

1 at a difference between wet and dry chemistry here in some  
2 ways.

3 My presentation is more focused from a  
4 formulator's perspective, how we think a formulator would  
5 benefit from these technologies. To give you a sense of  
6 what these tools are, here is an example of gasoline  
7 analysis. On the top, you have four different attributes  
8 being tested by different methods. You have octane engine  
9 taking 40 minutes, RVP analyzer, a GC method, and a density  
10 meter. All of those attributes can be measured on line or  
11 quickly with near infrared with the same spectra. So, one  
12 method is able to characterize or to gather information  
13 about various physical and chemical attributes.

14 So, in this case, the difference here is you  
15 essentially use pattern recognition tools to understand the  
16 relationship between the spectral attributes and those  
17 physical or chemical attributes of interest. Based on that  
18 calibration curve or the statistical model, you have a  
19 system that can evaluate a new sample that comes along.  
20 So, that's the framework under which many of these process  
21 analytical chemistry tools operate.

22 I have taken this from a website of a company,  
23 which I have obviously blocked the name out, for  
24 pharmaceutical applications. Here from the website it  
25 says, "from incoming raw material inspection to final

1 product release, instruments, software," and all these  
2 technologies have been available. You can see the progress  
3 that has occurred in this area over the last 10 years.

4 These obviously are available but are being  
5 currently used as an alternate. These are not generally  
6 regulatory methods. These are alternate methods which are  
7 in addition to the regulatory testing.

8 I would like to focus my thoughts on what I  
9 perceive as the impact on product quality could be by  
10 adoption of some of these technologies. In my opinion, the  
11 current situation begs us to take a hard look at this at  
12 this time. Combinatorial chemistry and high throughput  
13 screening essentially have created a scenario where the  
14 number of interesting, promising new chemical entities is  
15 humongous. As a result, development, including product  
16 formulation development, is becoming rate limiting.

17 There are two aspects which are challenging.  
18 Formulation development has always been considered as a  
19 black box because of the inability to reliably predict  
20 product performance changes when formulation/process  
21 variables are varied. Also, variable physical functional  
22 attributes of raw materials that are known to conform to  
23 USP or NF standards. Compendial standards have always  
24 focused only on chemistry, not on the physical attributes.  
25 So, functionality of excipients has not been a public

1 standard, and it's not likely to become a public standard  
2 because of the complex nature of the excipients, as well as  
3 multiple uses of excipients. It's a very difficult process  
4 to build public standards based on physical attributes.

5 Process analytical chemistry tools focus both  
6 on physics as well as chemistry at the same time and at the  
7 right place actually. So, here is an opportunity which in  
8 pharmacy at least we have not, in my opinion, taken full  
9 advantage of. The number of publications are humongous.  
10 Some of those you have seen in your handouts, and they're  
11 very impressive. But I think in terms of evolution, I see  
12 bringing these technologies in would really help move  
13 pharmaceutical manufacturing to the next stage quickly.

14 From my way of looking, over the last 100  
15 years, tablets that we make today are the same as we made  
16 100 years ago. In fact, aspirin is over 100 years old, the  
17 first tablet ever made. So, we have been making tablets  
18 and capsules essentially in the same way, the same process  
19 as for the last 100 years.

20 But during those 100 years, we have transformed  
21 pharmacy from an art to more of a science and engineering  
22 based profession. In the last 30 years, you have seen  
23 application of physical chemistry and chemistry principles  
24 coming in and engineering principles coming in, but we're  
25 not there yet. We still develop our formulations through a

1 trial and error approach, although that's a guided trial  
2 and error approach where you have a formulator with vast  
3 experience and can guide the formulation development  
4 program quickly.

5 But keep in mind, at least from the pharmacy  
6 school perspective, pharmaceuticals and other disciplines  
7 have sort of eroded away, and formulation development is  
8 not being taught in schools anymore, literally. So, the  
9 experience base and the knowledge base is to some degree  
10 eroding away. So, the trial and error has to be guided.  
11 In the absence of that, it becomes very difficult.

12 There has been a tendency towards moving to  
13 design of experiments with Professor Bancor and others who  
14 had initiated that, but 1994 Professor Shanguard did a  
15 survey of the pharmaceutical industry to see how many of  
16 them are utilizing statistically designed experiments to do  
17 formulation development. That number came to be 5 percent.  
18 So, the trend has not moved in that direction. So,  
19 although we would like to see more designed experiments and  
20 hopefully computer-aided design concepts to come in, they  
21 have not occurred.

22 Dosage forms have transformed drug delivery  
23 systems. The next stage is obviously intelligent drug  
24 delivery systems. If we are able to improve the  
25 formulation science, then we actually create more

1 opportunity to look at more creative options. Here's an  
2 opportunity. Batch processing to continuous and automated  
3 processing is obviously a desired next step in this  
4 evolutionary process.

5           However, coming back to the pharmaceutical  
6 product development process, here are some of the  
7 attributes that we have to address. It is multi-factorial  
8 and a complex problem. Significant reliance on formulation  
9 development is based on personal knowledge. Historical  
10 data is likely to have been generated by a guided trial and  
11 error approach. There are many choices of achieving target  
12 specification.

13           Therefore, I think from an FDA perspective, to  
14 evaluate some of those changes under SUPAC, for example,  
15 becomes a challenge. Without up-to-date information,  
16 there's a high potential for misjudgments, reinventing the  
17 wheel, and mobile institutional memory. We have seen in  
18 many situations approved products need frequent changes.  
19 They're not optimal.

20           So, if you look at the pyramid of  
21 pharmaceutical product development knowledge, I tend to put  
22 that knowledge base in low to medium in terms of level of  
23 sophistication in the details that it's able to resolve.  
24 The reason for that is most of our database is based on  
25 historical trial and error. Patent recognition and

1 generalization of that data is extremely difficult. We  
2 have heuristic rules of thumb and very few empirical models  
3 for developing formulation safety. With respect to  
4 mechanistic modeling, physical rules, we're not there yet.

5           How are we controlling unit operations now? If  
6 I take a simple unit operation, blending, the last two  
7 years I have been engrossed in blending problems and the  
8 criticisms received from industry of our guidance.  
9 Blending is a major thing in my mind right now, and  
10 therefore I have asked Dr. Raju to use blending as an  
11 example to illustrate some of the issues.

12           How do we control blending? We define the  
13 equipment, type, size, operating speed. We define a  
14 process time. Then we check whether the blend is  
15 homogeneous or not. So, you blend, put thieves in, collect  
16 samples, and check.

17           Wet granulation. We define equipment, define  
18 fluid addition, composition, volume, and process time, and  
19 check for moisture content after we dry those granules.  
20 These are fine but are limited in scope with respect to  
21 performance predictions.

22           Unit operations are intended to produce in-  
23 process materials that possess optimal attributes for  
24 subsequent manufacturing steps. We know that.

25           Do current controls always ensure consistent

1 | quality of in-process materials? They can't. One reason  
2 | is the physical attributes of the pharmaceutical raw  
3 | materials can be highly variable. We don't have a good  
4 | handle on that.

5 |           A consequence is processes do need to be  
6 | adjusted, and if you do adjust those beyond certain ranges,  
7 | you have to seek regulatory approval or some regulatory  
8 | evaluation is needed. So, it's an added level of scrutiny.  
9 | One of the whole initiatives of risk based is to reduce the  
10 | supplements.

11 |           So, the current situation, again to summarize,  
12 | in-process testing is the norm, not controlled. Blend  
13 | uniformity, for example, if I take that example, I'll stop  
14 | the blender, test, wait for the answer to go to the next  
15 | step. That's one way of looking at it. If it was  
16 | controlled, blending would have been done until it's  
17 | homogeneous and move on.

18 |           Process parameters and specification are set  
19 | based on limited data. Raw materials. We don't know their  
20 | functionality well. And a combination of all this. In-  
21 | process sample collection, testing, verification, and as a  
22 | result, a lot of exceptions that occur contribute to long  
23 | production cycle time. It was a bit of a surprise to me  
24 | that it could take 30 to 60 days to manufacture one batch  
25 | of tablets.

1                   Process validation. What are the limitations  
2 there and how are we doing that? I found this quote by  
3 Harwood and Molnar quite interesting. The publication was  
4 called Using Design of Experimental Techniques to Avoid  
5 Problems, published in Pharmaceutical Development  
6 Technology in 1998. They characterized current practices  
7 in validation as a "well-rehearsed demonstration that  
8 manufacturing formula can work three successive times." In  
9 their experience, "validation exercise precedes a trouble-  
10 free time period in the manufacturing area, only to be  
11 followed by many hours, possibly days or weeks, of  
12 troubleshooting and experimental work after a batch or two  
13 of product fails to meet specifications. This becomes a  
14 never-ending task."

15                   Clearly, companies would not release batches  
16 which fail specifications. It's the subject for recall.  
17 But here is a situation at least for temptation. If you  
18 your batches are failing, it leads to problems. And some  
19 of the court cases I was involved with dealt with these  
20 issues.

21                   I hope that is not a general observation. I'm  
22 sure it's not a general observation. But the example does  
23 illustrate what happens when quality is not built in, and  
24 quality cannot be built in till you really understand your  
25 processes and so forth.

1           The type of cycles times that you're looking  
2 at, which you will hear from Dr. Raju in more detail, are  
3 as follows. It takes 21 to 90 days to qualify a raw  
4 material. It takes about 60 days to manufacture and  
5 release a tablet formulation, and you'll hear more about  
6 this, so I will not deal with it.

7           So, what we are talking about right now is the  
8 next step in the evolution of process controls. When I  
9 started out in pharmacy school and my industrial training,  
10 this is how we did it. Reach out, grab some of the  
11 granules, squeeze them, see how they break, and then decide  
12 whether the granulation endpoint is reached or not. That  
13 was years ago. Things are different now, obviously.

14           But the next step in the evolution is to go  
15 more subjective, gather physical, chemical information  
16 about the granules to ensure that the granulation was  
17 optimal so the tableting next step would be as smooth as  
18 possible. And that's feasible now.

19           Modern in-process controls. I'll use near IR  
20 as an example because in our labs we have more experience  
21 with that right now. It's a noninvasive spectroscopic  
22 technique, and you could also use it as an imaging tool --  
23 and I'll show you some examples -- which has been in use  
24 for the last 10 years in the food and chemical industries.

25           It provides real-time control of processes

1 without having to collect samples.

2 One can potentially process material until  
3 optimal attributes are achieved, as opposed to stopping and  
4 testing.

5 And using pattern recognition tools, one can  
6 relate near IR spectra to both physical and chemical  
7 attributes of materials and hence be in a position to  
8 predict product performance and therefore improve product  
9 quality.

10 If I were to apply near IR technology to a  
11 tablet formulation, I chose a direct compression as an  
12 example. On the left-hand side, the conventional approach  
13 would be get the raw materials, do the compendial tests to  
14 make sure they meet the specifications, blend the product,  
15 test for blend uniformity, and keep in mind the only  
16 component that we test is the drug. One of the culprits  
17 that creates problems is magnesium stearate, very small  
18 amounts. We never test for that.

19 Compaction. We make the tablets. We check for  
20 hardness, thickness, weight, friability, and so forth,  
21 content uniformity and dissolution. All of those could be  
22 done literally at- or on-line with some of these  
23 technologies.

24 I'll give you an example of some of our work.  
25 Blend uniformity has been an issue and PQRI has actually

1 developed a proposal on how to address that. The proposal  
2 is posted on the PQRI website. But we wanted to look at  
3 the near IR imaging technique to see what can be done.

4 So, we were looking at tablets. These are  
5 furosemide tablets that I think were made at the University  
6 of Iowa. No. These are handmade tablets in our labs.  
7 It's a binary mixture of drug and excipient. What you're  
8 looking at is a chemical image. The tablets are white,  
9 colorless tablets. But the chemical image, the white areas  
10 are the drug, and the red spectrum is the excipient. So,  
11 looking at each of those pixels in the digital image, which  
12 was acquired in less than a minute, or actually in 30  
13 seconds, you get that picture. You can actually develop  
14 simple metrics to do the analysis.

15 Here is our University of Iowa product where we  
16 are looking at the scale of interest right now that's  
17 actually a small part of the tablet. So, with the current  
18 technology of blending, we can achieve uniformity far  
19 beyond what we had anticipated. So, blending should not be  
20 a problem. We are doing it right, but we are having  
21 trouble proving that we are doing it right right now.

