

## FOOD AND DRUG ADMINISTRATION

## ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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8:31 a.m.

Wednesday, November 28, 2001

Conference Room  
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Food and Drug Administration  
Rockville, Maryland 20857

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## P R O C E E D I N G S

(8:31 a.m.)

1  
2  
3 DR. LEE: Good morning. I am Vincent Lee. I'm  
4 the acting chair of the Advisory Committee for  
5 Pharmaceutical Science, and I'm calling the meeting to  
6 order.

7 I would like to go around the table to have  
8 everyone introduce herself or himself, and then I will turn  
9 it over to Nancy Chamberlin.

10 DR. SHARGEL: Good morning. I'm Leon Shargel  
11 at Eon Laboratories, representing the generic industry.

12 DR. SHEK: Efraim Shek from Abbott Labs,  
13 representing industry.

14 DR. HUSSAIN: Good morning. Ajaz Hussain,  
15 Office of Pharmaceutical Science, CDER.

16 MS. WINKLE: Good morning. Helen Winkle,  
17 Office of Pharmaceutical Science, CDER.

18 DR. LAYLOFF: Tom Layloff, SGE with FDA, and  
19 with Management Sciences for Health.

20 DR. MEYER: Marvin Meyer, former faculty  
21 member, University of Tennessee, now emeritus professor.

22 DR. VENITZ: Jurgen Venitz, Virginia  
23 Commonwealth University.

24 DR. CHAMBERLIN: Nancy Chamberlin, Executive  
25 Secretary.

1 | implications with respect to an entire class of products,  
2 | in accordance with 18 U.S.C., section 208(b)(3), all  
3 | committee participants with current interests in  
4 | pharmaceutical firms have been granted a general matters  
5 | waiver which permits them to participate in today's  
6 | discussions.

7 |           A copy of these waiver statements may be  
8 | obtained by submitting a written request to the agency's  
9 | Freedom of Information Office, room 12A-30 of the Parklawn  
10 | Building.

11 |           We would also like to note for the record that  
12 | Leon Shargel, Ph.D., Eon Labs Manufacturing; Efraim Shek,  
13 | Ph.D., Abbott Laboratories; Garth Boehm, Ph.D., Purepac  
14 | Pharmaceutical Company; and Tom Garcia, Ph.D., Pfizer are  
15 | participating in this meeting as industry representatives  
16 | acting on behalf of regulated industry. As such, they have  
17 | not been screened for any conflicts of interest.

18 |           In the event that the discussions involve any  
19 | other products or firms not already on the agenda for which  
20 | FDA participants have financial interests, the participants  
21 | are aware of the need to exclude themselves from such  
22 | involvement and their exclusion will be noted for the  
23 | record.

24 |           With respect to all other participants, we ask  
25 | in the interest of fairness that they address any current

1 or previous financial involvement with any firm whose  
2 product they may wish to comment upon.

3 DR. LEE: Thank you very much, Nancy.

4 I would like to point out that a number of  
5 committee members are not here, and I don't know whether or  
6 not they are listening. How can I tell? Because there's  
7 lots of background noise. They're not on yet. And the  
8 three members are Mary Berg from Iowa, Nair Rodriguez from  
9 the University of Michigan, and Patrick DeLuca from the  
10 University of Kentucky. So, they'll be joining us by audio  
11 throughout the day, or whenever they are available.

12 Next, I would like to call Helen Winkle, Acting  
13 Director of OPS, to introduce the meeting.

14 MS. WINKLE: Good morning. Before I start with  
15 my introduction, I do have one little presentation I wanted  
16 to make, and that's I wanted to present Kathleen Lamborn  
17 with a certificate of appreciation. This is going to be  
18 Kathleen's last meeting with us, and I wanted to let her  
19 know how much we've appreciated all her input over the last  
20 few years.

21 DR. LAMBORN: Thank you very much.

22 (Applause.)

23 MS. WINKLE: I also want to welcome Vince as  
24 our new chair of the advisory committee. We've already  
25 been working some with Vince in the past on various things,

1 and since we've asked him to be chair, he's been extremely  
2 full of ideas on how we can work with this committee and  
3 help make improvements, and we've just loved every minute  
4 of it. So, we know we're going to really enjoy working  
5 with Vince and we appreciate him taking on this additional  
6 task.

7 I also want to welcome some of the new members  
8 to the committee. First, I want to welcome Art Kibbe. We  
9 really appreciate Art participating with the committee.  
10 Art and I happened to run into each other last year in  
11 Indianapolis and got to talking about the committee, and he  
12 showed his interest in being part of it. So, here he is  
13 and we're really happy to have him here.

14 Also, Lem Moye isn't here yet. I don't know if  
15 he's stuck in traffic or what, but I also want to welcome  
16 him. He's being processed and is a member of the  
17 committee. And also Pat DeLuca from Kentucky, who is  
18 supposed to be on the phone eventually today. He also will  
19 be a new member of the committee.

20 Now that Steve Byrn has arrived, I have another  
21 presentation to make. Steve has been the chair of this  
22 committee for several years now. We've worked a lot with  
23 Steve. We've really enjoyed it. He's contributed a lot to  
24 the committee and to the various scientific issues that  
25 we've addressed during the years. And I want to present

1 him with a little certificate of appreciation as well.

2 (Applause.)

3 MS. WINKLE: I've actually put this chart up  
4 here for three reasons basically. I wanted to just remind  
5 the committee and the new members especially of what the  
6 Office of Pharmaceutical Science looks like. Basically,  
7 it's broken up into four offices: the Office of New Drug  
8 Chemistry, the Office of Generic Drugs, the Office of  
9 Clinical Pharmacology and Biopharmaceutics, and the Office  
10 of Testing and Research. Most of these groups, except for  
11 the research obviously, are doing parts of the review of  
12 new drugs and, of course, of generic drugs. I think this  
13 is really a very important part of what the Office of  
14 Pharmaceutical Science does, but I think there's a lot more  
15 to the office.

16 I see the office as really being the  
17 underpinning of the science base in CDER, and I think  
18 that's important for all of us to remember as we work  
19 toward the future on the various scientific issues that we  
20 have because I think this is where we want to be able to  
21 answer a lot of the questions and also look toward the  
22 future to scientific and technical issues we may have and  
23 may need to resolve. So, that's just one reason I have it  
24 up here.

25 The second reason is that I wanted to point out

1 | Dr. Ajaz Hussain. I think all of you here know Ajaz. He's  
2 | been working in the Office of Testing and Research for many  
3 | years now and in other parts of the center, but he recently  
4 | joined the staff of OPS as the Deputy Director for Science.  
5 | And in that role, I see Ajaz basically helping to instill  
6 | science throughout OPS and the rest of the center. I think  
7 | this is a very, very important role. I'm not saying that  
8 | science hasn't been in the center. Certainly. Don't take  
9 | me wrong, but I think that it needs to be better infused  
10 | into our daily activities, and I think we need to look at  
11 | how we can best improve and focus on scientific issues.  
12 | So, Ajaz is here to do that.

13 |           As part of that, he is overseeing major  
14 | scientific issues which are arising in OPS and the center.

15 |           He's also coordinating many of the science  
16 | issues that we have with outside groups. So, he's working  
17 | with various groups outside, the trade associations, with  
18 | PQRI, and other such scientific groups that are doing  
19 | research or doing some type of collaborative work to help  
20 | in sort of laying the basis for the OPS.

21 |           He's also overseeing the activities of this  
22 | advisory committee. I think he worked with many of you and  
23 | with the speakers in preparing for today.

24 |           And he's also working with the coordinating  
25 | committee.

1           So, you'll see a lot of Ajaz. You'll talk a  
2 lot to Ajaz on scientific issues. So, I just wanted to  
3 sort of bring that up today so you'd have a good idea of  
4 what his role is going to be.

5           Thirdly, I put this up just so you would see  
6 who in the organization does what. I think it's important  
7 to see who the various people in the offices are and who  
8 you will see from time to time as far as various dealings  
9 on scientific issues.

10           Next, I just wanted to put up the organization  
11 of this advisory committee. Basically it's just a reminder  
12 that this advisory committee continues to grow. We  
13 currently have two subcommittees, the Nonclinical Studies  
14 Subcommittee and the Orally Inhaled Nasal Drug Products  
15 Subcommittee. But we see several other subcommittees  
16 coming on line. The possibility of a Clin/Pharm  
17 Subcommittee, the possibility of the Drug Safety and Risk  
18 Management Subcommittee, and also we'll talk more today  
19 about the Emerging Technologies Subcommittee.

20           I think, though, the important thing is not to  
21 look at the structure, but I could take this chart and  
22 superimpose it on the organizational chart of OPS because I  
23 think the two groups have worked and will continue to work  
24 extremely closely together in basically laying that  
25 foundation for good science. And I'm really depending on

1 everyone sitting here at the table, as part of the advisory  
2 committee, to help in that endeavor.

3 As I was putting this together, it sort of  
4 reminded me of a story, and I'm not the best storyteller.  
5 But it just seemed to fit right in. These two men, Frank  
6 and George, were going out hunting for deer and they got  
7 out there and there was this great, big herd of deer out  
8 there. Boy, they were really excited. They got their guns  
9 up, ready to shoot. All of a sudden George says, I've good  
10 news and bad news. And Frank says, well, what, what? And  
11 he says, well, the good news is there's loads of deer out  
12 there; the bad news is they're being chased by a grizzly  
13 bear.

14 So, they looked and all of a sudden the grizzly  
15 bear was after them, and so they started running. Finally  
16 Frank just stopped, pulled his tennis shoes out of his  
17 backpack, and he put his tennis shoes on. George says,  
18 what are you doing? And he says, everything says you just  
19 can't outrun a grizzly bear. He says, I don't have to  
20 outrun the grizzly bear. I only have to outrun you.

21 (Laughter.)

22 MS. WINKLE: I think, though, there really is a  
23 purpose behind this story, and that's the fact if any of us  
24 take off and don't help the other, we're not really going  
25 to have the best foundation for science. And I think this

1 often happens. We're all sort of trying to get ahead of  
2 the other, and I think it's really important for us to work  
3 together with members of the advisory committee and with  
4 others outside of FDA so we can ensure that we are  
5 providing the best science for the regulatory aspects of  
6 the pharmaceutical industry and for FDA and basically for  
7 the public that we can. So, I think that's an important  
8 point that I just wanted to make.

9           Quickly let me go through what we're going to  
10 talk about today, and then I'll hand it back to Vince.

11           The first thing on the agenda is process  
12 analytical technology. Basically Ajaz is going to tell you  
13 a little bit about the meeting that we had on November 16  
14 with the Science Board. We made a presentation to them.  
15 We had several people in to help with the presentation.  
16 Dr. Woodcock was the initial speaker at the presentation to  
17 talk a little bit about where we are going with process  
18 analytical technology. And he'll give you an update on  
19 that.

20           We'll also talk a little bit about the process  
21 and forming of the new subcommittee. I think it's  
22 important that the advisory committee brainstorm about the  
23 objectives of this subcommittee and sort of define what we  
24 or the advisory committee expect from that subcommittee.  
25 So, that will be the first thing on the agenda today.

1           Next, we're going to talk about stability  
2 testing and shelf-life. The purpose of this particular  
3 topic is just basically to make the committee aware of some  
4 of the directions we're going, to let them know about the  
5 DOD shelf-life program that goes on in FDA, and also to  
6 talk a little bit about issues related to physical  
7 stability. I think this is important for us to talk about  
8 and I think some of the current issues of the day make it  
9 even more important that we at least look at this program  
10 and have a better idea as the committee may have to deal  
11 with future types of issues in this area.

12           Next on the agenda, I just put up quickly the  
13 PQRI organizational chart. I'm sure most of you are  
14 familiar with PQRI. I think in the past, even at the  
15 advisory committee, we've talked a little bit about PQRI.  
16 Basically you can see that various trade associations and  
17 FDA are part of the steering committee of PQRI, and PQRI is  
18 set up with technical committees and working groups that  
19 are focused on a variety of scientific issues, and they're  
20 basically issues to help improve or to enhance the  
21 guidances in FDA, guidances we already have out there, to  
22 actually provide information on new guidances that may help  
23 us better regulate, the idea being, across the board, is to  
24 reduce some of the regulatory burden on industry.

25           The first project we have under PQRI is

1 basically blend uniformity. When we were meeting on PQRI,  
2 we decided this was our low-hanging fruit. It was  
3 something that we could get a win on easily. It didn't  
4 work out that way. It's taken us several years to get  
5 where we are today.

6 But one of the things we wanted to do was to be  
7 able to discuss the proposal that PQRI is developing and  
8 the emerging recommendations from that proposal. We have  
9 two members from the Blend Uniformity Working Group of  
10 PQRI. Tom Garcia is going to talk. He's actually the  
11 chair of that working group. So, we would really like some  
12 input from the committee. When PQRI provides these  
13 emerging recommendations to us, when they send these  
14 recommendations, we in FDA want to be prepared to act on  
15 them. So, I think it's important that we go through what  
16 these recommendations are and again, as I said, get your  
17 input so that we're prepared when the time comes to receive  
18 these recommendations. And basically we'll talk a little  
19 bit about what the next steps are.

20 Nonclinical Studies Subcommittee. I thought  
21 Jim MacGregor was going to be here today. He's the one who  
22 basically started this subcommittee when he was at CDER.  
23 He's now at NCTR. Dr. Doull is going to give us an update  
24 on the subcommittee and the next steps.

