

## AFTERNOON SESSION

(1:30 p.m.)

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DR. LEE: Welcome back.

Let me introduce two guests in front of us.

Gary Boehm?

DR. BOEHM: My name is Garth Boehm. I'm from Purepac Pharmaceutical Company, and I'm a member of the Blend Uniformity Working Group.

DR. GARCIA: My name is Tom Garcia. I'm from Pfizer, and I'm the Chairman of the Blend Uniformity Working Group.

DR. LEE: Welcome. Thank you.

The next agenda item is the open public hearing. We have three individuals who signed up to speak. I think all have been told they have 5 minutes each to make their case, and 1 minute to respond to questions.

So, the first person I would like to call is Christopher Ambrozic from Umetrics.

MR. AMBROZIC: Thank you very much, Mr. Chairman.

I'd like to thank members of the committee, some of the directors especially, for allowing us to come in and present some of the work that is being done at Umetrics. I think over the course of this morning's discussion, we really looked at a lot of what's coming to

1 | fruition in terms of process analysis technology, and I  
2 | think some of the information that I'm going to show over  
3 | the next few slides can be very interesting to you.

4 |           If you're interested in the company, of course,  
5 | we have a web site. There are also slides for those in the  
6 | audience who wish to take a copy of this home.

7 |           The background is that obviously process  
8 | analysis technology provides valuable process information.  
9 | I think this was clearly defined this morning. We'd like  
10 | to focus on the concept and the idea that these new  
11 | opportunities to monitor the evolution of the batch or  
12 | monitor the evolution of your process can take advantage of  
13 | this PAT data and other information as well. So, one of  
14 | the issues that I'd like to talk a little bit about is that  
15 | we can take not only near infrared information, we can  
16 | combine that with process information, temperature flows,  
17 | et cetera, GC analysis, and bring that all together in the  
18 | form of a summary which allows us to make the best estimate  
19 | of your production in real time. This is a very important  
20 | point.

21 |           This, of course, necessitates a summarizing and  
22 | that really becomes a modeling of the data. There are  
23 | statistical methods that allow us to do this. The  
24 | resulting model parameters provide an improved  
25 | interpretation of the process. So, in terms of monitoring

1 | your batch, you no longer look at the spectral analysis of  
2 | an NIR, which has 4,000 individual digitized wavelets,  
3 | you're actually looking at a summary of the individual  
4 | batch. We'll see that actually in a few slides.

5 |           One of the nice things about the software, of  
6 | course -- and these techniques allow you to display this  
7 | information in terms of control charts. This is obviously  
8 | very advantageous to the people in our plants and the  
9 | people doing the work.

10 |           Today, right now, what we are faced with in  
11 | production facilities is batch data that is being  
12 | summarized on a one-level information only in the sense  
13 | that what we get is doing quality control only after the  
14 | batch has been completed. Some of the work that we're  
15 | looking at and others are obviously looking at right now is  
16 | clearly identifying how we take this information, as it  
17 | exists transiently across the batch, within-the-batch  
18 | information. So, you not only get batch-to-batch  
19 | information, which is very useful, but you get within-batch  
20 | information, which is obviously very crucial.

21 |           This is kind of a cornerstone slide here and  
22 | what this is what we're being represented with today, and I  
23 | see this a lot. We have this information right here. This  
24 | is data. Everybody has got it, and what we do and this  
25 | type of technology does is that it summarizes into this one

1 chart right here. What that is, if you were to understand  
2 that, is a summary of the entire batch from start to  
3 finish, dynamically as it changes from the beginning to the  
4 end. In some cases, we might call this the golden run.  
5 That would be the green line that we have here.

6 If we move on to the next slide, we can see  
7 here that we have summaries of this batch. We have  
8 summaries of our golden batch as they exist from the start  
9 of the batch through to the finish of the batch. At every  
10 single time point, we can also identify what kind of  
11 variability is acceptable and what kind of variability is  
12 not acceptable in terms of production, in terms of quality  
13 control, in terms of validation.

14 Let's take an example of this. I'd like to  
15 mention that some of this data, some of this analysis is  
16 being done in a number of pharmaceutical companies from  
17 AstraZeneca, GSK, Pfizer. All of these companies are  
18 definitely leading the charge with working with this type  
19 of data and this type of analysis.

20 When we put something on line and we are trying  
21 to monitor for a batch upset or some sort of upset, this is  
22 what happens. You can see here on this slide that our  
23 current batch that we're running right here has, for some  
24 reason, gone out of control. This is real-time  
25 information, as we bring it down into the system. What

1 we're able to identify is not only that a fault has  
2 occurred. We see that the fault has occurred. But we're  
3 also going to do the root cause analysis. So, it's fault  
4 detection and root cause analysis on top of that.

5 Here's the root cause analysis. It's called a  
6 contribution plot. It's to the right of your screens.  
7 Essentially what that is is clearly identifying with one  
8 single mouse click, to go from our black line, which is out  
9 of control, to identifying the root cause of the analysis,  
10 which is the green bar. In this case, it turns out that  
11 the level of this batch ramped up prior to when it should  
12 have. You can see here that this batch ramped up very  
13 early whereas it should have maintained a much more steady  
14 state through the beginning of that particular batch. So,  
15 this is how simple it is. This is how easy it is for our  
16 operators to execute this type of analysis and for us to  
17 correct batches as they occur in line.

18 I don't think I need to discuss too much about  
19 the opportunities for our companies because the advantages  
20 are obvious, being able to correct batches and reduce batch  
21 scrap, reduce batch variability, not to mention the  
22 advantages for the FDA in the ability to monitor these  
23 fingerprints because this really becomes what it is. It's  
24 a footprint. It's a fingerprint of your batch. It allows  
25 you to, in one snapshot, identify whether or not that

1 particular batch has been processed according to  
2 regulation.

3           From this point here, we continue to drill  
4 down. I come from a 10,000 foot level almost to a 1,000  
5 foot level, if you will, this being my 10,000 foot where  
6 I'm looking at the entire summary of the batch. I go  
7 through where I identified the individual problem. I can  
8 then go a level further and look at the actual variable  
9 itself. That really shows up right here. We can see that  
10 in fact this level really was the indication that caused  
11 this. This is a batch pharmaceutical process. It's  
12 actually a mixing stage that's going on. The company in  
13 question was having difficulties with their agitation, and  
14 that actually was due to level changes.

15           So, really, we introduced this concept and this  
16 idea, which is very prevalent in a lot of different  
17 industries, whether it's chemical engineering, semi-  
18 conductors and so on, this idea of real-time quality  
19 control. Being able to take the evolution of  
20 representative good batches and then monitor all of your  
21 information, we take all of the data. And I really want to  
22 stress all process analysis technology data, whether it's  
23 from in-line sensors, on-line sensors. We take flow  
24 information and so on and so forth. We saw there the  
25 example was an agitator and a level.

1            Obviously, we use the control charts to display  
2 this information. So, we represent it in a very simple way  
3 that makes it very easy for us to make conclusions when we  
4 have problems and difficulties.

5            Obviously, we monitor new batches as they are  
6 evolving, as opposed to just doing batch to batch. We once  
7 again introduce this idea of within-batch or within-run.  
8 And we detect problems and interpret the solutions on the  
9 fly. That really is the advantage of this type of  
10 technology.

11           The culprit variables in the problem batches  
12 are clearly identified -- I think we saw that -- very  
13 easily with the green bar of our contribution plot.

14           And the quality of the whole batch is predicted  
15 as it is evolving and at completion. This, of course, then  
16 allows us to implement possible 6 sigma control. Being  
17 able to implement this type of analysis is going to bring  
18 us to that level.

19           The technology, as it is, is based on a  
20 multidimensional informative data measured during the batch  
21 evolution and multivariate analysis. If you're interested  
22 in more of that, I can talk off-line with you, absolutely.

23           Finally, just some conclusions. Really, we're  
24 introducing not only multivariate statistical process  
25 controls, well-known with the SPC idea, but batch SPC where

1 | it exists on two levels. It exists within the batch and it  
2 | exists on an upper level.

3 |           One of the advantages is that we can not only  
4 | get information about the batches, but we also start  
5 | predicting the batch qualities halfway through the batch  
6 | completion. Let me just say that again. We actually start  
7 | predicting the batch quality data halfway through the batch  
8 | completion. The technology allows us to say, okay, our  
9 | density is going to be this, our viscosity is going to be  
10 | this, as we trend through the batch. Very useful  
11 | information, of course, because then if we can see it's  
12 | beginning to go out of control, we can then go back down to  
13 | the 1,000 foot level and direct it towards being within  
14 | target specifications.

15 |           Once again, I mentioned already really reducing  
16 | the scrap rates. Having to throw out batches I think was  
17 | well demonstrated Dr. Hussain's talk today. Really this  
18 | whole idea of facilitating compliance inspection, the  
19 | ability to monitor batches and in a snapshot look at this  
20 | fingerprint, look at this footprint, and be able to in one  
21 | clear picture identify whether the batch was made properly  
22 | and in control.

23 |           I'll take any questions at this point. I'd  
24 | like to thank especially Dr. Hussain for allowing us to  
25 | come in and the members of the committee as well.

1 DR. LEE: Thank you. We have time for maybe  
2 two questions. Steve?

3 DR. BYRN: Can you comment on the extent of  
4 this kind of data analysis being used in Europe? Does your  
5 company originate from Europe?

6 MR. AMBROZIC: No. Our company, yes, is  
7 originally from Europe. I have no background in that  
8 location.

9 DR. BYRN: Right. Do you know how much of this  
10 kind of analysis, what we were talking about earlier, is  
11 going on in the pharmaceutical industry in Europe compared  
12 to here?

13 MR. AMBROZIC: I would say that in most cases  
14 we're pretty much on the same level. This was something  
15 Steve and I talked about over the lunch break, that this  
16 idea that maybe the Europeans are ahead a little bit in  
17 some areas. I think that conceptually we're at the same  
18 location. The idea that it has to be implemented -- we  
19 want to get there eventually. But I wouldn't say that they  
20 are, in fact, running on real-time models in place.

21 DR. LEE: Marv?

22 DR. MEYER: This is probably terribly naive,  
23 but on the bad batch plot, it looked like, after some  
24 period of time, it converged and became a good batch.

25 MR. AMBROZIC: Yes.

1 DR. MEYER: Did it matter, therefore, that it  
2 diverged at the beginning?

3 MR. AMBROZIC: Well, that's of course going to  
4 depend on what ends up happening in terms of the quality.  
5 This is the lower level analysis. You're right. What  
6 happens is that the batch goes out of control to begin  
7 with, and then what happens is the operators, of course,  
8 realize that it, in fact, has done so. We can see that by  
9 this slide right here where they realized, in fact, they  
10 have risen the level too early.

11 The analysis at the lower level, we then take  
12 that to the upper and identify whether that has a clear,  
13 distinct impact on the quality of the batch. If it does,  
14 something like this would be unacceptable. If it doesn't,  
15 then something like this would acceptable. That is the  
16 definition that comes out when we start doing the analysis  
17 with the data.

18 DR. LEE: Thank you very much.

19 MR. AMBROZIC: Thank you very much.

20 DR. LEE: Next, I would like to invite Nancy  
21 Mathis from Canada, and she knows what she's going to talk  
22 about.

23 DR. MATHIS: Good afternoon. I'm here this  
24 afternoon to put together for you the morning session that  
25 you heard, as well as the afternoon session. What I'm

1 going to be talking about is on-line techniques for blend  
2 uniformity and specifically a technique that our company  
3 represents called effusivity.

4 If we agree that blend uniformity needs to be  
5 monitored and we agree that the best way to do this is on  
6 line, then this afternoon's presentation is going to be  
7 valuable for you.

8 Since we've all just had lunch and our bellies  
9 are full and we're getting a little bit groggy, I'm going  
10 to have you do an experiment. I'm going to have you do an  
11 on-line effusivity measurement with your hands. These are  
12 very accurate little sensors. I want you to reach under  
13 the table, especially for this group because I've already  
14 checked out your tables, grab the metal leg of the table,  
15 put your other hand on top of the table. For those of you  
16 sitting in the chairs, you grab the leg of your chair and  
17 it will also work. Tell me which thing feels colder. The  
18 leg feels colder. The metal feels colder to your touch.

19 You've just done an effusivity measurement.  
20 The legs of the chairs and of the tables are both at room  
21 temperature. What you've done is an interfacial,  
22 nondestructive measurement of effusivity which allows your  
23 hand to not detect the temperature of the item it's in  
24 contact with, but rather the rate of heat flow. The  
25 thermal conductivity and specifically the effusivity of the

1 table, the metal, is higher and it draws the heat away from  
2 your hand.

3 We have sensors that allow that to happen.  
4 Those sensors not only work with metal, wood, and solids,  
5 they also work with powders.

6 Effusivity. What is it? It's a combination of  
7 thermal conductivity, density, and heat capacity, and it's  
8 the root general principle that comes when two semi-  
9 infinite bodies come in contact. It's the property that  
10 drives the interfacial temperature, and that's what you  
11 just felt.

12 This is a commercially available instrument.  
13 It's been available for six years, right now private  
14 labeled through Perkin Elmer Instruments for the non-  
15 pharmaceutical application. So, this has been out there  
16 and the efficacy of thermal conductivity and effusivity has  
17 been proven.

18 This instrument works for solids, liquids, and  
19 gases.

20 The way the system works. Picture a sensor  
21 coming in contact with powder. There's a heating element  
22 that heats roughly 5 degrees Celsius, and during that  
23 heating period, the rate of the heat flow into the material  
24 is what's detected.

25 So, schematically you've got a sensor. What

1 shows in the red arrow is the heat flowing into your  
2 sample. The more conductive or the higher the effusivity  
3 of that sample, the more heat flows into it. And the  
4 smaller amount of heat that's left behind -- we measure the  
5 relative rate of temperature rise at that interface and  
6 produce the effusivity value.

7 Now, of interest in unit dose sizes, the longer  
8 you test -- and I'm talking the difference between 2  
9 seconds, 3 seconds, 4 seconds -- the further the heat wave  
10 penetrates into your sample. So, for a typical 2-second  
11 test, you'd be penetrating .6 millimeters into a particular  
12 powder bed or giving you roughly a volume of 150  
13 milligrams, a weight of 150 milligrams of material  
14 evaluated. If you wanted a larger sample size, you'd  
15 simply test longer with the same hardware.

16 This is something that can be retrofitted onto  
17 existing blenders. A hole, not a window, but a hole can be  
18 placed in a piece of blending equipment. The sensor can  
19 come down and come in contact with that and be retrofitted  
20 in. This schematic, this graphic has motion to it, which  
21 is not actually working. So, picture eight different  
22 sensors. I heard this morning, I think from Dr. Hussain's  
23 presentation, that they're envisioning six sensors for one  
24 technology. We're envisioning eight for this. Picture  
25 eight sensors at various locations all over a blender.