22 So, here is, for example, if you analyze each  
23 pixel, you can see the complete distribution of the drug  
24 and concentration and so forth and how symmetric it is when  
25 it's uniform. When it's not uniform, you can see how

1 things change. This information can be gathered in  
2 minutes, if not seconds.

3 I've used another example. Since I mentioned  
4 magnesium stearate, here is a slide that Steve Hammond from  
5 Pfizer shared with me and what can be done which we could  
6 not do before. Two blends, one with good flow properties,  
7 one with bad flow properties. Look at the distribution of  
8 magnesium stearate in that. So, you can easily associate  
9 problems to solutions and develop causal links quickly.

10 Just to go on as an example, near IR is not the  
11 only one. Raman. You could have a three-dimensional Raman  
12 spectroscopy of a tablet's surface and look at where the  
13 aspirin is and where the excipient is, and actually do  
14 quantitative analysis at the same time.

15 Here is a very recent publication from Dr.  
16 Lodder's group from Kentucky, published in the Pharm. Sci.  
17 Tech. of AAPS. Since it was available on the web, I  
18 downloaded this. Here you're looking at the ability to  
19 analyze aspirin and salicylic acid after it has been  
20 packaged. So, this is through a blister pack. You don't  
21 even have to wait. Through a blister pack you could look  
22 at aspirin and actually look at the moisture content of the  
23 tablet without having to open the blister pack.

24 So, the technology is maturing, but there are  
25 many challenges. One of the challenges I have heard,

1 talking to people from industry and in a recent trip to the  
2 U.K., the New Technology Forum, is the mind set is out  
3 there that FDA will not accept it. FDA will accept it if  
4 there's good science. Period. There's no question about  
5 it.

6 Also, I think the mind set is also in  
7 companies. Regulatory affairs departments within companies  
8 have to be convinced, and others have to be convinced.

9 There are challenges. Method suitability and  
10 validation approaches have to be developed, have to be  
11 agreed, a consensus has to be developed.

12 Chemometrics is something which traditional  
13 analytical chemists are not aware of, are not fully  
14 cognizant of, and don't have expertise in. So,  
15 chemometrics, pattern recognition will have to come in and  
16 we'll have to learn how to deal with that.

17 Also, mechanisms of regulatory introduction  
18 have to be developed so that investment costs and other  
19 cost issues can be managed properly.

20 So, to summarize, potential benefits for  
21 process analytical chemistry. I believe that manufacturing  
22 and quality control cycle times can be reduced and costs  
23 can be reduced. It can improve product quality, provide  
24 information during processing for feedback control. Direct  
25 sampling problems are eliminated and can facilitate

1 establishment of causal links between product and process  
2 variables and product performance.

3 Improve patient and operator safety. Keep in  
4 mind many of the products are very important, and operator  
5 safety is a concern.

6 And I firmly believe there's a win-win  
7 opportunity that will require out-of-the-box thinking on  
8 both FDA's and industry's side to move forward. I hope you  
9 would support my perceptions here, and I would like to hear  
10 your thoughts on this.

11 The second presentation will focus more on the  
12 opportunities that exist in reducing cost, time of  
13 development, and so forth.

14 Questions?

15 DR. BYRN: Questions for Ajaz? I'm sure we'll  
16 have a discussion after the second one, but are there  
17 questions for Ajaz right now?

18 DR. ANDERSON: Did you say that you are using  
19 near infrared in your laboratory?

20 DR. HUSSAIN: Yes.

21 DR. ANDERSON: Could you just take a couple of  
22 minutes and comment on it, on the results that you're  
23 getting?

24 DR. HUSSAIN: Actually I had planned to share  
25 with you some recent information. I had -- Robbe Lyon is

1 here -- the division director, to give me a comparison  
2 about HPLC and near IR. They are currently doing  
3 furosemide analysis content uniformity. They estimated  
4 time to do a USP analysis for furosemide tablets is 34  
5 hours, using the HPLC technique. It's 3 hours with near  
6 IR. The complete analysis takes 3 hours, everything.

7 The sample costs for a stability study that we  
8 are doing again. Costs per sample using near IR, again for  
9 the same drug, is about \$2.25 compared to \$47-something for  
10 HPLC. So, that's our experience in our hands.

11 Instrumentation cost is almost comparable. The  
12 instrument that we have is about \$75,000 for the near IR,  
13 and HPLC in high end is \$40,000 to \$50,000.

14 DR. HOLLENBECK: Ajaz, in the backgrounder,  
15 there was the statement that you made that went like this.  
16 The regulatory environment under which the pharmaceutical  
17 industry must operate is often suggested by many to be an  
18 impediment for introducing these tests. I think you just  
19 covered that in your slide by saying that FDA won't accept  
20 it, but can you expand on that a little bit more in terms  
21 of what impediments exist and what steps can be taken to  
22 get rid of them?

23 DR. HUSSAIN: The challenge here is I think  
24 uncertainty. We don't have a guidance out. There are many  
25 parts of the agency that have to deal with this from the

1 field to the center. So, that itself is a challenge.

2 I think the major challenge is validation in  
3 terms of how do you validate this. I'll use blend  
4 uniformity as an example. Sampling using a thief is a  
5 challenge. It creates this problem. But the mind set is  
6 to validate near IR, you have to compare it to that method.  
7 I think if you're looking at a modern technique, with the  
8 potential of becoming the gold standard, you have to  
9 compare that to some standard. We had that discussion this  
10 morning with clinical. The same issues cross over. So,  
11 again, I think we have to think outside the box how you  
12 validate some of these tools and bring those in without  
13 adding a burden.

14 What will we plan to do is to create a  
15 subcommittee. There are a number of challenging issues.  
16 In my letter to you all, I suggested that we really need a  
17 multi-disciplinary team to look at the feasibility and so  
18 forth. So, a subcommittee under this committee would be my  
19 proposal.

20 DR. BOEHLERT: May I just make a comment as  
21 well? Maybe we need to think even further outside the box  
22 when it comes to things like blend uniformity testing  
23 because right now things like the Barr decision are forcing  
24 manufacturers to take single dosage units, one to three  
25 times the size of the dosage units, take it off-line and

1 test it by a technique, and that creates the problems. So,  
2 testing is one aspect, but it's other things that are  
3 impacting what we have to do today.

4 DR. BYRN: Our next speaker is a good friend of  
5 mine, G.K. Raju, who is going to give a case study on in-  
6 line process controls.

7 DR. RAJU: I'm not sure if this is a good thing  
8 or a bad thing. I haven't been to an advisory committee  
9 meeting in my life. I'm not sure that it's a good thing.  
10 I'm not a pharmacist. I'm not a doctor, but I want to help  
11 make medicine cheaper, better, and faster for patients  
12 because I think it's a great thing to do, and I want to do  
13 whatever little I can to help do that. I am a chemical  
14 engineer, and think of the next few slides as a chemical  
15 engineer's view of the pharmaceutical industry.

16 This is the training I come with that affects  
17 how I look at things. That affects what I'm going to say  
18 when I look at these things. So, I'm going to summarize an  
19 outsider's look at the pharmaceutical industry at multiple  
20 levels. Hopefully I have something intelligent to say.  
21 I'm not really asking for anything. I'm asking really for  
22 you to lend me your eyes and ears and hopefully your mind.  
23 And this is a summary of what I think I'm going to say.

24 Since I'm new to this field and this audience,  
25 I'm going to tell you where I come from. I'm then going to

1 have two very high level looks very quickly at an industry  
2 at a very high level. I'm going to go through a lot of  
3 slides, and that's because I want to go through a lot of  
4 things quickly. So, don't worry if you don't get the  
5 details. You have it in your background slides.

6 I'm not from New York. I am from Boston, and  
7 I'm also from India so I can talk pretty fast.

8 (Laughter.)

9 DR. RAJU: So, this is the introduction to  
10 where I come from, sitting in the chemical engineering  
11 department and also in the business school at MIT. We then  
12 decided to work together in what we began to call the MIT  
13 Pharmaceutical Manufacturing Initiative. And our passion  
14 was to begin to describe and capture the opportunity to  
15 impact this part of this pharmaceutical industry.

16 What was that part? And we had to draw a  
17 diagram. That was one of the first things we were taught.  
18 Let's draw a diagram that represents that little block.  
19 That diagram has pieces over time and pieces over space.  
20 That's pharmaceutical manufacturing. There's the process  
21 development over time, and then there's routine  
22 manufacturing. We have the chemistry changing in the  
23 active ingredient. The dominant physics, which is what are  
24 the components. Small aspects of physics which is what  
25 form should these components be in and how do I package

1 around it. No chemistry. Physics in the middle two,  
2 chemistry here, sometimes biology, and some paper most of  
3 the time around it. That's what pharmaceutical  
4 manufacturing looked like.

5 So, if I was going to measure and characterize  
6 it, I had to measure it in terms of something, and we all  
7 know what dollars are. We can debate what quality is, but  
8 we have a pretty good understanding of what that is. Time  
9 means the same thing to everybody. It's the time on a  
10 clock. And safety can mean different things to different  
11 people.

12 For this presentation, I now have a choice  
13 which one of these to talk about. It seemed like the most  
14 neutral and seemingly communicative thing to do was to talk  
15 about time because all of us know what that is. It's  
16 pretty neutral. It's important. It's the same thing for  
17 everybody. So, for the rest of the presentation I'm going  
18 to talk about time, looking at it from two points of view.

19 Routine manufacturing. When we first looked at  
20 pharmaceutical manufacturing, it seemed like the word only  
21 meant routine manufacturing, which was this, and process  
22 development somehow was disconnected from it. So, routine  
23 manufacturing. The first question was, what is routine  
24 manufacturing and where is the time spent?

25 So, we said let's look at some blocks of

1 routine manufacturing. We got together a consortium of a  
2 lot companies. Over these I've worked with about 25  
3 companies representing 80 or 90 percent or more of the  
4 pharmaceutical business. One of the focus areas was the  
5 formulation of a particular consortium, and we said, let's  
6 start looking together at your plants from an outsider's  
7 point of view and measure where the time is spent.

8           Once we decided to do that, the question then  
9 became which products do I look at. Everybody makes  
10 different kinds of products. So, we said we can do high  
11 volume products. Those are the billion dollar products.  
12 We can do the complex ones, and we had some discussions  
13 about complexity, and then there were liquid lines which  
14 have totally different manufacturing and testing  
15 priorities. Which one do we choose?

16           Since we had no basis to choose, well, yes,  
17 about 80 percent of the products are solid, so we could  
18 look at the first category, but liquids were distinct. So,  
19 we wanted to know what they were about as well. So, we  
20 said we don't really have a basis to choose between, so  
21 let's do a little bit of all of them. Let's look at the  
22 high volume products, for example.

23           The first step I was taught was to draw a  
24 process flow diagram. From a chemical engineering view, we  
25 said let's draw so-called unit operations, what is

1 | happening in that step, chose the color blue. This is the  
2 | active ingredient that we don't study, and I showed you  
3 | that block on the previous slide.

4 |           The first thing that came to my mind is why are  
5 | these tests at the two ends of it. I began to understand  
6 | that, of course. But why is it that we don't measure  
7 | anything in between? We had two dominant places where we  
8 | did testing: at the end, at the beginning. We had very  
9 | minimal in-process testing in my opinion. I was surprised  
10 | at the very little testing that happened along the way. It  
11 | was something I wasn't used to, and I kept asking why.

12 |           I said, yes, we make a product that goes into  
13 | somebody's body. That's important. We have to make sure  
14 | its safe. We have to worry about its efficacy. I don't  
15 | know if it's 210 or 211 on your CFR documentation, but  
16 | these are the definitions about purity. I read them up and  
17 | I said, okay, this makes sense that you have to do these  
18 | tests because they mean something in the body. But why are  
19 | we doing it at the end? Yes. That's the last place we can  
20 | do it. We can be pretty sure that when it comes out, it's  
21 | done.

22 |           But what are the consequences of only doing it  
23 | at the end? Maybe we should think about that as well.  
24 | It's not just a zero sum game here. There are some  
25 | consequences, possibly, about measuring things here when

1 | the causes of that variability may be very early on.

2 |           Second, raw material testing. I was surprised  
3 | at how little implications of the physics of the process  
4 | were captured in that test. If formulation is all about  
5 | the physics of the process, the main test was really a  
6 | chemical test. And I wondered why. Again, as you wonder,  
7 | you start saying, let me look at a few more cases. Maybe  
8 | this is just one example.