25 I think before I had mentioned to the committee

1 that we were looking at possibly transferring this  
2 subcommittee into NCTR. We had a lengthy discussion at the  
3 last subcommittee meeting, and we're still exploring how  
4 we're actually going to handle this subcommittee. So, you  
5 will hear more about the future of this subcommittee. It's  
6 possible it could stay under this committee. There were so  
7 many things brought up, we've backed up and are  
8 reevaluating what we want to do.

9           Next, at the end of the afternoon today, we're  
10 going to have a training session, and I just wanted to  
11 mention it so that everyone would know what this session  
12 was set up for. Basically we're not going to discuss any  
13 scientific issues. We wanted to look at ways that the  
14 committee could interact in the future. Dr. Lee and myself  
15 and Ajaz have had several conversations about this. Dr.  
16 Lee has proposed several ways that we could improve on the  
17 process, including having principal reviewers, and we want  
18 to talk with the committee a little bit on how we would do  
19 that, what the expectations of these reviewers would be.  
20 So, we will be spending an hour or so later this afternoon  
21 in closed session basically training on this.

22           Tomorrow we only have two topics, but they're  
23 both very important topics and areas that we've been  
24 working on in CDER for quite a long time. They're issues  
25 that we really feel we need to go back and revisit.

1                   The first being dermatopharmacokinetics.  
2           Basically we will talk a little bit about the background.  
3           As I've said, we've been working on it since the early  
4           1990s. We have a draft guidance that was issued in June of  
5           1998, and we've had several joint meetings with the Derm  
6           Committee of the center. I think some of you actually were  
7           at the last joint committee. There are still lots of  
8           questions about the methodology and how it should be used.  
9           We're going to present some study data, and we have three  
10          issues for discussion which are on the agenda.

11                   Then I think really what we want from this  
12          committee is some advice on where to go with the draft  
13          guidance. We have talked about it internally within the  
14          organization. We feel like we probably need to withdraw  
15          that draft guidance because there are still issues that we  
16          need to resolve in this area and possibly even look at  
17          other ways of doing methodology for bioequivalence for derm  
18          products. But we'll talk more about that tomorrow morning.

19                   Last is individual bioequivalence. I think  
20          here this is an issue that we've discussed before this  
21          committee a number of times. We've issued a general BA and  
22          BE guidance that includes IBE. After a year of having that  
23          guidance issued, we'd really like to step back and  
24          reevaluate the use of IBE.

25                   We want to talk about replicate design studies.

1 We've found some real advantages to replicate design, and  
2 we want to bring that before the committee and talk about  
3 those as well.

4 We are also going to share with you the  
5 opinions of the scientific community. We have Les Benet.  
6 Actually Les was going to be here, and at the last minute  
7 he could not attend, but he will be on the telephone  
8 tomorrow during this discussion.

9 There are four discussion topics here, which  
10 are also included in the agenda. And basically what we  
11 would like to see from this committee is where do we go  
12 from here. I think this is really important. We're at a  
13 time where we have to make some decisions.

14 So, basically that's the agenda for the next  
15 two days. It's a pretty full agenda. We've actually  
16 debated a lot internally as to how many topics to put on an  
17 agenda for two days of discussion. I think all of today's  
18 discussions will be fairly easy to come to some conclusions  
19 or at least, as I said, one of them is awareness. But I  
20 think tomorrow's discussions may even continue some. We  
21 had hoped to get some decisions in both areas, but we'll  
22 just have to work and see where we get. And that may be  
23 something we want to talk about this afternoon when we meet  
24 on training, really how much we should bring before this  
25 committee, because we really do want your input and we want

1 to be able to get enough information to you that we do get  
2 adequate input. So, we can certainly discuss that later.

3 So, with that, I'll turn it back to Vince. I  
4 look forward to a really good two days and to coming to  
5 some conclusions. I appreciate it. Thanks.

6 DR. LEE: Thank you, Helen. I would like to  
7 thank Helen and Ajaz for the opportunity to chair this  
8 committee, and also I look forward to the opportunity to  
9 learn from everyone.

10 The reason I'm losing my voice was that I was  
11 staying up until 1 o'clock this morning watching the Lakers  
12 game.

13 (Laughter.)

14 DR. LEE: I don't know why. When I turned it  
15 on they were about 10 points behind. So, that's the story.

16 We have two very exciting days. You know I'm  
17 the chair without a tie, and I did come with a tie but it  
18 was confiscated by the security.

19 (Laughter.)

20 DR. LEE: No. I'm just making it up.

21 (Laughter.)

22 DR. LEE: So, the next item is on process  
23 analytical technology, and Ajaz is going to tell us what he  
24 has in mind. Those of you who were here at the last  
25 meeting might remember a presentation by the MIT

1 representative, and it was very exciting.

2 DR. HUSSAIN: Well, good morning. I did send  
3 you the slide presentations from the Science Board. The  
4 Science Board essentially is analogous to an advisory  
5 committee for the Commissioner's office. I have included  
6 some of those slides in my presentation, but I'll go  
7 through quickly to give you an update of how that  
8 presentation went.

9 The primary objective here for this discussion  
10 is to essentially develop the goals and objectives of the  
11 subcommittee we're ready to form now and also to  
12 essentially list or enumerate the expectations you have in  
13 terms of what the committee should be doing and how should  
14 it be reporting back to you and some sense of time lines  
15 and what time frame would be acceptable for defining that  
16 process.

17 So, the outline I have here is to provide you  
18 an overview, some background information. We have some new  
19 members on the committee, so I'll briefly discuss our July  
20 19th discussion on this topic, and then share with you the  
21 discussion that we had at the FDA Science Board meeting on  
22 November 16th and share with you then what we think that  
23 process analytical technologies can do in pharmaceutical  
24 manufacturing, a vision for the future, and propose or  
25 suggest some responsibilities for the subcommittee and time

1 | lines, and open that up for your discussion and your input  
2 | at that time.

3 |           When we met on July 19th, many of you were  
4 | present for that meeting, but some of you were not. That  
5 | meeting was designed to initiate public discussion on the  
6 | science of pharmaceutical manufacturing. The focus of the  
7 | presentation was modern process analytical technologies.  
8 | My interpretation of the discussion and the feedback I  
9 | received from you was extremely strong support to move  
10 | forward with that program and the recommendation to form  
11 | the Process Analytical Technology Subcommittee.

12 |           We also discussed a related topic on rapid  
13 | microbial testing and we had discussed on forming a  
14 | separate subcommittee on that. I'm not reporting any  
15 | progress to you on that topic at this meeting, but we will  
16 | bring this topic back to you in the next one with some  
17 | plans for moving the microbiology testing forward also.

18 |           The Science Board presentation was an important  
19 | milestone in this project for two reasons. One, the  
20 | project that we are about to undertake has the potential to  
21 | essentially change the whole system of manufacturing and  
22 | change the whole system of how we regulate. It has that  
23 | type of potential, and how we manage that is very  
24 | important. And we have to build consensus within the  
25 | agency, outside the agency as we move forward here. That

1 | was one of the underlying themes of taking this to the FDA  
2 | Science Board and getting their consensus on moving forward  
3 | also.

4 |           The other aspect was this project is somewhat  
5 | different. FDA is finding itself in a position that it has  
6 | to lead the scientific aspects on manufacturing, which is  
7 | somewhat difficult. I think generally we tend to be in a  
8 | reactive mode, responding to things being submitted to us.  
9 | Here we are changing that paradigm and saying we want to  
10 | move forward in this. So, there are two aspects that led  
11 | us to take this to the Science Board.

12 |           We had invited Doug Dean and Frances Bruttin  
13 | from Pricewaterhousecoopers to look at the cost issues and  
14 | the productivity issues in the pharmaceutical sector. Dr.  
15 | G.K. Raju made his presentation that he gave to you on July  
16 | 19. In addition, we had invited Norman Winskills, who's  
17 | the Vice President for Global Manufacturing Services at  
18 | Pfizer, and Steve Hammond to share their views from an  
19 | industry perspective. Dr. Woodcock obviously introduced  
20 | that and I sort of summarized some of the discussions we  
21 | had before.

22 |           Now, the response was actually very, very  
23 | strong. In fact, one of the comments was this is a no-  
24 | brainer. You have to move forward. So, there was strong  
25 | unanimous endorsement of the proposal, and also the Science

1 Board offered to help support the initiative through their  
2 own talks, seminars, and so forth. Also, I think one  
3 aspect is they would like to be involved in this process  
4 and would like to receive updates and progress reports.

5 Following this meeting, I had a meeting with  
6 the Office of the Commissioner and the message there was we  
7 have to move forward quickly on this.

8 I expect some questions from you on this  
9 presentation, and to keep the presentation short and leave  
10 you more time for discussion, I'm just going to flip  
11 through some of the slides that we used which I felt were  
12 key slides. So, I'm not going to spend much time on those  
13 slides.

14 Dr. Woodcock's presentation focused on the  
15 aspect of efficiency of manufacturing and efficiency of the  
16 associated regulatory processes. We think the quality of  
17 products is high, but I think the way we go about ensuring  
18 that quality can be improved and efficiency can have a  
19 tremendous improvement there.

20 There are problems in the manufacturing sector.  
21 These tend to come in the form of manufacturing related  
22 problems that we have seen over the last several years.  
23 There's an increasing trend. Low manufacturing and QA  
24 process efficiency is one of the major driving forces here.  
25 Innovation, modernization, and adoption of new technologies

1 | appears to be slow, especially in the U.S. sector, not in  
2 | the European. Most of these get applied in Europe, not in  
3 | the U.S. And there is a high burden on FDA resources also.

4 |           Dr. Woodcock essentially shared her view of how  
5 | did we get here. Pharmaceutical manufacturing this  
6 | committee is well aware of. We have moved from an art to  
7 | science and continue to move in that direction. But we  
8 | tend to have a lot of empirical approaches on how do we  
9 | define GMP standards and so forth. So, that is one  
10 | contributing factor.

11 |           We have moved towards harmonization of a lot of  
12 | our guidances and so forth, but these have been consensus-  
13 | based and I think the science tends to be secondary in  
14 | those discussions. The focus tends to be building  
15 | consensus across continents and move forward.

16 |           And also industry is risk averse and does not  
17 | want to take any risk in bringing new technology in if they  
18 | feel FDA or regulatory authorities are going to be not  
19 | receptive to such technology.

20 |           So, the challenges that we face are how to  
21 | encourage innovation while ensuring high quality, how to  
22 | successfully shift from empirical to more science-based  
23 | standards, and how to decrease reliance on pre-approval  
24 | review and physical evaluation, and how to recruit and  
25 | train the scientific work force that we'll need for the

1 shift.

2 The questions she posed to the Science Board  
3 are: Are you able to support this? What resources would  
4 you suggest that we have to draw upon? And what other  
5 aspects of quality should be considered?

6 Quickly, I think it was very good to see the  
7 presentation by Pricewaterhousecoopers in terms of the  
8 production cycle times and the efficiency numbers that they  
9 have, essentially matched with what Dr. Raju presented to  
10 you. And there are similar trends. There is lots of room  
11 for improvement and cost reduction by improving the  
12 technology of manufacturing. In fact, some of the numbers  
13 seem to support that. In some of their experience, a  
14 10-fold reduction in time and a significant reduction in  
15 cost has been achieved in other sectors.

16 The other aspect which is truly a win-win  
17 aspect is you not only improve quality but also you improve  
18 the efficiency at the same time. With the world-class  
19 standards being at 5 to 6 sigma, I think if we move in that  
20 direction, you not only improve compliance, but you improve  
21 productivity at the same time.

22 Quickly going through the presentation of G.K.  
23 Raju, he provided his analysis of the CAMP consortium  
24 members and the typical cycle times that he has seen in the  
25 pharmaceutical industry. For example, a tablet

1 manufacturer can take, after API has been screened and  
2 validated, about 60 days. But in reality, these numbers  
3 can be much longer. It can take half a year to get a batch  
4 of tablets out.

5 One of the reasons for the slow process is the  
6 off-line nature of our test. We complete a unit operation,  
7 stop, take samples, test before we go to the next step, and  
8 keep this process going. And the time spent is mostly in  
9 the paperwork, transferring material, and so forth, not in  
10 the process, not in the testing itself. It is the off-line  
11 nature that does that. But that's one contributing factor.

12 The other major contributing factor is out of  
13 specifications, when you have an exception. When he  
14 presented this -- or he did not present this to you -- he  
15 took the y axis off this slide. The reason is it's  
16 extremely sensitive. I know the numbers. The top is a  
17 year. I mean, you're looking at 300 days to get some of  
18 those batches out. That's what's happening.

19 One exception leads to investigation, leads to  
20 a paperwork trail, and so forth, and that leads to very  
21 long cycle times. Average cycle times for two products  
22 that he analyzed in detail were about 95 days and the  
23 standard deviation is more than 100 days. So, the  
24 productivity is getting products out is compromised and  
25 capacity utilization is low. So, really there's a need for

1 fundamental technology and a fundamental shift in the way  
2 we think about manufacturing.

3 This is new. I think the Pfizer presentations  
4 really hit the mark in many ways. Pfizer has been using a  
5 lot of these technologies for the last 20 years, and they  
6 have implemented this in many places but not in the U.S.  
7 Less than 15 percent of applications in U.S. sites. And  
8 they have been applying this to all of the drug product  
9 manufacturing from raw material testing to packaging,  
10 blending, and so forth, but not in the U.S.

11 They summarized their thoughts in two  
12 scenarios. There's a "don't use" scenario. They would not  
13 use it because of the uncertainty, regulatory risk  
14 associated, which leads to waste of resources, duplication  
15 of test methods for different sectors. This is  
16 unnecessary.

