DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Tuesday, April 13, 2004

8:30 a.m.

Advisors and Consultants Staff Conference Room
5630 Fishers Lane
Rockville, Maryland

PARTICIPANTS

Arthur H. Kibbe, Ph.D., Chair
Hilda F. Scharen, M.S., Executive Secretary

MEMBERS

Charles Cooney, Ph.D.
Patrick P. DeLuca, Ph.D.
Meryl H. Karol, Ph.D.
Melvin V. Koch, Ph.D.
Marvin C. Meyer, Ph.D.
Gerald P. Migliaccio (Industry Representative)
Cynthia R.D. Selassie, Ph.D.
Nozer Singpurwalla, Ph.D.
Marc Swadener, Ed.D. (Consumer Representative)
Jurgen Venitz, M.D., Ph.D.

SPECIAL GOVERNMENT EMPLOYEES

Judy Boehlert, Ph.D.
Paul H. Fackler, Ph.D., (Acting Industry Representative)
Thomas P. Layloff, Jr., Ph.D.

FDA

Ajaz Hussain, Ph.D.
Chris Joneckis, Ph.D.
Robert O'Neill, Ph.D.
Keith Webber, Ph.D.
Helen Winkle

C O N T E N T S

PAGE

Call to Order:
Arthur Kibbe, Ph.D. 4

Conflict of Interest Statement:
Hilda Scharen, M.S. 4

Introduction to Meeting:
Helen Winkle 8

Subcommittee Reports:
Jurgen Venitz, M.D., Ph.D. 34

Parametric Tolerance Interval Test
for Dose Content Uniformity:
Ajaz Hussain, Ph.D. 44

Moving Forward--An Approach for Resolution:
Robert O'Neill, Ph.D. 46

Committee Discussions and Recommendations 53

Process Analytic Technology (PAT)--Next Steps:
Ajaz Hussain, Ph.D. 70

Finalizing PAT Guidance, Training and
Certification:
Chris Watts, Ph.D. 89

Standards Development:
Ali Afnan, Ph.D. 100

Rapid Microbial Methods:
Bryan Riley, Ph.D. 110

Committee Discussions and Recommendations 135

Open Public Hearing
Leo Lucisano, GlaxoSmithKline 135
Parrish M. Galliher, Xcellerex 145
Troy J. Logan, Siemens 174
Robert Mattes, Foss-NIRSystems 185

PAT Applications for Products in the Office of
Biotechnology Products (OBP): Overview and Issues:
Keith Webber, Ph.D. 194
Christopher Joneckis, Ph.D. 213
Charles Cooney, Ph.D. 224
Kevin Koch, Ph.D. 248
Tom Layloff, Ph.D. 271

Committee Discussions and Recommendations 279

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

2 Call to Order

3 DR. KIBBE: Ladies and gentlemen, shall we

4 begin. This is the Advisory Committee for

5 Pharmaceutical Science. Today is April 13th. Those

6 of you who have not done your taxes, because you

7 are here working for us and the Federal Government,

8 you will get exactly no compensation to allow you

9 to do your taxes late.

10 Hilda.

11 Conflict of Interest Statement

12 MS. SCHAREN: Good morning. I am going to

13 start reading the Conflict of Interest Statement

14 for the Advisory Committee for Pharmaceutical

15 Science. I am Hilda Scharen with the Center for

16 Drugs, FDA. I am the Executive Secretary for this

17 committee.

18 The following announcement addresses the

19 issue of conflict of interest with respect to this

20 meeting and is made a part of the record to

21 preclude even the appearance of such at this

22 meeting.

23 Based on the agenda, it has been

24 determined that the topics of today's meeting are

25 issues of broad applicability and there are no

1 products being approved at this meeting. Unlike
2 issues before a committee in which a particular
3 product is discussed, issues of broader
4 applicability involve many industrial sponsors and
5 academic institutions.
6 All Special Government Employees have been
7 screened for their financial interests as they may
8 apply to the general topics at hand. To determine
9 if any conflict of interest existed, the Agency has
10 reviewed the agenda and all relevant financial
11 interests reported by the meeting participants.
12 The Food and Drug Administration has
13 granted general matter waivers to the Special
14 Government Employees participating in this meeting
15 who require a waiver under Title 18, United States
16 Code, Section 208.
17 A copy of the waiver statements may be
18 obtained by submitting a written request to the
19 Agency's Freedom of Information Office, Room 12A-30
20 of the Parklawn Building.
21 Because general topics impact so many
22 entities, it is not prudent to recite all potential
23 conflicts of interest as they apply to each member
24 and consultant and guest speaker.
25 FDA acknowledges that there may be

1 potential conflicts of interest, but because of the
2 general nature of the discussion before the
3 committee, these potential conflicts are mitigated.
4 With respect to FDA's invited industry
5 representatives, we would like to disclose that
6 Gerald Migliaccio is participating in this meeting
7 as an industry representative acting on behalf of
8 regulated industry. Mr. Migliaccio is employed by
9 Pfizer. Dr. Paul Fackler is participating in this
10 meeting as an acting industry representative. Dr.
11 Fackler is employed by Teva Pharmaceuticals U.S.A.
12 In the event that the discussions involve
13 any other products or firms not already on the
14 agenda for which FDA participants have a financial
15 interest, the participants' involvement and their
16 exclusion will be noted for the record.
17 With respect to all other participants, we
18 ask in the interest of fairness that they address
19 any current or previous financial involvement with
20 any firm whose product they may wish to comment
21 upon.
22 Thank you.
23 DR. KIBBE: Thank you. I am Art Kibbe. I
24 am Chairman of the Pharmaceutical Science's
25 Department at Wilkes University.

1 We have a tradition of introducing
2 everyone around the table, so, Dr. O'Neill, if you
3 will start.
4 DR. O'NEILL: I am Bob O'Neill. I am
5 Director of the Office of Biostatistics in CDER.
6 DR. HUSSAIN: Ajaz Hussain, Deputy
7 Director, Office of Pharmaceutical Science.
8 MS. WINKLE: Helen Winkle, Director,
9 Office of Pharmaceutical Science.
10 DR. VENITZ: Jurgen Venitz, Clinical
11 Pharmacologist, Virginia Commonwealth University.
12 DR. SELASSIE: Cynthia Selassie, Professor
13 of Chemistry, Pomona College.
14 DR. BOEHLERT: Judy Boehlert. I have my
15 own pharmaceutical consulting business.
16 DR. SWADENER: Marc Swadener, retired from
17 the University of Colorado at Boulder.
18 DR. MEYER: Marvin Meyer, Emeritus
19 Professor, University of Tennessee, now a
20 consultant in Boca Raton, Florida.
21 DR. KAROL: Meryl Karol, a Professor at
22 the University of Pittsburgh in Environmental and
23 Occupational Health.
24 DR. LAYLOFF: Tom Layloff, Management
25 Sciences for Health, a nonprofit, working primarily

1 in Africa on drug quality.

2 DR. KOCH: Mel Koch, Director of the

3 Center for Process Analytical Chemistry at the

4 University of Washington.

5 DR. COONEY: Charles Cooney, Department of

6 Chemical Engineering at MIT.

7 DR. DeLUCA: Pat DeLuca, Professor of

8 Pharmacy at the University of Kentucky.

9 MR. MIGLIACCIO: Gerry Migliaccio, Vice

10 President of Global Quality Operations for Pfizer.

11 DR. FACKLER: Paul Fackler, Teva

12 Pharmaceuticals.

13 DR. KIBBE: Thank you.

14 Next on our agenda is an Introduction to

15 the Meeting. Ms. Winkle.