9 |           So, I used the same colors now, and I simply  
10 | said instead of drawing a process flow diagram in space,  
11 | let's draw it in time. So, it's the same colors now. All  
12 | I did was say let's draw them in time and look at it from a  
13 | company's point of view. What came out instantly was an  
14 | observation that the red testing took significantly more  
15 | time than the making itself. Were we pharmaceutical  
16 | manufacturers or were we pharmaceutical testers? It's just  
17 | a general open question to ask. So, testing dominates what  
18 | we do. Clearly there are important reasons.

19 |           Is this just process A now? Maybe if you look  
20 | at a few more, we'll see if there's some pattern here.  
21 | Another big high volume. Usually now we're talking about  
22 | close to a billion dollars or more, so significant. I'm  
23 | not doing products that are not important. It looked like  
24 | a simpler process, the tests very much defined by the body  
25 | now. The tests are very much defined by what a tablet

1 | should do. And the place is in the same place again, very  
2 | little in the middle. The consequences in time look so  
3 | similar. Again, about 20 days from the beginning and the  
4 | end, less time in the actual making of the tablets. Then  
5 | there's the API which I don't even count and this inventory  
6 | afterwards that I don't even count.

7 |           Let's look at another one. Is there a pattern  
8 | here? Yes. The tests look very similar, almost expected  
9 | now. The times keep coming almost similar. So, it's not  
10 | the company. It's not the location. It's not the product.  
11 | Maybe it's just the high volume products that look like  
12 | that because that's what I've seen so far.

13 |           Here's another high volume product that looks  
14 | very similar.

15 |           Just to be sure, let's look at a fourth one,  
16 | and it looks very similar again. We take a couple of  
17 | months to go through the system, half or more than half of  
18 | the time testing it in some way. Does that testing take  
19 | that long? What drives the timer on those tests?

20 |           But before I go into that question, let's make  
21 | sure that we've seen a representative -- if you would go  
22 | back to the active ingredient manufacturing, you would see  
23 | a much longer time. And if you look at this time and you  
24 | add it up from the beginning to the end, you ask yourself  
25 | is this what we want to do in pharmaceutical manufacturing.

1 | What are the consequences of allowing us to do it? That  
2 | is, if there's some variability here and because of our  
3 | testing and the way we define it, we see it 100 days later,  
4 | how are we going to relate the cause and the effect, and  
5 | what happens to our problem solving of asking why we see  
6 | something? Does time affect that kind of a thought  
7 | process?

8 |           We finished high volume products. Maybe it was  
9 | just those billion dollar products that look like that.  
10 | Let's look at a complex process, complexity measured in  
11 | many ways. One measure would be the number of steps, which  
12 | in the previous presentation you said wasn't important. In  
13 | this case it clearly was a complex process. I try to make  
14 | sure they always fit on one slide, so I don't take too many  
15 | slides to explain it.

16 |           But again, you have a process that does a  
17 | number of things again and again. The way we measure how  
18 | well we do it is testing at multiple places. If you look  
19 | at that process in time, this is what it looks like.  
20 | Again, the testing dominates the time very much.

21 |           Let's say a liquid line, and liquids are  
22 | different in the sense the uniformity is a little easier to  
23 | establish. Micro-testing is a little bit distinct about  
24 | priorities in terms of testing. So, let's look at a liquid  
25 | line, although those are not the dominant dosage forms.

1                   Yes, the basic tests around it look very  
2 similar. The sterility test clearly is going to show up on  
3 the next slide. If we now say let's put the process and  
4 draw the time around it, you really start wondering why  
5 this ratio of the testing to process is so different. If  
6 you then say let me try to summarize and see if I can get  
7 something important around it, you ask where is the  
8 leverage.

9                   The first is to make sure you put all those  
10 products on one slide and ask do I see a pattern, and we do  
11 see a pattern and the pattern being that almost always the  
12 testing seems to take at least as much time as the making  
13 itself.

14                   What shall we do about that? First, we  
15 probably have to understand the testing itself. So, if  
16 that is at least the single biggest thing we should look  
17 at, maybe we should look at it in a little bit more detail.

18                   So, the big picture. Let's got to the next  
19 level of the picture for each of these red bars. So, we  
20 said let's look at those tests. What really are those  
21 tests and where is the time there? Let's look at any of  
22 those tests, at the beginning, at the middle, at the end of  
23 a process, and it always has a unit operation that ends.  
24 It stopped. You take a sample from the process. You hold  
25 the sample in the plant. You then document your sampling.

1 You transfer it to the lab. You then batch it in the lab.  
2 You then actually do your test right here, then data  
3 collect. You document. You transfer from review, and then  
4 you make a decision about what?

5 If you looked at your test itself, it's this  
6 tiny little thing here. And Ajaz says he was comparing  
7 HPLC with NIR. What kind of a difference does it make?  
8 But Ajaz also said at-line and in-line, and it's those  
9 aspects that the opportunity is there. It can be Raman.  
10 It can be laser-induced fluorescence. It can be NIR. But  
11 it's the fact that at-line and on-line is what takes care  
12 of these red bars. That's where the variability comes in  
13 in many cases because we as human beings don't like to do  
14 the same thing again and again for too long. Sometimes  
15 that shows up in many places. But yes, we can do something  
16 about the testing, but yes, this is where the pieces are.

17 So, if you look at the technology opportunities  
18 around it, the only way to attack this place completely is  
19 the word on-line. Along the way we go from off-line to at-  
20 line, in-line, and on-line. You can see the transition,  
21 and I think there's an opportunity for the whole industry  
22 to make that transition test by test, product by product,  
23 and I think that's a lot of time that we can do something  
24 about.

25 So, to repeat, it's not the test itself. It's

1 the before and the after of the test, which is 98 percent  
2 of time opportunity.

3           So, what did we say? We said if we were all  
4 about making quality, we measure it very infrequently. Why  
5 do we measure it so infrequently? Because it's a lot of  
6 work. It takes a long time. The scale of the test is  
7 based on the scale of the human being. The manual nature  
8 of the off-line test defines the cost-benefit tradeoff of  
9 doing that test. Hence, we do it at the end because we  
10 have to do it at least at the end we think.

11           But once we make it on-line, the tradeoff of  
12 number of tests to the cost of the tests has now changed  
13 fundamentally. So, one test and two tests are not  
14 necessarily once and twice more expensive in terms of the  
15 organization's time, cost, and possibly even quality. We  
16 want to make it more continuous. The FDA would be very  
17 happy. So would we because we would actually have  
18 differences in our times, we would have differences in our  
19 processes, and we would attack the off-line test once and  
20 for all.

21           So, that's the first message of a chemical  
22 engineer looking for a little bit of time at routine  
23 manufacturing over space. We covered different products.  
24 We thought we had some conclusions. But clearly I had to  
25 look at it over time, and there were so many things I could

1 | look at. From a chemical engineering perspective, I would  
2 | love to look at the active. There's something chemical  
3 | going on.

4 |                 But the consortium, when we sat together and we  
5 | said we said we can do all of this, we can study all of  
6 | this, they said look at blend uniformity. Why would we  
7 | want to do that? You blend for five minutes and all you  
8 | want to do is figure out whether you're done? That's  
9 | really boring. No. This is what we want you to do.

10 |                 (Laughter.)

11 |                 DR. RAJU: Okay, I'll do it.

12 |                 We did a lot of other things, but when Ajaz  
13 | invited me, I said I'm going to talk about all these  
14 | things. He said blend uniformity.

15 |                 (Laughter.)

16 |                 DR. RAJU: So, I said I'm gong to have to do it  
17 | here too. So, that's the next set of slides that I have.  
18 | It's blending.

19 |                 Let's define what blending is. What am I going  
20 | to try to find out? I've looked at space. Let's look at  
21 | time now just to be creative. I want to look at process  
22 | development and the measurement of quality, particularly  
23 | blend uniformity along the way.

24 |                 Here is my on-line sensor and then benefits are  
25 | a little less, but it's at-line and in-line compared

1 | against off-line. This sensor has many possibilities and  
2 | near infrared is one. A number of companies have worked on  
3 | it. We've patented a technology called laser-induced  
4 | fluorescence within this consortium of companies. There  
5 | are different aspects and different ways of measuring  
6 | uniformity. But the conventional way, we're all the same,  
7 | and we all do thieving because that's how we started off  
8 | doing it a long time ago.

9 |           But let's understand what blending is. Before  
10 | we figure out what on-line do, we've got to figure out what  
11 | blending is first. So, blending is actually not just the  
12 | mixing; it's actually a whole bunch of operations before  
13 | and after it. You clean a blend. You load the active  
14 | excipients. You then finally mix. Then you sample. You  
15 | transport to a lab. You analyze, and then you have results  
16 | about uniformity. You have different kinds of results.  
17 | You can be undermixed, and so you mix longer. You could  
18 | get it right, and there's a minimum specification. I think  
19 | it's RSD 6 percent, and you usually get 3 or 4 percent. I  
20 | was happy to see that.

21 |           But sometimes you have this thing called  
22 | overblending that I never learned in chemical engineering.  
23 | They call it desegregation. They said sometimes its  
24 | demixing. But something happens so it really is not a good  
25 | idea to go beyond that time too. Do we understand it? No.

1 Well, let's not get into that right now.

2 But let's look at the material and information  
3 flows. The material flows through as you go forward. The  
4 information all comes far away from the lab many, many,  
5 many, many hours away. You then make a decision about the  
6 material based on another organization, which is what is it  
7 about batching the HPLCs? Because they have only so many  
8 and they want to make best use of their samples. So, what  
9 are the consequences? So, that's blending.

10 If we agree that that's blending, let's see if  
11 we can do blending on-line. Here's an example of a  
12 collaboration between MIT and Purdue, two universities  
13 actually collaborating. We don't have a pharmacy school  
14 and we have a chemical engineering school and a business  
15 program. Here is a bin blender at Purdue University in  
16 their pilot facility. We do the lab scale trials in our  
17 laboratories at MIT, and when we scaled up in collaboration  
18 with near infrared and LIF together. And this is basically  
19 a light-induced fluorescence. There's no laser. It looks  
20 at uniformity in three different locations.

21 The question is a very simple one, which is  
22 when are you done? There is no deeper question about what  
23 are those patterns, what do they mean. When are you done?  
24 It's very clear that we could do it very easily and very  
25 robustly.

1           We were pretty happy about when we were done,  
2           and we said we're very excited. How do we know whether we  
3           got it right? You're going to know if you got it right  
4           when you compare it against thieving.

5           Okay, I know I'm uniform. I have to compare  
6           against thieving. You told me thieving was a problem with  
7           the sampling and the manual operation. Now, is it going to  
8           be difficult for me to compare a much superior test with an  
9           inferior test and that would be my benchmark? Can we look  
10          deeper about content uniformity? I can do a lot more  
11          tests. I can look at different places. I don't think  
12          that's going to work. You have to measure it against  
13          thieving.

14          So, we did and we were very lucky that that  
15          works well. This is the laser-induced fluorescence, and  
16          it's very similar for the near infrared. We can certainly  
17          talk about that as well. On average for different active  
18          concentrations, and we were able to go very low. For  
19          important products, I think we have a great answer. The  
20          endpoint was very consistent and less variable. Not  
21          necessarily a tradeoff between the FDA and the industry,  
22          between quality and cost, but we got them all less  
23          variable. What does that mean in terms of time and cost?  
24          Well, I told you I won't talk about cost, but I will try to  
25          talk about time.

1           So, if Ajaz represented some part of the FDA  
2           and he was looking for just this variation, hey, we're not  
3           doing too badly. But if we represented the companies, how  
4           would this help us? Why would we have to go through this  
5           pain of showing equivalence? Hopefully we'll get something  
6           out of it. Maybe it's cost. At least it has to be time.  
7           So, the answer is so what. We've got to get something out  
8           of it. It seemed like we had some variability reduction.

9           The "so what" comes down to let's compare --  
10          and I took one of those case studies now, one of these  
11          processes that three different excipients were added, one,  
12          two, three. Here is the conventional off-line test, and I  
13          have the on-line test. And I have the maker of this  
14          product, and I said what are your blend process development  
15          times.

16          But I said let me not stop there. We have a  
17          consortium of seven companies. Let's capture all of those  
18          times so that I don't have to then succumb to the argument  
19          that says it's just that company that doesn't blend very  
20          well or do the process development.

21          So, we collected blend process development time  
22          from all the seven companies and everybody was different.  
23          So, we said let's capture all their data, but let's start  
24          asking questions around the whole blending operation.  
25          Let's define the blending operation. The off-line one has

1 a number of components, brown representing the material  
2 flow, as I said before, blue representing the information  
3 flow. Brown, material. Blue is information. Information  
4 flow and material flow are two different tasks.