1           What we're doing when blending starts, it feels  
2 like this. When the sample is uniform, it feels like this.  
3 So, we're not measuring the absolute value so much as we're  
4 measuring the relative value of the effusivity.

5           Results. Eight measurements, 3 minutes into  
6 blending. You're going to see wide variation in the  
7 results because the effusivity for different powders  
8 varies. At some point, as blending continues and  
9 uniformity is reached, there's going to be a minimization  
10 of those results, and that's the tightest location  
11 indicated on this graph. We can actually see de-blending  
12 as well.

13           What you see in front of you, the schematic,  
14 the next one is actual results. This is on an eight-  
15 component, commercially available formulation, and the  
16 active that was assayed in this case was under 1 percent.  
17 You see a 4.5 percent variation at the beginning and at the  
18 end a .3 variation.

19           Now, to clarify, these samples that you see  
20 tested, each of these dots were actually thieved and tested  
21 off line. The on-line version will not available until the  
22 spring.

23           So, what I want you to think about is this is a  
24 relative measurement, not absolute. The absolute  
25 effusivity will depend on the excipient mix, the active

1 | mix, and the particle size. But what we're hoping for is  
2 | looking for that optimum value, which is the minimization  
3 | of the relative standard deviation between multiple  
4 | readings.

5 |           Our challenge is validation, and this morning's  
6 | conversation was very interesting to me. How do we  
7 | validate that this is actually measuring uniformity? To do  
8 | that, we've started the process by doing side-by-side  
9 | comparisons between thieved samples, tested for effusivity,  
10 | and thieved samples tested by current assay techniques for  
11 | percent label claim. On this graph, although we don't have  
12 | the early data for this set, you'll see that there is that  
13 | clear trend of looking at the de-blending from the percent  
14 | label claim results that we could also see, and in both  
15 | cases, this produced an optimum blend time of 10 minutes.

16 |           Issues addressed. As I've done these  
17 | presentations over the last year to different  
18 | pharmaceutical organizations, they've presented different  
19 | challenges. Some of them are listed here. There's  
20 | technical documentation available on our website that  
21 | addresses each of those and how they've been solved.

22 |           We've had a group of participants, including  
23 | GlaxoSmithKline in two locations and also Merck. Together  
24 | we've worked collaboratively with our organization, as well  
25 | as Patterson Kelly, to investigate effusivity as a blend

1 | uniformity monitoring technique.

2 |           These results were presented in Denver last  
3 | month, and some of the results are shown here. We can  
4 | differentiate between powders. This does have the ability  
5 | to be an ID potential.

6 |           2-second testing gives us 1 percent precision.

7 |           Insensitive to pressure after a certain  
8 | threshold point, which was one of the things on the table  
9 | of different techniques that was brought out. There is a  
10 | sensitivity to pressure, but over a certain threshold  
11 | refined.

12 |           The sample size is appropriate, 150 milligrams  
13 | and scaleable, and the benefit here is that we can retrofit  
14 | it onto current equipment without the need for new capital  
15 | equipment.

16 |           We're now in a phase of BUG 2. BUG 1 stands  
17 | for Blend Uniformity Group, and that's an internal group  
18 | that we've put together with the members I mentioned  
19 | earlier. We're now forming BUG 2 as a second phase, and  
20 | our goal in that is to build our portfolio of examples  
21 | where effusivity has been compared to percent label claim  
22 | so we can do that validation of this technique.

23 |           As I said, current members, GSK, Patterson  
24 | Kelly, and Merck.

25 |           For more information, there's my contact data.

1 I'm nancy@blend-tech.com. And www.blend-tech -- with a  
2 dash -- .com. I do have the technical literature that I've  
3 kind of alluded to on that site, and I would be more than  
4 happy to get questions and also participate with people  
5 after the fact and involve them in BUG 2.

6 Thank you.

7 DR. LEE: Thank you very much. We have time  
8 for maybe one question.

9 DR. MATHIS: Yes.

10 DR. ANDERSON: How large is that sensor?

11 DR. MATHIS: The sensor right now is 1 inch by  
12 a quarter of an inch. I'm Canadian, 25 millimeters by 5  
13 millimeters. I talk both languages.

14 The sensor is roughly the size of the end of  
15 your thumb and that can be scaleable if people want larger  
16 or smaller unit doses to blend with their time of  
17 penetration into the sample. That can be adjusted based on  
18 the needs of the user.

19 DR. ANDERSON: How do you know that the  
20 uniformity doesn't apply to the outside of the sensor when  
21 you're putting pressure on it with the sensor?

22 DR. MATHIS: You'll have to clarify that.

23 DR. ANDERSON: If you put the sensor in there,  
24 everything outside may be uniform and because you're  
25 putting pressure there, there may be a difference between

1 -- you understand what I'm saying?

2 DR. MATHIS: I understand what you're saying,  
3 and part of when we bring this on line, we'll have to have  
4 a determined homogeneous, uniform, single phase material  
5 that we would place in the blender and then you can  
6 basically baseline or tear out that effect.

7 DR. BYRN: Obviously, the blender is moving and  
8 so things are changing. How do you envision that? Are you  
9 just averaging over the 2-second time? You're averaging  
10 what's in the area? Is that the general thinking?

11 DR. MATHIS: That's where we're going to head.  
12 In April of this at Interphex, we hope to introduce a  
13 system that you actually blend, stop the blending, tie an  
14 umbilical cord back to the instrumentation, take a  
15 measurement, collapse that, blend again. The eventual  
16 version would be a moving system with radiotransmission.

17 DR. BYRN: Right now you're doing static.

18 DR. MATHIS: That's right. We're heading  
19 there, but we want to do this in steps because we think  
20 it's important to get a solution out there as quickly as we  
21 can.

22 DR. LEE: Thank you very much.

23 DR. MATHIS: Thanks very much.

24 DR. LEE: The last one is going to be by Steve  
25 Lonesky on behalf of GPhA.

1 MR. LONESKY: Good afternoon. My name is Steve  
2 Lonesky. I work for Teva Pharmaceuticals USA, and our Vice  
3 President Chris Palone was not able to be here this  
4 afternoon, so I'm going to try to fill in for him.

5 Teva Pharmaceuticals is a member of the Generic  
6 Pharmaceutical Association, or GPhA, and I'm going to speak  
7 on the association's behalf this afternoon. GPhA would  
8 like to thank the FDA for the opportunity to contribute to  
9 the dialogue concerning the issue of blend uniformity.

10 Briefly, the GPhA endorses the PQRI's blend  
11 uniformity proposal except for the 4 percent RSD compliance  
12 requirement. We believe that this requirement is  
13 unnecessarily limiting and will result in unwarranted  
14 investigations and testing of actually compliant product.

15 The generic industry views blend uniformity as  
16 a good tool for the development and validation phases of  
17 manufacture but must be carefully considered in light of  
18 well-documented problems associated with sampling phenomena  
19 of powder blends. We must have a way to deal with the  
20 occasional sample result that does not quite makes sense or  
21 fit the data set, which we know is most likely due to  
22 sampling. We can pick up a tablet and assay it. There's  
23 no question what the sample is or what the result  
24 represents. This is not true with a sample pulled from a  
25 powder blend that is in constant motion. To this end, we

1 must have a two-tiered approach. The investigators should  
2 also take this into account when reviewing product data and  
3 investigations performed by a firm when a result does not  
4 conform to an intended specification. Because this is only  
5 one tool to determine the quality of a product and there's  
6 a significant flaw associated with the process of obtaining  
7 reliable and consistent basis data, this method should not  
8 be applied to routine production of commercial product.

9 In addition, we are concerned with the unequal  
10 application of blend uniformity requirements by the agency.  
11 If in fact blend uniformity is, indeed, so important in the  
12 manufacture of quality drugs, it would seem prudent that  
13 the rules would apply to the submitters of NDAs as well as  
14 ANDAs.

15 Thank you very much for the opportunity to  
16 contribute to the generic industry's views on this issue.

17 DR. LEE: Thank you very much.

18 Are there questions?

19 DR. GARCIA: I have a question. I'm sort of  
20 confused here. You say that the GPhA is objecting to the 4  
21 percent RSD for the cGMP requirement during routine  
22 manufacture. In the next paragraph, you're talking about  
23 blends. Are those two points related or --

24 MR. LONESKY: The 4 percent --

25 DR. GARCIA: You realize the 4 percent is for

1 dosage units not blends.

2 MR. LONESKY: I thought it applied to the  
3 blends.

4 DR. GARCIA: No. We're getting into my  
5 presentation, but for readily complies versus not readily  
6 complies, that's dosage units.

7 DR. LEE: Maybe we should wait until --

8 DR. GARCIA: Yes. It will become clearer in a  
9 little bit.

10 DR. LEE: Thank you. So, please don't go away.

11 MR. LONESKY: I'll be here. Thanks.

12 DR. LEE: Thank you.

13 That's all the open hearing speakers there are,  
14 and we now move into the next session.

15 By the way, for those of you who are expecting  
16 a break at 3 o'clock, there won't be one. There will be  
17 one later on.

18 Ajaz?

19 DR. HUSSAIN: Let me sort of introduce this  
20 topic and the questions posed to the committee.

21 But two things before I give the introduction.  
22 One is this is a 100-year-old unit operation that we're  
23 dealing with. We're struggling with this. So, it's an  
24 interesting reflection on -- I don't know what.

25 The point, just to clarify, I had referred to

1 putting six different windows or things for near IR on a  
2 blender. That's not what I'm saying. It was meant to  
3 reflect the publication in J.Pharm.Science by Jim Drennen.  
4 I think just one window is enough. We have data. There  
5 are technical aspects to that, but let me just clarify that  
6 and move on.

7           What are we talking about here? Background.  
8 Blend uniformity analysis, the way we use it is not a  
9 control. It's an in-process test. What I mean by that is  
10 you will blend, stop the blender, collect 6 to 10 samples  
11 from different locations in the blender, assay, and then  
12 determine whether the blend is homogeneous. And if it's  
13 not, if you have a reprocessing, you'll blend for more  
14 time, or if you don't have a reprocessing protocol, you  
15 might have to start again. So, it's not a control. It's a  
16 test.

17           The way blend samples are collected. The  
18 picture there is from Sonja from Pfizer. She had provided  
19 that. In a lab scale, you poke a thief in different parts  
20 of the blender and try to collect small samples which are  
21 representative of the final dosage unit. Generally 1 to 3X  
22 is what we recommend.

23           What that picture reflects is it's probably  
24 easier to do that in the lab, but imagine some of the  
25 blenders are the size of the room. Collecting those

1 samples is not an easy task in many cases.

2           The subject has been intensely debated for the  
3 last 10 years. There was a code decision that triggered  
4 this. I'm not going to get into that code decision. But  
5 debate has focused on sample size, what is the right sample  
6 size. Should it be equal to the final tablet weight or  
7 should it be smaller, larger, and so forth? That has been  
8 a source of debate. Sampling errors are a source of  
9 debate.

10           When you collect blend samples, other  
11 processing steps follow. Segregation can occur after  
12 blending. We may not be controlling that by simply  
13 focusing our attention on the blend itself. And there are  
14 positions expressed that there's lack of correlation  
15 between the tablet content uniformity and blend samples.  
16 So, these have all been debated for the last 10 years, and  
17 in my presentation to the Science Board I said we probably  
18 have spent a couple of million dollars just talking about  
19 this and not getting a solution to the situation.

20           The story is an old story but was brought into  
21 focus with the issuance of a draft guidance for the generic  
22 applications, draft ANDA guidance on blend uniformity in  
23 August of 1999. That became the focus of research under  
24 the PQRI. You'll hear from that, but the story on blending  
25 -- the debate goes much beyond. It's older than the draft

1 guidance itself.

2           Very quickly, I'm not going to summarize the  
3 guidance. You have already received that guidance. But I  
4 just want to share with you some of the motivations. Some  
5 of these motivations are not listed in the guidance, but  
6 are underlying concerns that are being expressed in this  
7 guidance.

8           One reason for the draft guidance was to  
9 address some of the inconsistencies in the review practices  
10 with respect to supplements requesting deleting of blend  
11 uniformity testing. It was a minor administrative issue.

12           But the underlying concerns, the way I am  
13 expressing these concerns based on the discussions with the  
14 review chemists and so forth, is concern regarding drug  
15 content uniformity. Looking at the warning letters and so  
16 forth, you'll see a trend. There are cases where blend  
17 uniformity might be an indicator of content uniformity  
18 problems. A small number of examples but there are some  
19 examples.

20           But the point here is we have insufficient  
21 information to ensure quality is by design. I think that  
22 in my opinion is the fundamental cause. When an  
23 application comes in, we have one batch. We have  
24 information on one batch, and we have to make a decision on  
25 that batch. We have no other information, literally no

1 other information.

2           What is in that submission? With respect to  
3 this unit operation, we'll describe a blender type. We'll  
4 describe a capacity, and we'll describe an operating speed  
5 and maybe a time for blending. Generally, the information  
6 is the same for the proposed scale-up. The time would be  
7 the same. The blender capacity would be different and so  
8 forth.

9           The scope of this guidance was for products  
10 which require USP content uniformity test, and that is  
11 tablets or capsules which have 50 milligrams or less of  
12 drug or 50 percent or less of drug. For dosage units that  
13 have more than 50 milligrams or more than 50 percent, USP  
14 does not require content uniformity. It's just on the  
15 basis of weight. So, we don't do content uniformity tests  
16 for those. The guidance did not recommend blend uniformity  
17 testing for those.

18           For complex dosage forms, yes, we recommend but  
19 request speaking to the division to get more information.

20           And also the guidance recommends not to submit  
21 a supplement to delete a blend uniformity analysis when  
22 it's also used for compliance with cGMP. I think that is  
23 also a source of discussion. Is this a cGMP issue or is  
24 this a review issue?

25           Sampling size and procedure are briefly

1 described, and acceptance criteria and analytical  
2 procedures are described very briefly.

3           The point I want to make here is this.  
4 Performance of a solid processing unit or any processing  
5 unit depends on the underlying mechanisms. In the  
6 engineering world -- this is again a publication from the  
7 American Institute of Chemical engineers -- how would an  
8 engineer go about ensuring the right performance? Keep in  
9 mind what I just mentioned before. What information is  
10 available in the submissions, what the reviewers have to  
11 make a decision. It's the time, blender type, and so  
12 forth. The critical attributes, material characteristics,  
13 particle attributes, equipment design, operating condition,  
14 and how these impact on the forces on the particles and how  
15 the bulk mechanical properties are involved, none of the  
16 scientific aspects of blending or any other unit operations  
17 are discussed.