16 Introduction to Meeting

17 MS. WINKLE: Thank you and good morning to

18 all the committee members. I especially want to

19 welcome the members who have not attended before or

20 are just joining us for the first time.

21 That includes Dr. Cooney, Dr. Koch, and

22 Dr. Singpurwalla, who is not here yet, but will be

23 joining us later today, and also to Gerry and Paul

24 for helping us out as industry reps. We are really

25 pleased to have both of them here working with us.

1 [Slide.]

2 Today, I just want to give a short
3 update--it will probably be longer than short, but
4 it is supposed to be short--update on some of the
5 things that we are doing in OPS.

6 [Slide.]

7 Today, I want to talk a little bit about
8 the OPS mission, vision, and goals. I think it is
9 really important for me to go over these with the
10 committee because it helps all of us understand a
11 little bit more about where OPS is going in the
12 future. I think that as we talk about various
13 scientific issues, it will help put things in a
14 better perspective for the committee.

15 We have just recently finalized the
16 mission, vision, and goals, so I think it is
17 important that I share them.

18 I also want to talk a little bit about
19 what we are doing in OPS in developing a new
20 paradigm for CMC review in our Office of New Drug
21 Chemistry. This is really an exciting effort that
22 we have undergone, and I think there are a lot of
23 things that will be very beneficial to talk about a
24 little bit here.

25 A lot of this is built on the

1 Pharmaceutical Quality Initiative for the 21st
2 Century, so it helps put that in perspective, as
3 well as to what we are doing in the future in OPS.
4 I also want to mention some of the new
5 personnel that we have in OPS and then talk a few
6 minutes about the meeting agenda.
7 [Slide.]
8 The mission statement. Again, I think
9 this is very important because it sets forth what
10 OPS is currently focused on, and it is important
11 not only to those activities that we are engaged in
12 and working on very diligently in the organization,
13 they are also very important in supporting the
14 overall mission of the Center and mission of the
15 Agency.
16 Basically, our mission statement is to
17 ensure timely availability of high quality drug
18 products to U.S. patients. We are doing this
19 through effective and efficient scientific
20 assessment of relevant pharmaceutical and
21 biotechnology information in the submissions, and
22 by facilitating those scientific and technological
23 innovation that improve understanding of product
24 performance, quality, and efficiency of
25 development, manufacturing, and quality assurance

1 processes.

2 Many of these things that we have talked

3 about at past meetings, that we will talk about in

4 the future, fall very much within this mission

5 statement and some of the things that we are trying

6 to accomplish.

7 [Slide.]

8 Our vision is to be an international

9 champion. I think it is very important that we

10 talk about where OPS is going from an international

11 perspective because things are more global.

12 Obviously, now industry, many of the

13 things that we work on are global, and we need to

14 be part of that overall global involvement in

15 pharmaceutical science, but we really want to be

16 champions and leaders in the regulatory application

17 of contemporary scientific knowledge, and that

18 knowledge that affects the design, development,

19 manufacture, and clinical performance of

20 pharmaceutical and biotechnology products.

21 [Slide.]

22 Basically, the goals are for OPS programs

23 and projects to support the achievement of the

24 following attributes of drug products:

25 The drug quality and performance is

1 achieved and assured through design of effective
2 and efficient development and manufacturing
3 processes;
4 That regulatory specifications are based
5 on a mechanistic understanding of how product and
6 process factors impact product performance;
7 And that there is continuous "real time"
8 assurance of quality.
9 These are all very important objectives
10 that we are striving toward.
11 [Slide.]
12 Also, OPS will implement a review quality
13 system and procedures throughout the organization
14 that will:
15 Recognize the level of scientific
16 knowledge supporting product applications, process
17 validation, and process capability;
18 Apply a risk-based regulatory scrutiny
19 that will relate to the level of scientific
20 understanding of how formulation and manufacturing
21 process factors affect product performance, and the
22 capability of process control strategies to prevent
23 or mitigate risk of poor product performance.
24 [Slide.]
25 I wanted to talk a few minutes now that I

1 have talked about sort of the mission and the
2 goals, and you have a feel for where we are going,
3 I want to talk about some of the changes that we
4 are making. Specifically, I want to talk about the
5 changes we are making in CMC review.
6 To help set the stage for the future, I
7 wanted to go quickly through the FDA Strategic
8 Action Plan that Dr. McClellan initiated when he
9 came on board, I want to talk about the
10 Pharmaceutical Quality for the 21st century, which
11 is a really important initiative that is taking
12 place in the Agency, and is very important to us as
13 we move ahead in the Office of Pharmaceutical
14 Science and some of the things that we are trying
15 to accomplish.
16 I want to talk just a second about
17 resources in our CMC area, because I think without
18 mentioning the resources and the problems that we
19 have in resources, it is hard to understand why the
20 changes are necessary that need to be made in order
21 to improve on how we do review.
22 Also, I want to talk about a few other
23 influences that have happened since the
24 organization was first established in 1995.
25 [Slide.]

1 The FDA Strategic Plan - Responding to
2 Challenges and Opportunities. Again, as I said,
3 Dr. McClellan introduced this plan several months
4 after he entered the Agency. He was very focused
5 while he was here at the Agency on accomplishing
6 these particular aspects of all of the products
7 that are regulated by FDA.
8 Mainly, he focused on efficient risk
9 management, so that we were sure we were going to
10 get the most public health bang for our regulatory
11 buck.
12 He wanted empowering consumers. He felt
13 that I think all of us understand there is a lot of
14 interest on the part of consumers in their own
15 health care, and he wanted to be able to improve
16 health through better information to consumers, so
17 as they make decisions, as they look at their own
18 health care, as they even deal with their
19 physicians, et cetera, that they have a better
20 understanding of the medications, food, et cetera,
21 et cetera, that they need to take or use.
22 He wanted to improve patient and consumer
23 safety, protect America from terrorism, and more
24 effective regulation through a stronger workforce.
25 So, as we make changes in OPS, and we look

1 toward the future of things that we want to do
2 differently, and how we want to do those, we are
3 trying to incorporate many of the things that Dr.
4 McClellan incorporated in his strategic plan.
5 [Slide.]
6 Also, as I mentioned, the FDA Initiative
7 on Pharmaceutical Quality is an important
8 groundwork for some of the things that we are doing
9 now and in the future in OPS.
10 This particular chart is very helpful
11 because it shows the particular dimensions of the
12 plan for strong public health protection, for
13 international cooperation, for risk-based
14 orientation, science-based policy and standards,
15 and integrated quality systems orientation. These
16 are the really important aspects of the initiative
17 and where we are going.
18 [Slide.]
19 There are various directional vectors that
20 came with the initiative, and I won't go through
21 each of these. I think you can look through them,
22 but I think they are important as we look at OPS
23 and where we are going for OPS in the future, so
24 looking at our regulatory policies, making sure
25 that we incorporate new technology advances when we

1 do our regulation, that we are able to work with
2 industry, et cetera, in doing some of these, and
3 that we have consistency and coordination
4 throughout the whole drug quality regulatory
5 program.
6 [Slide.]
7 Here is basically the directional vectors
8 and many of the things that are being worked on
9 under the GMP initiative agencywide.
10 These include looking at a preapproval
11 inspection compliance program, dispute resolution
12 processes being established, a pharmaceutical
13 inspectorate that focuses specifically on
14 pharmaceutical products during the inspection
15 process that is being set up. We are hoping to
16 have product specialists on inspection process, and
17 we hope to start that very soon.
18 We have set guidance on CFR Part 11,
19 aseptic processing guidance, a comparability
20 protocol guidance. We have been doing a lot of
21 stuff with risk management and quality by design,
22 and, of course, PAT, which we have talked about.
23 But you can see where each of these sits on the
24 whole vector between risk and science. These are
25 all important aspects of the initiative.