5           When material is separate from information,  
6 what is the space in between called? It's called  
7 inventory. When you can combine material and information  
8 together, that's when you can deal with the fundamental  
9 drivers of inventory. You have to wait to get the  
10 information. You wait with the material. And that's  
11 called inventory. So, we wanted to get these two things  
12 together.

13           And then uniformity is done differently in  
14 manufacturing and is done differently in process  
15 development. Again, it's done differently if you're a  
16 generic versus a brand name. But in many cases, depending  
17 on the country, you don't necessarily have to do the  
18 content uniformity test at the end of the blend while  
19 you're manufacturing. You often do it during validation,  
20 often during process development. Some of the generics do  
21 it around the manufacturing as well. Some countries would  
22 do it in the manufacturing as well.

23           But let's look at process development now  
24 because that's what we're going to look at and figure out  
25 what is the material/information flow going to be for the

1 on-line technology. Where's the brown? Where's the blue?  
2 They are in the same place, and this is the decision. Here  
3 is the material/information flow, so complicated. Here is  
4 the simple flow. We measured it where the cause of the  
5 variability is, and we can do something about it.

6 So, let's collect data from all these  
7 companies, and we have the seven companies. How long do  
8 you take to clean? How long do you take to load? How long  
9 do you take to discharge, sample, transport, test, hold?  
10 And we had all the seven data entered in, and we said now  
11 let's simulate each of these case studies.

12 So, we said let's take each of these companies  
13 and do blend process development the way they did it. We  
14 said here's all these tests. We're going to represent all  
15 these tests based on the time of what they took. Here is a  
16 representation, a model of each of those steps. Modeling  
17 is a really not so commonly used thing in this industry as  
18 well. But let's look at each of these steps.

19 For example, this is the QC lab. You transport  
20 to the QC. I told you about all the components. You hold.  
21 You retrieve the samples. You prepare. You test. You  
22 analyze. That's inside the lab. Here's the actual  
23 blending. Here's the actual charging of the active  
24 ingredient and you can say you usually have to clean and  
25 then you have to load the active. And you represent all

1 | those steps.

2 |           This is now two years old, and when we were  
3 | presenting at the consortium of the pharmaceutical  
4 | companies, we said it's a few more months before it's the  
5 | start of the millennium. And I said let's start the  
6 | millennium -- this is way back from our time now -- the old  
7 | way. Let's do blend process development the way we did it  
8 | for now I don't know how many years. If aspirin was made  
9 | this way, then that's a lot of years. So, let's do it that  
10 | way.

11 |           So, we're going to start using the actual data  
12 | from each of these companies. Let's start and do blend  
13 | process development. And here's the actual time that it  
14 | takes, and you can see the 1st of January is now the 3rd of  
15 | January and we're waiting for our first batch to come out.  
16 | It's now the 4th of January. This is actual time based on  
17 | the data that we collected. Still waiting. This arrow  
18 | indicates that we got our first batch with an acceptable  
19 | RSD. Now, we got one. We are really happy now.

20 |           We look at our plant and we see a whole bunch  
21 | of samples waiting to be analyzed, so-called sample blends.  
22 | We don't know whether this is right. We don't know how  
23 | many we have to do. We make a lot and we're waiting for  
24 | the analysis. It's a whole other organization somewhere.  
25 | This is inventory space, information and material flow

1 | being disconnected.

2 |           Let's go inside our lab and see what they're  
3 | doing. We go inside our lab and you can see they have a  
4 | whole bunch of samples to deal with. They're working  
5 | unbelievably hard, and you can see that it's at different  
6 | places. Some are being held. Some are actually being  
7 | tested. Then you can see some are being analyzed.

8 |           You can now look at the QC people, and there  
9 | are QC/QA people in that organization, red indicating that  
10 | they're busy, and you can see they're very, very, very busy  
11 | in the lab. They're both very busy. We got our first  
12 | blend.

13 |           You can now look at all your HPLC equipment,  
14 | and if it's red, they're busy too. So, if HPLC is busy, if  
15 | people are busy, there's inventory in your plant, you got  
16 | one correctly.

17 |           Now, you have this interpretation of  
18 | validation, if you remember Ajaz saying in his  
19 | presentation. This is a lot of work. If I could just get  
20 | three right. So, you say I've done one. It's now the 4th  
21 | of January. Let's try to get a couple more. Oh, everybody  
22 | is working so hard. Everybody is so busy. What should the  
23 | right head count be? How many HPLCs should I have?  
24 | Terrible questions asked around a terrible technology. The  
25 | wrong questions.

1                   But you finished one. You got two. It's the  
2 5th of January. You took five days. You got it out. Now,  
3 there's some people in the organization, so-called  
4 processing people, who say you know what? We got it right.  
5 We got three done. You know, maybe we should do a few more  
6 so that we just understand the area around it.

7                   But then you have your marketing people. You  
8 have your business people who look at your plant.  
9 Everybody is so busy. You have the inventory. And they  
10 say it's all about time market.

11                   So, what are we going to do? Okay, everybody  
12 is busy. This is three runs in a row. This is content  
13 uniformity. This is blending.

14                   Let's go to the next step. We have an envelope  
15 around which we've done data. We have data. Now we're  
16 ready to go to the market, and that's now the 5th of  
17 January.

18                   As another alternative, I also challenged the  
19 companies and the consortium to say let's go back in time  
20 and start that same millennium, January 1st 12:00 midnight,  
21 run everything the same. That is, you clean the same way,  
22 you load the same way. The only thing you do differently  
23 is the monitoring of content uniformity. So, you start the  
24 same time too.

25                   Now you figure out what you want to do about

1 | it. So, you run your batches. You watch the clock and you  
2 | do everything else the same. It's 10 o'clock on the 1st of  
3 | January. I finished one. Let me just take a look at my  
4 | lab and see what they're doing. Red means they'll be  
5 | really busy. Wow. Now, is the question now should you not  
6 | have those QC people? No. You want your QC people to do  
7 | thinking jobs instead of doing jobs. This is an  
8 | opportunity for them to be auditors and trainers and QA  
9 | people. I think they're going to enjoy themselves more if  
10 | they don't have to move in batch samples.

11 |           Let's just take a look at our HPLC equipment  
12 | that Ajaz had I think underestimated at \$45,000. You just  
13 | freed that up too, but you did put a lot of investment  
14 | around your on-line sensor. But guess what? We're very  
15 | happy. We've only got one right. It was pretty fast.  
16 | Let's see if we can get a few more. We got two. It's the  
17 | first day. In about 24 hours, we just finished three and  
18 | now we're asked the question, you finished three, one is  
19 | random, two is minimally a pattern, three is a law in some  
20 | disciplines. Is this a law? Do we know a blending? Do we  
21 | know the uniformity of our blending?

22 |           Shall we do a few more? Yes. QC people are  
23 | there to analyze the data to figure out what your next run  
24 | should be. You don't have things sitting around. The  
25 | costs are making that decision of a few more. You know

1 | you're going to succeed. You can do some runs around it.  
2 | And maybe you can go back to the real deeper spirit of  
3 | CGMP. That's four. That's five. How many do you want to  
4 | do? Six. Okay, two days. We did seven runs. We did more  
5 | than twice as many in less than half as much time. This is  
6 | what technology can do for us.

7 |           Now I've asked the companies -- this is  
8 | obvious. The technology is in place now. This is your  
9 | data. I presented it to you. Why isn't it done? It's  
10 | been around for a long time. The first response is I've  
11 | done so much of this NIR stuff. I have so much data. But  
12 | the FDA just won't accept it.

13 |           I actually first met Ajaz at the PhRMA meeting,  
14 | and he presented right after me, which is when the idea for  
15 | this came up. I ran after him and I said, Ajaz, why  
16 | haven't you guys accepted it, and he just said I have not  
17 | seen one application with near infrared submitted to the  
18 | FDA yet.

19 |           Are they wrong? No. They're both right. It's  
20 | a perception. Number one. Second, it's a limitation of  
21 | saying you want to do a test-to-test comparison.

22 |           Together, I challenge this advisory committee  
23 | to break out of the box to see if we can break through that  
24 | barrier. I can see the logic for that test-to-test  
25 | comparison. I can do the same thing too. But let's look

1 back to why we had that test. What does it mean for all of  
2 us? A lot, just for that one step. I took the simplest  
3 possible step, and it gets better every time. Blending.  
4 On-line blending process development. Off-line whether you  
5 have one, two or three blends. A factor not 10 percent. A  
6 factor of 10 improvement to a factor of 15 improvement of  
7 that process development time just for blending.

8 But even better. There is a predictability of  
9 that time, which means you know when to start your blend  
10 process development, you know when to build your plant, you  
11 know how big to build your plant. That is about  
12 variability of the organization. It depends less on the  
13 organization now. This is the opportunity.

14 I listened to the presentations and everybody  
15 seemed to believe uniformity is an important issue. But I  
16 challenge that on that important issue, to make an  
17 important leap in working together to be able to capture  
18 some of these benefits together. I don't even talk about  
19 the quality variability issues because I said I will talk  
20 only about time today.

21 So, we looked at the top level routine  
22 manufacturing, and we quickly got some pictures that told  
23 us something and we said where do we look now. We then  
24 took the simplest possible operation and we said let's take  
25 the simplest technology -- and there are three or four of

1 | them -- and look at the opportunity that we have ahead of  
2 | us.

3 |           As I come to the end of my presentation, I'm  
4 | going to take off on a couple of things that I said before.  
5 | We want to monitor quality continuously. Because of the  
6 | cost of doing it today, we do it at the end. The  
7 | consequences are large and we all deal with it together as  
8 | companies and regulators and society. So, on-line  
9 | technology, at-line technology allows us to break that  
10 | tradeoff and measure continuously where we can all win  
11 | together.

12 |           We have extended this work beyond blending. In  
13 | fact, I would have rather talked about all of those. And  
14 | we've looked at different parts of the process. Being a  
15 | chemical engineer, I like the first part. But we looked at  
16 | a lot of these, including some microbial tests, flow,  
17 | tableting transport. We looked at high volume products.  
18 | Here is an example of some of the data that I deliberately  
19 | don't show you the axis on, but here is where you can  
20 | monitor in the active ingredient. Here's the blend  
21 | monitoring data. Here's the flow data, and you can measure  
22 | uniformity during flow and you can measure tablet  
23 | uniformity.

24 |           The challenge now is to ask yourself what is  
25 | content uniformity as the whole process. How do I show,

1 | when I bring in revolutionary technology, that I'm actually  
 2 | more uniform over the whole process? How do I get myself  
 3 | out of the way of saying it should be a test-to-test  
 4 | comparison when the case for the test and the manual aspect  
 5 | of a test is the technology problem? With all of these  
 6 | together, I showed you the opportunity for improvement  
 7 | here. I showed you the opportunity for improvement over  
 8 | just blending.

9 |           If you look at a three blending case -- I  
 10 | wanted to go back to that -- you can see as your off-line  
 11 | and on-line get to see more and more steps, the difference  
 12 | between on-line versus off-line gets bigger because the  
 13 | cause and effect gets separated. So, there's a cumulative  
 14 | benefit as you add on more of these things together.

15 |           With that challenge, I will end my presentation  
 16 | saying that I took one aspect of manufacturing performance  
 17 | and summarized many years of work around saying we can do  
 18 | something about it. I deliberately don't talk about those  
 19 | aspects, but obviously they're significant and you can  
 20 | imagine that time translates to money and quality.

21 |           I would gratefully acknowledge my colleague,  
 22 | Professor Charles Cooney from MIT who would have loved to  
 23 | be here, but is on the mountains of Peru and couldn't come.  
 24 | Now for the last five years I've worked very closely and  
 25 | very excitedly with Professor Steve Byrn at Purdue. This

1 is my first introduction with a pharmacy school, and it's  
2 been great fun.

3 And CAMP is the Consortium for the Advancement  
4 of Manufacturing of Pharmaceuticals that has more than half  
5 the pharmaceutical industry associated with it.

6 And in addition, I've also worked with the MIT  
7 program on the pharmaceutical industry. We worked with  
8 basically almost every one of these pharmaceutical  
9 companies in different ways.

10 Last, because I think I'm beginning to say  
11 something real about real processes. I feel bad to put  
12 this up but I felt I needed to. Nobody is liable for  
13 anything I say except me. Some of the data -- I  
14 deliberately take out the y axis when it's not relevant.