18           In many ways, I would say today trial and error  
19 is the norm. Reviewers have to look at one batch, two  
20 batches, three batches, at most the most data and make  
21 decisions. In the absence of a clear understanding and  
22 trial and error approaches, one has to ask the question.  
23 Do standard operating procedures that we have in place even  
24 reflect even the basic heuristics that underlie some of  
25 these processes? The answer is no.

1           To give you an example, in your handout packet  
2 I have a publication by Tom and Garth which has discussed  
3 the root causes of blending issues and so forth. They have  
4 tried to address that in many different ways.

5           Some of the heuristic rules that come into play  
6 that I've listed here -- I'm not going to read every one of  
7 those -- would have to be associated with an SOP. None of  
8 this, generally, is in any SOP.

9           In many ways, the question that we're dealing  
10 with is a question of representative sample, and let me  
11 give you an example. A major pharmaceutical company, in  
12 order to support the PQRI effort, started developing  
13 databases to submit to PQRI, and they shared this with me.  
14 I haven't had a chance to look at the PQRI data, so I'm not  
15 sure what data Tom is going to present, but this was  
16 submitted to me directly at FDA.

17           Here is a commercial product on the market, and  
18 the company wanted to provide information to PQRI and they  
19 did the proposed stratified sampling of this. Using blend  
20 sample analysis, beautiful results. Percent RSD is less  
21 than 1. We generally say less than 6 percent is  
22 homogeneous. USP content uniformity passes beautifully.  
23 All you do is take 10 tablets and that's your basis of  
24 that. But when you do a stratified sampling the way PQRI  
25 has proposed, you take samples repeatedly throughout the

1 run, this is the problem. The company actually had to go  
2 back and correct the problem. It would never have been  
3 detected until PQRI stratified came about.

4 So, the question in my mind is, is it a  
5 representative sample? I'll pose the questions to you and  
6 then invite Tom and Garth to make the presentations.

7 I have not seen the data, so I'm going to be  
8 looking at some of the data Tom is going to present for the  
9 first time with you. So, I have an overall impression of  
10 what the recommendations are likely to be, and that was the  
11 basis for these questions.

12 Is the current PQRI proposal appropriate for  
13 inclusion in the planned revised guidance? If no, we  
14 request you to provide suggestions so that Tom and others  
15 can work on those suggestions before the final  
16 recommendations come to FDA and we can have that  
17 accomplished in one cycle.

18 If yes, should the proposed stratified sampling  
19 and analysis plan be applied only for the bioequivalence  
20 batch and the validation batches? The validation batches  
21 are three batches at the commercial scale that people have  
22 to manufacture before they get to go on the market. And  
23 bioequivalence batch is the only batch our reviewers will  
24 get to see when they make a decision on approval.

25 DR. MOYE: Excuse me. Can I ask one question?

1 DR. HUSSAIN: Sure.

2 DR. MOYE: I'm sorry to interrupt.

3 What's the alternative for the answer to  
4 question 2? If the answer is no, then what other  
5 batches --

6 DR. HUSSAIN: Yes, I was getting to that.

7 DR. MOYE: Okay.

8 DR. HUSSAIN: If the answer is no, if the  
9 proposed stratified sampling and analysis is limited to  
10 dose, then how does one assure adequacy of mix for routine  
11 production batches? That's the question. So that you  
12 would do it routinely on every production batch.

13 So, that's the question, and I think what I  
14 would request Tom and Garth to do is to make their  
15 presentations and then we can open the discussion. Thanks.

16 DR. LEE: Let me interject. Who is on the  
17 phone?

18 DR. DeLUCA: I'm on the phone. Pat.

19 DR. LEE: I just wanted to make sure because I  
20 was told that one person is on line, and I don't know which  
21 one. Glad that you're here.

22 Please go ahead.

23 DR. BOEHM: Good afternoon and thank you for  
24 allowing Tom and I to come and present the work of the  
25 Blend Uniformity Working Group this afternoon.

1 DR. RODRIGUEZ-HORNEDO: I am on the phone.

2 DR. LEE: Nair, you're on the phone too.

3 Great.

4 DR. BOEHM: While we're waiting for the  
5 overheads to come up, the presentation this afternoon has  
6 three parts. The first part is a brief description of the  
7 background of the work of the Blend Uniformity Working  
8 Group, which I'm going to present. The second part is  
9 going through the draft recommendations, which the Blend  
10 Uniformity Working Group have come to. The third part is  
11 having a look at the data we have so far on the data mining  
12 exercise that was undertaken to challenge the  
13 recommendations that we made, and both of those parts will  
14 be presented by Tom.

15 At the start, it's reasonable to ask the  
16 question, why test blend uniformity? If blend uniformity  
17 is such a hot topic, you can avoid all of this aggravation  
18 by not testing at all.

19 The answer to why test it is found, I think, in  
20 two documents. The first and older of these is the section  
21 of the so-called GMP regulations, 21 C.F.R. 211.110, which  
22 reads in part, "to assure batch uniformity and integrity of  
23 drug products, written procedures shall be established and  
24 followed that describe the in-process controls, tests, or  
25 examinations to be conducted on appropriate samples of in-

1 process materials for each batch." And sub (3) under that  
2 introduces a term, "adequacy of mixing to assure uniformity  
3 and homogeneity."

4 There are two things in this that you need to  
5 take special note of. The first is this is referring to an  
6 in-process test or control of some sort, and the second is  
7 the use of the term "every batch." It doesn't say  
8 validation batches or 10 a year; it says every batch.

9 The second document to look at is the Office of  
10 Generic Drugs draft guidance, which was issued in late  
11 1999, on routine blend uniformity analysis. Now, it's  
12 important to note that this was not a new requirement from  
13 the Office of Generic Drugs. They had been requiring for  
14 some years that generic drug sponsors commit to performing  
15 blend uniformity analysis on routine production batches.  
16 However, the application of when to do that and the  
17 acceptance criteria that should be met were not even. And  
18 this guidance was issued to, as it were, level the playing  
19 field and let everybody know what was required. And it had  
20 three main parts.

21 The first is that it's required on solid dosage  
22 forms, less than 50 percent active or less than 50  
23 milligrams active; that is, that the USP would require  
24 content uniformity testing on.

25 The second was a suggestion to use 6 to 10

1 | samples of blend, and they should be 1 to 3 unit weights  
2 | per sample. That's weight for the dosage form.

3 |           And finally, the data that you generate must  
4 | meet a mean of 90 to 110 percent of label claim with an RSD  
5 | of not more than 5 percent.

6 |           The Product Quality Research Institute is a  
7 | collaborative effort -- you've heard about it before --  
8 | between FDA, industry, and academia. It's intended to  
9 | provide a platform where participants can set aside their  
10 | rhetoric and their some distrust of one another and  
11 | actually get down to looking at the basic science behind  
12 | some issues. Its mission is to provide a scientific basis  
13 | for developing regulatory policy, and one of its  
14 | initiatives was to set up expert working groups to look at  
15 | particular issues and analyze those issues with a view to  
16 | potential future regulatory policy.

17 |           I think the first working group set up was the  
18 | Blend Uniformity Working Group, which was established in  
19 | late 1999. The group is chaired by Tom and has members  
20 | from academia, FDA -- that's both from CDER and the  
21 | Division of Manufacturing and Product Quality -- and from  
22 | industry from both innovator and generic companies.

23 |           The group is charged with making scientifically  
24 | based recommendations on suitable procedures for assuring  
25 | batch homogeneity.

1 PQRI is a public effort. What it does is meant  
2 to be publicly available. So, I'd like to run briefly now  
3 through a list of the actions that the Blend Uniformity  
4 Group has taken from its formation to get to this point.

5 It has conducted an industry practices survey,  
6 which I'll talk about briefly. Published the Uniformity  
7 Troubleshooting Guide in pharmaceutical technology. It's  
8 held a public workshop on blend uniformity testing issues.  
9 It's held several numerous working group meetings and  
10 teleconferences. The group has written a draft proposal on  
11 the use of stratified testing of dosage units as an  
12 approach to batch homogeneity, and we have sought data from  
13 industry with which to challenge our proposal.

14 The industry practices survey was conducted to  
15 find out what was actually going on in industry. In order  
16 to have people give us honest answers, we conducted this  
17 survey in an entirely blinded manner. We have no idea who  
18 replied and who did not reply. It was sent to all solid  
19 dose sponsors with at least one approved NDA or ANDA that  
20 could be located. That's a poorly worded sentence. It's  
21 the sponsors we had to locate, not the applications. And  
22 it was designed to elicit information on general practices  
23 regarding blend uniformity sampling and testing.

24 134 surveys were sent out. We received 28  
25 replies, approximately 20 percent, which was somewhat

1 | disappointing given that this was an issue that generated  
2 | some heat in industry. Most of the replies came from large  
3 | manufacturers. That should be borne in mind since most of  
4 | the sponsors, in fact, are small manufacturers.

5 |           The survey asked questions on demographics,  
6 | what sort of company replied in general terms; on blend  
7 | sampling, what was done for routine testing, what was done  
8 | for validation testing; on causes of failure for blend  
9 | uniformity testing; on costs associated with the test; and  
10 | on new technology.

11 |           The full survey with the results filled in can  
12 | be found at PQRI's website, and a summary was published in  
13 | the August 2001 Pharm Tech, and I believe you have a copy  
14 | of that article in the handouts that you have.

15 |           The picture that emerged from the survey was  
16 | one of a conservative or perhaps very conservative  
17 | industry, that samples with conventional sampling thieves,  
18 | taking 1 to 3 unit dose sample sizes. It tests those with  
19 | conventional wet analytical methodology, HPLC type methods,  
20 | and it uses established acceptance criteria to test the  
21 | data with.

22 |           About two-thirds of those who replied for  
23 | testing of routine production batches were prepared to  
24 | defeat failing blend uniformity testing results with some  
25 | form of enhanced testing. There were many different

1 variations of this, but it amounted to enhanced testing.  
2 About a half of those who replied were similarly prepared  
3 to defeat failing blend uniformity results that were found  
4 in validation batches the same way.

5 Most respondents reported having trouble with  
6 about 10 percent of the products they manufacture and that  
7 that trouble was apparent right from the start, right from  
8 the point of validation. Or to look at that the other way  
9 around, 90 percent of the products they deal with give them  
10 no trouble.

11 Most of them think failures are due to sampling  
12 or analytical error. Very few people, apparently, think  
13 their failures are due to nonuniform blends, which is  
14 interesting.

15 And virtually all of them have not adopted any  
16 technology. They cite various reasons, among them that  
17 there is a fear of regulatory acceptance.

18 So, that was the picture that we got from the  
19 industry practices survey.

20 Fairly early on in the discussions that we had  
21 as a Blend Uniformity Working Group, I think it became  
22 apparent to us that there was no concise guide available  
23 for diagnosing blend or dosage form uniformity problems.  
24 There were some publications which addressed one situation  
25 or another, but nothing was pulled together.

1 Jim Prescott and Tom Garcia took the task of  
2 writing the guide, which they did, and designing a  
3 companion chart, which you can get from Jim and can use as  
4 a tool, a very useful tool, to diagnose uniformity problems  
5 really. That was published in the March 2001  
6 Pharmaceutical Technology.

7 The public workshop was based around the theme:  
8 Is blend uniformity testing a value-added test? It was  
9 intended to be somewhat controversial since the purpose of  
10 holding the workshop was to draw out information from the  
11 participants and not for us to hear ourselves talk. It was  
12 held in September of last year and approximately 200 people  
13 attended the workshop. It's form was that there were  
14 several presentations on aspects of blending, blend  
15 sampling, acceptance criteria, new technology, and there  
16 was a report also on the progress the working group had  
17 made to date. And the summary of the workshop was  
18 published in the September 2001 Pharmaceutical Technology.

19 The presentations that were given to set the  
20 theme for the workshop were based around the following:  
21 that blending of solids is a poorly understood process, and  
22 unlike blending of liquids, it's very poorly understood.  
23 It's very difficult to sample a static powder bed with  
24 conventional sampling thieves. That sampling errors that  
25 can occur, when you do try to sample powder beds, are

1 common and can occur both ways. Now, what I mean by both  
2 ways is the familiar one is when the sample indicates that  
3 the blend is not uniform and you're convinced that it is.  
4 However, it's easy to show. You can take a deliberately  
5 nonuniform blend and have a sample pulled out of it which  
6 indicates uniformity, which is perhaps the more dangerous  
7 issue. And post-blending segregation can be a serious  
8 problem, particularly for some of the newer types of bin  
9 blenders.

10 The major part of the workshop involved  
11 breakout sessions to elicit feedback from the attendees,  
12 and each attendee was able to rotate around three of these  
13 breakout sessions. Those three were based on the  
14 following. Is blend uniformity testing on every batch a  
15 value-added test? How do you validate a process when you  
16 have a sampling problem? And what new technologies are  
17 available to assess blend uniformity?

18 The conclusions that the workshop reached were  
19 as follows. I think it was unanimous or almost unanimous  
20 that blend uniformity testing on every batch is not a  
21 value-added test. That was also, however, almost unanimous  
22 that appropriate and meaningful blend uniformity testing  
23 should be conducted during development and validation. So,  
24 the workshop doesn't conclude the test is not of any value  
25 at all. It's not a value-added test in routine production.

1           Lastly, probably we had nobody at the workshop  
2 from any QC, we all decided that higher costs are  
3 acceptable if they yield meaningful results, although  
4 nobody has asked anyone who works in the lab whether they  
5 think that's true.

6           So, we've reached the point of having written  
7 our draft proposal. We decided in heading into this that  
8 it should have the following three attributes. The test  
9 should be simple to perform and not involve any complicated  
10 equipment, and it should maximize the use of the data  
11 that's gathered. Acceptance criteria to be applied should  
12 be easy to evaluate and interpret. And finally, acceptance  
13 criteria should demonstrate when lack of homogeneity is  
14 suspected.

15           I'll now hand over to Tom who will discuss the  
16 recommendation in detail.

17           DR. GARCIA: What I'd like to do now is just go  
18 over the recommendation that we're getting ready to  
19 finalize and pass on to the steering committee for their  
20 review and eventual forwarding on to the FDA if they  
21 approve it. This is more or less the culmination of all  
22 the preparatory things that the group did over the last  
23 almost two years now into our final approach that we think  
24 is reasonable.

25           First of all, I'd like to start with saying

1 that we do use stratified sampling. Stratified sampling is  
2 really a statistical term that refers to selecting your  
3 sample points, whether it be in a blender or during a  
4 compression or filling operation. You select distinct  
5 points in that blender or that run that will target  
6 problematic areas. For example, if you've got a  
7 compression run, you'll probably want to take samples at  
8 the very beginning of the batch, as well as the end of the  
9 batch. If you have multiple bins or hoppers that are being  
10 emptied onto the press, you'll want to catch the changeover  
11 there because that's where you can typically get  
12 segregation.