1 [Slide.]
2 But the most important thing to me about
3 the initiative is it afforded us in OPS, a lot of
4 opportunities to change the way that we do
5 business. It has opened up a window of time for us
6 to really look at how we do business and make the
7 changes that are necessary to move forward into the
8 21st century.
9 This is not easy, and I will go through
10 some of the challenges what we have had, but first
11 of all, I want to talk about some of these
12 opportunities and just mention them to you, because
13 I think they are really important.
14 We really have the opportunity now to
15 strategize more on how we are going to ensure
16 product quality. This is ensuring product quality
17 across all of the Center, and it is the first time
18 we really have thought about the whole aspect of
19 product quality and what needs to be done to ensure
20 in the future that we are focused on the right
21 aspects of that.
22 We need to revisit our processes. This is
23 a really good opportunity for us to do that. We
24 have built processes over the last 20, 25 years,
25 not only in review, but in inspection, as well, and

1 this gives us an opportunity to look at all of the
2 processes that fall under pharmaceutical quality
3 regulation, and to incorporate best practices.
4 We need to focus more on manufacturing and
5 associated issues relating to the quality of
6 products, one of the things that was very apparent
7 to us when we went in and looked at the review
8 processes, that we did not pay as much attention to
9 the actual manufacturing of products and how it
10 affected the quality of the products.
11 So, this is a really good opportunity for
12 us to do that. We have a lot to learn and we have
13 to work with a lot of people because obviously, we
14 don't have as much understanding as we need, but we
15 are doing a lot and looking at manufacturing
16 science and trying to get a better understanding of
17 that. I think that has been very apparent in some
18 of the things that you have talked about with PAT,
19 we will talk about even more today.
20 We need to focus both on review and
21 inspection, and we need to put more science into
22 those. A lot of times, and it has been said time
23 and time again, we have not used really good
24 science in making the decision, and sometimes we
25 have had a lot of complaints from industry and

1 others about that lack of really scientific
2 understanding on inspections, so this is a really
3 good opportunity for us to ensure that that science
4 exists, but it is really important that we ensure
5 that it is part of the review process, as well, and
6 it is going to take time, but I think working with
7 our people and others, we will get there in the
8 future.
9 We need to enhance the interactions
10 between review, inspection, and compliance. One of
11 the things that was very interesting to me right
12 before we started the initiative is we met with a
13 number of people from trade associations, and it
14 was made very clear, the gap between what happens
15 in review and what happens in inspection, and who
16 is sitting in the middle but industry with a lot of
17 questions on how policy was set or what the policy
18 means, and dealing with the inspectors day to day
19 who really don't have an understanding of that
20 either, so we really need to ensure better
21 interaction between review and inspection.
22 We need to foster communication with
23 industry. In the review, we have been very
24 hesitant to talk much to the industry and to work
25 with the industry, not only on specific

1 applications, but on science in general, and there
2 is a lot of science in the industry that can be
3 very beneficial to us in the Agency to understand
4 the processes and understand manufacturing and
5 pharmaceutical quality, and we need to do more of
6 that.
7 We need to have early discussion on CMC
8 questions. As I already mentioned, we have a
9 dispute resolution process that we are setting up,
10 which we feel will be very helpful to give industry
11 an opportunity to talk with us when they have
12 scientific issues or questions.
13 We need to leverage resources for the best
14 bang for the buck. This is a real problem, and as
15 I said, I am going to talk a little bit more about
16 resources.
17 We need to simplify the regulatory
18 requirements and we need to be able to find ways to
19 reduce some of the regulatory burden. We have
20 talked here before at the committee about the
21 number of supplements that we get in the
22 organization, we are really drowning in
23 applications in supplements, and all of them are
24 treated basically the same, and we need to really
25 step back and look at ways that we can put more

1 emphasis or more responsibility on industry and try
2 and work with them to have better understanding of
3 things, and not get as many applications.
4 We need to eliminate the "check box"
5 approach that we have. What we do basically in
6 review is we go through and do you have this, do
7 you have that, do you have this without a real
8 understanding of what the process is, the
9 manufacturing, the whole important aspects of
10 pharmaceutical quality.
11 [Slide.]
12 We need to enhance training opportunities,
13 and we now have this opportunity under the GMP
14 initiative, as well as some of the things that we
15 are undertaking in OPS. We are in the process of
16 working with several of the pharmaceutical
17 industries to set up plant residency programs for
18 some of our chemists.
19 We have other cross-training opportunities
20 that we are discussing, and then we have the
21 pharmaceutical inspectorate, and the reason I put
22 this here is not only will we be able to train our
23 inspectors better as far as some of the aspects or
24 manufacturing science, will it be able to take
25 advantage of those from the review standpoint, as

1 well, and I think this will be extremely helpful
2 and useful to us in our future regulatory
3 activities.
4 [Slide.]
5 We need to enhance FDA's knowledge
6 regarding new technologies in manufacturing, and we
7 need to encourage innovation, and again this goes
8 back to PAT.
9 We need to develop processes that are
10 focused more on product risk, which we have not
11 done. As I said before, almost every product has
12 the same weight, same level of review, and we
13 really need to look more at the risk aspects of the
14 product.
15 We need to revisit how quality of products
16 relate to ensuring safety and efficacy, and
17 especially ensuring clinical relevance.
18 We need to alleviate industry's concern
19 regarding reprisal. I hate to put this up, it's a
20 bad word "reprisal," but that thought is out there
21 often in industry, I hear it time and time again,
22 and I am hoping through better interactions with
23 industry, with better understanding of the science
24 and the ability to discuss the science, we can
25 begin to eliminate some of these concerns.

1 We need to enhance our international
2 involvement. We are working on pharmaceutical
3 development and risk management in international,
4 but we need to do more of this, because again it's
5 a very global world out there, and we need to be
6 sure that we are involved in everything that is
7 happening on the international front.
8 [Slide.]
9 I did say I wanted to mention resources
10 real quickly. I thought this would give you a
11 better perspective again as to why we want to make
12 some of the changes in CMC. The workload is really
13 difficult for our CMC reviewers in new drugs.
14 We got, in 2003, 159 NDAs, 342 commercial
15 INDs, 507 research INDs, 1,858 CMC supplements, and
16 that doesn't include efficacy or labeling
17 supplements, and 1,132 annual reports. This is a
18 lot of work to take on, and this is a lot of work
19 because we have fewer and fewer review staff.
20 We have constantly been over the last few
21 years hit by reductions in resources, so we are
22 doing more work with less people, and we have
23 really got to think of ways to streamline the
24 process and to be able to get some of this done in
25 a more efficient and effective manner.