15 But I think the basic message has to be very  
16 clear. I know the way to deal with that message. It's not  
17 obvious and not trivial, but that's what we're here for.

18 With that, I'm going to actually see if maybe  
19 Steve can have a few thoughts on this because we actually  
20 have gone well beyond some of this. Maybe he can decide  
21 whether he wants to talk about it or not.

22 DR. BYRN: Thanks, G.K.

23 One thing I should say, before we start and we  
24 talk about this, is Purdue is heavily involved in research  
25 and developing intellectual property in this area. So, you

1 should know that when I talk about my comments.

2 But G.K. touched on these areas because with  
3 one of his slides especially -- and this is probably the  
4 only comment I'll make -- we think there's tremendous  
5 potential for these technologies, on-line/at-line  
6 technologies, to reduce time to market of drugs. That  
7 could be achieved by starting using these technologies in  
8 development and then moving them through scale-up because  
9 you can get instant feedback when something is going wrong,  
10 and by using multiple sensors, multiple at-line/in-line  
11 techniques. So, there is a huge potential public health  
12 benefit because if we can reduce time to market and, like  
13 G.K. showed, ensure quality at the same time, then that's a  
14 very exciting game.

15 I think that's probably all I need to say.

16 I think we need to have a discussion now.  
17 Ajaz' proposal was to, I think, establish a subcommittee of  
18 this group to look at these technologies in more detail and  
19 report back. But let's have a discussion and see if there  
20 are questions for G.K. and go from there. Yes, Vince.

21 DR. LEE: I think this is very intriguing. Is  
22 there any other industry using these technologies?

23 DR. BYRN: Yes. I think G.K. can answer that  
24 one.

25 DR. RAJU: This is probably one of those really

1 extreme industries where testing takes a lot longer than  
2 processing. It usually takes a much smaller fraction.  
3 There are many good reasons for it. It's the legal nature  
4 of the test, the fact that we're making medicine.

5 But actually I think if we do it right, by  
6 moving it up, we can actually capture all of those. We can  
7 actually make -- I hate to say the word "better," but we  
8 can make equivalent, in a real way equivalent product I  
9 think. And we can all be a lot happier and have more fun  
10 doing manufacturing. I'm not sure I want to be  
11 manufacturing if all I do is doing. I want to do some  
12 thinking, and that's part of improving the process along  
13 the way within the constraints of the CGMP, of course.

14 DR. BYRN: Just to give one example, Vince, as  
15 far as we know, Lay's Potato Chips uses near IR to monitor  
16 the water content in a potato chip. They use many more  
17 units than we do.

18 DR. LEE: Let me ask one more question. Can  
19 you build into dissolution as part of the --

20 DR. BYRN: We do need to be fair. There are a  
21 few tests that are more difficult to put at-line or on-  
22 line.

23 DR. HUSSAIN: Steve, let me answer that.  
24 Vince, I think in the handout there's an article on  
25 predicting dissolution rate of carbamazepine. We in a

1 sense can essentially predict or control every parameter or  
2 variable that affects dissolution. So, dissolution can  
3 essentially come at-line in terms of the predictive mode.  
4 You're not actually doing the dissolution, but you're  
5 essentially ensuring that dissolution would be acceptable.  
6 So, we'll have to think out of the box how to address that.

7 DR. BYRN: Yes. To put the actual test on-line  
8 would be difficult, obviously, because you've got a time to  
9 dissolve.

10 DR. LEE: You still need personal intervention.  
11 Right?

12 DR. BYRN: There are automated units where you  
13 can kick a tablet out. You can run a dissolution test  
14 automated.

15 DR. HUSSAIN: In our labs actually in St.  
16 Louis, we have actually predicted dissolution, just near IR  
17 when you know what the dissolution is. Tennessee has been  
18 doing some of that right now. So, predicting dissolution  
19 from spectra, information gathered from tablet surface.  
20 That's a very important point for us. There's potential  
21 for misuse of the technology too because now I can predict  
22 the dissolution of a tablet without doing the dissolution.  
23 Then therefore it raises the question of selectivity in  
24 terms of what gets reported to FDA. That's a concern that  
25 we have to worry about.

1 DR. LACHMAN: Has anyone considered the  
2 validation implications of this activity?

3 DR. HUSSAIN: That is a major issue I think  
4 we'll have to deal with, and part of the reason for  
5 requesting a subcommittee is to discuss those aspects, how  
6 one should go about doing this.

7 DR. LACHMAN: That's going to be something  
8 that's going to be very important to address.

9 DR. BYRN: Yes, and G.K. was touching on that.  
10 One of the problems in this blending area is how do you  
11 validate what we think is a more precise method, which is  
12 at-line monitoring, with a less precise method, thieving  
13 and off-line analysis. We need to talk to statisticians  
14 about how to do that.

15 DR. LACHMAN: I think you have to have the  
16 various computer assisted activities and electronic  
17 documentation and records that you're developing. So, it  
18 gets quite complicated for the validation activity.

19 DR. HUSSAIN: I think the patent recognition  
20 and the statistical validation would be a challenge.

21 DR. LACHMAN: Right.

22 DR. BOEHLERT: I was just going to mention that  
23 I'm aware of at least one company in this country that  
24 makes vitamin blends that has been using near IR since the  
25 mid-1980's to test and release product and quite

1 | successfully. I don't know if they'd be willing to share  
2 | that with the group, definitely --

3 | DR. HUSSAIN: I'm aware of the OTC and other --

4 | DR. BOEHLERT: And that's analogous to a  
5 | pharmaceutical blend.

6 | DR. HUSSAIN: I understand, yes.

7 | DR. RODRIGUEZ-HORNEDO: Two points. The first  
8 | one is I cannot find it now, but in the reading materials  
9 | you sent us, there is something in the European  
10 | Pharmacopeia regarding the use of NIR. So, what do we know  
11 | about Europe using these techniques?

12 | DR. HUSSAIN: The European Pharmacopeia  
13 | introduced the chapter on near IR in 1997. We are working  
14 | with USP to try to get a chapter in USP.

15 | EMEA, our counterpart, has a draft position  
16 | paper, and that position paper is in your packet also. In  
17 | their position paper, they have outlined some of the  
18 | regulatory challenges that they feel would need to be  
19 | addressed before it comes in. I'm aware of one company  
20 | which has essentially adopted a lot of this in a new plant  
21 | in Germany. So, probably Europe is ahead of us in this  
22 | regard.

23 | DR. RODRIGUEZ-HORNEDO: I think it's a great  
24 | opportunity to have control of the processes by monitoring  
25 | in-line.

1                   Regarding dissolution and the example of  
2 carbamazepine you gave us, I'm not sure if the sensitivity  
3 to the dissolution is due to the solid state  
4 transformation. Are you able to also capture differences  
5 in effective surface areas that may affect dissolution?

6                   DR. HUSSAIN: Predicting dissolution is sort of  
7 a black box. I don't have a mechanistic understanding of  
8 that, but based on what I have seen so far, porosity -- you  
9 can actually predict hardness of that. All those things  
10 are being captured.

11                   So, the mechanism by which we are predicting  
12 dissolution I'm not sure I understand that, but that's the  
13 focus of our lab right now. We asked the labs to focus on  
14 how are we predicting dissolution, what attributes that we  
15 are getting from the tablet surface are related to that.  
16 So, I think as we understand that, more confidence would be  
17 developed in this area.

18                   DR. RAJU: There's also a more recent public  
19 news that the Australian regulatory agency approved NIR for  
20 release just a few weeks ago.

21                   DR. BLOOM: The other aspect of these  
22 techniques is that you can use them off-line also for  
23 troubleshooting. In some cases there have been  
24 publications of Raman and near IR trying to find some  
25 troubleshooting.

1 DR. HUSSAIN: One such example I presented from  
2 Pfizer, Steve Hammond, on the bad flow was the  
3 troubleshooting.

4 DR. LEE: This is not a quality control  
5 question, but how much retooling has to be done to  
6 implement this?

7 DR. HUSSAIN: I don't have a good answer for  
8 that. That's one of the reasons I thought we will need to  
9 gather more information on that. We have done it crudely  
10 in our labs. We are doing it off-line. We're using the  
11 same. So, it's buying HPLC or buying this, so it's not  
12 that. But in terms of putting it on-line, I think G.K.  
13 probably will have more information on that.

14 DR. RAJU: I think that people have been doing  
15 it in stages and different companies have made significant  
16 progress, more than one step at a time. The interface with  
17 the regulatory agency, because of perceptions, has been  
18 kind of delayed. But the phase has been to first do it at-  
19 line and in-line before on-line because you get half the  
20 benefit or a little bit more before that. When you go  
21 close to the process, the operators start asking questions  
22 about the data. Why is it that we call it uniformity?  
23 They start looking at patterns, for example, that say, oh,  
24 this is probably because we top-loaded the excipient versus  
25 bottom-loaded. As soon as they can remember the data and

1 ask why around it, because cause and effect in the same  
2 human being gets analyzed and the process gets -- so, it's  
3 coming in phases and on-line has been kind of the last step  
4 and not everybody has done it yet.

5 DR. BYRN: Other comments from the committee?  
6 Is there general consensus that a subcommittee should be  
7 formed to pursue these concepts and work with the agency  
8 and so on?

9 DR. HOLLENBECK: Ajaz, could you comment a  
10 little bit more on the direction you'd expect the  
11 subcommittee to take?

12 DR. HUSSAIN: There were three stages in my  
13 mind in terms of how this could unfold. One is simply an  
14 understanding of the current state of technology. Vince  
15 asked about what does it take to do this. Because if that  
16 is too a high cost, obviously, it's going to be a slow  
17 process and so forth. An understanding of the feasibility.

18 Second would be I think probably understanding  
19 of validation procedures. Without that, I think it will be  
20 difficult.

21 Thirdly, I think some mechanistic understanding  
22 because I think we probably should gather information on  
23 how much this is generalizable so that we build confidence  
24 in what we are looking at because patent recognition, use  
25 of chemometrics and so forth is a different way of looking

1 at chemistry than we have done before. So, we really need  
2 to build confidence and understand the mechanistic basis,  
3 especially, say for example, about dissolution. If I'm  
4 able to predict dissolution, how am I doing this? If we  
5 are replacing one with another black box, we need to be  
6 careful.

7 DR. BYRN: Any other questions?

8 (No response.)

9 DR. BYRN: Let's take a break till 4:00. We're  
10 not very far behind. I think we're in pretty good shape.  
11 So, let's take a break till 4:00.

12 (Recess.)

13 DR. BYRN: I think we can begin.

14 I'll introduce the speakers as we go along  
15 today, and we should just continue till the end. I know  
16 we're running behind, but we're okay I think because we  
17 were supposed to finish at 4:45. So, we'll just finish  
18 around 5:00.

19 This session is on microbiology. The first  
20 speaker is Dr. David Hussong.

21 DR. HUSSONG: Good afternoon. The last time I  
22 was up here, we were nearly an hour behind. Now we're only  
23 15 minutes behind, so I'd like to congratulate the panel  
24 for shortening the cycle times and getting things rolling.

25 (Laughter.)

1 DR. HUSSONG: I'm here to initiate a discussion  
2 of applying new technologies to microbiological testing in  
3 the pharmaceutical industry. Now, many of these  
4 technologies have been around for quite a while. Some have  
5 come from a clinical arena and some from academia. But I  
6 wanted to give a real quick history. This is microbiology  
7 history 101. So, if you'll bear with me for a minute.

8 Historically, to measure growth of  
9 microorganisms, you use medium. To detect them, you use  
10 medium. Everything is growth-based, and it depends on the  
11 medium. So, if you don't have the right nutrient, you  
12 don't detect it. You don't get the right nutrient, you  
13 can't count them.

14 There are other methods and they will often,  
15 when used, show different populations. Now, the USP  
16 methods, the compendial methods, for microbiology are very  
17 much the simplest and people can do them in most any  
18 laboratory. Because they are simple, anybody will do them.  
19 They can be standardized, but I don't think that they're  
20 necessarily the best.

21 Now, we've been looking at bacteria for over  
22 300 years, and in the last 100 years, we have played with a  
23 lot of different methodologies. Certainly there has been  
24 some pressure driving us to get into the use of them.  
25 Towards that end, the Parenteral Drug Association was able

1 to put forth Technical Report 33, a multiyear effort. It  
2 came out in May 2000 telling the pharmaceutical industry  
3 how to bring these methods on-line.