13 It does not necessarily mean that you take  
14 evenly spaced samples throughout the batch. In fact, what  
15 we tend to advocate is that you want to probably target  
16 more samples around these changeovers at the beginning or  
17 the end of emptying a hopper, to pick those areas where  
18 you're most likely to find a problem.

19 The recommendation applies to process  
20 validation and routine commercial batches for solid oral  
21 dosage forms. It applies only to those products where the  
22 active ingredient or ingredients are added into the blend.  
23 For example, if you are adding an active ingredient into  
24 the film coating suspension or solution, spraying it onto  
25 tablets, this recommendation does not apply to that

1 particular drug. It would apply to the drug that's in the  
2 core, but not the one in the coating.

3 It does not apply to those instances where you  
4 could use weight uniformity to demonstrate content  
5 uniformity per the USP.

6 The advantages of the approach that we are  
7 advocating are it's much more accurate and more relevant of  
8 the true uniformity of both the blend, we feel, and the  
9 dosage units that are going out the door.

10 It eliminates all blend sampling errors,  
11 especially when you start monitoring for routine  
12 production.

13 The third thing is it will detect segregation,  
14 and the slide that Ajaz put up a couple minutes ago shows  
15 that exact thing. By targeting more samples toward the end  
16 of the batch, you're more likely to pick up those outliers  
17 that are probably the result of segregation of the drug.

18 Finally, it eliminates those instances where  
19 you've got to break containment. If you've got a highly  
20 potent or toxic drug, you could take the tablet cores out  
21 of there rather than cracking open the blender and exposing  
22 your operators to the toxic effects of the substance.

23 The disadvantages are some people say, well,  
24 it's too late. Once you compress the batch or fill the  
25 batch, how are you going to adjust to improve your

1 | uniformity? Others have said it's not consistent with  
2 | quality by design or parametric release. This one I have a  
3 | little issue with because I think it really is. The other  
4 | thing is, is it a control or is it a test? If it's a  
5 | control, you should be able to make some adjustment during  
6 | the batch. If it's a test, it's more of a pass/fail thing.

7 |           The actual recommendation itself is split up  
8 | into three parts. The first one addresses process  
9 | development. We want to make it clear that the stratified  
10 | sampling approach is not an excuse to do poor development,  
11 | particularly when assessing your blends for uniformity.  
12 | You should be defining your sampling techniques and the  
13 | equipment that you use to sample it. For example, you want  
14 | to get a very thorough scheme, so you map that blender to  
15 | make sure that you got all dead spots. You want to look at  
16 | multiple sampling devices because there are indications in  
17 | the literature where you could have one thief pull samples  
18 | on the same blend and get an RSD that's twice as high as  
19 | samples obtained with a different thief, for example, a  
20 | plug thief versus a grain thief.

21 |           Your sampling technique. How do you insert it?  
22 | Do you spin the thief around? Do you wiggle it? All these  
23 | things need to be defined before you go in and start your  
24 | validation.

25 |           Finally, one big thing that we wanted to make

1 | sure we covered is the Blend Uniformity Group acknowledges  
2 | that sometimes you cannot sample 1 to 3X dosage units  
3 | weights. Therefore, our approach is that you should start  
4 | at 1 to 3X, but if you cannot get representative data  
5 | there, you should go up in the weight until you can  
6 | identify the smallest weight of sample that is truly  
7 | reflective of the blend.

8 |           The next thing is the process validation  
9 | approach that is in the guidance document. We start out by  
10 | sampling at least 10 locations from your blender and taking  
11 | triplicate samples from each location. I just want to add  
12 | a little thing here. 10 locations are for tumble mixers  
13 | such as a deblender, tote, things like that. If you get  
14 | into a convective mixer such as a ribbon blender where you  
15 | have more dead spots in it, actually we do advocate that  
16 | this number is increased to 20 locations just because there  
17 | are a lot of dead spots in those blenders.

18 |           You assay one sample per location. The RSD is  
19 | if it's less than or equal to 5 percent. And all  
20 | individuals are within plus or minus 10 percent of the mean  
21 | absolute. This is another little change we made here. We  
22 | are not saying 90 to 110 percent here. The reason is we  
23 | acknowledge that blend sampling bias can occur in a very  
24 | constant, consistent reproducible manner either inflating  
25 | or deflating the mean. The true measurement of uniformity

1 of blend is the RSD. The blend uniformity test is not the  
2 time to determine potency. So, we have incorporated this.  
3 All individuals are within plus or minus 10 percent of the  
4 mean, and that's an absolute number. For example, if your  
5 mean is 90 percent, your range is 80 to 100 percent, not 81  
6 to 99. We don't calculate it based on that exact mean.

7 DR. MOYE: Excuse me. Just so I can be clear.  
8 I'm sorry.

9 You are suggesting that precision should take  
10 precedence over accuracy here? Is that what you're  
11 suggesting?

12 DR. GARCIA: We're saying that basically it's  
13 the RSD. We're not looking at the absolute values because  
14 those could be consistently biased, high or low.

15 After testing, one sample from each location,  
16 if you fail, we ask that you test the second and the third  
17 samples from that location. Basically now what you're  
18 doing is an out-of-spec investigation. If you look at this  
19 data and you identify that it is truly related to a mixing  
20 problem, then your blend is not uniform and you've got to  
21 go back to development and figure out what went wrong.

22 However, if your investigation points to  
23 sampling bias, which could be demonstrated through  
24 component variance analysis or some other attributable  
25 cause not related to mixing, then you go over to stage 2

1 testing of the dosage units.

2 If you pass this criteria, you proceed to stage  
3 1 dosage unit testing.

4 The big thing here is you don't want to go down  
5 this route and do a lousy job on your blend uniformity  
6 sampling techniques because the number of samples you're  
7 going to test here are a lot greater than here. So, there  
8 is a penalty to pay. But at least we have identified a  
9 means to get around the classic case where you have poor  
10 blend uniformity but great cores.

11 This is the second half for validation. This  
12 addresses the content uniformity of dosage units. You can  
13 see how it ties in.

14 During a compression or filling operation, we  
15 advocate that you take 20 locations throughout that batch,  
16 once again stratified locations. From each location, you  
17 take at least 7 dosage units. Now, stage 1 is right here  
18 where you assay 3 dosage units per location. So, you're  
19 looking at a total of 60 for stage 1.

20 The acceptance criteria is the RSD of all  
21 individuals is less than or equal to 6 percent. Each  
22 location mean must be between 90 to 110 percent label  
23 claim. We're absolute here now. No more plus or minus 10  
24 percent of the mean.

25 Finally, all individuals have to be within 75

1 to 125 percent.

2 If you pass this criteria, then  
3 congratulations. That batch is validated.

4 If you fail it, assay the other 4 dosage units,  
5 and this is stage 2 right here. So, you're looking at a  
6 total of 7 units for each of the 20 locations. So, you can  
7 see if you do a lousy job on your blend uniformity  
8 development work, you're going to pay the price in assaying  
9 80 more samples when it comes to validation. So, it's in  
10 your best interest to get the blend down.

11 You assay it again. The acceptance criteria  
12 are the same as up above. Pass, you're okay. That batch  
13 is validated. If you fail, then the blend is not uniform  
14 or segregation or something is happening during the  
15 compression run.

16 Briefly, how do we justify the number of  
17 samples here? The 10 locations for the tumbling blender,  
18 as I said before, the Blend Uniformity Working Group felt  
19 that that was adequate to map the blender. But notice  
20 below that when you get into the convection mixers, we  
21 advocate going to 20 locations. As I said earlier, you  
22 need to take replicates so that if you do fail the first  
23 step of the blend evaluation, you could do your analysis to  
24 see if you have sampling error or bias in there.

25 The number of dosage unit samples during the

1 | compression or the filling operations, the 20 locations and  
2 | the 3 or 7 dosage units to test. These all came through  
3 | operation characteristic curves that were generated using  
4 | Monte Carlo simulations. What we did when we generated  
5 | those OC curves is we looked at things like weight  
6 | variation, assay variability, between-location error, and  
7 | within-location error for each one of your sampling points.  
8 | We also used the USP content uniformity test as our  
9 | benchmark for reference.

10 |           This is an example of one of the OC curves that  
11 | we use. This particular one is looking at within-location  
12 | RSD; in other words, how do those 3 or 7 tablets vary  
13 | within a given location. Basically if you look at our  
14 | criteria for PQRI, you can see that we start breaking it  
15 | about 5 percent, I think it is. It starts going down  
16 | pretty steep. Whereas, the USP test is about 6 percent.  
17 | So, the PQRI criteria is more discriminating than the USP  
18 | test.

19 |           The other thing is you notice that this is a  
20 | pretty steep curve, which is good. It says as soon as you  
21 | hit some sort of a threshold, you're going to start failing  
22 | batches. So, that's another indication of the  
23 | discriminating power of our test.

24 |           This particular one as well assumed the  
25 | population mean was 100 percent, and we added a 1.5 percent

1 RSD for our weight.

2           The next slide I want to put up here looks at  
3 between-location. In other words, you got 20 locations  
4 throughout your, say, compression run. How does the data  
5 vary from each location? Once again, we're assuming a mean  
6 of 100 percent. What we did here is the weight is still at  
7 1.5 percent. We also threw in an assay variability of 1.5  
8 percent here. On the bottom this is you're between-  
9 location. RSD ranges from 1 to 10.

10           What you can see here, if you have between  
11 location variability, you're going to start rejecting  
12 batches a lot quicker. It's a lot more severe of a penalty  
13 than within-location. Basically at about 3.7 percent I  
14 believe is the exact number, you're at the 95 percent  
15 probability of passing the acceptance criteria. So,  
16 roughly around 4 percent you're going to start sliding  
17 down. Once again, you can see we are more discriminating  
18 that USP.

19           This goes back to Steve's question. Where did  
20 the 4 percent come from? It's right here. This computer  
21 simulation is what we will use later on to say whether you  
22 readily pass validation criteria or marginally pass it.  
23 But here it is. It's actually 3.7 was the exact number.  
24 We rounded it up to 4 percent. As soon as you go above 4  
25 percent for your RSD, you're going start failing batches.

1 So, that's where it comes from.

2 Justification for our dosage unit acceptance  
3 criteria. The RSD of 6 percent is consistent with stage 1  
4 of USP.

5 The one that you're going to fail on is all  
6 locations means between 90 to 110 percent. This is for  
7 each of the 20 locations. What you're basically going to  
8 detect here is drifting in the process, dead spots, or  
9 segregation in the batch, either at the beginning or the  
10 end of it. This is the one that's really going to probably  
11 have the most impact of all the criteria.

12 We also added the 75 to 125 criteria in there  
13 just in case we should detect a stray outlier, a  
14 superpotent or a subpotent tablet. We felt that if you did  
15 have one of those and by some miracle you still were able  
16 to pass the mean, that batch doesn't have any business to  
17 be accepted.

18 For the dosage unit test, we also use a two-  
19 stage test which is consistent with the USP. You notice  
20 that stage 1 and stage 2 criteria are the same. Basically  
21 what we're doing is if you have an 89 percent mean, we're  
22 giving you one more chance to get it right and salvage the  
23 batch.

24 The final part of the document addresses  
25 routine manufacturing and primarily the cGMP component that

1 Garth mentioned earlier. The dilemma we had in PQRI is  
2 we're supposed to be reducing regulatory burden. So, how  
3 could we incorporate the USP test and the cGMP test without  
4 any real additional testing.

5 So, after some thought, what we ended up doing  
6 is we said could we pull the sampling procedure for the USP  
7 test as an in-process test. It looked pretty good until we  
8 figured what happens if you got a coated tablet. You're  
9 going to be doing the USP test on coated tablets, and USP  
10 says it's got to -- excuse me. You're going to do in-  
11 process tests on uncoated tablet cores, and USP says it's  
12 got to be done on finished dosage forms. So, we had to get  
13 around that, and I think we have.

14 Basically we're advocating pulling 30 tablet  
15 cores in process at 10 different locations, 3 per location  
16 at least. For the cGMP compliance, you assay those 30  
17 tablets and you normalize the data for weight. Why are you  
18 normalizing for weight? You're looking for uniformity of  
19 the blend here. We're not interested in weight  
20 variability.

21 To satisfy the USP test, you don't normalize  
22 for weight.

23 So, you see what we're doing? We're testing  
24 the same 10 or 30 dosage units, performing two calculations  
25 on it to satisfy two tests. So, the actual analytical

1 testing work and sample preparations is zero. Granted, you  
2 got to do two calculations on it, unless you want to roll  
3 the dice and just try to satisfy GMP compliance without  
4 normalization.

5 Here's the key thing. I've got to read this  
6 because I want to get it straight because it was worded  
7 really carefully. If the in-process sample is not the  
8 finished dosage form -- i.e., a core for a coated tablet --  
9 you must demonstrate during validation that the in-process  
10 results provide the same or better control as the content  
11 uniformity data generated during release testing of the  
12 corresponding finished dosage form, i.e., the film coated  
13 tablets. If you could demonstrate this relationship, you  
14 could do this up on top. So, there's how we took care of  
15 two birds with one stone and met our requirement of  
16 minimizing regulatory burden.

17 Now, in routine manufacturing, you're going to  
18 see on the flow chart the term "readily complies" versus  
19 "marginally complies." Products that readily comply are  
20 those that for your ANDA exhibit batches and/or the  
21 validation batches, the RSD is less than 4 percent for the  
22 dosage units, not for the blend. All the mean results are  
23 within 90 to 110 percent for those batches, and we don't  
24 have anything outside the 75 to 125 percent range. If you  
25 readily comply, you go to stage 1 testing.

1                   Now, for products that do not readily comply --  
2                   i.e., marginally comply -- this is where your RSD is  
3                   between 4 and 6 percent. You have to go into stage 2  
4                   testing where you test 30 dosage units.

5                   So, here it is, the flow diagram for your  
6                   batches. You make your decision, do these products readily  
7                   comply. If so, come down to stage 1, test one tablet  
8                   sample out of 10 locations, 10 tablets. If they do not  
9                   readily comply, you go to stage 2 where you test 3 samples  
10                  per each of the 10 locations. So, you're looking at 10  
11                  versus 30 for stage 1 and 2.

12                  Obviously, if you pass stage 1, adequacy of mix  
13                  is demonstrated, you then perform your second calculation  
14                  if you weight correct it to verify that that particular  
15                  batch meets USP criteria.