1 [Slide.]
2 Other influences, though, too, that bring
3 about the necessity for change, as I said, in 1995,
4 when ONDC was established, it was collocated with
5 the clinical divisions, and this seemed to work
6 really well for a couple of years, but a lot of
7 things have happened within the Center, within the
8 Agency, within the world, that really affect how we
9 do the CMC reviews, so we really need to rethink,
10 based on these influences and changes, how we do
11 things.
12 Some of the influences includes shorter
13 PDUFA deadlines, FDAMA, again harmonization and
14 globalization, such changes in our regulatory
15 processes, such as SUPAC, BACPAC, new technologies
16 in pharmaceutical manufacturing.
17 [Slide.]
18 PAT, counterterrorism, counterfeit
19 products. We were just talking about the fact that
20 we can't even begin to keep up with counterfeiting,
21 we have to find better ways to do that.
22 BSE and other crisis, such as that. There
23 has been a greater focus on generic drugs, and
24 tomorrow we will spend a lot of time talking about
25 some of the issues that we have with regulating

1 generic products, and it is really important that
2 we begin to focus more on some of these issues and
3 how we need to ensure that we incorporate other
4 thinking from the new drug side into how we are
5 going to regulate generic products in the future.
6 There have been a lot of changes in
7 industry, more globalization mergers, et cetera.
8 There has been electronic submissions. We are
9 working very hard to hopefully enhance the
10 efficiency of our processes through electronic
11 submissions, and there has been more focus on risk
12 management and quality systems.
13 [Slide.]
14 So, basically, what we need to do is to
15 change the paradigm for CMC review. I have talked
16 about that we have the opportunity to do this. The
17 things that we really need to focus on based on
18 those opportunities is really to develop a
19 risk-based CMC review.
20 I think this is really important, and I
21 think we are going to need help. This is not going
22 to be an easy thing to determine risk.
23 I think products are going to come and go
24 that are risky, we see that all the time, products
25 that you don't expect when it comes on the market

1 to have any risk, then, things are found out later
2 on, so it is not going to be an easy process to
3 develop, and it is going to take a lot of thought
4 and probably a lot of help even from the committee,
5 but this is definitely a direction that we need to
6 head in.
7 We need to establish quality systems which
8 help set the framework for ensuring that we do have
9 a dynamic organization and that we can handle the
10 complications of the regulatory processes.
11 We need to focus resources towards efforts
12 that improve quality, and not hinder and interfere
13 with innovation, and I think that is very
14 important, and we need to focus on all aspects of
15 CMC.
16 We need to look at chemistry, we need to
17 look at manufacturing, and we need to look at
18 controls, and we have not done as good a job of
19 this in the past.
20 [Slide.]
21 The advantages of the new paradigm, for
22 FDA, we will have more product and process
23 knowledge, which can be shared by industry, so that
24 we have a better understanding of the products that
25 we regulate.

1 We will have more efficient resource
2 allocation for review and inspection, and we can
3 increase our trust and understanding of industry
4 decision making.
5 [Slide.]
6 The advantages for industry is hopefully,
7 that we will have fewer, more efficient,
8 science-based inspections, faster, more consistent
9 reviews.
10 There is a potential for reduced
11 regulatory burden, for managing changes with less
12 FDA oversight, for focused resources on critical
13 issues, flexibility to focus on what should be
14 done, not what can be done, and to improve
15 communication with FDA.
16 [Slide.]
17 But most of all, the ultimate beneficiary
18 is the public, and we hope through some of the
19 changes that we make, that we can increase the
20 availability of drugs on the market, we can have
21 faster approval of new products, we can have
22 continued assurance of high quality products, and
23 we can increase the public's confidence in the work
24 that we are doing in FDA, and hopefully, reduce
25 costs, which isn't, of course, our business, but

1 something we hope is going to come out of some of
2 the changes that we are making.
3 [Slide.]
4 The new paradigm will include developing
5 strategies to recruit and train reviewers. One of
6 the things that we realize is that we have a real
7 gap in the qualifications that our reviewers have.
8 We need more that have understanding of
9 drug discovery, analytical chemistry,
10 pharmaceutical engineering, and we are going to be
11 looking at recruiting and training people in these
12 areas.
13 We need to build a learning organization,
14 one that is skilled at creating, acquiring, and
15 transferring knowledge. This is one thing we have
16 not done an adequate job of in the past, and we
17 really need to work on, probably not only just in
18 OPS, but throughout the whole Center.
19 We need to set specifications based on
20 science and process understanding. We need to
21 reengineer the process, so that we have the best
22 practices, metrics, and that we are customer
23 oriented.
24 This is another thing that we have not
25 paid a lot of attention to in the past, which we

1 really need to look toward in the future, is who
2 our customers are and what they need.
3 [Slide.]
4 We need to increase emphasis on
5 manufacturing science, we need to ask the right
6 questions at the right time. We need to implement
7 peer review by FDA scientists and clinicians.
8 Establish a program to better integrate
9 review and inspection, develop processes which
10 ensure regulatory relief based on process
11 understanding and control, quality systems in
12 manufacturing, and continuous improvement is very
13 important, and we need to create a better work
14 environment and promote job satisfaction within our
15 organization.
16 [Slide.]
17 As I said, there is a lot of challenges.
18 The current culture, both inside and outside of
19 FDA, is definitely the biggest challenge we have.
20 It is very difficult to get people to think
21 differently. They have worked in a certain culture
22 for years and years, and changing that culture is
23 not easy. We see that both inside the Agency, as
24 well as outside.
25 Hiring is not easy, it is very difficult

1 to find people with the right skills that want to
2 come to work for the Government, and this is a big
3 challenge that we have ahead of us.
4 Establishing performance metrics is also a
5 challenge because we have really never had the
6 metrics to measure anything except for the amount
7 of work we get, and we are really going to have to
8 step back and look at this differently.
9 We need to identify gaps in requirements.
10 We need to reevaluate the review process again to
11 be sure we are asking the right questions that
12 ensure product quality.
13 We need to understand what is relevant
14 science.
15 We need to determine what is needed for
16 pharmaceutical development data to assist in a
17 better understanding of manufacturing process.
18 We need to develop a science-based risk
19 model, and we need to integrate better into the
20 inspection process including participating on
21 inspections.
22 This is a lot of work we have ahead of us,
23 and the reason I am sharing it is because I think a
24 lot of these issues are going to come up in the
25 future where we are going to need the committee's

1 input on how to tackle some of these challenges,
2 some of the things that we need to incorporate into
3 our review and our processes to make sure that we
4 are doing what is necessary to have the best
5 regulatory processes available.
6 Again, I feel that this is important that
7 you all have an understanding of where we are
8 going, and we will look forward to talking about
9 many of these things in the future.
10 [Slide.]
11 Before I go into the agenda, I just wanted
12 to mention some of OPS's new additions that we
13 have. We are really fortunate to be acquiring a
14 lot of new staff lately, and some of the people I
15 think that are very important, that will be working
16 with us very closely, I wanted to talk about today.
17 First, is Dr. Vince Lee. I think all of
18 you know Dr. Lee since he was once chair of this
19 committee. We are very happy to have Vince with
20 us, and we feel that there is a lot of things that
21 he is going to be able to help us work on as we
22 move towards changing some of our regulatory
23 paradigms.
24 Also, we will be adding Dr. Mansor Khan
25 from Texas to our staff. He is going to be our