4 So, today's speakers I'd like to introduce. We  
5 have Dr. Bryan Riley, an FDA review scientist, who will  
6 give us an introduction to the alternate technologies used  
7 in microbiology.

8 We have Dr. Ken Muhvich, who is a consultant to  
9 the pharmaceutical industry, and he has a lot of experience  
10 with the validation of methods, both the standard methods  
11 and the new methods.

12 Dr. Jeanne Moldenhauer is with us who is also a  
13 consultant, and she has a tremendous scope of industry  
14 experience, and she will discuss her experiences as a user  
15 of some of these technologies.

16 We're hoping Roger Dabbah will be able to join  
17 us. He seems to be a little late. But he's from the USP  
18 and he can provide us some comparative information relative  
19 to the compendial methods.

20 So, with that, I'd like to introduce questions  
21 that we'll have at the end. What I'd like to have the  
22 committee do is keep these questions handy.

23 Question 1. You can see I have a little bit of  
24 bias in these methodologies. Considering the advantages  
25 demonstrated by some of the new microbiological testing

1 | technologies, should FDA take steps to facilitate the  
2 | pharmaceutical industry's use of these technologies?

3 |           Then question 2. Since various guidances and  
4 | compendia offer test acceptance criteria in terms of  
5 | colony-forming units, is it appropriate to permit changes  
6 | to the numerical limits to reflect the sensitivity of tests  
7 | that measure microorganisms using these properties?

8 |           So, with that, I would like to have Dr. Riley  
9 | take over.

10 |           DR. RILEY: Good afternoon. I'd like to spend  
11 | about the next 10 minutes or so taking a brief look at the  
12 | methods used for microbial limit testing. What we'll do is  
13 | look at both the current methods that are now in use, as  
14 | well as a couple of the new technologies.

15 |           First I'd like to look at the compendial  
16 | methods, which in this case means USP. There are  
17 | essentially two types of compendial methods used for  
18 | microbial limit testing.

19 |           The first are called plate counts, which give  
20 | us colony-forming units, also known as CFUs. This is  
21 | probably the most common method used for microbial limit  
22 | testing and is probably the most accurate of the ones used  
23 | so far. In this case, the samples are applied to a solid  
24 | medium. The medium is incubated. The microorganisms that  
25 | are capable of growing on this media will grow, form

1 colonies. These colonies can be counted, and then the  
2 results are expressed as either CFUs per ml or per gram of  
3 the sample.

4 The other method is called the most probable  
5 number method, or MPN. It's based on the statistical  
6 distributions of organisms in a sample. It is considered  
7 less accurate than the plate count, but it is used  
8 sometimes when plate counts can't be used.

9 What you do is you take a parallel series of  
10 serial dilutions of a sample in liquid medium. You do  
11 these at least in triplicate. So, what you might have, for  
12 example, are three tubes of a 1 to 10 dilution, three tubes  
13 of 1 to 100, and three tubes of 1 to 1,000, and so on. You  
14 incubate these tubes, and then you look for evidence of  
15 growth. You take note of how many tubes at each dilution  
16 have growth. Then you refer to an MPN table which will  
17 give you the most probable number of organisms in that  
18 original sample.

19 The advantages of the compendial methods, as  
20 Dr. Hussong mentioned a minute ago, is they're very simple.  
21 They don't require fancy equipment. Any microbiology lab  
22 should be able to perform them. They're sort of tried and  
23 true.

24 Also an advantage is it only counts viable or  
25 living organisms, which is important because that's really

1 | all we're worried about in this case. Are these organisms  
2 | alive or not, can they multiply?

3 |           The disadvantages are the incubation time.  
4 | Despite the fact this says 48 to 72 hours on this slide, it  
5 | actually can be longer. It can be up to about 7 days or so  
6 | depending on the organism you're looking for.

7 |           The other disadvantage is not all organisms  
8 | will grow on a single medium. So, you're really just  
9 | getting a subset of the possible viable organisms in a  
10 | sample.

11 |           Again, we're only interested in the viable or  
12 | live organisms. Therefore, the new method must be able to  
13 | count or differentiate between live and dead, and also must  
14 | not count microorganisms shaped particles or anything like  
15 | that. You only want viable bacteria or fungi. Therefore,  
16 | you need some sort of viability indicator, and I'm going to  
17 | talk about two different indicators that are used in these  
18 | two new methods.

19 |           The first method is called esterase detection.  
20 | The example I'm going to give is a test called ChemScan  
21 | from a company called Chemunex. Esterase is an enzyme  
22 | that's ubiquitous in microorganisms. It's present in all  
23 | of them. The reagent that is used is called Chem-Chrome,  
24 | which is a nonfluorescent compound which can be passively  
25 | taken up by microorganisms. Esterases in these organisms

1 will then cleave that substrate, which will give you a  
2 fluorescent compound. The viability is demonstrated by the  
3 presence of the esterases in the microorganisms, as well as  
4 the intact cell membrane that is necessary to help contain  
5 the fluorescein after the Chem-Chrome reagent has been  
6 cleaved.

7 To perform the procedure, you sample the filter  
8 through a membrane. You expose the membrane to the  
9 reagent. You then analyze the membrane by laser scanning,  
10 looking for the fluorescence. You will count particles  
11 that fluoresce at the appropriate wavelength and also at  
12 the appropriate size of the microorganisms that you're  
13 looking for.

14 The time for this test is an hour or two from  
15 start to finish.

16 The next method I'm talking about is ATP  
17 bioluminescence. The examples are the MicroStar and the  
18 MicroCount tests by Millipore. This test looks for ATP,  
19 which is the primary energy source for all organisms. The  
20 reagent used is a combination of luciferin, which is a  
21 substrate, and luciferase, which is an enzyme, which will  
22 react with the ATP that you're assaying, as well as oxygen  
23 to produce light. And you can measure the light.

24 To do the MicroStar procedure, it's similar to  
25 the ChemScan procedure. You filter the sample. In this

1 case, you then replace that membrane onto a solid medium  
2 for a brief incubation. This incubation could be 6 to 12  
3 hours. It's not as long as if you're looking for total  
4 growth. The reason for the incubation is it amplifies the  
5 signal by increasing the amount of ATP that's present.

6 You then disrupt the cells to release the ATP.  
7 You add the bioluminescence reagent to the membrane. You  
8 can then detect the spots of light using a charge-coupled  
9 device camera and computer analysis, and then you can  
10 analyze the number of light spots you get and count your  
11 organisms.

12 The time, again 6 to 12 hours or so for the  
13 incubation part, and an hour or so for the analysis.

14 That's all I wanted to say this afternoon, and  
15 we'll go to our next speaker.

16 DR. BYRN: Are there any questions?

17 DR. MARVIN MEYER: Steve, the handout listed  
18 some advantages and disadvantages to the standard methods.  
19 Do you have similar statements for the proposed two new  
20 methods?

21 DR. RILEY: I think time is an obvious  
22 advantage. As I sort of mentioned, we're looking at  
23 probably a larger subset of the viable organisms that are  
24 present because you're not looking just at growth on a  
25 single medium.

1 DR. MARVIN MEYER: No disadvantages?

2 DR. RILEY: There are probably some  
3 disadvantages, but I'm not going to get into a lot of the  
4 detail at this point.

5 DR. BARR: Is it likely that this could replace  
6 the traditional method?

7 DR. RILEY: It could potentially replace the  
8 traditional method, yes.

9 DR. BYRN: Our next speaker is Dr. Kenneth  
10 Muhvich, who's going to talk about validation issues.

11 DR. MUHVICH: Being a former FDAer it's a  
12 pleasure for me to be here today to talk to you about my  
13 views. Since I left the agency, I've worked almost four  
14 years in the pharmaceutical industry, and a large part of  
15 what I do is audit sterile manufacturers, and I'm always in  
16 a micro lab somewhere. So, that's given me a perspective  
17 that I want to share with you all. I'm not going to take  
18 too much time. I'll really try to give you take-home  
19 points on where I think these technologies can be used and  
20 their efficacy.

21 I've heard it twice today -- and I use it and a  
22 lot of FDA investigators use it -- the common saying that  
23 you can't test quality into product, especially for sterile  
24 products. That typically refers to a final drug in its  
25 final container. Instead, one must use validated

1 sterilization processes and use a proper aseptic technique.

2           That being said, I think that there are a lot  
3 of instances and/or points in a manufacturing process where  
4 appropriate microbial testing will provide invaluable  
5 information and provide a greater sense of control over the  
6 manufacturing process. It's not waiting to the end to find  
7 out what the quality of your sterile product is like.

8           The bullets on this slide show areas that I  
9 think are really ripe, if you will, for use of the new  
10 technologies which are really old to me. I used a lot of  
11 them as much as 25 years ago. They just haven't been used  
12 in this industry and the time is now.

13           Water for formulation; water used for  
14 processing, cooling water in autoclaves and washing of  
15 stoppers and so forth; raw materials; in-process bulk  
16 solution or intermediates. A lot of folks that are making  
17 biologics have intermediates sitting on the shelf for  
18 months, and they might not be of the same microbiological  
19 quality as when they were put up. Microbial limits  
20 testing, which Bryan already talked about for a couple  
21 minutes. A lot of people use that as an in-process test.

22           I put the final product release testing at the  
23 end for a reason. Jeanne Moldenhauer and I had a talk the  
24 other day, and I'm going to quote her. I'm not going to  
25 take the line for myself. We both think that use of these

1 tests needs to be in some in-process testing areas where we  
2 can do some comparison testing and get a real feel for the  
3 efficacy of these tests with pharmaceuticals. So, we need  
4 to walk a little bit before we're going to run with what  
5 everybody really wants them to be used for, which is  
6 product release testing.

7 I'll go with a simple definition of validation.  
8 It's a process or a test that will, with a high degree of  
9 assurance, consistently give the intended results.

10 Now, in the case of one of these type of tests,  
11 the validation of a rapid method is going to demonstrate  
12 that small numbers of microorganisms -- and I should have  
13 put viable there because we can't underscore that enough.  
14 These are viable organisms that can grow -- can be detected  
15 in the presence of their intended solution. What I mean by  
16 that is in the vehicle that they're going to be  
17 administered to the patient in, whether that be an in-  
18 process solution or the final product solution in the  
19 container.

20 Leon Lachman beat me to this one. The key  
21 issue in my little talk here is about validation, but the  
22 key issue for these is that they need to be validated.  
23 Trust me, this is a lot easier than computer validation.  
24 It's just work that needs to be done. They need to be  
25 validated and used, in my mind, for in-process testing to

1 gain some experience with the testing. We need to know  
2 what circumstances are likely to yield a false positive  
3 result and that these will be readily recognized. They  
4 should only be used for product release when a high level  
5 of confidence has been gained with these methods.

6 I want to talk about a couple of case studies.  
7 These are real and these are instances that I plucked from  
8 my experience both when I was here at the FDA and since  
9 that I think are real instances where these types of  
10 methods could have been utilized to prevent problems. I'm  
11 not doing a Hillary. I'm not saying could have, would  
12 have, should have. I'm just pointing out that these are  
13 detrimental events that happened that, if technologies like  
14 these are explored aggressively, are not likely to be  
15 repeated.

16 The first case is a sample from a bulk  
17 solution. This is a very high count. It's 10 to the 5th  
18 CFUs of *Ralstonia pickettii* per ml of product. This  
19 organism is well recognized that it will go through a  
20 sterilizing filter. A lot of people have switched to .1  
21 micron filters when they recognize that this organism is in  
22 their manufacturing environment.

23 Several hundred thousand units of this sterile  
24 product were manufactured before they recognized that this  
25 organism had been in their bulk solution. All of this

1 | product, which represented a product that was needed on the  
2 | market and had a value to the manufacturer of the product,  
3 | was rejected. Then they also had to do quite a cleanup in  
4 | the facility before they could do any more manufacturing.

5 |           The second case probably needs no introduction  
6 | to any long-term FDAer. This is the Copley case, the  
7 | contamination of the albuterol sulfate solution. The  
8 | reason that the contamination was undetected is because the  
9 | microbial limits testing, as was performed for this  
10 | product, as a release test has a dilution in it. The  
11 | product had a very low level contamination which escaped  
12 | the microorganisms' detection during routine release  
13 | testing. And deaths and serious illnesses occurred in the  
14 | patients. I feel strongly that if a validated rapid method  
15 | was available for low level detection, that this type of  
16 | thing would never happen again.