16                  If it doesn't pass stage 1 -- and notice that  
17                  your mean is between 90 to 110 percent, RSD is 5 -- you go  
18                  to stage 2. You test all 3 samples per location. Your  
19                  acceptance criteria is still 90 to 110 for the mean, but  
20                  your RSD has gone up to 6 percent. Then if you pass, the  
21                  same box as over here. If you fail, then adequacy of mix  
22                  is not demonstrated and the batch is rejected.

23                  Now, if you come down this route, you got a  
24                  product that marginally complies, and you do 5 batches in a  
25                  row where you pass, then you could revert to stage 1

1 testing and reduce the burden.

2 The sample size and the number of locations for  
3 routine manufacturing are based on USP tests. We're trying  
4 to keep the 10 plus 20 approach.

5 The GMP acceptance criteria of an RSD less than  
6 5 percent and the mean between 90 and 110 percent was  
7 consistent with the validation approach, although for  
8 validation they want individuals. We talked John Dietrick  
9 into just letting us get away with a mean between 90 and  
10 110.

11 That concludes our recommendation. But I want  
12 to just put up the one last slide. This is just one way to  
13 demonstrate that the blend and the dosage units are  
14 uniform. There are other means out there, and in  
15 particular, the on-line monitoring, NIR, those new  
16 techniques that are coming out. That's the ultimate that  
17 we should be striving for. This is more like a band aid  
18 that will take care of the problem at hand right now.

19 We also had a number of individuals on the  
20 Blend Uniformity Working Group that were carryovers from  
21 PDA 25. PDA 25 is a very, very good, very strict means to  
22 also look at this problem, and there are no reasons why you  
23 shouldn't be able to use that either. It's a very good way  
24 to do it.

25 Of course, for the brave ones out there that

1 want to continue sampling every blend, go ahead. But as  
2 Fernando Muzzio said, when you fail, don't come hollering  
3 at us.

4 So, this concludes this particular section on  
5 the actual recommendation that is coming out.

6 The next thing I want to talk about is the  
7 results of the PQRI data mining effort. This information  
8 is really only about a week old. Actually two of the  
9 slides in the packet that have been handed out are already  
10 out of date. I actually made the adjustments right before  
11 I left for the airport yesterday, so I'll point those out.

12 The objectives of our data mining effort were  
13 really threefold. First, we wanted to test the hypothesis  
14 that blend uniformity testing is not value-added testing  
15 for the products.

16 The second thing is we wanted to test the  
17 assumption we made during the Monte Carlo simulations that  
18 the means both within-location and between-locations were  
19 normally distributed because basically that's how we  
20 establish our acceptance criteria.

21 And finally, we wanted to compare the various  
22 criteria that are out there ranging from our criteria to  
23 the OGD, the FDA, the USP, and the modified USP, and see  
24 how they stacked up when comparing the same sets of data.

25 A call for data went out. I think it was in

1 July. We solicited companies to send us solid dosage form  
2 information in a number of categories. We wanted to get  
3 products that had an active ingredient of less than 5  
4 percent and those between 15 and 25 percent to see if low  
5 potency products performed any worse than the higher  
6 concentrations of drugs.

7 The other thing that we wanted to look at was  
8 products made by various processes, namely direct  
9 compression, wet granulation, and dry granulation.

10 We also wanted to look at both capsule dosage  
11 forms, tablets, and if could get any sachets or powder  
12 fills, that would have been nice too.

13 Finally we wanted to look at large and small  
14 batches.

15 We had a total of eight companies submit the  
16 data to us. We got 149 batches. For those members of the  
17 audience whose companies submitted data, thank you very  
18 much. We would have like to have seen more, but we feel we  
19 had a fairly good representation to get some confidence.

20 This slide is one of them that I replaced  
21 yesterday. We had 149 batches for tablets, 0 for capsules.  
22 So, we missed that objective.

23 The number of direct compression products out  
24 of 149 was 12 batches. We had, I think it was, 67 batches  
25 that were made via wet granulation and 70 batches that were

1 made by dry granulation.

2 I don't have this data for potency or the batch  
3 sizes summarized yet. As I said, we're still in the middle  
4 of finalizing the data and information from the study.

5 This slide ignore, so I'm just going to go  
6 right on to the next one and read the other one.

7 The test for the normality of means -- as I  
8 said earlier, we wanted to test both within-location and  
9 between-locations. The way that the consultant did it, he  
10 did Wilk-Shapiro test for normality. For between-location  
11 means, to see if those were normally distributed, we found  
12 out that about 11 percent of the 149 batches had at least  
13 one value that was statistically different or deviated from  
14 normality. Most of those 11 batches that had this problem  
15 had that point either at the beginning or the end of the  
16 batch. So, you see the power of stratified sampling to  
17 detect these changes.

18 Now, for within-location differences, about 15  
19 percent of the batches had at least one value that was  
20 statistically different.

21 The conclusion for both of these, though, is  
22 that -- first of all, most of the data out there was  
23 normally distributed, but even though some of it wasn't,  
24 the computer simulations that we used to estimate rejection  
25 criteria rates will yield slightly smaller values than

1 rejection rates based on the actual data. For example, we  
2 may say that 3.2 percent of the batches are going to be  
3 rejected, when in reality it's going to be about 3.5 when  
4 you start looking at the data. So, it's slightly  
5 different. The take-home message is here, yes, we're off  
6 by a little bit, but in general using the computer  
7 simulations is legitimate and the acceptance criteria that  
8 were identified are going to be sound.

9 The second thing is to compare the blend and  
10 dosage unit content uniformity data. Really what we're  
11 doing here is we're testing the hypothesis that blend  
12 uniformity is not value-added testing. The plots I'm about  
13 to show you are really interesting.

14 First of all, we compared them by plotting  
15 blend RSD on the x axis and dosage unit RSD on the y axis,  
16 and we did it for all 149 batches.

17 Here's the plot right here. Notice we have a  
18 line going up here at a 45 degree angle. If you have a  
19 true prediction of a blend for how the dosage unit is going  
20 to be, you're going to get a 45 degree angle. In other  
21 words, if your blend RSD is 5, your dosage unit RSD is 5,  
22 similarly up the line. What you can see is we got a lot of  
23 points off the line.

24 The second thing I want to point out on this  
25 plot is we divided it into three distinct areas: RSDs less

1 | than 3 percent, RSDs 3 to 5 percent, and then RSDs greater  
2 | than 5 percent. That's what I'm going to go into now.

3 |           If the RSD is less than 3 percent for the  
4 | blend, we got a decent correlation of the data. I think we  
5 | had something like 112 data points here. I can't remember  
6 | exactly what it is. For about 100 of those, we did see a  
7 | fairly decent -- probably within statistical acceptable  
8 | limits -- a real good correlation between the actual blend  
9 | RSD and the dosage form RSD. You can see a lot of points  
10 | are very close to this line.

11 |           We do have, I think, 12 or 10 points up here  
12 | where the dosage unit RSD is higher. So, what could be the  
13 | possible cause of that? One thing that came up is you got  
14 | weight variability in there now. If it's a tablet, how  
15 | much weight variation is included into this RSD. The  
16 | second possibility is, is this particular product  
17 | segregating? So, you can see that there is a little bit  
18 | value in further analyzing these particular points.

19 |           Now, when we go to 3 to 5 percent RSD, we start  
20 | to lose that correlation. Everything should be bunched  
21 | around a line right up here. But what you see is the blend  
22 | RSDs are a lot higher than the corresponding dosage form  
23 | RSDs. Roughly it's about 1 to 2 percent higher for the  
24 | blend. So, we're starting to lose that meaningful  
25 | correlation and starting to question the value of blend

1 data.

2 Now when we go above 5 percent, everything  
3 blows up. Basically if you got a blend RSD greater than 5  
4 percent, you have no correlation to what you're going to  
5 get in the dosage unit. These are the products that are  
6 very prone to sample bias.

7 So, if you put it all together, unless you got  
8 an RSD less than 3 percent, your blend uniformity is of no  
9 value to predicting what the uniformity of the final dosage  
10 form is going to look like. So, we did meet our objective  
11 for that, to test that hypothesis based on this data.

12 Finally, the last thing I want to talk about is  
13 the comparison of the acceptance criteria. We put all 149  
14 batches up against the PQRI validation criteria, the OGD  
15 criteria, and FDA.

16 The FDA validation criteria was the most  
17 restrictive, and the reason for that is, remember, that you  
18 had to have an RSD less than 5 percent, but also all the  
19 individuals had to be between 90 and 110 percent for the  
20 blend. If you had any bias in there, you're going to start  
21 to have batches less than 90 or greater than 110. You're  
22 going to start failing it. So, that's the cause of this  
23 right here.

24 The OGD and the PQRI validation approach.  
25 Really, there's probably no statistical difference between

1 those numbers there. So, they were on a par when it came  
2 to passing it.

3 For the PQRI routine, USP, the ICH, and PDA 25,  
4 we only tested 88 batches of the 149. The reason for the  
5 fewer number of batches being tested was because 88 of them  
6 had at least 10 sampling points during the compression run.  
7 The other ones only had like beginning, middle, and end.  
8 Even though we advocated 20 sampling locations in our  
9 recommendation, we felt that we needed at least 10 to  
10 perform this analysis. So, it's a lesson that you learn  
11 when you do data mining after you set the number of sample  
12 locations and tablets you want. We're at the mercy of what  
13 we got. So, these 88 batches had at least 10 sampling  
14 locations.

15 Basically for the first three, you see there's  
16 really no difference in the percentage of batches that were  
17 passing it. However, you can see PDA 25 is much, much more  
18 discriminating and will reject about 30 percent more  
19 batches.

20 One other thing I want to put up finally is  
21 going back to the marginally versus readily complies data.  
22 Of the batches that passed in the previous slide, 79 of the  
23 83 batches that passed PQRI validation acceptance criteria,  
24 79 readily complied, 4 of them marginally complied. So,  
25 that will give you a flavor for how many tablets you're

1 going to have to test for routine production.

2           Finally, I just wanted to acknowledge a number  
3 of people. From here on up is the Blend Uniformity Working  
4 Group, a great bunch of guys and girls. They worked really  
5 hard. It was really nice to see people from various  
6 aspects of the industry come together in a united way to  
7 come up with this.

8           Finally, Laura Foust, who is not on the Blend  
9 Uniformity Working Group, probably did more work towards  
10 this proposal than anybody on it. So, this is actually all  
11 the brain power behind the final recommendation.

12           That's the last slide.

13           DR. LEE: Thank you.

14           Any questions for the speakers? Because we do  
15 have a couple of questions to address.

16           DR. VENITZ: In your data mining efforts, were  
17 all those batches that actually passed? Because it appears  
18 to me that if you look at your overall plot, that all the  
19 dosage form RSDs are less than 6 percent. Right? So, you  
20 didn't include any failing --

21           DR. GARCIA: No. All the dosage form RSDs were  
22 less than 6 in 149 batches.

23           DR. VENITZ: Do you think that your  
24 interpretation, in terms of the predictiveness of the  
25 blends, would change if you had included failing batches?

1 In other words, right now you know a priori that all your  
2 batches are going to pass your dosage form requirements,  
3 but if you had included the ones that failed, would that  
4 change your interpretation?

5 DR. GARCIA: Yes, probably. I couldn't see how  
6 it wouldn't.

7 DR. VENITZ: You're arguing that the blend RSD  
8 predicts the dosage form RSD only for the low RSD. Would  
9 that be true if you included your failing ones?

10 DR. GARCIA: What's the hypothesis we're  
11 testing though? Blend uniformity is not value-added. Look  
12 at the number of batches that had RSDs greater than 5  
13 percent, some of them up around 20 percent for the blends.  
14 If you were going to say that there is a correlation there,  
15 then that batch is not uniform. The hypothesis we're  
16 testing, the data fit it because we had batches of blend  
17 that definitely failed, and some grossly failed. But yet,  
18 the dosage forms were uniform.

19 DR. VENITZ: And if you had included the  
20 failing one, I think that would have been even more  
21 apparent. I think it would have even more confirmed your  
22 hypothesis that your blend does not predict your dosage  
23 form performance.

24 DR. GARCIA: Possibly.

25 DR. LEE: Nair, do you have any questions for

1 | the speakers? Dr. Rodriguez? Dr. DeLuca?

2 | DR. DeLUCA: No. I'm okay.

3 | DR. RODRIGUEZ-HORNEDO: Question.

4 | DR. LEE: So, Nair, go ahead.

5 | DR. RODRIGUEZ-HORNEDO: I have a question for  
6 | the speakers. My question is the relative standard  
7 | deviation on the blend in all these studies that have been  
8 | reported may very well be reflecting the error in sampling.  
9 | Am I correct in that?

10 | And if that is so, we need to be careful  
11 | because if the sampling technique is really not  
12 | representative of the whole sample, that is really not a  
13 | good test for whether blend uniformity would be a good  
14 | endpoint for dosage form uniformity. So, I'm wondering if  
15 | any of these were done with in-line or on-line monitors.

16 | DR. GARCIA: We don't have that information  
17 | whether or not the companies that submitted the data were  
18 | also using on-line monitoring. I doubt it, though.

19 | DR. LEE: Nair, are you satisfied with the  
20 | explanation?

21 | (No response.)

22 | DR. LEE: Judy?

23 | DR. BOEHLERT: My understanding is the eight  
24 | companies from whom you received data were mostly large  
25 | companies, or were they smaller as well? My concern always

1 | when we change a standard is what is the impact on  
2 | previously released product, product that met the old  
3 | standard and is it going to be an adverse impact for the  
4 | large variety of products that are out there?

5 | DR. GARCIA: To answer your first question, we  
6 | don't know the size of the companies. The companies that  
7 | submitted the data were totally blinded.

8 | DR. BOEHLERT: Totally blinded.

9 | DR. GARCIA: Right. The way we did it is they  
10 | submitted the data to Sylvia Ganton, who is our executive  
11 | secretary of PQRI. She entered it into a database after  
12 | acknowledging that it was from a legitimate company,  
13 | removed any reference of product name, company name from  
14 | the data, and then forwarded it on to the statistician and  
15 | subsequently to the working group.

16 | DR. BOEHLERT: Did you encourage companies to  
17 | submit batches that weren't so good?

18 | DR. GARCIA: We tried.

19 | DR. BOEHLERT: Or is it likely they sent their  
20 | best?

21 | DR. GARCIA: We tried but that was a question  
22 | that came up.

23 | DR. BOEHLERT: Yes, it's always a question.  
24 | I'm going to send you my best data. I don't want my  
25 | company to look bad even if you don't know who I am.

1 DR. GARCIA: But if you look in the slide where  
2 you got the blend RSDs greater than 5 percent, obviously  
3 somebody had some guts to send us that.