17 And the other aspect is "don't tell." They'll  
18 do it in parallel. In addition to the regulatory test  
19 requirement, they'll do it in parallel and rely on their  
20 methods and then provide the data to FDA to support the  
21 regulatory requirements. So, why would we really need such  
22 a duplication?

23 And they proposed certain aspects in a win-win  
24 scenario. This was to start bringing modern process  
25 analytical technology in through a process which improves

1 | our understanding in industry as well as in companies.  
2 | They suggested that we sponsor joint forums and a  
3 | discussion, develop an effective process to evaluate new  
4 | technology, and participate in dummy submissions in a  
5 | sense. Because of the risk associated, they don't want to  
6 | delay the approval of drugs. They proposed dummy  
7 | submissions. My thoughts are why dummy? We could work in  
8 | real time and make it happen. So, there are other aspects  
9 | to this.

10 |           But let me now sort of shift gears. What we  
11 | are talking about really is shifting the manufacturing  
12 | paradigm here through a process, stop, test, process, stop,  
13 | test to continuous monitoring of attributes which are  
14 | related to product quality and performance on line and in a  
15 | continuous fashion. I mean, that's the shift in paradigm  
16 | that we're talking about. So, it really has to bring about  
17 | rethinking of our current way of review and inspection.

18 |           The issue that I presented was that really we  
19 | find ourselves in a position that we have to lead or we  
20 | have to facilitate introduction of new technology. We do  
21 | that for two reasons. One is from a public health  
22 | objective you want to have the most efficient system from  
23 | an economic and quality perspective. But the other  
24 | underlying theme is, five years from now, if you don't do  
25 | this, who will get blamed? We will get blamed. FDA did

1 not allow this to happen. Obviously, that's not the case  
2 and we haven't seen one submission at all. So, we have to  
3 break that barrier and move forward.

4           Some of the challenges are with new technology,  
5 you have new questions. You have old products. If you  
6 have new technology, you have new concerns. You see some  
7 things which have already been. How do you address those  
8 problems? And really the mind set is that FDA will not  
9 accept it.

10           We presented this as a win-win opportunity to  
11 improve quality and manufacturing efficiency, reduce the  
12 likelihood of scrap and recalls. But in my mind I think it  
13 really adds value in terms of bringing more science and  
14 engineering into the process, as well as improving the  
15 scientific and engineering basis of our debates. We will  
16 continue to debate, but I think hopefully we'll do it more  
17 on scientific grounds.

18           So, here was our proposal. What should FDA do  
19 to facilitate introduction of PAT? We need to eliminate  
20 regulatory uncertainty, and the official position FDA has  
21 always had is FDA will accept new technology that is based  
22 on good science. The key here is defining and building  
23 consensus on what good science would be. So, development  
24 of standards for process analytical technology in terms of  
25 method suitability and validation.

1           One key aspect is multivariate statistical and  
2 computer pattern recognition. We have traditionally  
3 addressed quality issues as univariate statistical  
4 criteria, but you're dealing with a multivariate system.  
5 You have to think of new tools, and all pattern recognition  
6 tools have to be sort of brought in and discussed.

7           We have to redefine and rediscuss critical  
8 process control points and how do you establish  
9 specifications for these.

10           Changes. How will you manage changes in this,  
11 and how will you deal with out-of-specification results?  
12 So, we have to reexamine and rethink the whole scenario.

13           In order to define clear science-based  
14 regulatory process, I think one aspect which we believe in  
15 is the current system is adequate for intended use. So, I  
16 think that becomes the floor that gives you a platform upon  
17 which to build. So, introduction of process analytical  
18 technology will not be a requirement. It's an option. It  
19 is based on the scientific and economic drivers that a  
20 company may have. So, we would support that from that  
21 perspective.

22           And we really need to define conditions under  
23 which process analytical technology may replace current  
24 regulatory release testing because if you keep adding new  
25 tests and keep holding on to the old tests, you will not

1 accomplish what you're trying to accomplish.

2           And we have to develop a process for addressing  
3 existing invisible problems in the marketed products, which  
4 will become apparent when you bring new technology on.

5           We need review and inspection practices based  
6 on science, and eventually we'll have to deal with  
7 international harmonization issues.

8           We have limited institutional knowledge and  
9 experience at FDA in this area, so we have to seek input  
10 and collaboration. We did that with you on July 19th, and  
11 we are ready to form the subcommittee. We are looking at  
12 aspects of collaborating with individual companies if we're  
13 ready to bring this on line, and clearly we'll work with  
14 academic pharmaceutical engineering programs and process  
15 analytical chemistry programs, and PQRI.

16           That was sort of an update and some background  
17 information. I just want to sort of position the rest of  
18 the talk to help your discussion in terms of defining the  
19 subcommittee's objectives.

20           A perspective on process analytical technology.  
21 In my mind it is one piece of the puzzle. It's not the  
22 entire system. So, we're discussing one piece of the  
23 puzzle. In my way of looking at it, I think here is an  
24 opportunity to go from "I know it when I see it" -- that's  
25 the current system. You have to test for blend uniformity

1 before you know it's uniform. Vision 2020 is "I can see  
2 clearly now" which entails quality and performance by  
3 design, plus continuous real-time monitoring of quality,  
4 specifications based on mechanistic understanding of how  
5 formulation and process factors impact product performance,  
6 leading to high efficiency and high capacity utilization.  
7 But also I think an important aspect that we have to deal  
8 with and plan for is real possibility of real-time review  
9 and inspection and do that from sitting in our offices. I  
10 think this technology opens the door for that possibility.

11 One of the presentations in the open session at  
12 the Science Board was from AstraZeneca. Bob Chisholm from  
13 AstraZeneca made a presentation on their plant that they  
14 have actually put on line right now in Germany, and that  
15 real-time inspection is a possibility. So, that production  
16 facility is on line for German products.

17 So, the key elements that I think we need to  
18 consider for this emerging program and our initial thoughts  
19 are -- this is a draft. What I feel is we really need to  
20 start defining general principles guidance on process  
21 analytical technology. We need to articulate an FDA  
22 position on process analytical technology. By that I mean  
23 the acceptance and definition and terminology. We are  
24 introducing a whole host of new terms, and I think we  
25 really have to start from scratch and say here is this

1 common language that we'll speak in this program.

2 Outline a regulatory process for introducing  
3 process analytical technology. Here there are two aspects:  
4 pre-approval phase and post-approval phase. What I hear  
5 from companies is it's unlikely that a company will  
6 introduce this in the pre-approval phase because of the  
7 pressures of getting the drug approved and potentially  
8 delaying or raising questions with new technology in an NDA  
9 or ANDA application. So, many may opt for bringing new  
10 technology in in a post-approval phase. Unfortunately, you  
11 really have to build the quality in. So, data has to be  
12 collected throughout. But we'll have to work around those  
13 things.

14 Addressing existing invisible problems I  
15 mentioned before, and creating a team approach for review  
16 and inspection. In our minds, the process would be a total  
17 team approach, but our review chemists from the center will  
18 actually visit and be part of the inspection program to  
19 bring the folks together.

20 From a science perspective, the type of  
21 experimental evidence and justification that will be  
22 needed, the thoughts are as follows. There are two ways of  
23 bringing this technology in: as an alternate or as the  
24 primary control or test. I'll explain that in a minute.

25 The other aspect is you will have, in some

1 cases, direct measurement of attributes of interest and in  
2 other cases, you have a correlation-based control of that  
3 attribute. Again, I'll explain that in a minute.

4 We would need to have an appropriate level of  
5 redundancy or backup systems to make sure we cover  
6 failures, if any.

7 And we will have to debate on-, in-, and at-  
8 line release testing. The concept of parametric release  
9 comes in and I'll explain that in a minute too.

10 Types of test and controls. Alternate control  
11 and test. A process analytical technology tool may be  
12 validated by comparison to a traditional in-process test  
13 using development data and/or data from routine production  
14 for a period of time. Number of batches. And traditional  
15 in-process test discontinued after sufficient data has been  
16 collected to support the validation. So, that's one  
17 approach.

18 So, an example of that would be on-line blend  
19 uniformity using, say, for example, near infrared analysis  
20 that would be validated using data from blend samples  
21 obtained using a sampling thief. Once you compare that as  
22 acceptable, that may be one way of looking at it. But it's  
23 not an ideal situation. When you compare a modern, more  
24 efficient, better technology to something which is  
25 problematic, that's not the solution.

1           So, we really have to create new gold standards  
2           and a new way of looking at it. I think we have many ideas  
3           of how it should be done, but I think the subcommittee  
4           should start thinking in those terms. It could be a  
5           primary control/test, and a process analytical tool is  
6           developed and validated on its own merits, moving to its  
7           first principles maybe. Here I think we'll have to  
8           reassess how we define that in terms of accuracy,  
9           precision, specificity, and all the terms that we use for  
10          validation of an analytical test.

11           Continuing on types of tests and controls, I  
12          just want to share some thoughts on correlation-based  
13          controls and tests.

14           Many times I think you have an option of  
15          looking at an infrared spectra or a fingerprint and  
16          deriving information about attributes indirectly. So, you  
17          may have to build a correlation model for that. Here use  
18          of chemometrics or pattern recognition methods to identify  
19          and develop a correlation between measurement and product  
20          attribute would come in. An example that I'll share with  
21          you is prediction of tablet hardness or dissolution rate  
22          from, say, near infrared spectral fingerprints. It's not a  
23          direct test of dissolution, but it is a correlation to  
24          dissolution.

25           And from a validation perspective, there are

1 two options. Validation based on predictive performance  
2 only. For example, our in vitro/in vivo correlation  
3 guidance that we have for dissolution is a validation based  
4 on predictive performance only. That is, you develop three  
5 formulations, you establish a correlation, and the  
6 correlation gives you prediction within plus/minus 10-15  
7 percent, it's okay. So, that's the way we handle in  
8 vitro/in vivo correlation.

9 But here I think there's an opportunity to  
10 improve upon that. What I'm suggesting is validation based  
11 on predictive performance of a correlation, plus  
12 mechanistic justifications owing to its causal links. Let  
13 me explain that.

14 The data I have here is percent dissolved  
15 versus time for seven experimental formulations. The drug  
16 is metoprolol, and you're looking at the USP dissolution  
17 test here. The data is from our University of Maryland  
18 research project. All of those products, by the way, are  
19 bioequivalent.

20 But now how do we establish a dissolution test?  
21 We simply say, if 70 percent dissolves in 30 minutes,  
22 everything passes. So, that's how we do it.

23 With simple experimental procedures, here is  
24 the half-factorial experiment that we did. We actually  
25 know every factor that affects dissolution. In fact,

1 | percent dissolved at any given time could be predicted with  
2 | very high precision, and it was related in this case to  
3 | magnesium stearate, microcrystalline cellulose, and sodium  
4 | cromoglycolate.

5 |           So, what I'm showing here is at different time  
6 | points we have ability to predict dissolution based on  
7 | formulation and process components. So, you have  
8 | established and defined the critical variables and  
9 | developed an empirical but mechanistic causal link saying  
10 | these are the reasons why dissolution changes according to  
11 | this, and so forth.

12 |           Now, with technology on line with imaging and  
13 | others, you can actually measure magnesium stearate. You  
14 | can actually measure microcrystalline cellulose, and all  
15 | those attributes separately. So, in addition to a  
16 | correlation, you have the ability to monitor all those  
17 | excipients and all other attributes that affect  
18 | dissolution. So, that's what I mean by correlation plus a  
19 | causal link approach.

20 |           Let me share with you some thoughts on  
21 | parametric release. This term has been hotly debated and I  
22 | think in Europe it's widely accepted but not in the U.S.  
23 | What is parametric release and release test? Parametric  
24 | release is used in the U.S. only for parenteral dosage  
25 | forms that are terminally sterilized.

1                   Let me explain what this is from a USP  
2 perspective, and the quote there is from USP. The  
3 information there is directly from USP. Let me read that.  
4 When data derived from the manufacturing process sterility  
5 assurance validation studies and from in-process controls  
6 are judged to provide greater assurance that the lot meets  
7 the required low probability of containing a contaminated  
8 unit, any sterility test procedure adopted may be minimal  
9 or dispensed with on a routine basis.

10                   Suppose it is a sterilization process that uses  
11 steam, autoclave. The parameters that you validated would  
12 be temperature, pressure, time. So, if you have confidence  
13 in those parameters, then you don't wait for sterility test  
14 to approve the product. The logic is simple in the sense  
15 if you have 5 percent contamination in the thing, to  
16 identify and to find out that level of contamination, you  
17 actually have to test three lots of the material. So, the  
18 limitations of sampling, the statistical limitations -- it  
19 does make sense to do that test.

20                   So, that what is parametric release in a  
21 parenteral sense. But I think what we can do with process  
22 analytical technology is far superior, far better, and I  
23 think we have to redefine parametric release in this  
24 context.

25                   The European guidance on parametric release

1 | defines that term as follows. It's a system of release  
2 | that gives assurance that the product is of the intended  
3 | quality, based on the information collected during the  
4 | manufacturing process and on compliance with specific GMP  
5 | requirements related to parametric release. This is sort  
6 | of a broad, regulatory definition.

7 |           But this guidance, which is now effective since  
8 | September of this year, extended the concept of parametric  
9 | release to other dosage forms, including tablets and  
10 | capsules.

11 |           So, building on the example I showed you with  
12 | the dissolution, what would parametric release for  
13 | dissolution look like? Simply creating a hypothesis,  
14 | visualizing what this might look like down the road.