17 |           It's well known. People in the FDA have  
18 | published that they think it's high time that we move on  
19 | with some of this technology. I would encourage the  
20 | committee to at least support having a day or so to really  
21 | take a hard look at what the FDA can do to help the  
22 | industry in terms of moving this type of testing into the  
23 | real world of product in-process testing and release.

24 |           Thank you so much for your time.

25 |           DR. BYRN: Our next speaker, while we're

1 getting ready, is Dr. Jeanne Moldenhauer, who's going to  
2 give an industrial perspective.

3 DR. MOLDENHAUER: I'm probably a little  
4 different from most of the folks that work with rapid  
5 methods in micro in that I've worked both on the regulatory  
6 side and the scientist side. So, I have some different  
7 concerns in some cases than what some of the others may  
8 have.

9 From an industry perspective, business  
10 objectives are really what drive us. Laboratory compliance  
11 to FDA requirements is a major concern because our products  
12 don't get approved without them. One of the big concerns  
13 we have is the ability to understand in advance how  
14 investigators are going to look at rapid methods,  
15 particularly when there's no guidance from the reviewing  
16 division that supports us. When we get in the case  
17 studies, I'll tell you about why that became of interest.

18 In fact, it was such a big interest to me, that  
19 in one of the companies that I worked at, we brought the  
20 FDA in for their drug school to go through some of the  
21 rapid methods that were available. They're a fear because  
22 they're not familiar with the methods.

23 We have a business objective to be a low cost  
24 provider for high quality products. Lost cost providers  
25 have to look at the cost in the total process.

1 Microbiological testing causes significant delays in the  
2 release of product. That becomes an issue if you look back  
3 at when parametric release was approved for the first time  
4 by Baxter, and they eliminated a 7-day sterility test and  
5 had millions of dollars of annualized savings. Well, that  
6 does reflect back into the product cost.

7           Sterile products all require some sort of  
8 sterility test. And there's a major reticence on the part  
9 of FDA to encourage people to go to other forms of  
10 parametric release, and they've documented that in many  
11 cases. We're looking for other ways to accomplish the  
12 sterility testing and still achieve some of the benefits of  
13 reduced inventory hold time. It becomes particularly  
14 important in the case of aseptically filled products where  
15 you're talking about a 14-day sterility test and there  
16 isn't any option for parametric release.

17           Reduced inventory hold time contributes  
18 significantly to the total cost of the product, cost in how  
19 much warehousing space we need and storage space as well.  
20 In the case of parametric release, when they reduce from a  
21 7-day hold time down to less than a day, they were able to  
22 do just-in-time production with 6 hours from filling to  
23 release the product. So, from a business objective point  
24 of view, that's a big issue to pharmaceutical  
25 manufacturers.

1                   We're also looking for expedited product  
2                   approvals. Here's where the kick comes in looking at rapid  
3                   methods. On one hand, people want to submit rapid methods  
4                   and get them approved, but the great fear is that it's  
5                   going to be the only thing holding up their product  
6                   approval. So, there's a balance between wanting to use  
7                   state-of-the-art technology and condemning your product  
8                   that's in for approval.

9                   There are other concerns over rapid methods.  
10                  One of the biggest ones is that the regulatory expectations  
11                  are not clear. The reason PDA had the major task force is  
12                  that everybody wants their new product approved from a  
13                  vendor point of view. Pharmaceutical manufacturers have a  
14                  big business objective to want to use those technologies,  
15                  and no one really knows who is going to approve or not  
16                  approve them.

17                  The cost of the equipment for doing these tests  
18                  is significantly high. I'm most familiar with the ChemScan  
19                  technology. That averages somewhere in the vicinity of  
20                  \$300,000 just to buy the piece of equipment. Then by the  
21                  time you get the accessories and that that you need, that's  
22                  about another \$100,000 and somewhere in the vicinity of  
23                  twice that cost to validate it. So, when I go in and try  
24                  to get that approved through my management, they're looking  
25                  for returns on investment. The return on investment comes

1 | from reduced inventory hold times, but there's a perceived  
2 | high regulatory risk because there's very little guidance  
3 | on what it will take to get those methods approved.

4 |           There are compliance issues versus submission  
5 | issues. If you choose the route of picking a less critical  
6 | test, if you will, than the final product release test,  
7 | because you want to ease people into the technology, then  
8 | you have the issue of convincing compliance to deal with  
9 | them. I'm going to talk about that exact thing in one of  
10 | the case studies that we talk about.

11 |           The other thing is that in terms of regulatory  
12 | guidance, the thing that we always here is that you can do  
13 | two methods that are equivalent. Most of these new  
14 | technologies aren't equivalent because they have superior  
15 | technology. So, when you go and try to explain that you  
16 | want to do something, it won't be equivalent, but I'd still  
17 | like you to get it approved, there are some concerns on  
18 | that.

19 |           There are also scientific issues with them on  
20 | top of everything else that's a regulatory issue that would  
21 | be useful to obtain some guidance on.

22 |           The first one I want to talk about -- and these  
23 | are two real life case stories. Fortunately, I got to  
24 | participate in both.

25 |           As a result of the PDA Committee, everyone

1 pretty much agreed that water testing -- and we had several  
2 FDA, USP kind of folks on this committee -- was probably  
3 not a product release test, and you could probably do this  
4 and get it approved as a compliance issue.

5 I'm a daring kind of person, so we went ahead  
6 and tried that. We met with the local district, told them  
7 we bought this equipment. We wanted to talk about it. We  
8 specifically wanted to address in advance the issues of it  
9 not being equivalent, as well as how many tests they would  
10 buy into or what strategy they would look at for testing.

11 Their first reaction in the first meeting was  
12 no way would we even consider it. But we got past that  
13 because I went in and explained, did you ever hear of this  
14 organism Campylobacter? You won't ever detect it in any of  
15 your tests, and by the way, it kills people. Now are you  
16 interested in a new technology?

17 They were willing to do that, and they agreed  
18 that it would probably raise the bar. Unfortunately, they  
19 also told me compliance is not likely to make any quick  
20 decision on this and, in fact, they'd get back to me.

21 Well, return on investments, business  
22 objectives. I've got to justify why I have a \$500,000  
23 piece of equipment that's validated that I want to use for  
24 a method, and I was starting up a new plant at the time.  
25 So, the benefit to me was to be doing all my water testing

1 | during the validation when you had thousands of tests to  
2 | do.

3 |           Well, six and a half months later, I still  
4 | didn't even get a follow-up phone call from the meeting,  
5 | and went back and talked with them some more. The bottom  
6 | line is no one wanted to make a decision, and we ended up  
7 | not using the technology for that test method because they  
8 | couldn't even agree on what it would take to convince them  
9 | that the technology might be okay to use. And by the way,  
10 | even if you did use it, don't ever use it as water for a  
11 | raw material for your product because that wouldn't be  
12 | okay. And we were talking about making sterile water for  
13 | injection which, by the way, is grandfathered. So, that  
14 | was water testing.

15 |           The next thing that we looked at is, okay,  
16 | we'll go a different route. The folks in Washington have  
17 | seen new technologies. Maybe they'd be more agreeable.  
18 | So, we went to look with developing a test where we could  
19 | get it approved through Washington, validate it, submit it  
20 | with a drug. And you know how you do some drugs and you  
21 | always know that there's going to be a deficiency anyway?  
22 | Well, we picked one of those to submit it with because we  
23 | didn't want it to be the only thing holding up the  
24 | submission. And we also were going to do parallel testing  
25 | so that if it died, you could just take the new technology

1 out.

2 We had looked at a USP stimuli for revision  
3 that talked about one of the new technologies, and it said  
4 that the method was suitable for bacteria, fungi, and  
5 spores. So, we thought, hey, BIs. That's a really good  
6 thing. If we wait 7 to 14 days to qualify the sterilizer,  
7 that's still a big inventory hold time. We started to  
8 develop the method.

9 We had problems on the very first one with the  
10 counts being erratic, had to go back to the vendor,  
11 modified the tests multiple times because we were finding  
12 counts that were lower than you would expect. Don't  
13 forget, I read all these things that it worked great for  
14 spores. Well, not really injured spores.

15 So, we eventually were able to modify it, got  
16 it to work, we thought. And my counts were 4 logs higher.  
17 Well, if you're talking about a sterilization cycle, that  
18 becomes a big issue. Does this indict all the  
19 sterilization cycles you've been running and is your  
20 product really not sterile? Next new problem. Not good.  
21 We weren't really sure how we were going to handle that and  
22 what to do with the sterilization model.

23 Intuitively I never believed the results. So,  
24 we did some follow-up studies and we looked at with  
25 controlled kill times were you seeing the kind of

1 logarithmic reduction that you would expect to see with the  
2 heat. And we did. It approximated the D-value within a  
3 hundredth of the count. So, that made me still believe  
4 that counts weren't true.

5 We were eventually able to find out that there  
6 was a scientific issue that had to do with clumping, and we  
7 were able eventually to get it down to be about a half log  
8 difference in counts. But from an industry point of view,  
9 there's no guidance that tells me when do I stop the test.  
10 What if I had stopped it at the point where it was 4 logs  
11 higher? I very easily could have done that because I had  
12 data that printed out and routinely told me it was 4 logs  
13 higher.

14 So, there are scientific issues that are also  
15 needing to be addressed along with the regulatory issues,  
16 and the perception out there is I just can't do it. I get  
17 routine calls, because I presented a paper on this, that  
18 you really would think that FDA might maybe think about  
19 considering to approve this. People are frightened to  
20 death to do this, and we're being bombarded because these  
21 technologies are used in all kinds of other industries.  
22 So, the higher management in your company knows that there  
23 are technologies out there to resolve our problems, and  
24 everybody is scared to death that FDA will not make a  
25 decision or will not approve them.

1 DR. BYRN: Thank you very much.

2 Questions?

3 DR. DOULL: In your presentation and in the  
4 previous one, you talked a great deal about validation, and  
5 you may recall in Dr. Holt's presentation this morning he  
6 talked about ICCVAM, which is a multi-agency organization  
7 that has undertaken this task of validation. They're  
8 concerned primarily with validation of biomarkers, but they  
9 have a group that's part of that that's looking at the  
10 microbiological and I know the food people at Food and Drug  
11 here are, with Listeria and all the ones that they're  
12 looking at. Food and Drug is one of the members of ICCVAM,  
13 of course, and they're a player and, therefore, are  
14 somewhat involved and obligated by where they go and what  
15 they decide.

16 So, it seems to me that it's crucial that we  
17 have the ability to, in fact, validate these procedures and  
18 to get some kind acceptance of that process of validation  
19 in order that we can all move ahead in an efficient manner.  
20 ICCVAM wouldn't buy into this definition in here of  
21 validation because ICCVAM is more pointed towards the  
22 argument that validation involves getting the right answer  
23 from the test. If you don't have that built in in some  
24 way, you're not really validating the procedure.

25 But it would seem to me that because that's an

1 area of concern that's pretty widespread, it would be  
2 something that we would all benefit from if we could have  
3 some utilization of validation procedures and some  
4 agreement as to our ability to accept those once they have  
5 been shown to give us the right answer.

6 DR. BYRN: Any other questions or comments?

7 (No response.)

8 DR. BYRN: Should we address the questions that  
9 were raised? The first question is not on our sheet. The  
10 second question is kind of on our agenda. The first  
11 question is, considering the advantages demonstrated by  
12 some of the new microbiological testing technologies,  
13 should FDA take steps to facilitate the pharmaceutical  
14 industry's use of these technologies? I guess translated:  
15 help develop validation or be involved in validation or  
16 work with people that are doing validation.

17 Does anybody disagree with that?

18 DR. MARVIN MEYER: I don't disagree with it.

19 I'm ignorant of the process. When some new  
20 technology becomes available that looks reasonable and  
21 people are interested in it, when we say let's get the FDA  
22 to buy into it, who are we really talking about at FDA?  
23 Does this vary or is there a group that gives final  
24 blessing, or how does that work?

25 DR. HUSSONG: One of the problems is FDA is a

1 multi-part organization. So, when you're trying to get FDA  
2 to buy into something, it depends on who regulates what.  
3 Sometimes that becomes a turf battle.

4 In the example that Dr. Moldenhauer gave to us,  
5 a procedure was included in a new drug application and it  
6 was part of a validation of another process or if it was a  
7 procedure in the application that provided for a finished  
8 drug product test, then that would be controlled by the  
9 center. If, however, it's just limited to process testing  
10 in the line -- the example would be Jeanne's water testing  
11 -- that would be done by ORA and the field people. So,  
12 when we try to get buy-in, we need buy-in from everyone who  
13 would be involved in that method. This is something of a  
14 dilemma for us because, obviously, no single buy-in is  
15 going to work. It has to be across the board.