4 DR. BOEHLERT: Well, but USP -- the current  
5 limit on content uniformity is 6 percent for RSD on the  
6 first 10.

7 DR. GARCIA: There are some 12, 15, 20's in  
8 there too.

9 DR. BOEHLERT: That would be my concern. If  
10 they're currently close to that 6 percent, what's the  
11 impact of going down in RSD in the future?

12 DR. GARCIA: One question I think that came up  
13 at AAPS that may be related to yours is, is this going to  
14 be applied to some of the older products where we don't  
15 have blend uniformity? Is that what you're getting at?

16 DR. BOEHLERT: Yes, absolutely. What's the  
17 impact on old products? New products is something else.  
18 You validate them using these standards, but old products  
19 were validated many years ago in some cases.

20 DR. GARCIA: Do you want to handle that one,  
21 Helen or Ajaz?

22 DR. HUSSAIN: I'm here to seek the  
23 recommendation from the committee.

24 (Laughter.)

25 DR. BOEHRM: Well, I'll have a go at it. We did

1 discuss this and the representatives of DMPQ indicated that  
2 the current rule would still apply. If it's an old  
3 product, you leave it alone. If you don't make any  
4 changes, you don't do anything, then you don't need to  
5 produce any more information. But as soon as you touch  
6 something to improve it or shift it, then they have the  
7 right to ask for today's standard.

8 DR. BOEHLERT: Another reason for not going to  
9 new technology I guess. Right?

10 DR. LEE: Kathleen, you have comments to make?

11 DR. LAMBORN: I guess I have sort of a follow-  
12 up to some of the things that are being said about the  
13 basis on which these batches were coming forward because  
14 you could argue that if you wanted to try to convince  
15 people that the blend uniformity standard was not useful,  
16 the first thing you would do would be give some examples  
17 that looked just like the graph that we saw.

18 And then the results that you're getting. I'm  
19 assuming that you're recognizing that the biases that come  
20 into the -- I mean, there's no way that this necessarily  
21 describes the frequency with which things would pass if you  
22 were to get a "random" sample of things that come in from  
23 the field. I think you recognize that.

24 The other question I have is could you have  
25 predicted pretty well the order in which you would have

1 | seen the passage rate just by knowing the differences in  
2 | the criteria that were set? You said, for example, that  
3 | the FDA validation results in fewer acceptance. Then you  
4 | said, well, of course, that would be expected because they  
5 | have a narrower range.

6 |           So, I guess my question to the group is, have  
7 | you learned anything that you would not have really known  
8 | already just by contrasting the differences in the criteria  
9 | as you knew that they were? I mean, you knew that the FDA  
10 | criteria on that component of it was stricter. So,  
11 | anything that passed the FDA is by definition going to pass  
12 | the other ones.

13 |           DR. GARCIA: Right. What we were trying to do,  
14 | though, is what are meaningful specifications. That's the  
15 | thing. Now, the FDA specification is for individual dosage  
16 | units. All of the other ones are for means. That's why  
17 | you got more selectivity. If you got an 89 percent blend  
18 | sample, on the FDA criteria you're going to fail; whereas,  
19 | in the PQRI, if you got an 89, a 90, and a 91, you're going  
20 | to pass.

21 |           DR. LAMBORN: I realize that's what you're  
22 | saying. All I'm saying is that you didn't need data in  
23 | order to conclude that.

24 |           DR. GARCIA: Well, all of our acceptance  
25 | criteria are based on Monte Carlo simulations, and when we

1 originally went down that road, the steering committee was  
2 not comfortable with us using computer generated data. The  
3 results of that data were the OC curves that I put up  
4 there. So, yes. Could we predict how many were going to  
5 fail? Absolutely. The OC curves did it. But what we  
6 wanted to do, per the DPTC and the steering committee's  
7 request, was to get a reality check on what is actually out  
8 there and how was it going to conform.

9 Does that answer your question? I don't think  
10 it does.

11 DR. LAMBORN: Partially. That's okay.

12 DR. BOEHM: Perhaps I could add one more thing.  
13 The FDA validation criteria, as it's being called here,  
14 comes from an old compliance document, and it has blends  
15 only. It has no stratified sampling criteria associated  
16 with it. So, it just sits out there alone as a blend  
17 uniformity criteria in the middle of nothing else.

18 DR. LEE: Ajaz?

19 DR. HUSSAIN: Vince, a couple of comments and  
20 corrections. Garth in his presentation said CDER and  
21 Division of Manufacturing and Product Quality. That's part  
22 of CDER. The Office of Compliance is within CDER. The  
23 Office of Regulatory Affairs is probably what you were  
24 confusing.

25 Also, I'm seeing the struggle here I think that

1 | you will have to face in terms of providing recommendations  
2 | to the questions because you're looking at a traditional  
3 | approach to validation and test, test at every stage.  
4 | That's the traditional mentality, and I think what the  
5 | recommendations that Garth and Tom have provided are in a  
6 | sense essentially keeping track of where the samples are  
7 | coming from in a larger way. That's what is being  
8 | reinforced here. In terms of number of samples and so  
9 | forth, I think you still see very similar approaches to the  
10 | traditional approaches. The number of samples are  
11 | essentially fixed, not based on the batch sizes, not  
12 | related to the process and so forth. So, that's the  
13 | traditional way of thinking about this.

14 |           As you start deliberating, I think keep that in  
15 | mind. In a sense, here we have removed the emphasis from  
16 | the sampling thief, taken the emphasis to end product  
17 | testing, although increasing the number of end products  
18 | more so than we generally might be doing. And at the  
19 | validation stage, you have a means of providing  
20 | justification that the thief is giving you the wrong  
21 | answers. That's in a nutshell the proposal here.

22 |           DR. LEE: Thank you very much.

23 |           Let me give you some idea of where I'd like to  
24 | take it. I think that this committee is ready for a  
25 | timeout, and what I propose to do is hold all the

1 | questions, take about a 15-minute break, and return for  
2 | another 30-minute discussion on answering these questions.  
3 | The questions are posed very clearly here and I think that  
4 | we might need some time to clear our heads and come to some  
5 | sensible answers. So, let's reconvene in about maybe 10  
6 | minutes, about 3:15. Thank you.

7 | (Recess.)

8 | DR. LEE: We are ready to continue.

9 | Based on our conversation during the break, I  
10 | think it is very clear that we need to continue with the  
11 | questions before we address the questions posed to us.  
12 | Leon, you were about to raise a question before the break.

13 | DR. SHARGEL: Yes, I had a question. It sort  
14 | of continues what Dr. Boehlert said about old products. I  
15 | wasn't clear what your answer was on that, whether blend  
16 | uniformity was needed on products that have been  
17 | manufactured for a number of years. So, if you can answer  
18 | that, then I'll go to my next question.

19 | DR. BOEHM: I'm not sure if I can answer  
20 | whether it's needed or not. My point was that it was my  
21 | understanding that compliance's view of old products is  
22 | that as long as they remain exactly as they are, that they  
23 | will not ask for additional information. If old products  
24 | didn't have any blend uniformity, I interpret that to mean  
25 | that they wouldn't be asking for it. But if any change is

1 | made, including a change in manufacturing site or  
2 | equipment, then the product needs to meet current  
3 | requirements.

4 |           DR. SHARGEL: The follow-up is, I checked with  
5 | a number of manufacturers on the generic side who go along  
6 | with your conclusions in your public workshop, one, that  
7 | blend uniformity testing is not a value-added test. It  
8 | seems to be the consensus which I got, and also that blend  
9 | uniformity testing was more for the validation and the  
10 | development.

11 |           Now, the sense that I get also from my  
12 | colleagues is that if you're able to reproduce your batch  
13 | in manufacturing and you eventually get a body of  
14 | knowledge, does this new product become eventually an old  
15 | product that you're very confident in making and do you  
16 | really need to continue with blend uniformity testing  
17 | forever and ever, or is it possible to get a body of  
18 | knowledge -- I'm pulling 10 out of the sky because it's a  
19 | nice number -- and maybe do it on every tenth batch or some  
20 | other approach?

21 |           So, the first question I really have, which  
22 | differs maybe from Dr. Hussain, is not on here. Is there a  
23 | time or a place where we can not do blend uniformity on  
24 | every batch once we've manufactured it successfully for  
25 | some time?

1 DR. HUSSAIN: Vince, let me just share with you  
2 some information that might be helpful here. The current  
3 good manufacturing practices -- the "c" in the current good  
4 manufacturing practices is a continuous improvement and  
5 keeping current with the technology and standards. That  
6 often becomes a roadblock, for example, bringing new  
7 technology in. Old problems become invisible. The "c" in  
8 cGMP is that argument. And to extend this to on-line  
9 technology, if two companies do it on line, blending for  
10 example, does that become the current standard for the rest  
11 of the industry? That's the debate here.

12 Now, with this proposal, how do we address  
13 older products which have been there on the market? So, I  
14 think I don't have a firm answer for that, but I think we  
15 are looking at that. At least my personal approach to that  
16 has been let's look at improving without penalizing as much  
17 as feasible. If there are problems associated, then I  
18 think we have to correct those problems. But if those  
19 standards have been used and applied for the last 20-30  
20 years, there has to be a rational reason for updating that.  
21 So, I think that's the internal struggle. I don't have the  
22 official answer for that right now, but I think we will  
23 carefully look at that and make sure we address it right.

24 Leon had suggested that -- and I think the  
25 proposal here is -- we do it for product development. We

1 do it for validation. But why continue doing for routine  
2 production? There are two aspects to that. One  
3 interpretation of the regulations is, yes, that has to be  
4 done for every production batch. The first or second slide  
5 said that. So, that's one interpretation of that.

6 But what is the scientific basis for that? I  
7 think I just want to share with you my interpretation of  
8 the underlying science or gaps in the science which would  
9 say that probably should be done.

10 What is validation? Validation is a series of  
11 qualifications of the equipment process and so forth that  
12 culminate into the three commercial batches. A product  
13 essentially is validated when you successfully demonstrate  
14 three commercial batches meet the specification, plus the  
15 supporting development data that goes behind that. So,  
16 that's what validation is.

17 In the absence of a clear understanding of the  
18 mechanisms of each unit operation, the discussion and the  
19 debate focuses on three batches. All the information you  
20 have or the manufacturing history are those three batches  
21 before you allow market access.

22 What would be the problem in the current  
23 system? I'll give you two examples. One would be  
24 excipients. Excipients in USP are totally dictated by  
25 chemical purity. USP NF or lactose NF from different

1 | sources could differ considerably in their physical  
2 | attributes.

3 |           To give you an example, magnesium stearate.  
4 | Magnesium stearate is a very significant challenge in terms  
5 | of its physical attributes and we still don't know how to  
6 | really do a functionality test for magnesium stearate.  
7 | I'll quote a thing from Dr. Kibbe's handbook. One of the  
8 | culprits with magnesium stearate is the impurity sodium  
9 | stearate which defines the hydrophobicity and lipophilicity  
10 | of that molecule, and that is so critical for dissolution.  
11 | We don't even have a test for that in the monograph. So,  
12 | one source of magnesium stearate will have the same NF  
13 | stamp on it but have very different physical and functional  
14 | attributes.

15 |           Now, in your validation run, you have used  
16 | generally -- validation -- in practice what it has become,  
17 | in my opinion, is you do everything as homogeneous as  
18 | possible to prove that three batches would work because  
19 | that's your ticket to commercialization. That should not  
20 | be the case but in fact in some cases that is the case.  
21 | So, you are using the same raw material for the three  
22 | batches, and then subsequently the raw materials might  
23 | change. So, that would be a sort of scientific argument  
24 | saying that raw material attributes are changing during  
25 | subsequent manufacturing and we have no way of assessing

1 | whether that had an impact or not.

2 |           The release tests are very much limited in  
3 | terms of the sample size. Content uniformity, 10 tablets  
4 | is the basis of releasing a product which could be 1  
5 | million tablets or 20 million tablets or 30 million  
6 | tablets. That's sort the in-built dilemma that we face all  
7 | the time.

8 |           DR. SHARGEL: I agree with you that when you do  
9 | validation, you have a limited body of knowledge. Then as  
10 | you go into commercial production, you begin to gain a lot  
11 | more knowledge with making the process over and over again.  
12 | The issue is not in change of excipients or such. If I'm  
13 | making it the same way with the same excipients, using the  
14 | same raw materials, is there a time and place where I no  
15 | longer have to do this particular test? Can I be assured?  
16 | If I'm changing raw materials and then I get into a SUPAC  
17 | type of issue or some other annual report or something of  
18 | that sort, I am assuming that I have to make a statement.  
19 | Then I might --

20 |           DR. HUSSAIN: Leon, the argument I've placed is  
21 | you're using the same monograph material, but it's  
22 | changing. You don't even know it's changing. That's the  
23 | point.

24 |           DR. SHARGEL: If I'm using the same supplier.

25 |           DR. HUSSAIN: Even if you're using the same

1 | supplier, because the specifications on raw materials don't  
2 | address physical attributes.

3 |           DR. BYRN: Yes. In mag stearate, I know that  
4 | the same supplier doesn't control the physical attributes,  
5 | hydration, other things. So, company X's mag stearate is  
6 | not a constant thing.

7 |           DR. KIBBE: Nor is it depending on where they  
8 | shipped it to you from.

9 |           DR. BYRN: Right. I've even heard that certain  
10 | companies that make raw materials, when they're approached  
11 | with this problem, say, well, we'll ship you a drum. You  
12 | can test it. If it's what you want, you can manufacture  
13 | with it. If you don't, just ship it back to us. We'll  
14 | ship you another drum. And it's continued through that  
15 | process until you get a raw material that works. All these  
16 | raw materials that were shipped to you meet USP, but they  
17 | won't manufacture.

18 |           I know ahead of time I need a mag stearate that  
19 | has a certain property. I can't guarantee that that's  
20 | shipped to me. So, what the raw material supplier says,  
21 | I'll ship you a drum. You test it. If it's the way you  
22 | want, you can keep it and make it into a product.

23 |           DR. KIBBE: And different products require  
24 | different strict control of the mag stearate. With some  
25 | products, it doesn't matter as much. So, then the company

1 | isn't going to put the energy into keeping track of that.

2 |           DR. SHARGEL: I'd just like to replay to that,  
3 | if I may on the excipient differences.

4 |           DR. KIBBE: Go ahead.