15 |           One way of defining parametric release, or  
16 | whatever we call this term when we define this term, if  
17 | that method provides a greater assurance, compared to  
18 | current dissolution test methods, that lots will meet  
19 | established typical dissolution specification, or we can  
20 | think out of the box, forget the routine dissolution  
21 | testing. Just link it directly to the bio if lots can be  
22 | assured to meet the bioequivalence criteria. That would be  
23 | one way of saying this is a better test.

24 |           What data would be needed for that? I think  
25 | processes that utilize in-process controls that can measure

1 and control all critical variables that affect dissolution  
2 -- we will need to have those test methods. And we would  
3 need appropriately designed manufacturing process  
4 validation studies, such that validation based on  
5 predictive performance, plus mechanistic justification,  
6 could be the foundation on which this could be based. So,  
7 moving towards all the critical variables, moving towards  
8 understanding of the mechanisms of dissolution, moving  
9 towards more science-based.

10 Let me share with you an example. How do we do  
11 dissolution testing, lot-release testing now? Under USP  
12 conditions, you take 6 tablets out of a lot, do the  
13 dissolution test, meet your one point, and you're done.  
14 That's 6 tablets. It could be a million lot, 2 million, 25  
15 million lot of tablets. That is what it is today.

16 Here's an example from a major company which  
17 sent this to me. It's also linked to blend uniformity.  
18 They were having dissolution problems. When they first  
19 marketed, there was no problem. There was a sampling issue  
20 because non-homogeneous distribution of magnesium stearate  
21 was the culprit here, and if you look at the dissolution as  
22 a function of the production itself, the box number itself,  
23 tablets being collected as the production is ongoing, you  
24 can see dissolution failures either early or late. Using  
25 technologies, such as near infrared on line, or other such

1 | technologies, laser-induced fluorescence maybe, you can  
2 | actually do this and have a homogeneity with respect to  
3 | magnesium stearate, all excipients, and so forth. So,  
4 | looking at 6 tablets and being happy with that and looking  
5 | at the entire lot, which would we prefer? So, that's the  
6 | message.

7 |           I'm going to skip this I think and share with  
8 | you that on the 25th of October, we had a Federal Register  
9 | notice on Process Analytical Technology Subcommittee.  
10 | We're requesting names of qualified individuals in the area  
11 | of process analytical chemistry, pharmaceuticals, industrial  
12 | pharmacy, chemical engineering, pharmaceutical analysis,  
13 | chemometrics, pattern recognition, expert systems, IT, and  
14 | statistics. So, we know this is going to be a multi-  
15 | disciplinary approach. We want to bring all these talents  
16 | together to help all of us work together. So far we have  
17 | received 27 applications. I have not fully gone through  
18 | those applications, but we have 27. The deadline for  
19 | submitting is the 30th of this month.

20 |           The Federal Register notice stated that this  
21 | subcommittee would report on scientific issues related to  
22 | application and validation of on-line process technologies  
23 | such as near infrared. I keep repeating this. Near  
24 | infrared is just one example. I tend to use it more  
25 | because I'm more familiar with it. But this is not the

1 | only technology. In fact, at the back of your handout, I  
2 | have a list of all the technologies, and the list is two  
3 | pages long. So, near infrared is only one example in my  
4 | mind. I'm just using that for presentation clarity. But  
5 | the whole host of technologies available is mind-boggling.

6 |           We have requested focus on both drug substance  
7 | and drug product manufacture, also asked for feasibility of  
8 | parametric release concepts, potential risks and benefit  
9 | analysis of this, and as I said, applications are due the  
10 | end of this month.

11 |           My proposal to you is what should the  
12 | subcommittee report to you on? The proposal is this. If  
13 | we can have the subcommittee focus on the following:  
14 | current status and future trends in process analytical  
15 | technology, especially in pharmaceutical development and  
16 | manufacturing, not just manufacturing, but starting from  
17 | the development aspect itself. Provide information on  
18 | available technologies, capabilities, advantages,  
19 | limitations. Also application in U.S. versus non-U.S.  
20 | plants and why the difference. Perceived and/or regulatory  
21 | hurdles.

22 |           General principles for regulatory application.  
23 | Principles of method validation, specifications and out-of-  
24 | specification, but general principles, not in terms of  
25 | getting at the nitty-gritty at the first stage, but in the

1 long run, we will have to.

2           Appropriate use and validation of chemometric  
3 tools.

4           Feasibility of parametric release concepts,  
5 also to redefine this in this context. Parametric release  
6 is actually less of a standard compared to what we are  
7 doing here.

8           Case study. Should the group use a case study  
9 like vibrational spectroscopy, near IR? It's a question  
10 mark. I don't know whether we need to have the  
11 subcommittee focus on one tool or have a much broader look  
12 at the situation.

13           And also some input on research and training  
14 needs within the FDA and in industry.

15           One of the concerns which I expressed at the  
16 Science Board was the pharmacy schools -- the erosion of  
17 pharmaceuticals/industrial pharmacy programs and pharmacy  
18 schools -- may not be there to help bring the people we  
19 need for this. We have to think of going outside pharmacy  
20 schools. What the trend has been is the Michigan chemical  
21 engineering program now has a pharmaceutical engineering  
22 program. Rutgers has one. So, there are a number of  
23 pharmaceutical engineering programs that are coming up and  
24 somehow support that through the National Science  
25 Foundation. Steve has one program in his. We have to

1 | build the pharmacy programs and refocus some of the  
2 | industrial pharmacy programs to help meet the needs of the  
3 | individuals that we'll need in this area.

4 |           With that, I'll stop and give it back to Steve.  
5 | Hopefully, that presentation was not too long and was  
6 | helpful to initiate the discussion.

7 |           DR. LEE: Thank you very much, Ajaz.

8 |           Any questions for Ajaz?

9 |           Before I do that, I'd like to welcome a  
10 | prospective committee member. Dr. Moye, would you please  
11 | introduce yourself?

12 |           DR. MOYE: Of course, good morning. My name is  
13 | Lem Moye. I am a physician and a biostatistician from the  
14 | University of Texas School of Public Health. I have served  
15 | on one advisory committee before this and that was the  
16 | Cardio-Renal Advisory Committee.

17 |           DR. LEE: Thank you very much.

18 |           Questions for Ajaz?

19 |           DR. MEYER: Ajaz, what's your sense of the best  
20 | way to move forward? If you try to, let's say, reinvent  
21 | industrial pharmacy in an academic setting, it will be 10-  
22 | 15 years before you have any progress to show.

23 |           It seems to me, as you noted, some firms are  
24 | already doing this in Europe and would, therefore, easily  
25 | be able to adapt it in the U.S., if it weren't for the FDA

1 | constraints that they perceive. Is that correct?

2 |           So, maybe if you had some kind of mechanism  
3 | like an RFP where companies could respond and say, we're  
4 | willing to give this a shot, and you're willing to train a  
5 | select group of FDAers in monitoring their progress, and  
6 | you work together on a small basis, one product, one firm,  
7 | two products, two firms, whatever, you might make some real  
8 | progress that could then rapidly be disseminated rather  
9 | than trying to solve all the problems all at once and make  
10 | lists and so on and so forth.

11 |           DR. HUSSAIN: No. Marv, that actually was a  
12 | message I got from the Office of the Commissioner also, a  
13 | similar message. The folks from Pfizer shared with us  
14 | their success with getting this introduced in Australia,  
15 | and the question was raised, why Australia, and why not the  
16 | U.S.? So, the technology, the SOPs, the regulatory aspect,  
17 | review aspect, outside the U.S. is already there.

18 |           One option -- we have to discuss this  
19 | internally more, but I think we have initiated the  
20 | discussion -- is actually to have a parallel process to the  
21 | subcommittee and invite companies who would like to do this  
22 | and provide a means or mechanism whereby a review and  
23 | inspection team could be formed and can make that happen  
24 | starting today, if need be.

25 |           So, we would need some expertise in-house. We

1 | have a lot of expertise in-house in terms of analytical.  
2 | We have to rethink in terms of on-line approaches in terms  
3 | of control, and we actually will hire a few people also on  
4 | the OPS level and strike a move forward in this parallel  
5 | track also.

6 |           But I don't have the whole program laid out,  
7 | but that's something they're looking at.

8 |           DR. LEE: Let me define the boundaries here, if  
9 | I may. We have about an hour to discuss, and assisting us  
10 | in discussion is Tom Layloff over there. I gather what you  
11 | would like us to do, Ajaz, is to define the charge of this  
12 | subcommittee. Right? So, it seems to me that this is a  
13 | trend that is somewhat irreversible, and let's hope that we  
14 | can accelerate the process and make it a reality.

15 |           So, Steve, since your name was mentioned, would  
16 | you like to lead off the discussion?

17 |           DR. BYRN: Yes. I should say before we go too  
18 | much further, though, that Purdue has been doing a lot of  
19 | work in this area, and there's some intellectual property  
20 | involved. So, you need to realize that the comments I'm  
21 | going to make are in that context.

22 |           I wanted to comment on what Marvin said first  
23 | and also Ajaz on the breadth of this area. I was just  
24 | writing down, but I think the area involves at least four  
25 | major components or educational or background. One would

1 | be pharmaceuticals, manufacturing pharmaceuticals, that part of  
2 | pharmaceuticals. One would be analytical chemistry, almost  
3 | straight, which Tom would represent, almost straight, and  
4 | Judy. One would be informatics because we're going to have  
5 | to be able to deal with an awful lot of data. And the last  
6 | one would be regulatory affairs, validation, all that kind  
7 | of thing. So, it's really an interdisciplinary program  
8 | area, and the educational part of it is extremely difficult  
9 | I think to get people that can work in this area. It's  
10 | going to require a special kind of interdisciplinary  
11 | program.

12 |                 So, I don't know whether we want to start on  
13 | that, Ajaz. But maybe we should brainstorm the educational  
14 | background that's going to be required to achieve this.

15 |                 I put engineering in there with pharmaceuticals  
16 | and manufacturing.

17 |                 DR. HUSSAIN: Steve, I understand the long-term  
18 | educational needs, definitely. But instead of focusing on  
19 | that, there's very little at this meeting we can do for  
20 | that. I think we have to start brainstorming and  
21 | developing this program.

22 |                 But what we have at hand right now is the  
23 | subcommittee is ready to form. In fact, we have set the  
24 | date for the subcommittee meeting as February 22nd and  
25 | 23rd. So, before that subcommittee gets started, I think

1 we need to define the charge or the work plan and what you  
2 expect from that subcommittee so that we can move forward  
3 on that aspect.

4 DR. LEE: Okay. Since we're talking about  
5 technical issues, Art?

6 DR. KIBBE: Yes. I have just a couple of  
7 questions. From your presentation, we clearly have  
8 leadership in Europe on this issue, both the companies  
9 being willing to go forward with it partially because of  
10 the regulatory environment, and second, the regulatory  
11 bodies being willing to accept this and seem to be slightly  
12 ahead of the curve, if what you say is true.

13 Wouldn't it be prudent for us to have people  
14 from our side of the Atlantic in the regulatory field get  
15 educated by the regulators who are willing to accept this  
16 kind of technology in Europe so that they know the pattern  
17 of acceptance of that information? And then what we're  
18 really talking about, if it is ongoing in Europe ahead of  
19 us in terms of developing this process, transporting that  
20 technology here.

21 So, the first step in my mind is to get a clear  
22 understanding of how they go about validating these systems  
23 and accepting these systems in the European situation, and  
24 then just transposing that methodology here and modifying  
25 it so that we make it work easily here. That would, in my

1 | mind, move our time table up, rather than starting from  
2 | scratch and trying to reinvent the entire process. I  
3 | recognize the four areas you talked about are extremely  
4 | important in terms of educating all of us on how to go  
5 | about doing this, but to make the system work faster, I  
6 | think importing the information is better.

7 |           DR. HUSSAIN: The information we have is what  
8 | we have heard from the companies. We have not directly  
9 | contacted the regulatory agencies, and I think we will.  
10 | We'll try to get some information. So, I don't have any  
11 | more information on the acceptance and then how that  
12 | happened. I think it's very important for us to understand  
13 | and capture some of that information. Definitely.

14 |           The MCA, our counterpart in the U.K., is very  
15 | active in this area, and I have spoken to folks there and  
16 | they have expressed frustration that nothing has happened  
17 | in the U.K. It has happened in Germany and Australia for  
18 | some reason. So, we will try to get that information and  
19 | see how that has happened.

20 |           DR. KIBBE: I'd be more than happy to go with  
21 | you and spend a few weeks in Switzerland to research this.

22 |           (Laughter.)

23 |           DR. BYRN: I just want to comment on that too.  
24 | Of course, having done a lot of work in this area, we've  
25 | been trying to look for public information. There's very

1 little public, unless Tom knows of something that I don't.  
2 But if you search the literature on parametric release or  
3 any of these terms, there's virtually nothing published.  
4 So, all of this information in Europe is private sector  
5 information.

6 So, one of the things the committee I think  
7 ought to do is try to get as much information as they  
8 could. I think that's one of the charges probably, to try  
9 to figure out how much information there really is in this  
10 area.

11 DR. LEE: And at the same time, to find out  
12 what are the hurdles and the resources required, and items  
13 such as those. Right?