16 DR. MARVIN MEYER: I raised the question  
17 because that was a recurring theme with both the infrared,  
18 as well as this. Maybe it's a matter of some structuring  
19 or some group assigned responsibility for final blessing,  
20 rather than kind of helter-skelter, depending on who gets  
21 to look at it first.

22 DR. SHARGEL: I have sort of a comment about  
23 the pharmaceutical industry and it particularly deals in  
24 the compliance side. When one manufacturer adds a test or  
25 changes a test, then at times the field inspector feels

1 perhaps everybody should do it and raises that bar and buys  
2 into it. There is probably in industry a worry if one  
3 company starts doing this. Does that mean that everybody  
4 should be doing it or would they be held responsible for  
5 not doing it? You can word it better, if you understand  
6 what I'm getting at.

7 DR. HUSSONG: I understand. It's a  
8 philosophical question. Really it boils down to what's the  
9 difference between good manufacturing process and best  
10 available technology. Certainly in the technologies we're  
11 addressing, you can use the most advanced technology, but  
12 if you don't apply it to the right circumstances, it's not  
13 what you should be doing.

14 Good manufacturing practices are conceptually  
15 to me a long way off from using the most cutting edge or  
16 best available technology. There is a difference. The  
17 situation you're describing has been a serious problem with  
18 the perception of regulators. It goes beyond the U.S.  
19 regulatory agencies as well.

20 DR. MUHVICH: I'll give you an example. It's  
21 not quite technology, but it's something that somebody did  
22 that was new. There are only two companies in this whole  
23 country that use parametric release for release of  
24 pharmaceutical drug products. Other people are able to do  
25 this, but they don't put in the effort and get the data

1 that shows that they can do it. The other two companies  
2 have a huge number of microbiologists and they took the  
3 time and effort to submit the data that would allow the FDA  
4 review microbiologists to approve that. But all the other  
5 people kind of whine about it and everything, but they need  
6 to do the same thing. It's just a matter of effort. It's  
7 not a matter of black box technology or anything. It's  
8 just that they need to do it. If they want to do it, they  
9 should do it. They just need to make a corporate decision  
10 as to what they're going to do basically.

11 DR. BYRN: Back on the original question, it  
12 seems like there's consensus that we should do this or we  
13 should encourage FDA to do it. We just don't know how it  
14 can be done. Is that what we're saying?

15 DR. HUSSONG: I'd sure like to know how to do  
16 it.

17 DR. BYRN: Yes. Maybe we can just go on record  
18 as encouraging FDA. I'm not sure we can tell FDA how to do  
19 it. Right?

20 DR. HUSSONG: Well, if you could tell me,  
21 please do.

22 (Laughter.)

23 DR. BYRN: I'm pretty sure we can't.

24 DR. BARR: Maybe as a follow-up to Marv's  
25 inquiry, to make sure that all the decision making groups

1 are together, to encourage a formation of a committee that  
2 would have those people who would ultimately be involved in  
3 making the decision.

4 DR. BYRN: Ajaz.

5 DR. HUSSAIN: I had proposed a subcommittee  
6 sort of a thing. Maybe this would also be amenable to  
7 that, a subcommittee model for this issue also. I was  
8 actually tempted to have one larger subcommittee dealing  
9 with technology issues altogether. There are enough common  
10 things there. A separate committee might be a better  
11 approach for that.

12 DR. BYRN: So, what Ajaz is saying is maybe  
13 this committee that we already said we would form, we'd  
14 just expand the duties of that committee to deal with all  
15 new technology and how to validate it. Okay, that sounds  
16 great.

17 Any other comments on that question?

18 (No response.)

19 DR. BYRN: The second question is on our  
20 agenda. I think I'll just read it. Well, I'll paraphrase  
21 it. Most of the guidances and compendia use CFU, use  
22 colony counts. Is it appropriate to permit changes to  
23 establish acceptance limits that use new technologies  
24 rather than colony counts? Can we replace colony counts  
25 with new technologies?

1           Maybe this is something else we send to this  
2 committee because it's interrelated, but let's see if  
3 there's discussion of the committee.

4           DR. SHARGEL: That would strike me almost like  
5 finding new impurities at times on an old product. I'm  
6 thinking now on an old product that has been out for many  
7 years and everybody is happy with it and it has not shown a  
8 problem. But using a new technology, you notice new  
9 counts. Should the manufacturer, if it's a small product,  
10 have to come up to that new bar?

11           DR. MARVIN MEYER: Then kind of following up on  
12 a previous comment, if not everyone adopts the new  
13 technology, will you then have different limits at  
14 different companies?

15           DR. BYRN: I don't know, but now you can think  
16 about the USP has parallel tests in certain areas. We're  
17 not the USP obviously. I don't know whether the agency has  
18 a mechanism to do that or not. I assume it could be done  
19 in the USP.

20           DR. BOEHLERT: It certainly allows the use of  
21 alternative technology that's equivalent to or better.  
22 Under that umbrella, certainly it could be used. But I  
23 would agree with Leon, that on old products, if you  
24 suddenly start applying a new standard, you don't want to  
25 go putting them off the market if they've been acceptable

1 for many years. And that applies to a lot of changes in  
2 technology and limits.

3 DR. BYRN: In the USP, couldn't you have an  
4 entry that would have this test or that test?

5 DR. BOEHLERT: Its limits for that test. But  
6 the old test with its limits would still be acceptable.

7 DR. BYRN: That's one way to deal with it.

8 DR. BOEHLERT: But right now USP, I don't  
9 think, very often has alternative tests to measure the same  
10 parameters. They have alternative tests where the endpoint  
11 is different.

12 DR. BYRN: Well, they have different  
13 dissolution media. They have a couple of these famous  
14 ones.

15 DR. BOEHLERT: It's too bad Roger is not here.

16 DR. BYRN: Jeanne has been wanting to say  
17 something.

18 DR. MOLDENHAUER: I had two things.

19 One was, first off, in the case of  
20 microbiology, these new technologies are no different than  
21 doing an endotoxin test versus pyrogen test where you had  
22 different limits. So, that existed already.

23 In addition, in the case of microbiology, many  
24 of our tests are not product release tests, but they have  
25 limits and those limits are different from company to

1 | company anyway in the case of things like environmental  
2 | monitoring and that. So, I think you're adding in  
3 | commentary that really is not as relevant in the case of  
4 | microbiology.

5 | DR. MUHVICH: I'll make a comment about that.  
6 | As microbiology with the regulatory authorities that exist  
7 | today, right now you're not rejecting batches on in-process  
8 | bioburden limits. However, your sister agency, CBER, is  
9 | coming to that, and they're coming to it fast. They want  
10 | reject limits for product in process, bulk. So, I don't  
11 | know where that's going to leave us all, but I just wanted  
12 | to let you know that.

13 | DR. BARR: I think this is a very important  
14 | area and I think it's something that requires very careful  
15 | study. I certainly don't feel qualified to make a judgment  
16 | if I had to make a vote on this, but I would hope that we  
17 | would move this to a committee that would be more qualified  
18 | and would have the time to consider it to make a wise  
19 | decision on it.

20 | DR. BYRN: It seems to me that this committee  
21 | could handle these issues and maybe get some consultants  
22 | that could deal with some of these nuances and handle the  
23 | new technology in a general way.

24 | DR. HUSSAIN: Steve, there are many common  
25 | elements I think. The committee I had in mind probably

1 | would cover the common elements of validation, who does  
2 | what. But there are technical issues which are very  
3 | specific issues to microbiology. So, you probably would  
4 | need a separate group for that.

5 | DR. BYRN: I'm sorry, Ajaz. Are you thinking  
6 | now about a separate group or a subcommittee of the  
7 | subcommittee?

8 | DR. HUSSAIN: No, a separate group might be a  
9 | better approach.

10 | DR. BYRN: A separate committee. So, we'd have  
11 | two committees.

12 | DR. HUSSAIN: Just for microbiology, right.

13 | DR. BYRN: One would be microbiology, but they  
14 | would have sort of a similar general charge. I think  
15 | however the agency would like to structure it -- well,  
16 | let's see what other people think is fine with us. Is  
17 | there any comment on that? I don't think it makes a  
18 | difference whether it's two separate committees or one  
19 | committee. That's up to you I think. We're just saying we  
20 | like the idea of having committees that study these areas.

21 | (Laughter.)

22 | DR. DOULL: But I don't think it should be  
23 | limited to microbiology because the issue is once you  
24 | validate a procedure and show that it's more predictive  
25 | than what we were using before, then that technique or

1 procedure needs to have some ability to be incorporated  
2 into the regulatory process. And that's not just for  
3 micro; it's for a whole bunch of areas. It's a very  
4 important issue. Whether that's a working group or a  
5 subcommittee or a committee or whatever, it clearly is, as  
6 you said, Bill, an area that needs to be addressed.

7 DR. BYRN: Vince?

8 DR. LEE: Yes, I think I might be repeating  
9 what John said, that it looks like that we have on the  
10 horizon a number of new technologies, and it seems to me  
11 that somewhere, sometime soon that we need to come to grips  
12 with what to do with them. In addition to that, we have  
13 two specific technologies on the plate. So, it seems to me  
14 it is very important for us to take a look at how to deal  
15 with new technologies.

16 DR. BARR: I don't know how the structure of  
17 this works, but it seems if there are places for outside  
18 experts or consultants to be on these committees, that it  
19 probably would be worthwhile to have one or two of the  
20 members of this committee, at least somebody there that  
21 would be sitting in on that that could come back and give  
22 us some of the details of the interactions.

23 MS. WINKLE: You're right. Actually every  
24 subcommittee has to have two members of the advisory  
25 committee as members of the subcommittee. So, you guessed

1 | it right. So, that's what we'll plan on doing. Whether we  
2 | have two different subcommittees or one subcommittee that's  
3 | going to handle both of these issues, we will actually ask  
4 | members of this committee to be on that.

5 | DR. BYRN: I think this committee could perform  
6 | a tremendous service if we were involved in dealing with  
7 | new technologies and how regulatory changes could  
8 | accommodate those technologies. Maybe we'd have  
9 | presentations like we've had today and then decisions would  
10 | be made, it goes to this existing committee or another new  
11 | committee is set up. Since it's hard to predict new  
12 | technologies, it may be better just to let everything come  
13 | to this committee and then a decision be made whether it  
14 | goes to one of the existing committees or another new  
15 | committee is formed. But anything like this I think will  
16 | be tremendous for the industry and the agency.

17 | Any other comments?

18 | (No response.)

19 | DR. BYRN: I think we turned over the issue of  
20 | the different counts to this committee indirectly. We had  
21 | some input on that, but I think we deferred that issue,  
22 | unless somebody else wants to comment. We deferred the  
23 | issue of the differences in CFU and the other data that are  
24 | given to this new committee. Is that what everybody  
25 | understands?

1 Any other questions or comments? Yes, Gloria.

2 DR. ANDERSON: Mr. Chair, it seems to me like  
3 there's a fundamental issue here that maybe the committee  
4 might want to think about making a recommendation related  
5 to, and that is whether or not in fact the FDA, as a matter  
6 of policy -- and I don't know enough about FDA to know  
7 where this goes. But from what I've heard this afternoon,  
8 it seems to me like there's apparently some resistance, for  
9 whatever reason, to move into the 21st century with the new  
10 technology.

11 I would just like to see us explore the  
12 possibility, if it's within whatever it is this committee  
13 has to do, to go on record as supporting any explorations  
14 of new technology that would improve the regulatory  
15 process, to the extent that this committee is empowered, so  
16 that we don't limit it to NIR or one particular thing.  
17 That would form the basis for any future applications.

18 DR. BYRN: Gloria, I'm just informed that the  
19 best mechanism would be to use subcommittees. I don't know  
20 whether we need a motion or we can just take this as part  
21 of our charge, but I think what Gloria is saying and what  
22 everybody is saying is this committee will become involved  
23 in new technology development.

24 So, do we think we need a motion or can we just  
25 take it as our charge, Helen, just directly?

1 MS. WINKLE: I think you can take it as your  
2 charge directly.

3 DR. BYRN: Okay.

4 Any other comments or questions?

5 (No response.)

6 DR. BYRN: Then we'll adjourn until 8:30  
7 tomorrow in this room.

8 (Whereupon, at 5:02 p.m., the committee was  
9 recessed, to reconvene at 8:30 a.m., Friday, July 20,  
10 2001.)

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