5 |           DR. SHARGEL: Again, if I'm doing a couple  
6 | years or five years or 10 batches or whatever it takes,  
7 | then the excipients, as you say -- I just learned  
8 | something, that the mag stearate I'm getting is not exactly  
9 | the same every time I get it for those batches. But then I  
10 | know that my method is robust enough that it really didn't  
11 | make much of a difference because my end product has tested  
12 | very well all the way through. So, that starting material,  
13 | as far as the mag stearate or whatever I'm using, didn't  
14 | really make much of a difference. I'm still getting the  
15 | same answer. So, I haven't made any major changes in  
16 | process. I have only ordered from the same supplier what I  
17 | think is the same excipient. I just learned it's not quite  
18 | the same excipient, but my end product is still the same  
19 | end product by all my tests. So, does it still make a  
20 | difference?

21 |           DR. BYRN: You're saying you have an  
22 | established, robust product.

23 |           DR. SHARGEL: I think I have if I'm making it  
24 | for 10 years and whatever mag stearate you send me, you  
25 | send me.

1 DR. LEE: I think we are beginning to drift.

2 DR. KIBBE: Let me get back onto dissolution  
3 and batch selection and what have you.

4 One of the things I've noticed from all the  
5 data you gave us is that poor uniformity in the batches  
6 that you had information on didn't predict poor uniformity  
7 in terms of the tablet product that you made. Then I'm  
8 left with one of those wonderful theoretical conflicts, you  
9 know, where you have a beautiful theory that a uniform  
10 powder will make a uniform product, and then you have a  
11 wonderful fact that says that this uniform powder will make  
12 a uniform product. So, I'm struggling with whether my  
13 theory is no good, which is that you have to have a uniform  
14 blend in order to make a uniform capsule or tablet, or that  
15 there's something else going on.

16 I'm a little concerned that one of the problems  
17 we continually face is that we are not expert at sampling  
18 blends for a lot of reasons. I don't know whether you feel  
19 that those blends that were 15 and 20 percent, or quite  
20 large compared with an ultimate tablet, was because we  
21 don't know how to sample blends in general or because the  
22 companies that did it had an old sampling method and they  
23 stuck with it.

24 DR. GARCIA: We don't know the answer to that  
25 question. This is not my data. It's not Garth's. It was

1 just submitted blind.

2 DR. KIBBE: I just wanted to get a sense of  
3 where you were on it.

4 DR. GARCIA: Right. All that we do know is  
5 this is the blend RSD. They were high. We don't know the  
6 reasons they were high. If you go back to our validation  
7 flow diagram, did they even perform some sort of  
8 investigation into the cause of the RSD to determine is it  
9 sampling error, is it segregation, is it remixing further  
10 on down the process? Those things we don't know the answer  
11 to. To do that is beyond the scope of this particular  
12 exercise. But, yes, I acknowledge your point.

13 DR. KIBBE: A theoretical question then. If  
14 that data is real, then the agency can't depend on blend  
15 uniformity data to predict anything. So, why capture the  
16 data? And if that data is real, why do blend uniformity?  
17 Which to me flies in the face of what we were talking about  
18 this morning about trying to have in-process validation of  
19 all our things and quick turnaround time and quick release  
20 of batches. So, I'm wondering how we're going to resolve  
21 that.

22 DR. GARCIA: My own personal opinion on this --  
23 this does not necessarily reflect PQRI or the Blend  
24 Uniformity Working Group -- is based on the data you saw  
25 right up there, whether you think that's enough batches or

1 not, this is the data that we have to work with and I'm  
2 going to make the statement based on this. It's clear that  
3 blend uniformity data is useless. It does not represent  
4 what is really going on in a number of cases where you have  
5 sampling errors. The sampling technology today is not  
6 capable of extracting small quantities of blend. When you  
7 get below 200 milligrams, you get all sorts of problems if  
8 you're in that 1 to 3X range. That's fine if you got a 500  
9 milligram tablet, but when you start getting down to a 50  
10 or 100 milligram tablet, you're in some trouble.

11 So, based on your question, why are we doing  
12 it, good question. That is why we are testing the  
13 hypothesis, though. Blend uniformity is not value-added

14 But in the interim, we also released this  
15 guidance document. Actually, the guidance document was  
16 done before the data mining.

17 One of the things that we did feel, though, is  
18 the company should put forth some effort to show that your  
19 blending process is under control. And if you notice in  
20 the acceptance criteria, we said that we wanted individuals  
21 to be within plus or minus 10 percent of the mean, rather  
22 than 90 to 110 percent.

23 What we're basically saying there is the true  
24 measure of uniformity of a blend is an RSD, not potency.  
25 Once again, you're getting into the sample bias. If it's

1 centered around 100 percent, great. You've got a really  
2 fantastic sampling thing. But if you have a mean of 120  
3 percent and an RSD of 3 percent, obviously something is  
4 wrong here, and subsequent tablets made from that batch are  
5 centered at 100 percent, you obviously have a sampling  
6 error.

7 Up until this document that's been proposed and  
8 until it gets incorporated into a guidance document, you're  
9 basically stuck because you cannot check off that blend  
10 uniformity box during your validation exercise. So, we're  
11 trying to take all these things into consideration.

12 But is it worthwhile during process  
13 development? Yes, I think it is. But on a routine basis?  
14 It's got some serious flaws.

15 DR. BOEHM: Perhaps I could just briefly add to  
16 that. The survey suggested that manufacturers have trouble  
17 with about 10 percent of their products, about 1 in 10. We  
18 haven't been through and looked at that data to see if that  
19 is what we're looking at here, but it looks by eye to be  
20 pretty much what we are looking at.

21 DR. GARCIA: 16 out of 149.

22 DR. BOEHM: Yes. It's 1 in 10, which is what  
23 they reported in the survey, give them trouble. So, we're  
24 looking at a picture where they use the same old-fashioned  
25 ways of sampling blend, and 9 times out of 10 that's fine.

1 | 1 time out of 10 it doesn't work.

2 |           DR. BYRN: I can't capture all of this and some  
3 | of it is not published and so on, but at Purdue we've done  
4 | a lot of comparison of on-line data versus thieving. Maybe  
5 | not a lot but a significant amount. There's no question  
6 | that the errors are much higher in thieving, and the errors  
7 | are like Tom is talking about, the amount you're thieving,  
8 | how they're handled, how they're transferred. All of us  
9 | know of consulting situations where electrostatics of the  
10 | active cause it to not be at chemophore. And there are all  
11 | these stories. But on-line data is generally much better,  
12 | way, way better, than thief data.

13 |           So, my thought of all this is that thieving is  
14 | always going to be problematic. I'd like to see us go to  
15 | on-line data. The main barrier is that we're going to have  
16 | to validate the on-line data with the thief data, which may  
17 | be a complete result of artifacts. I'm not sure it's  
18 | complete, but there could be quite a few artifacts. I  
19 | think that's what you're saying. I don't know whether you  
20 | want to jump in here.

21 |           DR. GARCIA: You may be able to validate the  
22 | on-line data and get a correlation with the dosage form  
23 | data.

24 |           DR. BYRN: Yes. That may be the solution.  
25 |           So, ultimately my view is that this is actually

1 a big advantage of on-line data and that the more we can go  
2 on line, the more we'll really know "what's happening."

3 And then another major factor of going on line  
4 is going to be that we can troubleshoot when something goes  
5 wrong. That's another advantage of doing every lot is when  
6 something goes wrong, we can troubleshoot.

7 Ajaz didn't get a chance to go into this. He  
8 just mentioned it, but there's a lot data that part of the  
9 major costs of pharmaceuticals is the warehousing of  
10 samples, as Ajaz said, the OOS or the nearly OOS. If we  
11 have all this on-line data, we may be able to say, oh, yes,  
12 something happened in that sample that we don't know about  
13 now because of the problems that we're all talking about in  
14 thieving.

15 So, that's my optimistic view of the whole  
16 thing.

17 DR. KIBBE: If thieving is this problematic and  
18 we're not ready for everybody to go on line, why are we  
19 still collecting thieving data?

20 DR. BYRN: I don't think we can completely  
21 prove that it's completely problematic, but certainly it  
22 doesn't sound very good. Maybe Ajaz wants to comment.

23 DR. HUSSAIN: I agree with what Tom and Garth  
24 have presented in many ways, but I think I would state it a  
25 bit differently. When Tom says blend uniformity is not a

1 value-added test, in my way of looking at it what he's  
2 saying is blend uniformity testing the way we do it with a  
3 thief is not adding any value. That's what my  
4 interpretation of that is.

5 But Dr. Kibbe expressed some dichotomy of what  
6 we talked about in the morning and what we are saying right  
7 now. I don't see it that way, and let me explain why.

8 The regulatory concern that we were trying to  
9 overcome with the blend uniformity data was the limited end  
10 product testing for content uniformity. I think the  
11 limited end product testing was the motivation behind all  
12 of this exercise for the last 10-15 years, that being the  
13 10 tablets that is the basis of releasing a batch, and  
14 those 10 tablets may not represent the 20 million tablets  
15 that they're coming from. So, that's a fundamental  
16 concern. The approach that was used was to say that every  
17 unit operation has to be controlled precisely for us to  
18 rely on those 10 tablets.

19 In reality, I think the 10 tablets is not a  
20 true concern from one way. The concern truly is that a  
21 representative sample. The PQRI proposal essentially  
22 addresses that in a more formal way where you're expanding  
23 or increasing the number of end product tests. If we had  
24 made that proposal from FDA, I think we would be in front  
25 of the Congress probably explaining how are we increasing

1 that number of tests. Having PQRI makes our job a bit  
2 easier.

3 But to go back on the issue of dichotomy and  
4 what we talked about, on-line technology and this, I could  
5 make the case in many different ways. The current proposal  
6 for PQRI is still advocating for the validation development  
7 to use blend uniformity analysis. Right now it's sampling  
8 thieves. The MIT data, which we presented on July 19th --  
9 I did not summarize it again. Do you know how long it  
10 takes to validate just one unit operation? On average, 20  
11 days to do thief analysis and validation. And the range  
12 could be 1 day to 30 days because of the sampling errors  
13 that are coming in. So, going on line, you improve that  
14 process efficiency itself. You do it in a day. But that's  
15 not the only point.

16 All the focus has been on one component of the  
17 complex mixture. That's the drug. What about magnesium  
18 stearate? I showed you an example of what non-homogeneous  
19 distribution can do to dissolution. Guess how many tablets  
20 we test for dissolution before we release. 6 tablets, less  
21 than content uniformity.

22 So, building quality in starts at every step,  
23 and I think going to on-line will tremendously, in my  
24 personal opinion, improve our understanding of the  
25 processes and the quality.

1 I could easily extend the blend uniformity  
2 discussion to say, all right, when you validate, I would  
3 like to see dissolution data for those many tablets. 6  
4 tablets may not be sufficient. It's every attribute that  
5 comes in. All we have talked about is content uniformity  
6 today.

7 So, in my opinion, there's no dichotomy. Tom  
8 said this correctly. This is a band aid right now. It's  
9 correcting a problem that we have debated for the last 15  
10 years. It's a band aid. It's not a fundamental solution  
11 to the overall problem because as we go to the more complex  
12 dosage forms, excipient homogeneity becomes critically  
13 important for many controlled-release formulations.

14 DR. LEE: Thank you.

15 I think Marvin wants to say something.

16 DR. MEYER: Naively, because this is not my  
17 area, it seems to me that if your concern -- and I was glad  
18 to hear you mention that the PQRI has come up with  
19 increased end product testing. It seems that if your real  
20 issue is that end product testing is inadequate and you go  
21 to an even less adequate test to support your end product  
22 testing, that doesn't prove anything. What you ought to do  
23 is simply go to more end product testing. I would think  
24 that dissolution might be more difficult, but content  
25 uniformity -- if you took a sample somehow at the

1 beginning, the middle, and the end of a run and had 30  
2 tablets or 50 tablets, with today's modern analytical  
3 capability, you can run 60 tablets, I would think, fairly  
4 quickly compared to 10. It's a negligible. That would be  
5 easier than doing a blend uniformity because that's a  
6 second step. That's a second process that's different than  
7 the tablets themselves. So, it seems like the solution is  
8 to increase what really counts and put less stock, if any,  
9 into the blend uniformity.

10 DR. HUSSAIN: Marv, I just want to make sure I  
11 clarify the situation. When I said 10 tablets, the stage 1  
12 USP testing is the 10 tablets. The key question there is  
13 representative samples, and I think the proposal of PQRI  
14 addresses that. It focuses on collecting a representative  
15 sample. All of our GMP guidelines, even USP, state it has  
16 to be a representative sample. But in practice we may be  
17 missing some of that.

18 DR. GARCIA: First of all, I want to address  
19 the question, are we adding more testing into release of  
20 the product. For validation, yes. For routine production,  
21 no.

22 I also want to answer your question of about 10  
23 minutes. I didn't get a chance to chime in. When do you  
24 stop testing it? The approach that we're putting forth  
25 really doesn't matter because we have not added the burden

1 | for release testing. All we're doing is pulling those  
2 | samples in process. You're going to have to do USP content  
3 | uniformity release testing on it anyhow. The cGMP  
4 | requirement is what's mandated to do the blend adequacy of  
5 | mix component in there. According to our proposal, we're  
6 | not increasing any additional testing. So, given that,  
7 | it's more or less a moot point. You got two calculations  
8 | possibly, but hopefully that clarifies that.

9 | I just lost my train of thought.

10 | DR. BOEHM: Perhaps I could just also clarify.  
11 | The Blend Uniformity Working Group and the outcome of the  
12 | workshop -- people believe that blending operations should  
13 | produce uniform blends and that situations where nonuniform  
14 | blends are made uniform by something like a tablet press  
15 | are inherently dangerous and should be avoided. That's why  
16 | we advocate doing the blend uniformity testing in  
17 | validation but then switching. So, we do not favor  
18 | situations where potentially nonuniform blends produce more  
19 | uniform dosage units.

20 | DR. GARCIA: I just remembered the third thing  
21 | I was going to say. By going to stratified sampling of  
22 | dosage units, we are putting the emphasis of the testing  
23 | where it gives you the most value and the true read of the  
24 | uniformity of the product.

25 | The other thing is if you have a uniform blend

1 going onto your compression machine or filling machine and  
2 it segregates, you have a lot greater chance of catching  
3 that problem, which is just as bad as having a nonuniform  
4 blend coming through. You have a greater chance of  
5 catching that using the stratified sampling approach.  
6 That's another plus of pulling your USP samples in process.

7 DR. LEE: Kathleen?

8 DR. LAMBORN: I wondered if you could just go  
9 back and walk us through precisely what your proposal is  
10 because I've gotten confused. I'm looking at attachment 1  
11 which looks like one of your slides. But that specifically  
12 says mix and content uniformity for ANDA and talks about  
13 validation. Now you said validation is different from  
14 routine batches, but I was having trouble finding the slide  
15 that described routine batches. So, could you just sort of  
16 take us back through that and also specifically how it has  
17 changed from the current?