14 DR. BYRN: Yes, all of the above. I think Tom  
15 is going to say something about that.

16 DR. LAYLOFF: I was going to make a couple of  
17 comments.

18 First of all, in the pharmaceutical business,  
19 the manufacturing operation ends up as a control process,  
20 and most of the academic efforts have been in the discovery  
21 area. There's been a general trend in academics to move  
22 more towards discovery and less in the area of control.  
23 So, we see a decline in emphasis on any analytical process  
24 at all, anything that's concerned with control, and so the  
25 industry has had to bite the bullet and actually train

1 | their own personnel. And I'm sure FDA is going to have to  
2 | do the same sort of thing for process analytical  
3 | technologies also. I don't see a big bloom coming out of  
4 | people who are in discovery shifting to control efforts.

5 |           As Steve noted, these issues are proprietary.  
6 | There's significant investment in developing and validating  
7 | them, and I'm not sure that anybody who is in business is  
8 | going to be willing to give up their investment to other  
9 | people. It's a proprietary advantage to have these things  
10 | in place, and I don't think they're going to be willing to  
11 | give them away. They're probably going to be more  
12 | protective of the process technologies than they are of the  
13 | development technologies.

14 |           DR. HUSSAIN: Vince, I misstated the planned  
15 | dates for the subcommittee. It's February 25th and 26th.

16 |           DR. LEE: Are those better days?

17 |           (Laughter.)

18 |           DR. LEE: Ajaz, do you have any idea how soon  
19 | you want to have a report back?

20 |           DR. HUSSAIN: I'm just looking at the people  
21 | who have applied. There's a good mix of people from Europe  
22 | who are willing to participate on this committee. So, that  
23 | is a good sign.

24 |           At the same time, I just want to share with you  
25 | the Royal Pharmaceutical Society has a new Technology Forum

1 | Section, and I participated with that. It's like their  
2 | PQRI, but they are linked to MCA. So, they have been very  
3 | active in this area. And some folks from there also have  
4 | applied to be on our committee. So, I think there are  
5 | linkages that are emerging which should be very, very  
6 | useful not only in terms of learning and getting  
7 | information, but also simultaneous harmonization efforts.

8 | DR. LEE: I used the word "irreversible" very  
9 | deliberately, but I have not defined the speed to get  
10 | there.

11 | I see that Efraim has his hand up over there,  
12 | and maybe he's ready to speak.

13 | DR. SHEK: Yes. The way I look at it it's a  
14 | real revolution if we go this direction, and it's another  
15 | impact of the technology of information being to utilize  
16 | it. Since it's such a revolution, one aspect for the  
17 | subcommittee to look at it is the implementation. If we  
18 | don't look at what will be the end result, it might take a  
19 | long process. It requires investment, resources, both  
20 | intellectual as well as equipment. I personally believe  
21 | that it's the right direction to go, but somehow from the  
22 | subcommittee, as they deliberate, look how it's going to be  
23 | implemented. For example, how do you validate those issues  
24 | from an old technology to a new one? We have in other  
25 | areas where you cannot show comparability because you

1 compared two different aspects.

2 So, those details I think will be extremely  
3 important to move this process fast. If the subcommittee  
4 can deliberate sometime and learn from others or come with  
5 their own ideas how can we implement it faster, I think  
6 would be very, very important.

7 DR. LEE: Leon, you're sitting right next to  
8 Efraim. Would you like to make a comment?

9 DR. SHARGEL: Yes. I have sort of a question  
10 something really we all brought up in terms of proprietary  
11 methods. Many companies may have methods that are  
12 proprietary, and we also have to consider public standards,  
13 such as our friends up the street, USP, which often sets  
14 monographs and public standards.

15 Now, as this committee begins to approach new  
16 technology, it strikes me that the information needs to be  
17 disseminated publicly. I think that's a sensitive area and  
18 how that's done, that it can be publicly debated among  
19 industry, academics, and other interested people, to see  
20 whether this has applications that would be suitable in  
21 their own industry. I'm not sure how that would be done,  
22 but I'd like the subcommittee to consider that in how we  
23 can discuss this in an open forum.

24 DR. LEE: Good. I think what you're suggesting  
25 is that we need to identify the major players.

1 Other questions? Steve?

2 DR. BYRN: I think that's a really good idea.  
3 I think if you look at the proprietary, just in a general  
4 way, there's proprietary equipment, information handling  
5 software. All these things in this area are potentially  
6 proprietary. And if we can get private sector companies --  
7 for example, no company can manufacture their own near IR  
8 equipment, validate it, develop the software to do the  
9 chemometrics, et cetera. That's not a feasible thing, I  
10 don't think, for each company to do.

11 So, we're going to have to figure out a way in  
12 this process to attract instrument manufacturers. That's  
13 the way to be involved in this, and they're going to have  
14 to be able to -- and this is just one example -- run their  
15 business somehow. You talk about high technology. This is  
16 really a critical issue, how we involve the highest  
17 technology, the best people, and have some system that they  
18 can feel like they can run their business with it, and yet  
19 we can advance drug product quality and all the things we  
20 want to do.

21 DR. LEE: Yes, Ajaz.

22 DR. HUSSAIN: Vince, there were several  
23 comments that came to my mind. I think Leon mentioned  
24 public standards. Let me just share with you my thoughts  
25 on that.

1 I'll again use the example of near infrared.  
2 In my mind that is not a tool which could be used as a  
3 reference tool for analysis of the content uniformity of  
4 all tablets. It's not designed for that. That's not the  
5 intention. That's the reason the focus is on line for  
6 control. So, what that does is it actually creates a dual  
7 system. For public standards, you still have to rely on  
8 HPLCs and other traditional methods. That would be your  
9 foundation for public standards, not infrared as an assay  
10 in uniformity.

11 So, that's the reason the focus is on line.  
12 So, these will be alternate, additional methods. You still  
13 have to meet the requirements of public standards. But  
14 since you would possibly be raising the quality so much,  
15 that public standard is actually not a concern anymore.  
16 So, that's one aspect which I think is important to keep in  
17 mind.

18 Because of some of these methods look at both  
19 the physical and chemical attributes together, formulation  
20 is very specific. This would be very specific to  
21 formulation. So, everything has to be specific to a given  
22 manufacturer. So, private standards are what we are  
23 focused on.

24 The second question I think Steve raised was  
25 the proprietary nature of this, and actually the same

1 question was raised at the Science Board to the Pfizer  
2 folks. Pfizer's response was none of those instruments and  
3 so forth -- they're working with instrument manufacturers  
4 for commercial use. So, none of that would be sort of  
5 blocking anybody else from using those instruments. So,  
6 that's one aspect.

7 From the AstraZeneca presentation at the  
8 Science Board, the entire system that they have is based on  
9 commercially available equipment, not something that's  
10 proprietary to this.

11 So, right now, for example, infrared  
12 proprietary issues are not that significant. What is  
13 significant is how one applies it to their process and  
14 their use. The instrument, the calibration, the software  
15 are commercially available. In fact, the software is also  
16 part 211 compliant. So, it complies with the software  
17 validation and other aspects too.

18 But as new technology emerges -- this is just  
19 scratching the surface -- you will have so many new  
20 technologies that come in that we will have to deal with  
21 that issue.

22 DR. LEE: So, Ajaz, is it your sense that some  
23 industry is already moving ahead in that direction?

24 DR. HUSSAIN: Yes. I think the instrument  
25 manufacturers are quite active and many technologies are

1 coming.

2           What is missing right now is the mechanical  
3 engineering aspect in the sense of where do you put the  
4 sensor on the blender, how many. There's a recent  
5 publication by Jim Drennen in the last month's  
6 J.PharmScience, and he argues that you need six different  
7 positions on the blender where you need a near infrared  
8 probe. That doesn't make sense.

9           But again, do you need one port or you need six  
10 of them? When you shine in a laser light and retrieve  
11 information, what amount of sample are you reading? So, it  
12 brings the unit dose sample. What is the size of the  
13 sample that you're getting? So, all that has already  
14 started. I think we'll have to deal with those debates.

15           DR. LEE: Tom?

16           DR. LAYLOFF: I would like to agree with Ajaz  
17 that the technologies that we're talking about on process  
18 control are actually consistency assessments. We're going  
19 to need an orthogonal public standard for assessing the  
20 quality of the product once it's released into public  
21 commerce because the base on which the release is going to  
22 be made is going to be proprietary and very closely linked  
23 to the configuration of the technologies and the  
24 information systems that are tied in there.

25           Also, it is true that there has been a lot of

1 focus on near infrared and the technology. The companies  
2 there have moved in and basically made near infrared a COTS  
3 type system, commercial off the shelf. The software is  
4 validated and you just pick it up and use it.

5           However, there are other assessment  
6 technologies which are out there, acoustic, photon  
7 migration, which will give you more information on the  
8 consistency of processes, and those have not yet matured to  
9 the same level as near infrared, but they are out there and  
10 they are moving up quickly.

11           DR. LEE: Very well.

12           Judy?

13           DR. BOEHLERT: I would agree with Tom that we  
14 need an orthogonal public standard. The company also needs  
15 that public standard because, indeed, you may get back  
16 samples from the field after it's released and need to test  
17 them and verify the quality of that material.

18           I think organizations such as USP can help in  
19 this process not on a monograph-specific basis, but perhaps  
20 some general chapters that deal with some of these on-line,  
21 in-line, at-line analytical techniques.

22           The other thing I would point out is back in  
23 the early 1990s I was at a scientific meeting where a  
24 number of companies made presentations on how they were  
25 going to do all of this good stuff, parametric release for

1 solid oral dosage forms and all of that. As far as I'm  
2 aware, except for the European sites, very little has  
3 happened in this country, and why didn't it happen? Well,  
4 the expense, because very often they had to redesign their  
5 manufacturing process, the regulatory uncertainty. They  
6 weren't sure it would be approved. So, they haven't gone  
7 forward.

8 We have to get past that. We need to find some  
9 folks that are willing to take the risk and move forward in  
10 this regard because Europe is doing it.

11 DR. LEE: Joe, do you have any comments to  
12 make?

13 DR. BLOOM: Well, I think the issue to use new  
14 technology to improve all the manufacturing processes is  
15 good. But as Marvin was saying and taking the arguments of  
16 Dr. Kibbe here, we should focus on one or two technologies  
17 basically. These things are new and we're throwing punches  
18 in the air in a lot of aspects. What we should do is if we  
19 want to go forward, we've got to get some company that  
20 would cooperate with the FDA, and the instrument companies  
21 will cooperate too because if an instrument company knows  
22 that this new instrument is going to be used in a new  
23 technology, they might have a future in their production of  
24 the instruments. So, we should take one or two new  
25 technologies and try to implement them in a pharmaceutical

1 | atmosphere because this is going to take a long time. It's  
2 | not going to be an easy process.

3 |           Actually the NIR that Ajaz was discussing, one  
4 | of the things is the validation process. There's a lot of  
5 | people talking about different ways of validating the  
6 | technique. So, this is going to be a big issue.

7 |           The other issue is proprietary information. If  
8 | this is going to be a setback, we should look into it  
9 | because if we're going to establish this subcommittee and  
10 | the proprietary issue is going to come about, that might be  
11 | like a stop sign for the subcommittee to move forward. We  
12 | should move forward all together, the industry, the FDA,  
13 | and the instrument companies. We should come together  
14 | otherwise we're not going to move forward.

15 |           We should get one of the issues to move  
16 | forward. Just take NIR which is being used and try to get  
17 | a company to establish it and validate it, and then get  
18 | another new technology and do that.

19 |           The other thing is we cannot focus on  
20 | photoacoustic and NIR and all other new techniques and take  
21 | a whole bunch of new techniques and try to move forward.  
22 | We should focus on one or two of them so the subcommittee  
23 | should focus on that aspect.

24 |           DR. LEE: Ajaz?

25 |           DR. HUSSAIN: I think I'm hearing some concern

1 | with the proprietary nature and how that might interfere in  
2 | the process. Somehow I'm not getting the same concern. At  
3 | least I don't have the same concern for two reasons. One  
4 | is most of the things that get submitted to FDA are  
5 | proprietary technology. So, we handle that. So, it's not  
6 | an issue from that angle. The proprietary aspect becomes  
7 | an issue when you have to build guidances and science and  
8 | so forth.

9 |           But in many ways, there are two things here.  
10 | One is the reason we're focusing on on-line is you still  
11 | have the floor defined by the current quality standards.  
12 | So, you have the fall-back situation. So, you have a  
13 | method that would improve on the existing quality, and  
14 | that's the basis of justifying that method. All we need to  
15 | do is understand the basic principles of how will we define  
16 | that process. Then each company does that under the  
17 | umbrella of those basic principles for their particular  
18 | product. So, that becomes proprietary. The general  
19 | principles should be fine. So, that's the reason I'm not  
20 | so concerned with the proprietary aspects.

21 |           DR. BYRN: Maybe I could comment too on that.  
22 | I didn't mean to set this off on a big discussion of  
23 | intellectual property.

24 |           I think it's pretty simple. Let's think of a  
25 | spreadsheet. Now, somebody writes a computer program and

1 | they have a spreadsheet and that's proprietary. But yet,  
2 | that spreadsheet is made available, and they do that so  
3 | that they can fund the development of it and the  
4 | improvement. But that spreadsheet program, whether it's  
5 | Microsoft or whoever, then is made available to everybody  
6 | else, and they use that program to improve whatever they're  
7 | doing.

8 |           In the same way, a company might have a  
9 | proprietary technology of some sort that would be developed  
10 | that they would then sell to everybody else. Each person  
11 | would use that and operate on their system, but yet there  
12 | has to be, I think -- I'm not an economist, but I think  
13 | there has to be a way that we draw instrument manufacturers  
14 | into this field so that they can justify significant  
15 | investment in developing some of these technologies. So,  
16 | we have to allow a system, which I think we've already got  
17 | set up.