1 director of our Division for Product Quality
2 Research in our Office of Testing and Research, and
3 he will be joining us next month.
4 We are looking forward, too, to having Dr.
5 Khan. I think he is going to add a lot and help us
6 a lot in some of the areas of research that we need
7 to be focused on in order to accomplish some of the
8 things that we want to accomplish.
9 Also, I wanted to mention that Dr. Moheb
10 Nasr has become the permanent director of the
11 Office of New Drug Chemistry. I think many of you
12 know Dr. Chiu has retired. Dr. Nasr so kindly came
13 from St. Louis to take this job, and has been
14 working very diligently on some of the changes that
15 we are trying to make.
16 Dr. Chi Wan Chen has joined him as the
17 deputy of the office.
18 Also, I wanted to announce that Dr. Keith
19 Webber, who is sitting over here, too, is the
20 Acting Director of the Office of Biotech Products.
21 We appreciate Dr. Webber stepping in and taking on
22 this very challenging group that has recently
23 joined us in the Office of Pharmaceutical Science.
24 [Slide.]
25 Just to finalize my presentation, I just

1 wanted to quickly go through the meeting topics. I
2 think this is going to be an extremely exciting
3 meeting. I think that the topics tomorrow are
4 especially stimulating, topics that I think will
5 add a lot to our future thinking in these areas.
6 Today, we are going to have subcommittee
7 reports. We are going to have a discussion of the
8 proposal on PTIT. That is parametric tolerance
9 interval test for dose content uniformity. We have
10 talked about this before. We have a proposal now
11 on how we want to finalize our thinking in this
12 area.
13 Then, we want to talk about PAT. We want
14 to give an update, talk about some of the things
15 that we have done, and also talk about how PAT is
16 going to be implemented in our Office of Biotech
17 Products.
18 Tomorrow, as I said, I think the topics
19 are very stimulating, I think we will have some
20 really good discussion on bioequivalence topics.
21 We want to talk about highly variable drugs, about
22 bioINequivalence. This is very important.
23 We have a lot of areas here of thought
24 that we need to bring forward and discuss with the
25 committee, and we want to talk about topical

1 products.

2 Also, time allowing tomorrow, we have an

3 awareness topic, and this is nanotechnology that we

4 want to introduce.

5 With that, I am going to finish up and

6 hand it over to Dr. Kibbe, and I look forward to

7 hearing the discussion in the next two days.

8 Thank you.

9 DR. KIBBE: Thank you, Helen.

10 We are pretty close to being on time, so

11 we will turn it over now to the subcommittee

12 reports. The first one is from Clinical

13 Pharmacology. Jurgen is moving rapidly to the

14 podium, so here we go.

15 Subcommittee Reports

16 DR. VENITZ: Good morning. I am here to

17 report back from a meeting that the Clinical

18 Pharmacology Subcommittee had last November.

19 [Slide.]

20 Just in terms of review, this committee is

21 serving to provide expertise in three different

22 areas to this parent committee: pharmacometrics or

23 exposure-response modeling, pediatrics, and

24 pharmacogenetics. As you see, those were the three

25 topics that we discussed.

1 [Slide.]

2 Our first topic in the November meeting
3 was a proposal by Dr. Lesko from OCPB to institute
4 End of Phase 2a Meetings. Those are meetings that
5 are currently not recommended or that are currently
6 not required by the FDA.

7 He, as well as Dr. Lee, presented the
8 FDA's perspective, and then we had three FDA
9 staffers giving us case reports where those
10 meetings may be helpful in finding optimal doses
11 early on and identifying key issues.

12 [Slide.]

13 The committee appreciated that this was a
14 pilot program that is intended to improve dose
15 findings over a few years. There was some
16 discussion as to how we assess the success of a
17 program.

18 The committee noticed that there would be
19 additional FDA resources required to implement this
20 very program, but on the positive end, that this
21 End of Phase 2 Meeting Program would allow
22 integration of preclinical information both in the
23 PK and PD area and particularly to identify early
24 on the use of biomarkers in Phase 2 and Phase 3
25 studies that may help streamline the dose finding

1 process.

2 The committee also felt that a meeting

3 such as this would be very useful in identifying

4 key issues early on and discuss them between the

5 sponsor and the FDA, as well as define what we call

6 "utility" functions, which are basically measures

7 of the potential consequences of either safety or

8 efficacy issues which are essential to come up with

9 an optimal dose.

10 There was, as I said before, some

11 discussion as to how you would measure the success

12 of such a program, and the committee felt that

13 probably the overriding metrics to measure the

14 success would be customer satisfaction, the

15 customer being both the sponsor, as well as the

16 FDA.

17 Possible, but more difficult to measure

18 outcome would be the need to have post-approval

19 dose changes. Again, if we can minimize that, that

20 would indicate that there is success in this

21 program.

22 So, while the committee was in support of

23 this program, and as far as I know, it is being

24 implemented as speak.

25 [Slide.]

1 The second issue relating to
2 exposure-response was the issue about clinical
3 trial simulations specifically with the intent to
4 assess the liability of drug products to induce QT
5 changes which are thought to be associated with
6 fatal cardiac arrhythmias, we had Dr. Lee give the
7 introduction, Dr. Bonate from the outside review
8 modeling that he had done, clinical trial
9 simulations, and then Dr. Kenna from the FDA review
10 ongoing project within the FDA.
11 [Slide.]
12 There was a lively discussion on this very
13 topic. The committee I think still felt that the
14 QTc correction methods, those are ways to correct
15 the QT interval for change in heart rate, that
16 those methods are still questionable, we still
17 don't have a gold standard on that.
18 We felt that despite the trial simulations
19 presented to us, it still appears very difficult to
20 separate drug-induced changes from baseline changes
21 in those EKG intervals.
22 There was some discussion as to what
23 constitutes a meaningful QTc change. Right now the
24 perception is that a 6-millisecond average QTc
25 change would be relevant. There is some concern in

1 the committee or there was some concern stated in
2 the committee that that might be too conservative,
3 however, there was acknowledgment that using
4 clinical trial simulation to get to the issue as to
5 what the QTc liability is of a new product may
6 provide a more rational risk/benefit assessment.
7 One issue that was brought up that is
8 currently not being explored is the fact that some
9 drugs, not only interact at the kinetic level, but
10 also the dynamic level, which may lead to QTc
11 changes on the PD level.
12 [Slide.]
13 The second major topic related to the
14 pediatrics component of the committee, here, we
15 reviewed the pediatric decision trees. We had
16 several speakers. We had Dr. Hinderling and Dr.
17 Chen giving case reports. Those were drugs or drug
18 products that were reviewed for the pediatric use,
19 used what is a called a "pediatric decision tree,"
20 that allows PK or PK/PD studies to support efficacy
21 and safety.
22 We had Dr. Machado giving a statistical
23 overview on what methods might be useful to compare
24 pediatric exposure-response to see whether there
25 are any age-related differences.

1 Then, our committee member Dr. Kearns gave
2 his perspective on how those studies actually are
3 being done in practice and what some of the
4 shortcomings are of the current pediatric decision
5 tree, and this was followed by Dr. Rodriguez giving
6 the FDA experience with the decision tree that has
7 been in place for a few years.
8 [Slide.]
9 There was some discussion about the age
10 appropriateness of some of the endpoints that are
11 currently required to measure the pharmacology of
12 drugs in children, whether the endpoints are
13 related to the mechanism of action of the drug
14 and/or the pathophysiology of the disease, are
15 those meaningful endpoints and what do they tell
16 us.
17 There was some discussion, because that is
18 part of the decision tree, as to what evidence
19 supports that the disease progression in children
20 is similar to the one in adults, which would then
21 allow it to transfer information from adults to
22 children.
23 There seemed to be consensus that
24 nonclinical information, such as data from primate
25 studies or in-vitro studies may be very useful in

1 supporting the pediatric decision tree.