18 DR. GARCIA: Do you have the presentation fired  
19 up over there? Yes, put it up.

20 DR. LEE: You're not going to run through that  
21 again, are you?

22 (Laughter.)

23 DR. LEE: I can see that when Helen was  
24 introducing the meeting, she mentioned this seems like a  
25 piece of cake. It took years for PQRI to come to today,

1 and I think that we're witnessing the same phenomenon here.  
2 We need to come to closure. But I think Kathleen's  
3 question is very important.

4 DR. LAMBORN: I think we need that in order to  
5 address the question that's been asked of the committee.

6 DR. LEE: That's right.

7 DR. GARCIA: Attachment 1 is this slide, and  
8 this addresses the blend portion of it, the top half of  
9 attachment 1. By attachment 1, I'm referring to the actual  
10 proposal. The bottom half of it is in this slide. That's  
11 over two slides in my presentation.

12 DR. LAMBORN: But this refers to validation  
13 blend.

14 DR. GARCIA: Right. This is for validation.

15 DR. LAMBORN: So, both of these are recommended  
16 for validation only.

17 DR. GARCIA: Right.

18 Then you'll notice we're advocating -- well,  
19 first of all, we don't advocate blend sampling for routine  
20 manufacture.

21 The second thing is we are saying you have to  
22 have 20 locations here, test either 3 for stage 1 per  
23 location or a total of 7 for stage 2 per location. So,  
24 you're looking at 60 or 140. But this is validation.  
25 You're supposed to be stressing the product to make sure

1 | that the unit operation is producing consistent quality  
2 | product.

3 |                 Now, attachment 4 is this slide right here and  
4 | the recommendation, only not as colorful.

5 |                 DR. LAMBORN: You're saying it's for routine  
6 | manufacture.

7 |                 DR. GARCIA: This is for routine manufacture,  
8 | right.

9 |                 DR. LAMBORN: And yet, it says "or validation  
10 | batches."

11 |                 DR. GARCIA: No. The first step is for the  
12 | ANDA or exhibit validation batches, all the data you  
13 | generated per attachment 1. If you got the RSD less than 4  
14 | and all those other things, this is where you determine  
15 | readily comply versus not readily comply. You're only  
16 | looking at 10 tablets for a stage 1 or 30 for a stage 2,  
17 | versus 60 and 140. Is that clear?

18 |                 DR. LEE: Thank you.

19 |                 DR. BYRN: One thing that Tom and I discussed  
20 | just related to all this because on-line validation is  
21 | going to be completely different from this. So, that's a  
22 | whole new problem. Maybe Tom wants to expand on this, but  
23 | maybe I'll try and then you can correct. It's stated in  
24 | the proposed guidance that you can use on-line methods, but  
25 | you'll have to develop your own validation package because

1 obviously, especially on the previous one, 20 samples --  
2 one interpretation of that would be 20 sensors, and that's  
3 a lot of sensors by any criteria. So, people just need to  
4 realize if we're thinking about on-line validation, it's  
5 going to be significantly different from this.

6 DR. GARCIA: Yes. We state that on-line  
7 monitoring is actually the way to go, we feel. But we're  
8 not going to tell anybody how to do that. It's up to the  
9 firms to figure out how they're going to sample, where  
10 they're going to sample, where they're going to put the  
11 sensors. And as you said earlier, how are you going to  
12 validate that? What are you going to use as your  
13 benchmark?

14 DR. LEE: Nair, are you with us?

15 DR. RODRIGUEZ-HORNEDO: Yes, I am here.

16 DR. LEE: Are you ready to take us through this  
17 series of questions?

18 DR. RODRIGUEZ-HORNEDO: Yes, I can, but realize  
19 that due to the connection on my end apparently, there is a  
20 delay. So, we can try but it may be difficult to have an  
21 ongoing discussion.

22 DR. DeLUCA: I don't get a delay from my end  
23 here, Nair.

24 DR. RODRIGUEZ-HORNEDO: Okay. Well, let's try.

25 DR. LEE: Why don't you give it a try?

1 DR. RODRIGUEZ-HORNEDO: Okay. The questions I  
2 believe are the ones that Ajaz mentioned at the beginning.  
3 Am I correct?

4 DR. LEE: That's correct.

5 DR. RODRIGUEZ-HORNEDO: Which are the issues  
6 for discussion. First, is the current PQRI proposal  
7 appropriate for inclusion in a planned revised guidance?  
8 The first one is, if no, please suggest modifications for  
9 improvements that would be necessary prior to any  
10 regulatory application.

11 So, is there any discussion?

12 DR. BOEHLERT: Can I just ask a question?

13 DR. LEE: Go ahead.

14 DR. BOEHLERT: Is it the intent on the revised  
15 guidance to put that out as a draft?

16 DR. HUSSAIN: Yes. Also, just to make a point,  
17 sampling in many cases works right now in the sense we have  
18 a lot of data which says for many products the thief  
19 samples also work well. So, our intention is, as we go  
20 forward, you have many choices now. If you have a problem,  
21 you have an alternate way of doing that. So, it doesn't  
22 mean that everybody has to do it this way.

23 DR. LAMBORN: Can I ask a point of  
24 clarification? For the routine process, if I understand it  
25 correctly, the proposal, as you're doing it, is deleting an

1 existing requirement? Because currently there is an  
2 existing blend requirement or is there not an existing  
3 blend requirement?

4 DR. BOEHM: For most ANDA applicants, there is  
5 an existing requirement that they conduct blend uniformity  
6 testing on routine batch manufacture. It would be the view  
7 of the Blend Uniformity Working Group that substituting  
8 stratified in-process testing would be a better solution.

9 DR. LAMBORN: Thank you.

10 DR. BYRN: I think that the committee put a lot  
11 of work into it. So, it seems like a reasonable thing to  
12 go forth with this proposal. It's out for comment. There  
13 would be a comment period and then there would be  
14 additional time to review those comments.

15 DR. BOEHLERT: I think that would also give all  
16 of the companies that didn't submit data an opportunity to  
17 look at the impact on their product lines.

18 DR. LEE: So, what I'm hearing is that there is  
19 some -- I'm reading the minds of the rest who didn't speak.  
20 Is there some consensus on this? So long as this is the  
21 draft guidance.

22 DR. VENITZ: I second.

23 DR. LEE: Then let's get it out there and  
24 stimulate, motivate discussion and learn in the process.  
25 So, the answer to the question is yes.

1 DR. MEYER: Vince, which is quite different  
2 than endorse the proposal or the proposed guidance. Simply  
3 get it out there, let's hear what comes in, and then review  
4 that. Is that correct?

5 DR. LEE: So, Dr. Meyer is going to have a  
6 friendly revision.

7 DR. MEYER: No. I don't have any revision  
8 right now. I would hate to try to overturn what well-  
9 trained people have done over a period of months and what  
10 an untrained person has done in a period of an hour. But I  
11 think it's worthwhile to have it out there because they've  
12 obviously put a lot of work into it, and it seems to make  
13 sense.

14 DR. BYRN: And comments will come in and we'll  
15 have another meeting, and there will be a public hearing.  
16 Right, Helen and Ajaz? There could be.

17 DR. HUSSAIN: It depends in the sense --

18 DR. BYRN: There could be. It depends on what  
19 they are.

20 DR. HUSSAIN: Right.

21 DR. BYRN: And it could end up like  
22 dermatopharmacokinetic that continues for a very long time.

23 DR. HUSSAIN: No.

24 (Laughter.)

25 DR. BYRN: They're assuring us not, but I'm

1 | just saying that's a possibility. So, deliberation could  
2 | continue for a very long time. It may not, but we're just  
3 | starting the process. Right? That's our proposal. By  
4 | answering yes, we're just starting the process. We're  
5 | going to have plenty of input. We're not going to have a  
6 | lack of input into this process.

7 |           DR. HUSSAIN: No. Don't associate DPK with  
8 | this. We want to have a different process, a more  
9 | efficient process, and we are process mapping everything we  
10 | are doing inside too.

11 |           DR. MOYE: One question, if I could. Is there  
12 | any way that the committee could vote an answer to this  
13 | question that portrays the reservations the committee has  
14 | about this process? I'm just not sure how to do that based  
15 | on the phrasing of the question. If the committee has  
16 | reservations about the implications of the proposed plan,  
17 | I'm just not sure how they would express those reservations  
18 | in the answer to that question.

19 |           DR. LEE: I think that Steve Byrn more or less  
20 | summarized the sentiment. Here's a proposal. Let's put it  
21 | out there and stimulate input, have another discussion, and  
22 | go from there.

23 |           DR. MOYE: Well, it just seems if we put the  
24 | proposal out -- again, I'm naive about this. I'm just not  
25 | sure how putting the proposal out would be separate from

1 endorsing it. That's what my concern is.

2 DR. KIBBE: You want us to approve it with  
3 reservations.

4 DR. MOYE: Well, I was wondering whether we  
5 could vote to approve or not.

6 DR. LEE: I don't think we have to vote on  
7 this.

8 DR. MOYE: Okay.

9 DR. LEE: I think we're just expressing our  
10 opinion.

11 Kathleen, you have a point to make?

12 DR. LAMBORN: I think I was just following up  
13 on the same concept which I think is that we are, in a  
14 sense, not answering the question as posed. We are simply  
15 recognizing the amount of effort that's gone in and  
16 encouraging everyone to get this out for public comment and  
17 then come back. I think beyond that, all the discussion  
18 that's gone on so far gives some sense to the people about  
19 some of the questions we have, and I don't know that the  
20 committee is even ready to say exactly what their concerns  
21 might or might not be. But I think the key thing is not to  
22 -- we're not saying yes, the proposal is appropriate.  
23 We're saying, yes, this proposal is appropriate to get more  
24 input on, and in fact, it's been well formulated in terms  
25 of getting the discussion started.

1 DR. LEE: Therefore, the implication is that  
2 it's premature to answer the rest of the questions.

3 DR. HUSSAIN: That's not a problem at all. The  
4 process that we will follow is as follows. The official  
5 recommendations from PQRI would come in. We wanted to have  
6 this discussion up front so there are any  
7 reservations/concerns, those are expressed now so that Tom  
8 and others can go back and incorporate those reservations  
9 and address those reservations. So, as we go through the  
10 process of getting the PQRI official recommendations ready,  
11 those are already incorporated. So, when these come to FDA  
12 as official recommendations of PQRI, we already have the  
13 input in that.

14 What that does is it helps us to move forward  
15 quickly. It incorporates the proposal into our draft  
16 guidance, which will come out as a draft and go through the  
17 process of public comment before it gets final.

18 So, if answering the question yes or no is  
19 difficult, that's not the major concern that I have. I  
20 think if there are reservations that are expressed now,  
21 they get incorporated. So, it helps the process.

22 DR. KIBBE: I think my reservations are for  
23 those 10 percent of products where batch uniformity is not  
24 predictive for tablet or product uniformity. I think we  
25 need somehow to stimulate a different testing method for

1 | those kinds of batches and in-process testing or something  
2 | because I'm reluctant to say that as long as it works 90  
3 | percent of the time, it's a good tool. Do you understand?

4 |           If the current methodology of sampling powder  
5 | batches with thieves fails 1 out of 10, then there ought to  
6 | be something in the guidelines that says something about  
7 | those conditions when it's no longer an appropriate  
8 | sampling method and that the company ought to look for a  
9 | way of solving that problem on their individual batch  
10 | somehow. If I had an analytical method that correctly  
11 | assayed a tablet 9 times out of 10 and the 10th time got it  
12 | wrong, I don't think anybody would like to my analytical  
13 | method, and that's where I'm struggling.

14 |           DR. HUSSAIN: Let me sort of answer that. I  
15 | actually went through the same deliberation in my mind in  
16 | the memo. In fact, in the memo there was one more  
17 | question, which I left out in my presentation, and that was  
18 | that question.

19 |           In looking at an alternate method, we do have  
20 | an opportunity to incorporate some aspects of on-line  
21 | technology in the revised guidance. Let me expound on  
22 | that. Data that has been collected with MIT, Steve, CAMP,  
23 | using near infrared, as well as laser-induced fluorescence,  
24 | data that we have seen from Pfizer, data we have seen at  
25 | AstraZeneca -- there are at least six different sources of

1 good data on how to use on-line process for blending. We  
2 do have a sub-working group in PQRI which is supposed to be  
3 working on that aspect. We could accelerate and actually  
4 get those data submitted so that as the revised draft comes  
5 about, we have a suggestion of how to do on-line blending  
6 as a part of that guidance itself. So, there is a  
7 possibility.

8 But the reason I pulled that question back was  
9 not much progress has been made in PQRI on that front. I  
10 didn't want to hold the draft guidance just for that. That  
11 was the reason I pulled that question back.

12 DR. GARCIA: I'd like to just address your  
13 point. We had 16 batches with an RSD between 3 and 5  
14 percent. It's like the third slide I put up there in the  
15 series. Out of those, 12 of those 16 batches did not have  
16 a correlation between RSD of the blend versus the dosage  
17 form. In other words, the blend RSD was 1 to 2 percent  
18 higher than the tablet dosage was. Then, of course, at the  
19 end there were 13 blend RSDs that were greater than 5  
20 percent, and of all of those 13, the dosage forms were 5  
21 percent or less. So, really what you have is a total of 25  
22 batches in the data out of 149 where we do not have a  
23 correlation between blend data and dosage form data.

24 I'll go back to the hypothesis, is blend  
25 testing value-added? About 80 percent of the time, yes; 20

1 | percent of the time, no. Given that 20 percent of the time  
2 | it fails, is that a value-added test? In other words, is  
3 | your failing because of false negatives I guess. My answer  
4 | to that is no. So, we have accomplished, in this data I  
5 | think, to successfully test that hypothesis.

6 | DR. KIBBE: I'm not arguing that you tested the  
7 | hypothesis. What I'm saying is if we're going to put out a  
8 | criteria for manufacturing process and we have an in-  
9 | process measure that's supposed to give us an understanding  
10 | of the quality and it's not predictive 20 percent of the  
11 | time, then it's not a good measure.

12 | DR. GARCIA: Okay. But our whole proposal is  
13 | based on that. We are putting the emphasis on dosage form  
14 | content uniformity and down playing the effect of blend  
15 | uniformity. So, I don't see how we're putting out a  
16 | recommendation that's going to fail 20 percent of the time.  
17 | Our recommendation is being put out to ensure that you're  
18 | not going to have false failures 20 percent of the time,  
19 | and it also will add further confidence that the batch is  
20 | good 80 percent of the time where you would do blend and  
21 | dosage content uniformity. So, I think we're really  
22 | addressing what your concern is.

23 | DR. LEE: So, are you saying that the PQRI has  
24 | reservations about this?

25 | DR. GARCIA: No, no. Not at all. I'm saying