18 |           I think I completely agree with Ajaz. It's not  
19 | any different from using particle size analyzers or  
20 | anything else that are required by guidances. Those are  
21 | still proprietary and people sell those. It's just that  
22 | people need to realize that when we move into a new area  
23 | like this, there's going to be a lot of involvement of  
24 | proprietary companies in this. So, I don't think it will  
25 | hurt us. I think it will actually help us if we just let

1 | the current system work.

2 | DR. LEE: Kathleen?

3 | DR. LAMBORN: I can't say I know very much  
4 | about this area, but just listening to the discussion, it  
5 | seems to me that we're bouncing back and forth between  
6 | particular technologies and the concept of what rules  
7 | should we set for validation. I think this is, Ajaz, what  
8 | you were trying to say. If we set the rules for what  
9 | constitutes a sufficient validation for an alternative  
10 | process, then that would encourage everybody to use  
11 | different technologies and to develop proprietary  
12 | components because they would have been told what rules you  
13 | have to meet.

14 | So, it seems to me the place to start for the  
15 | subcommittee is to be looking at the general rules that  
16 | have to be met. This is where the concept of going to the  
17 | folks in Europe, if they've approved it, and saying, all  
18 | right, what rules have you had and what was the science  
19 | behind the concept, and to start there and then go back and  
20 | use specific examples to make sure that we would agree that  
21 | the level of assurance that they put in place is one that  
22 | we'd be comfortable with. But I think if we stay with  
23 | that, then we would avoid this problem.

24 | DR. LEE: Thank you.

25 | Art.

1 DR. KIBBE: I agree with you. I think that's  
2 where I was trying to get to at the very beginning.

3 DR. LAMBORN: That's what I thought you were  
4 doing.

5 DR. KIBBE: There are going to be lots issues  
6 that we can't even face or can't think of out of whole  
7 cloth, but there have been companies who have gone this  
8 route with regulators in a highly developed situation. So,  
9 if we could identify the companies and the products and the  
10 regulators that have already gone this route in Europe and  
11 Germany and the company sees a monetary gain for being able  
12 to do the same thing here and we can talk to the regulators  
13 about their guidelines and modify them with our own  
14 concerns here and put them in place and partner up on those  
15 products, we will be able to glean from that general  
16 guidelines for everybody else regardless of the technology  
17 they're using. That's where I would start.

18 I was half kidding about going to Switzerland  
19 with you, but I think that's what you need to do is go and  
20 visit with them.

21 (Laughter.)

22 DR. KIBBE: No, I think you need to take a  
23 couple of people from the agency over there and find out or  
24 bring them here and have us meet with them.

25 DR. LEE: I would like to give another minute

1 for discussion before summarizing the discussion. Jurgen?

2 DR. VENITZ: Yes. I'd like to add to the  
3 committee charge to deal with what you call the existing  
4 but invisible problems. In other words, if the current  
5 technology seems to pass a particular product, but then you  
6 use a new technology and all of a sudden there are some  
7 outliers that would lead one to believe there's a problem  
8 that we don't know about using current technology, I think  
9 that to me is a big hurdle for companies to even wanting to  
10 touch this. So, I think the committee should deal with  
11 that. What are you going to do in the circumstance?

12 DR. BYRN: I'd like to broaden that out because  
13 it's essentially the same problem just restating: trying  
14 to validate a really good method with a bad method. In  
15 other words, do you have a bad method that you're using now  
16 and let's say somebody comes up with a good method of blend  
17 analysis, how do you validate that new method, that better  
18 method, against a bad method? This is a fundamental  
19 analytical issue.

20 DR. LEE: Thank you.

21 Gloria, you have a point to make?

22 DR. ANDERSON: I'd just like to come back to  
23 the last slide, I guess it is, in your presentation. If  
24 I'm understanding this correctly, you have a question mark  
25 at the end of this, and that suggests to me that you're

1 | wanting some input on these three areas, whether or not we  
2 | feel that these are areas the subcommittee should consider  
3 | and report back on, as well as the subcategories under  
4 | here.

5 |           I think that these probably summarize what such  
6 | a subcommittee would want to do. It seems to me like we  
7 | should start with what's available, what's being done, what  
8 | the regulatory hurdles are, if such information exists, and  
9 | then try to look at where we want to go from there.

10 |           I have a question about the near IR. I want to  
11 | talk to you about it after this discussion because it may  
12 | be that we might not want to just look at near IR. We may  
13 | want to look at something that's complementary to that. I  
14 | looked at the sheet that you have, and there are a lot of  
15 | yeses and noes, and it may be a good idea to look at that  
16 | matrix and see if there's something complementary.

17 |           Apparently NIR has been used I guess more  
18 | frequently than anything else. It has a lot of good  
19 | characteristics, but there may be something that's  
20 | complementary so that we don't just look at one thing and  
21 | in the end find out it doesn't do what we want it to do.

22 |           DR. HUSSAIN: Thank you. I think that's  
23 | exactly what I was trying to do here. This is your  
24 | subcommittee, and I can propose and hopefully you will  
25 | accept it, but in a sense this committee will report back

1 | to you and the advice then comes to us. So, you really  
2 | have to define for the subcommittee what the charge would  
3 | be or the work plan would be.

4 |           There were two things which I just wanted to  
5 | share with you. One is near infrared is about 20-year-old  
6 | technology. It has been in application since 20 years ago  
7 | in other sectors, not in pharmaceuticals. The petroleum  
8 | and other chemical industries have used this, but it  
9 | doesn't mean that something that's applicable to petroleum  
10 | would be applicable to pharmaceuticals. We would have to  
11 | go through that evaluation process.

12 |           But the commercial availability and all the  
13 | other aspects have been worked out, and that's a leading  
14 | technology in terms of on-line applications. Raman is  
15 | close behind. So, vibration spectroscopy is a product  
16 | term. I think mid-IR and others are ready for  
17 | implementation. Acoustics and other technologies are in  
18 | the research state, and I think they'll come about soon.

19 |           So, focus on general principles and then  
20 | removing the uncertainty through general principles would  
21 | be my way of moving the first step.

22 |           I just want to clarify what has happened in  
23 | Australia and what has happened in Germany with AstraZeneca  
24 | in Germany and Pfizer. These tend to be new plants. I  
25 | think the AstraZeneca plant is a brand new facility which

1 is on-line throughout. Putting something on line in an  
2 existing facility, I think there are more challenges to  
3 that. So, I think we'll have to look at that aspect also  
4 in the sense of what might work in a new facility may not  
5 work in an older facility. It may not be ready for that.

6 But just to summarize, I think what I've heard  
7 is essentially a lot of issues that I have laid out are  
8 also on your radar screen, and I'll wait for Vince to  
9 summarize that.

10 DR. LEE: Any other comments, input before I  
11 attempt to summarize what I have heard?

12 DR. DOULL: Vince, I have just one general  
13 comment. It's interesting. This is a new committee that  
14 hasn't really even been formed yet, and yet I hear some of  
15 the same kind of problems that Nonclinical Subcommittee has  
16 already encountered, problems about proprietary information  
17 and how that's presented, publication of the results, for  
18 example, funding. In the Science Board, you talked about  
19 where the resources would come from. And it isn't clear to  
20 me exactly what kind of resources.

21 I guess what I'm saying is that this committee  
22 needs to be sure that when we lay down guidelines that  
23 those are guidelines which are useful across the board  
24 because we have the same kind of issues, same kind of  
25 problems with all of our subcommittees. If we add three

1 | more new ones, we'll probably have the same kind of things.  
2 | We need general guidelines is all I'm saying.

3 |           DR. HUSSAIN: Vince, this is not a research  
4 | subcommittee. I think NCSS was created to do research and  
5 | actually is supposed to be fact finding, but that was a  
6 | PQRI sort of a model. We're not going in that direction  
7 | with this committee at all. The research, the funding,  
8 | PQRI, our own, company collaboration, and so forth. This  
9 | is not a research subcommittee. So, that's the difference  
10 | here.

11 |           DR. LEE: Bill, do you wish to make any  
12 | comments?

13 |           DR. JUSKO: No.

14 |           DR. LEE: Anybody else?

15 |           (No response.)

16 |           DR. LEE: Let me attempt to summarize what I  
17 | have heard, and then I would have the committee to  
18 | formalize the charge to the subcommittee.

19 |           Obviously, this is a trend which is  
20 | irreversible. We don't know how fast we're going to get  
21 | there, but hopefully we would be on top of this process.

22 |           Steve Byrn mentioned a scientific foundation of  
23 | this idea.

24 |           I also heard about the players in terms of  
25 | institutions, ethical companies, generics, FDA, and USP,

1 and maybe many others.

2 I heard about gathering information, learning  
3 from others who already have been there.

4 I also heard about the disseminating of new  
5 information, in other words, educating the stakeholders.

6 What else? And also, I think Gloria mentioned  
7 very nicely that perhaps the charge to the subcommittee is  
8 already summarized in some of the slides and we should take  
9 a look at that.

10 John mentioned about the resources that it  
11 would take. For example, if this subcommittee is going to  
12 go forth and do some fact finding, would they have access  
13 to the facilities.

14 So, those are the things that I heard. Have I  
15 missed something? Yes.

16 DR. MOYE: This is a very unique conversation  
17 for me because typically I'm in situations where the  
18 pharmaceutical companies are essentially overwhelming the  
19 FDA with new technology and its implementation. It doesn't  
20 appear to be the case here. I think I've heard two  
21 obstacles, and perhaps you were going to get to these.

22 One I heard was cost because the pharmaceutical  
23 company will have a great deal of early investment and  
24 they'll want to recoup that, naturally. I don't know if  
25 that's an appropriate purview for the committee, but that's

1 going to be a very important issue for the pharmaceutical  
2 companies.

3           The second, of course, is the uncertain  
4 regulatory environment. The pharmaceutical companies will  
5 need to know, I think, clearly that if they can meet these  
6 regulatory stipulations, then they will not have a problem.  
7 Pharmaceutical companies oftentimes have their hands full.  
8 They have a product coming to market that itself may be  
9 controversial. Maybe the disease for which it's treating  
10 isn't well recognized. Perhaps the pivotal studies haven't  
11 been as persuasive as they had hoped. They often have an  
12 armful of problems coming into the FDA. I don't think they  
13 want to add to that the additional problem which would not  
14 have been a problem in the past, but the additional new  
15 problem of blend issues primarily because of a change in  
16 the regulations and stipulations. That needs to be lock-  
17 solid for them.

18           So, the degree to which the committee can  
19 address those two issues, recouping cost and easing the  
20 regulatory concerns, I think would remove the major  
21 obstacles from the pharmaceutical companies.

22           DR. LEE: Right. Thank you. I think this is  
23 exactly what Jurgen was hinting at about the problems and  
24 possible solutions.

25           Also, I think what you mentioned triggered

1 | thoughts. The pharmaceutical business is a global  
2 | business, and therefore how the regulatory agencies around  
3 | the world ought to work together is something we might want  
4 | to consider.

5 |           So, I have a list of items, and now we need to  
6 | identify somebody who's very good at crystallizing these  
7 | thoughts. Art, you seem to be very good at that. And I  
8 | had asked you this morning why is he sitting to my right?

9 |           DR. KIBBE: The greatest thing that can happen  
10 | to you, of course, is great expectations. He says I'm  
11 | going to crystallize all of this.

12 |           The thing that came to mind to me while you  
13 | were speaking is why would the companies do this. That's  
14 | the driving force of the regulatory agency anyhow. If the  
15 | companies are finding that this is a way of an economic  
16 | benefit, then they're going to move in this direction. And  
17 | then the question is, is the agency prepared to accept that  
18 | change and make it a viable change for the companies so  
19 | that everybody moves smoothly forward? And that's really  
20 | what the subcommittee is all about, to get the agency well  
21 | enough educated about how it can be done and what are the  
22 | pitfalls in regulating it so that when the companies are  
23 | here, prepared to move in that direction, they don't move  
24 | into a vacuum, because they're certainly not going to move  
25 | if we're not ready to accept that information. The first

1 step being then finding out how it has been done.

2           The second step -- if we had an economist here  
3 -- what is the economic benefit to an individual company  
4 and to the overall health care costs of the United States  
5 of having an agency lead the industry in this direction  
6 rather than responding to the industry? In other words, if  
7 we're going to, as an agency, put in regulations that  
8 encourage companies to move to this process of validating  
9 their products, what are all of these benefits going to end  
10 up with? So, I think the subcommittee needs to have a good  
11 argument because if we are, as you correctly point out, out  
12 in front of the companies on this issue, they're going to  
13 need a reason to move with us. I think that could come out  
14 of discussions with other regulatory agencies and companies  
15 that have gone in that direction. As you pointed out,  
16 Pfizer and AstraZeneca have done it with new plants, but  
17 are they willing to refit old ones to do that?

18           Something that hasn't been brought out, which I  
19 have kept in the back of my mind, is if we don't move,  
20 companies are international. Are they going to take  
21 manufacturing and put it someplace else because they can do  
22 it better there and not do it here? I don't know whether  
23 we need to be sensitive to that, but I think in terms of  
24 the United States' leadership in the development of new  
25 drugs, we need to be prepared for those kinds of things.

1                   So, I think Vince has correctly listed some of  
2                   the things. I think your last slide, as Gloria pointed  
3                   out, really does it. And what my input would be is that we  
4                   need to help you put priorities on those elements, and from  
5                   my perspective, the first priority is the regulatory  
6                   situation where it is working and then the second is to  
7                   delineate how the benefits will pan out for the companies  
8                   who are willing to step forward and jump into the water  
9                   with us.