2 However, there was extensive discussion on

3 whether there has to be extensive interaction and

4 discussion between both the clinical pharmacology,

5 the OCPB, as well as the reviewing divisions on the

6 pediatric decision tree and its use in a particular

7 drug product area.

8 There was some discussion also on the

9 limitations of the exposure-response in terms of

10 some of the PD differences that are very difficult

11 to be captured in the current paradigm.

12 I think there was overall an appreciation

13 that the pediatric decision tree is still

14 work-in-progress and additional updates may be

15 necessary to review or start discussing any changes

16 to it.

17 [Slide.]

18 The last area that we discussed related to

19 the pharmacogenomics and the metabolic drug

20 interaction area, so we had two outside speakers,

21 Dr. Flockhart and Dr. Neuvonen talk about two

22 relatively novel cytochrome p450 isoenzymes that

23 start to emerge as part of drug metabolizing

24 enzymes, and the issue was here what is the current

25 state-of-the-art, what can FDA use as basis of

1 review for new incoming NDAs.

2 [Slide.]

3 There was acceptance by the committee for

4 cytochrome P4502B6, that we do have both in-vitro,

5 as well as in-vivo, substrates, model substrates

6 that can be used for drug interactions.

7 We don't have, on the other hand, any

8 specific clinical inhibitors, and somewhat

9 questionable in-vitro inhibitors. On the other

10 hand, for cytochrome P4502C8, we do have both

11 in-vitro, as well as in-vivo, inhibitors, as well

12 as substrates, so we can characterize any

13 interaction potential for cytochrome P4502C8.

14 Discussion by the committee followed that

15 went beyond the specific isoenzymes where the

16 committee emphasized that it is becoming more and

17 more essential to look at population-based clinical

18 studies to primarily assess, not the incidence of

19 drug interactions, but their clinical significance.

20 In other words, we have enough science to

21 support the likelihood of drug-drug interactions,

22 but we are not always sure about what the clinical

23 consequence would be or consequence would be.

24 Along the same line, the committee made

25 the recommendation to encourage sponsors to review

1 databases that exist, medication-use databases, to
2 look for this very issue, what are the clinical
3 consequences of drug-drug interactions especially
4 if you go beyond two interactions.
5 [Slide.]
6 The last topic that we discussed related
7 to pharmacogenomics. Again, this is an ongoing
8 discussion that we had. In this case, we were
9 discussing how to integrate that in the drug
10 development and what kind of labeling may be
11 necessary to reflect information collected during
12 the development process.
13 We had committee member Dr. Flockhart and
14 Dr. Relling give their academic, as well as
15 clinical, perspective, and Dr. Hockett give the
16 industry perspective.
17 [Slide.]
18 To summarize the committee discussion, I
19 think there was acceptance of the fact that we need
20 additional population-based studies meaning
21 large-scale studies to look at the prevalence for
22 some of the rare genetic polymorphisms, in other
23 words, for some of those polymorphisms that may be
24 important, we do not know how many patients have
25 those specific genotypes.

1 There was recognition that we do have or
2 at least start to emerge having a lot of
3 mechanistic and quantitative understanding that is
4 necessary for labeling.
5 In other words, we collect a lot of
6 information and we know a lot about how likely some
7 of those pharmacogenetic differences are and what
8 the kinetic or dynamic consequences are.
9 The discussion then really focused on what
10 is the impact as far as risk/benefit is concerned,
11 in other words, how do we translate changes in drug
12 levels or change in the pharmacology of the drug,
13 how do we translate that into safety and efficacy
14 information.
15 There was, shall we say, a lively
16 discussion of how to label pharmacogenetic
17 information in drug package insert, and I don't
18 think there was any consensus.
19 We had experts telling us we need to label
20 very extensively, on the other hand, clinicians
21 were concerned about overloading information that
22 is not being used by the ultimate consumer, and
23 there was recognition that pharmacogenetics or
24 pharmacogenomics is going to be different from some
25 of the other clinical covariates in the sense that

1 it has multidimensional nature, in other words,
2 there are lots of different pharmacogenetic
3 polymorphisms that may be relevant for a given drug
4 product.
5 I would be happy to entertain any
6 questions that you may have.
7 DR. KIBBE: Okay. Jurgen will be with us,
8 so if you want to ask questions later, if topics
9 come up that we need to get back to him on, we can.
10 Thank you.
11 Now, I know you are fumbling through your
12 things looking for the slides for the next speaker,
13 but there aren't any, which gives us great hope
14 that it will be a short and direct presentation.
15 Dr. Hussain.
16 Parametric Tolerance Interval Test for
17 Dose Content Uniformity
18 DR. HUSSAIN: No, I do not have slides for
19 this part of my introduction. The topic that will
20 be discussed as a proposal to you is that of
21 parametric tolerance interval test.
22 As we have discussed this several times
23 with you, in particular at the last meeting, in the
24 previous meeting that we had, the challenge is how
25 do you move forward with adopting a more rigorous

1 scientific, statistically sound approach to dose
2 content uniformity of inhaled products.
3 We believe that parametric tolerance
4 interval test that is being proposed by IPAC-RS is
5 an improvement over the current method, and we
6 would like to sort of move forward in sort of
7 resolving some of those issues which have lingered
8 on, and sort of adopting it as soon as possible.
9 But the challenges are not trivial, and I
10 tried to sort of summarize those challenges to you
11 in the memorandum along with the paper that we
12 wrote.
13 We felt that in order to move this process
14 faster and move it forward more quickly, the
15 proposal to you is that we will form a working
16 group under this advisory committee.
17 This working group will report to you with
18 their findings and provide a way forward to
19 resolving the issues that have lingered on for
20 three years, and come up with a very well
21 structured process to resolve in a timely fashion.
22 So, the proposal is a very straightforward
23 proposal that this working group will report to
24 you, and you will define the goals and objectives
25 for this group, and you will define also the

1 timeline for this group, and the proposal will be
2 presented by Bob O'Neill, who is going to head for
3 FDA working group members.
4 Bob.
5 Moving Forward -- An Approach for Resolution
6 DR. O'NEILL: Good morning.
7 [Slide.]
8 My name is Bob O'Neill, and as I indicated
9 earlier, I am the Director of the Office of
10 Biostatistics, and Ajaz and Helen have asked me to
11 chair this group, which Ajaz has indicated is going
12 to be reporting to you all.
13 This is the process for coming to
14 resolution on what you know to be a discussion that
15 has been going on at least for three years under
16 the specifications for delivered dose uniformity
17 for inhaled and nasal drug products.
18 [Slide.]
19 I am going to be proposing how we are
20 going to be going about doing this and asking for
21 your advice and concurrence, so we can move forward
22 on this.
23 So, what we have thought about, and we
24 have met several times with the IPAC-RS group, and
25 this is the proposal. We will have a joint working

1 group under this particular committee, and it will
2 be populated by senior representatives from FDA and
3 from the Oral and Inhaled Nasal Drug Product
4 industry, and that is mainly the IPAC group that we
5 have been working with.
6 [Slide.]
7 The folks from FDA, I will get into the
8 names in a moment, but essentially are representing
9 sort of the clinical risk side of the house, the
10 statistical side of the house, the generic drug
11 side of the house, and the Office of New Drug
12 Chemistry side of the house, so all the major
13 players in terms of how this particular solution
14 impacts the way we go about doing business.
15 This particular proposal is essentially a
16 way forward, so that we have a defined process with
17 identified objectives, with identified ways of how
18 we are going to communicate with each other, in
19 terms of the mechanism, some timelines, some
20 milestones, and how are we going to get some
21 resolution on some of the issues that might be sort
22 of sticky or still needing further discussion.
23 So, the overall working group objective is
24 to agree on a mutually acceptable parametric
25 tolerance interval test for delivered dose

1 uniformity, and these are the folks, and if they
2 are in the room, I would ask them to stand up.
3 On the lefthand side are the FDA folks.
4 It is myself, Dr. Chowdhury, I believe Badrul is
5 here. He is the Pulmonary Division Director.
6 Moheb Nasr, I believe is out of the country, you
7 probably know him. And Lawrence Yu, I don't know
8 if Lawrence is here--there he is, and he is the
9 Director for Science in Office of Generic Drugs.
10 On the industry side, I think Michael is
11 here, Michael Golden from GlaxoSmithKline. Kristi
12 Griffiths, I don't know if she is here, from Eli
13 Lilly. Bo Olsson from AstraZeneca. Dar Rosario
14 from Aradigm. Dennis Sandell from AstraZeneca
15 also. We have met with these folks and we plan on
16 meeting in the future, and I will go through the
17 timeline.
18 [Slide.]
19 So, just to reiterate, the objective of
20 this working group is to develop a mutually
21 acceptable, standard DDU specification, both the
22 test and the acceptance criteria, for these
23 products with a proposal to come back to you folks
24 by the end of this year, by the end of 2004.
25 [Slide.]

1 So, the process that we are going to
2 follow is pretty much trying to get the
3 communication and the coordination of this effort,
4 which is not going to be trivial, straight among
5 all of us.
6 We have identified that we will have a
7 project manager that will help us as a working
8 group stick to agendas, minutes, meeting materials.
9 We plan on having monthly meetings at FDA beginning
10 in May.
11 The first one is probably in a few weeks,
12 and in May, what we will plan to do is to review
13 the feedback that you all give us today in terms of
14 your blessing and what other suggestions you might
15 have for how we would fine-tune this particular
16 process.
17 We are going to need to rely on working
18 groups within the industry and within the FDA to
19 further deal with the statistical issues here, the
20 clinical issues, the CMC issues, and whatever else
21 is on the plate, so there is likely to be some
22 technical projects that will be assigned to folks,
23 and the leadership and the project management of
24 those particular projects will be overseen by the
25 folks on the working group.

1 [Slide.]

2 So, again, just to reiterate the timelines
3 and the milestones, we expect to have a status
4 report back to you folks in the fall, in the
5 meeting in the fall, in October, and hopefully to
6 submit recommendations to you by the end of 2004
7 that you can act on and come back to us on.

8 [Slide.]

9 Here is where we think we are to date. We
10 have discussed these issues at length and here is
11 what we think we have reached consensus on.

12 That the parametric tolerance interval
13 approach is an improvement on the current test. It
14 is a concept that requires refinement and further
15 development to address the regulatory requirements.
16 There are still things that need to be fine tuned.

17 We believe that there has been a lot of
18 work, productive work, a lot of understanding, but
19 it is time to move forward and come to closure
20 particularly on this particular test.

21 So the working group is formed to devote
22 the necessary time and the resources to get this
23 thing done, and that is through review of
24 additional data analyses, especially some of the
25 appropriate statistical procedures.

1 [Slide.]

2 We also recognize that there is some stuff
3 hanging out there that needs consensus. You have
4 probably seen a presentation and heard about a
5 presentation with regard to the different operating
6 characteristic curves, the parametric tolerance
7 interval test versus sort of the zero tolerance
8 test, and there is a gap that essentially is the
9 difference between the producer and the consumer
10 risk, and it sort of differs in the middle over
11 what you might assume to be the standard deviation
12 of some of the measurements.

13 That is essentially where a lot of the
14 discussion has been. Much of the discussion has
15 been around what the performance characteristics
16 are of the different tests under assumed scenarios.
17 Another way of saying assumed scenarios is the
18 simulated data, so if this, then that.

19 So, if the data were to perform this way
20 or lay itself out this way, then, this is what the
21 operating characteristics of that particular test
22 procedure are.

23 So, we are actually also interested in
24 seeing what real data is, so there is a number of
25 issues with regard to actual data that is not in

1 our hands, not in FDA's hands, which would lead us
2 to say, well, how many situations are there where
3 the standard deviations start to push out to 12,
4 13, 14, 15, because those are the areas where you
5 may be wanting to have a little more information
6 because if you are not in the symmetric situation,
7 your outliers are going to be where your problem
8 cases are.
9 So, there is some more work to be done in
10 this area, so talking about that and marrying both
11 the zero tolerance interval concept with the
12 parametric tolerance interval idea is essentially
13 where the statistical details of the test are
14 likely to be focused over the next few months.
15 Obviously, this issue of the applicability
16 to non-normal distributions, asymmetric bimodal
17 distributions, which essentially may be very much
18 characteristic of manufacturing processes of, you
19 know, large and small particles, and things like
20 this, which is not an unusual statistical scenario
21 when you have mixtures of populations, so that is
22 from the statistical perspective.
23 [Slide.]
24 The next steps are to ask you folks to
25 endorse this idea or to suggest some refinements to

1 it. We will come back to you with a status report
2 as to where we are in October, and the working
3 group is planning to submit recommendations to you
4 all by the end of this calendar year.
5 With that, I think I am done. I would be
6 willing to take any questions, and I think anybody
7 on the working group would also be willing to chime
8 in.
9 Committee Discussion and Recommendations
10 DR. KIBBE: We have time now for
11 questions, it's on our schedule, so ask questions.
12 DR. SINGPURWALLA: Well, just out of
13 curiosity, what is the DDU test?
14 DR. O'NEILL: Delivered dose uniformity
15 test. It is essentially a measurement of, it's
16 content uniformity, how much of the dose is
17 delivered in, let's say, a spray or these nasally
18 inhaled products, so it's a matter of if this was a
19 pill, you would be crunching it up, you would be
20 looking at what its content is, you would have a
21 measure of that, and the test is essentially that
22 you agree what the goalposts are for an acceptable
23 amount of variability for the active ingredient,
24 and if it's in that zone, it's acceptable; if it's
25 not in that zone, it is not acceptable, so it's a

1 variant.

2 That is the whole concept behind the

3 delivered dose uniformity, that the product has to

4 have some consistent uniform characteristics to it.

5 DR. SINGPURWALLA: So, how would it differ

6 from the parametric tolerance interval?

7 DR. O'NEILL: Well, first of all, it

8 differs in a number of ways. I don't want to go

9 through the test, that there has been a

10 presentation on this, and there is a lot of

11 background stuff on this.

12 The key difference between the zero

13 tolerance is it's a zero/1 kind of thing, it's

14 either in or out, and it doesn't take the standard

15 deviation into account.