10                   Does that help you any, Vince?

11                   DR. LEE: Does it help you, Ajaz?

12                   DR. HUSSAIN: Yes.

13                   DR. LEE: Go ahead.

14                   DR. HUSSAIN: One aspect is I think I had  
15                   talked to some of you and some of you had expressed  
16                   interest in being part of that subcommittee. I think one  
17                   of the things which would be helpful is if you can identify  
18                   who from this committee would like to be on that committee,  
19                   and then we can build the rest of the group around that.

20                   DR. KIBBE: If we're meeting in Switzerland, I  
21                   want to.

22                   (Laughter.)

23                   DR. LEE: Are you happy with the names  
24                   submitted in those 27? Not the names but the expertise.

25                   DR. HUSSAIN: Yesterday, for example, I think

1 we were missing a few areas. I think statistics,  
2 chemometrics was low, and I requested some names from the  
3 National Institute of Standards and others, and I think we  
4 have received some.

5 What the list is right now are people who have  
6 actually done it.

7 DR. LEE: I think, Ajaz, the Federal Register  
8 is not something that I read every day. You need to get a  
9 message out to another group that can help you, I mean,  
10 another forum.

11 DR. HUSSAIN: What we did was we used AAPS and  
12 the American Chemical Society and AIChE to send this to key  
13 individuals that share. Also, the National Institute of  
14 Standards and other government agencies which have done  
15 this in other sectors have personally sent e-mails out to a  
16 lot of the folks.

17 DR. LEE: Let me declare a conflict of interest  
18 and then I'll make a statement and request, perhaps that  
19 you might want to write an editorial for Pharmaceutical  
20 Research. I'm the editor of the journal.

21 (Laughter.)

22 DR. KIBBE: Share that with J.Pharm.Sci. and  
23 you could be in both places.

24 DR. LEE: So, we have 10 minutes left. Let me  
25 put forth some charge, and then the committee ought to be

1 comfortable with the charge to the subcommittee.

2 Number one perhaps is to understand the state  
3 of the art, just learning from the people who have been  
4 there before.

5 Maybe before that, we need to define what is to  
6 be gained by embracing this new phenomenon. So, that's the  
7 first thing. What is the benefit?

8 Number two is the state of the art.

9 Number three is what are the problems, the  
10 hurdles, and possible solutions.

11 And perhaps number four is maybe the most  
12 important. How should the regulatory agency be prepared  
13 for this?

14 Now, these are very broad, not specific at all.  
15 We can fill in the blanks by going to some of the slides in  
16 the portfolio.

17 Steve?

18 DR. BYRN: One idea is to see if we have  
19 anything to add to these and then fill in the blanks?

20 DR. LEE: Yes.

21 DR. BYRN: One thing we might want to add --  
22 and I'm just throwing this out -- is educational issues. I  
23 don't know. In other words, if this is implemented, as  
24 Ajaz said, how do we educate people in this area since  
25 there are no existing programs, I don't think, anywhere

1 | that do this. So, how would the education be carried out?  
2 | Would it be done with AAPS? You know, the whole thing.

3 | DR. LAMBORN: Could I suggest that that could  
4 | fit in two places under the existing list? One is  
5 | education is a problem. Then when it comes to where do we  
6 | propose people go, then any proposals for improving  
7 | education would fit under that.

8 | DR. LEE: I think education certainly is an  
9 | important process, who to educate in the short term and the  
10 | long term.

11 | Other comments?

12 | DR. HUSSAIN: I was told Pat DeLuca is on the  
13 | phone in case he has a comment.

14 | DR. LEE: Where are you Pat? Pat, are you  
15 | there?

16 | (No response.)

17 | DR. LEE: I don't think he heard us. I think  
18 | we need some new technology for this meeting.

19 | (Laughter.)

20 | DR. LEE: Can anybody read back those four  
21 | things that I said?

22 | DR. HUSSAIN: Let me try. To start out with,  
23 | essentially defining the benefits and what we will gain  
24 | with this. Defining the state of the art. Identifying the  
25 | problems and hurdles and providing solutions. And then how

1 | should we prepare ourselves to move in this direction.

2 |           I just wanted to add to that. In terms of  
3 | training needs, the National Science Foundation has  
4 | established one center already at the University of  
5 | Washington. This is the process analytical chemistry  
6 | division at the University of Washington, and I think there  
7 | are some other centers that NSF is going to form. We are  
8 | hooking up with them right now.

9 |           DR. LEE: Is everybody comfortable with those  
10 | four points? Should we add more?

11 |           (No response.)

12 |           DR. LEE: All right. The next thing is two or  
13 | three other points.

14 |           Volunteers from this committee. Do we want to  
15 | do that now or should we do that behind closed doors?

16 |           DR. HUSSAIN: We can do it.

17 |           DR. LEE: Where are we going to meet?

18 |           DR. KIBBE: I'm ready.

19 |           DR. LEE: Art, are you serious?

20 |           DR. KIBBE: Listen, if we're going to  
21 | Switzerland, I'm ready.

22 |           (Laughter.)

23 |           DR. LEE: He has a Swiss account.

24 |           (Laughter.)

25 |           DR. LEE: How many people do you need?

1 DR. HUSSAIN: Well, I think traditionally a  
2 minimum of two and one consumer rep. That's how we have  
3 done it and then supplemented that from the industry and  
4 others.

5 DR. LEE: May I propose that those who might be  
6 interested -- well, you can do it two ways. You can either  
7 do it by a show of hands now or we can do that during the  
8 break. Traditionally, the chair of the subcommittee has to  
9 be from this committee. Isn't that right?

10 DR. HUSSAIN: Not necessarily. Tom is an SGE  
11 and I think he'll be part of that committee and sort of  
12 coordinate and manage that part. I think we're hoping we  
13 will accept him for that role.

14 DR. LEE: So, do you want some names now?

15 DR. HUSSAIN: It would be nice, but we can  
16 wait.

17 DR. LEE: So, who would be interested to be  
18 considered? Joe, Judy, Art, Steve.

19 DR. HUSSAIN: Steve, you're not on the  
20 committee anymore. I'm just kidding.

21 (Laughter.)

22 DR. BYRN: Yes. I'm not on the committee, so  
23 it doesn't really count.

24 DR. KIBBE: Well, you could serve on the  
25 subcommittee.

1 DR. LEE: Who else?

2 (No response.)

3 DR. LEE: Okay, good.

4 The next thing is the time line. Would two  
5 weeks be enough?

6 (Laughter.)

7 DR. HUSSAIN: What I was hoping is we'll  
8 prepare them and they should come with all the answers on  
9 February 25th.

10 DR. LEE: And 26th.

11 DR. HUSSAIN: Right.

12 DR. LEE: How soon would the Science Board like  
13 to hear back from you?

14 DR. HUSSAIN: The Science Board meets every six  
15 months. So, if we can have some information to feed back  
16 to the Science Board, that would be a driver in my mind.

17 DR. LEE: It seems to me that this task, if  
18 focused, ought to come to some kind of a conclusion in 6 to  
19 12 months, don't you think? I think as soon as we form the  
20 subcommittee, then the chair will recognize the scope of  
21 this task. Many issues that we have not talked about might  
22 emerge.

23 DR. MEYER: Vince, you might ask how long will  
24 it take you to get to Germany and Australia and back with  
25 the fact finding paper.

1 DR. HUSSAIN: I'm not flying. I have not taken  
2 the steps necessary to make the contact, but I will do so  
3 immediately and get back to you. I don't have an answer.

4 DR. MEYER: It seems to me that's critical.  
5 The technology apparently is there, although it's in  
6 Europe. And the regulatory information is in Europe. What  
7 we need to know is how to apply it here, but we don't know  
8 what we're trying to apply yet.

9 DR. BYRN: Marv, the general technology is  
10 there, but if you look at the last of Ajaz's slides, where  
11 you start looking at these new sensors, that's not there.  
12 In fact, this is a huge excitement I think of this field,  
13 the potential to develop sensors, better and better sensors  
14 that tell you more and more about what's happening. In a  
15 sense, it will be an evolving field. The goal would be to  
16 have a sensor, as Tom has said, right on this step that's  
17 absolutely critical, that if anything goes wrong, it senses  
18 it immediately and you stop the production or whatever and  
19 fix the problem. And that's going to be an evolving goal.  
20 So, I think what they have in Europe is the initial  
21 airplane, if you will, but they don't have the finished  
22 product yet. That's my impression.

23 DR. MEYER: That may be true, but I don't think  
24 this committee is being set up to develop technology or to  
25 enhance technology.

1 DR. BYRN: No.

2 DR. MEYER: It's to use current technology.

3 DR. BYRN: I think all the committee is doing  
4 is trying to set up the regulatory environment that would  
5 allow this to happen.

6 DR. LEE: Tom?

7 DR. LAYLOFF: In defense of the agency, I would  
8 like to say that the FDA many years ago approved the use of  
9 near infrared as an alternate technology for the release of  
10 ampicillin trihydrate for the moisture determination,  
11 identification, and assay, many, many years ago.

12 DR. LEE: Ajaz, this is a feasibility question  
13 for you, being chair for the first time. Would it be  
14 reasonable to ask the subcommittee to publish the report in  
15 journals?

16 DR. HUSSAIN: I think that's an excellent idea.  
17 It definitely is a public document. It will be published  
18 through our transcripts and so forth. A version of that  
19 written by the chair or the group of the members that would  
20 be more in tune with the journal I think would be an  
21 excellent idea. So, I would like to see that happen.

22 DR. LEE: It doesn't have to be Pharmaceutical  
23 Research.

24 (Laughter.)

25 DR. LEE: We are at the point of a break. Are

1 | there any other questions, comments?

2 | (No response.)

3 | DR. LEE: If not, thank you very much.

4 | DR. HUSSAIN: Vince?

5 | DR. LEE: I'm sorry.

6 | DR. HUSSAIN: Just to understand the 6 to 12  
7 | months, I think what we're hoping for that time frame is  
8 | general principles and so forth. But in my mind once we  
9 | have that, then more detailed aspects could be gotten into.  
10 | So, the committee might continue in a different direction  
11 | from that point.

12 | DR. LEE: That's correct. I can only speak for  
13 | myself that I have no idea what is the eventual scope of  
14 | this project.

15 | When we come back, we're going to talk about  
16 | stability testing and shelf-life. Thank you.

17 | (Recess.)

18 | DR. LEE: We have Dr. Pat DeLuca on the phone.  
19 | I understand that he was on the phone but he was not able  
20 | to speak. So, he heard everything that we talked about.

21 | Pat, are you still there?

22 | DR. DeLUCA: Yes, I'm here.

23 | DR. LEE: Great. The reason you were not able  
24 | to hear us was because we were too noisy.

25 | Pat, when you have a point to make, will you

1 | please identify yourself? So far you are the only one on-  
2 | line. There may be two others coming on-line. Pat, would  
3 | you please introduce yourself, who you are and where --

4 | DR. DeLUCA: Yes. I'm Patrick DeLuca. I'm at  
5 | the University of Kentucky College of Pharmacy.

6 | DR. LEE: Thank you.

7 | We have a new, quote/unquote, member around the  
8 | table. Dr. Chris Rhodes, would you please introduce  
9 | yourself?

10 | DR. RHODES: My name is Christopher Rhodes.  
11 | I'm at the University of Rhode Island.

12 | DR. LEE: Thank you very much, and welcome to  
13 | this discussion.

14 | The next session is on stability testing and  
15 | shelf-life. Once again, Ajaz Hussain would like to define  
16 | the issues for us.

17 | DR. HUSSAIN: Thank you, Vince.

18 | This is somewhat of a different discussion  
19 | topic. We're not truly posing questions to you but we're  
20 | presenting this as an awareness topic, an awareness topic  
21 | from the perspective of opportunity, concern, together  
22 | creates an awareness issue in my mind.

23 | Stability is always a contentious debate that  
24 | we always have and we continue to have debate. I'm not  
25 | bringing those debates to you for discussion, but a topic

1 on physical stability.

2           The way we are going to present different  
3 perspectives here are I'll introduce a topic, and I've  
4 invited Professor Chris Rhodes to share the scientific  
5 perspective on physical stability. Then Dr. Chi-wan Chen  
6 will provide an overview of current stability requirements  
7 and hopefully by then you'll have sufficient information  
8 for some discussion. I pose a broader question towards the  
9 end of my presentation. I'll come back to pose that after  
10 Dr. Chen makes her presentation.

11           Just to move on, the awareness topic. I think  
12 regulatory stability testing requirements are effective in  
13 minimizing stability problems. I think that's the general  
14 consensus and I think the data bears that out. So, why are  
15 we discussing this topic today?

16           There are lingering concerns that certain gaps  
17 exist with respect to ensuring physical stability,  
18 especially with more complex products such as parenteral  
19 controlled-release dosage forms. They are few in number,  
20 but their numbers are increasing. And changes in physical  
21 stability -- and if there is a recall, do we take the  
22 plants out? We have to struggle with those questions. So,  
23 as more dosage forms get more complex physical attributes,  
24 changes, and so forth comes on our radar screen as a  
25 concern that the current approach may have to be improved.

1 That's the lingering concern.

2 At the same time, on the opposite of that  
3 concern, one could ask do such concerns contribute to  
4 excessive stability testing. We often get criticized for  
5 our stability requirements, but I think what I would like  
6 to show is that our stability requirements actually are  
7 doing an excellent job, and there are certain reasons for  
8 why they are what they are.

9 But also, is there an opportunity to further  
10 improve regulatory utility of pre-formulation and product  
11 development data to understand mechanisms of physical and  
12 chemical changes? So, that's sort of a broad introduction.

13 Let me focus on concerns from my perspective.  
14 Physical stability I believe -- and I think you'll agree --  
15 is a critical quality and performance attribute. I'll use  
16 dissolution changes as an example. Changes in dissolution  
17 rate that occur in the absence of detectable chemical  
18 changes would be in my mind an example of physical changes  
19 for tablets and capsules. For other dosage forms,  
20 suspensions, resuspendability and other aspects of changes  
21 that occur. So, there are many different physical  
22 attributes which are important.

23 For the last six years, we have tried to track  
24 dissolution changes and recalls that occur because of that.  
25 And dissolution related recalls are even number one or

1 number two quality related problems that we see. The  
2 numbers are small. The numbers are not big. I think this  
3 year we had 22 products being recalled because of  
4 dissolution failures, and many of those failures are class  
5 3, not a significant safety and efficacy concern. But  
6 there are recalls that occur for certain products on a  
7 continuous basis.

8 Carbamazepine. Marv has done a lot of work on  
9 bioavailability dissolution failure on that in the 1980s.  
10 Those dissolution failure problems still continue. So,  
11 those problems have not gone away. So, it's a lingering  
12 problem.

13 The other concern here is accelerated stability  
14 test conditions are more reliable for identifying the  
15 potential for chemical changes. Essentially the basis of  
16 Arrhenius equation and so forth are for chemical changes  
17 and so forth. And if we don't understand the mechanisms of  
18 physical changes, how do we know that the Arrhenius type of  
19 equation would work for some of that? Is it even  
20 appropriate?

21 Just to give you an example for that, cross-  
22 linking of gelatin capsules was a significant issue 5-10  
23 years ago, and the stability conditions actually induced  
24 that change, but it was not an issue from a bio  
25 perspective. So, in some cases, the test might be more

1 sensitive to potential problems where there may not be a  
2 safety and efficacy concern. But having a test which is  
3 more sensitive and giving false positives or false  
4 negatives can be a problem.

5 Mechanisms governing physical changes are not  
6 well understood or characterized. Dissolution rate changes  
7 may occur due to a change in morphic form of a drug and/or  
8 excipient -- I think generally we ignore the excipient --  
9 and a change in processing. This could be triggered by a  
10 change in processing conditions, packaging, and so forth.  
11 It's a complex set of variables that one has to deal with.

12 One aspect of recalls that tend to bother me at  
13 least personally is recall investigations often do not  
14 result in identification of a root cause. So, if you see a  
15 dissolution problem, now recalled, the same thing will be  
16 recalled again. So, that cycle perpetuates. In order to  
17 solve that problem, that problem keeps coming back again  
18 and again.

19 As I said earlier, increasing number of  
20 parenteral controlled-release products comes on my radar  
21 screen as something that we need to be prepared for because  
22 more protein peptide drugs are being developed and more of  
23 them are coming in microspheres, implants, and so forth.  
24 We can deal with recalling tablets rather simply, but what  
25 about something that's implanted and so forth? We have

1 | actually dealt with some of those situations the last  
2 | couple of years.

3 |           At the same time, I think there is a concern,  
4 | but I think there is also a sense of opportunity. We do  
5 | know there have been significant advances in pre-  
6 | formulation and material characterization aspects and  
7 | optimization. I think new tools, x-ray diffraction, are  
8 | more commonly used and there are many tools available for  
9 | characterization and understanding of the physical  
10 | attributes. So, we have improved ability to identify and  
11 | eliminate problems, but are they being fully utilized?  
12 | That's a question mark I have.

13 |           Can we use this information to reduce the need  
14 | for stability testing and prior approval supplement  
15 | process? That's a program you have heard about from Dr.  
16 | Yuan-Yuan Chiu. That's our risk-based chemistry. So,  
17 | there is already a thought process ongoing, and you have  
18 | some presentations to that effect. So, I'll not get into  
19 | that right now.

20 |           But let me bring an example in. I was planning  
21 | to bring a couple of case studies, carbamazepine as a case  
22 | study, and so forth, but it's difficult to do that in terms  
23 | of the proprietary nature of some of the data that might  
24 | have two products. So, I shied away from creating those  
25 | case studies.

1           But I want to share with you some data from our  
2 own program that we have in collaboration with the  
3 Department of Defense, and this is our program, what we  
4 call Shelf-Life Extension Program. So, the stockpile that  
5 we maintain, we keep extending the shelf-life through  
6 testing. Let me share some results with you. This is a  
7 major cost-saving to the taxpayer. It's millions of  
8 dollars that we save by not throwing out the stockpile  
9 every year.

10           So, some results from that that we have. We  
11 have done analysis on about more than 1,000 lots of 96  
12 products. And what do we see in this program? 84 percent  
13 of the lots were extended, the shelf-life was extended on  
14 an average of 57 months past the original expiration date.  
15 About 14 percent were terminated due to failure, but many  
16 are still active. 22 products showed no signs of failure  
17 at all. So, these are essentially solid as a rock.  
18 Nothing happens to them. But about 10 percent of the  
19 products that we have are unstable and have difficulty  
20 meeting even the expire date. So, extensions are not  
21 feasible.

22           But what is striking -- and I'll show you some  
23 data on this, which in my mind supports why we have to be  
24 very conservative with the shelf-life and why our stability  
25 requirements are the way they are -- is the stability

1 | period is highly variable from lot to lot. I cannot say  
2 | the shelf-life of this lot is going to be this. Let me  
3 | show you some examples.

4 |           Here is an example of an injection, diazepam  
5 | injectors. On your y axis, you're looking at length of  
6 | extension beyond what was established as the shelf-life,  
7 | and we're extending beyond. So, you're looking at months  
8 | beyond the original expire date and the extension. On the  
9 | x axis, you're looking at different lots. There's nothing  
10 | different. It's a different lot of that material. You'll  
11 | see that it's so variable. Can one lot be extended to 120  
12 | months or 96 months? We don't know until we do the  
13 | testing. So, this is an ongoing testing program that we  
14 | routinely test the stockpile material.

15 |           But one of the aspects is you'll see chemical  
16 | degradation, physical changes too, so pH, maybe a chemical,  
17 | physical, or a combination. But look at the  
18 | recrystallization and the problems with precipitation of  
19 | these injections. That is a reason for not being able to  
20 | extend certain lots at all. But it's so unpredictable.  
21 | That means we have to do testing for every lot to maintain  
22 | this program.

23 |           Why are there such big lot-to-lot differences?  
24 | I don't have an answer for that, but I would like to seek  
25 | some answers for that.

1           Here's one more example, tetracycline capsules.  
2           The lot designated H is still ongoing. It's beyond 120  
3           months after its expire date.

4           Just to let you know, the expire date are under  
5           controlled conditions. This is not for in-use type. It  
6           was storage conditions.

7           And dissolution failure in this case is also  
8           quite apparent on occasions, and there are certain products  
9           on the stockpile right now which we know will fail  
10          dissolution. So, we actually have an ability to identify  
11          products that might fail dissolution, maybe becoming models  
12          to understand what the mechanisms are.

13          I was going to hold the questions after you  
14          heard from the other two speakers. I'll come back to these  
15          questions later on.

16          DR. RHODES: Thank you very much, indeed. It's  
17          a great pleasure to be here. I greatly enjoyed the  
18          discussion we had before break. I have promised not to  
19          mention the near IR.

20          Basically, my first point I want to make is  
21          looking back, I think we can rightly congratulate ourselves  
22          -- and by ourselves, I mean industry, regulatory bodies,  
23          and academia -- on the general progress that we have made  
24          in stability testing. Of course, stability testing is one  
25          of the areas where harmonization has been remarkably

1 | successful.

2 |           However, unfortunately, I still meet many  
3 | people in industry, where I work as a consultant, who  
4 | believe basically that the only role of stability testing  
5 | is to test potency. If the drug meets label claim with  
6 | respect to potency, that's their only concern. And that is  
7 | something which all of us have got to do something about.

8 |           This morning we were heard and I as an EU  
9 | pharmacist was flushed with pride to hear that the EU is  
10 | somewhat in advance in some areas. I must say this. I  
11 | spend about three or four months in Europe. I think -- I  
12 | haven't got hard data -- that there probably is rather more  
13 | understanding of the problem that physical stability cause  
14 | in Europe than is here. And I'm hopeful that one of the  
15 | results of the discussions we will have this morning is to  
16 | raise the level of awareness of potential stability  
17 | problems and then perhaps to decide what kind of action is  
18 | required.

19 |           So, stability testing should take as its  
20 | purview the quantification of any functionally relevant  
21 | attribute that can change with time and that may modify the  
22 | safety, efficacy, or patient acceptability of that  
23 | particular product. It, therefore, certainly includes many  
24 | stability problems.

25 |           As a consultant, I can tell you that some of

1 | the worst stability problems I have ever had to deal with  
2 | or attempt to deal with are physical stability problems,  
3 | and I'd like to endorse very strongly what Ajaz has said  
4 | about batch-to-batch variability.

5 |           We all know that batch-to-batch variability can  
6 | be a problem with chemical stability. Again, without hard  
7 | data, my own personal impression, it is a much more serious  
8 | problem with certain types of physical stability. I've  
9 | worked with suspensions where every 12 or 15 batches run  
10 | very well, and then one batch fails for some reason. And  
11 | when you have that problem, I regret to say that there are  
12 | some who would like to use the SUC, "sweep it under the  
13 | carpet," and forget about it. I do strongly believe that  
14 | physical stability problems for a number of reasons are  
15 | less well studied, they are cases where in some instances  
16 | we certainly have no understanding of the mechanism, and it  
17 | may well be that all we see at the moment is the tip of the  
18 | iceberg. The problems may be more significant than we  
19 | realize.

20 |           Some of the possible adverse effects of  
21 | physical stability clearly are modification in release  
22 | rate, and that could be increasing the release rate or  
23 | decreasing the release rate. We've already heard that this  
24 | is relatively common. It can lead to certainly a class 3  
25 | and in some cases class 2 recalls.

1                   Aggregation of proteins, aggregation of  
2 dispersed material in emulsions and suspensions can be very  
3 important. Adsorption on packs or infusion sets certainly  
4 can be a clinically significant problem. Deliquescence can  
5 lead to such problems as content uniformity difficulties,  
6 tablet weight difficulties. Migration of one or more  
7 molecular species either in a drug delivery system, in a  
8 pack or in a label can cause problems. You can get, for  
9 example, loss of adhesion in a transdermal. You can get  
10 loss of label adhesion on a plastic bottle, or you can  
11 simply get the ink running because of migration.  
12 Obviously, if the patient can't read what is on the label,  
13 it's very hard in my opinion to argue that that product is  
14 safe and effective.

15                   Some of the other effects that you'll see are  
16 loss of back-off torque on a plastic bottle with a plastic  
17 cap. In most cases, when we put tablets in bottles, the  
18 resin we use for the bottle is not the same as that we use  
19 for the cap, and therefore, when the temperature rises,  
20 either the bottle or the cap expands more than the other  
21 component. And if you have this stress, eventually you can  
22 lose your back-off torque, t-o-r-q-u-e.

23                   Similarly, certain physical changes, aging on  
24 plastics, can lead to loss of package integrity, and that  
25 of course, can affect the microbiological status of the

1 product.

2           And then we come on with this lovely term, loss  
3 of pharmaceutical elegance. Now, you might say, well, is  
4 that really important? Yes, it is. If the patient sees or  
5 smells a perceived difference in a batch of tablets from  
6 the previous batch, very often they will not use it, they  
7 will take it back, they will miss doses. Therefore, when  
8 we talk about quality of products, safety, efficacy, and  
9 patient acceptability are all important.

10           Now, why don't we give sufficient attention to  
11 physical stability? Quite frankly, I think that in many  
12 cases ignorance is bliss because in many cases we haven't  
13 looked to see if there are any changes and we assume that  
14 everything is okay. The scope of the problem, the  
15 mechanisms of the problem are, in many cases, quite  
16 unclear.

17           One of the areas that I have published on is  
18 change in dissolution, and I would suspect that there are a  
19 number of different molecular mechanisms that can lead  
20 either to a premature release of drug, in other words, the  
21 dissolution is too rapid, or to slow a release or an  
22 incomplete release.

23           Some of the techniques that can be used to  
24 investigate this problem. One technique, which is -- now  
25 there are some companies developing equipment for

1 | pharmaceutical purposes, and in particular I think that  
2 | technique has very considerable potential for evaluating  
3 | prolonged-release pharmaceuticals, some of the new  
4 | complicated dosage forms that have been referred to.

5 |           Unfortunately, I think insufficient attention  
6 | has been given by regulatory bodies to physical stability.  
7 | I think too often the test methods used for physical  
8 | stability vary from company to company and you don't really  
9 | know whether the data is comparable or not.

10 |           Universities are at fault. We already heard  
11 | this morning about the decline of programs in industrial  
12 | pharmacy. Steve, I'm now going to give a commercial, since  
13 | I am also a boilermaker. There are still some universities  
14 | which are giving this type of training and they are to be  
15 | commended, but in many cases, it isn't getting the  
16 | attention that it deserves.

17 |           Of course, as I've already said, very often  
18 | these problems are intermittent in nature and we hope they  
19 | will go away.

20 |           What are some of the common misconceptions  
21 | about physical stability testing and physical stability  
22 | problems? There are still some people who quite  
23 | confidently assert to me, when I say to them, I looked at  
24 | your protocol for evaluating tablets, and why are you only  
25 | doing hardness? Don't you realize that FDA is interested