16 The parametric tolerance interval approach

17 is probably, assuming that you have something close

18 to normality, and it is essentially basing the test

19 both on the estimate of the mean and the estimate

20 of the standard deviation, and then depending upon

21 the combination of both of those guys, it is

22 essentially a zone of equivalence, but the

23 distinction between the two tests is one sort of a

24 zero/1, you are either all in or all out, but it

25 doesn't estimate the standard deviation.

1 The work that has been done on the
2 parametric tolerance interval approach
3 statistically is intended to be a more powerful,
4 more precise, take more of the information into
5 account.
6 DR. SINGPURWALLA: So, would you say that
7 the DDU test is not a statistical test, it has no
8 statistical basis?
9 DR. O'NEILL: No, I would not say that at
10 all. In fact, both of them have statistical bases.
11 In fact, the zero tolerance test is essentially the
12 USP test that is used for all content uniformity,
13 it is a variation on that.
14 Take 10, see whether they are in the
15 limits or out of the limits, if not, take another
16 20. If they are in the limits or out of the
17 limits, and you are done, up or down. That is what
18 the test has been for years.
19 What this is, is essentially to say,
20 well, I am not using all the information, I am not
21 finding out actually what the variability of the
22 process is, so I want to get some handle on what
23 the standard deviation of the process is, so I want
24 to estimate that also, and I also want to estimate
25 what the mean is.

1 So, if you were to back up and sort of
2 look at this within the mainstream of process
3 control, you sort of want to look at where you are
4 in the standard deviation world, where you are in
5 the mean target close to what the center of the
6 distribution is.
7 So, both of these are statistical in the
8 sense that they have probabilities of consumer risk
9 and regulatory risk, but it is that part of it that
10 is the statistical aspect of it.
11 DR. SINGPURWALLA: So, if I were to
12 understand what you are saying, the DDU test seems
13 like a binary test, it's a sequential binary
14 process.
15 DR. O'NEILL: Well, what we are talking
16 about, we are talking about the parametric
17 tolerance interval test versus what is--I don't
18 know what its best name is--but it would be like
19 the zero tolerance interval test. That test is
20 binary. The other one is--
21 DR. SINGPURWALLA: Is not binary.
22 DR. O'NEILL: --is not binary. It takes
23 more of the information into account. That is the
24 conceptual idea.
25 DR. KAROL: Could you tell me how much

1 real data you have and what is the source of the
2 real data?
3 DR. O'NEILL: Well, we have, our folks, I
4 know that there are folks maybe in the audience who
5 have looked at data that we have from the industry,
6 but it is not necessarily the data that is all the
7 data.
8 I mean what we have is data that is
9 submitted to us in applications and in annual
10 reports, and often that is data that has already
11 been screened in the sense that it either passes or
12 doesn't pass, so in some sense, we are seeing data
13 that is less variable than the data that these
14 tests are intended to apply to uniformly.
15 I believe that is where our comfort level
16 is in terms of trying to understand how much
17 variability is in the data, and I think it's a
18 conceptual thing getting back to the way Helen
19 talked about.
20 For years, for years, I think the process
21 was let's set the goalposts and then see whether we
22 can manufacture it to fit the goalposts as opposed
23 to the other way around, sort of saying what is the
24 process capability and then fix the goalposts for
25 the process capability.

1 Under continued process improvement, the
2 idea is to be closer to the target mean and to be
3 closer and tighten down your variability. It may
4 be if you can't do any better, that's what you are
5 left with.
6 So, our situation is understanding that,
7 and what we are seeing now is I believe, if I am
8 not speaking for our chemists, our folks are seeing
9 relatively tight standard deviations in the 5, 6, 7
10 area, and the idea that there could be some
11 standard deviations that are hanging out in the 12,
12 13, 14 area is how come. We are not necessarily
13 seeing all of that.
14 So, we want to see a little more data
15 along those lines. So, that is sort of
16 conceptually where the gap is in terms of trying to
17 move transitionally from the current test into a
18 test that we believe has a lot more merit for
19 several reasons.
20 One, it captures better a handle on the
21 variability of the data, and, secondly, you should
22 be rewarded for taking more samples than less
23 samples. So, this test needs to reward you for
24 having better estimates of what your variability is
25 rather than less. That is another conceptual part

1 of this.

2 DR. MEYER: I might be mistaken because I

3 don't normally read the USP, but it seems from my

4 recollection there are some tablet products that

5 have a specification for variability, as well,

6 warfarin being an example, where you do 10, then

7 you do 20, but you also look at standard deviation

8 or coefficient of variation as some marker for

9 approval or not.

10 Is that correct?

11 DR. O'NEILL: Ajaz.

12 DR. HUSSAIN: Right, I think, Marv, you

13 are right, in the sense the traditional approach,

14 in the pharmacopeial approach, which are market

15 standards, and they were never intended to be

16 release standards, and that is the purpose they

17 serve, are to maintain the market standard.

18 In the case of tablets and solid dosage

19 forms, you have a non-parametric approach to that,

20 and, say, you have your goalposts 85 to 115 for 10

21 tablets, and if one is outside that, you go to 75

22 to 125 with 20 additional ones.

23 For those, you have an estimate of

24 standard deviation. I think it's 6.6 person at the

25 second stage, so you have to meet that.

1 The test we have for dose content
2 uniformity or delivered dose uniformity for
3 inhalation products right now, the FDA guidance
4 doesn't have a value of standard deviations. It
5 simply says take, if it's 85 to 115, if one is
6 outside that, take 20 more, and they all have to be
7 within 75 to 125.
8 So, the term "zero tolerance" actually is
9 not really a meaningful term, and I think we
10 discussed that at the previous committee, but if
11 you really look at it, Jurgen had one set of
12 comments at the end of that meeting, and our
13 statisticians there had a very different set of
14 comments on that, so we were very divided on that,
15 because zero tolerance is for that sample, and that
16 is, in my opinion, a big hindrance to continuous
17 improvement because it forces industry to do only
18 30 tests.
19 If they do more, they are at risk, so that
20 is not conducive to PAT, that is not conducive to
21 the 21st century process that we want to move
22 forward, so this actually is a model or the
23 framework for what we would like to do for all
24 specification, because clearly, the compendia,
25 there is no movement.

1 I don't see much movement in the compendia
2 to change that, so we will have to move forward and
3 change that, because if the compendia don't change
4 that, they are going to be hindrance to PAT and
5 everything else that follows.
6 DR. BOEHLERT: Just as a follow-up to
7 that, I believe under ICH, the compendia are
8 looking at harmonizing general chapters, and one of
9 the ones they are looking at is content uniformity
10 and should there be a tie-in somewhere with that
11 group and what they are looking at and what they
12 are doing, so you don't go two separate ways in two
13 separate directions.
14 DR. HUSSAIN: I agree, but compendia are
15 still a market standard, they are not a release
16 standard, so from a regulatory perspective, that
17 has always been the case.
18 DR. BOEHLERT: That has always been the
19 case.
20 DR. KIBBE: Tom.
21 DR. LAYLOFF: I was going to say also
22 there is a market standard in the way--you end up
23 in a contradiction if you test the whole lot, it
24 will always fail, because of the standard
25 deviation, so you can't really do that.

1 But in the regulatory laboratory, what we
2 used to do is if we found one out of limits, then,
3 we would submit it for check analysis, and if it
4 passed check analysis, then, it was okay. So, you
5 sort of got around that contradiction in the limit
6 setting.
7 DR. KIBBE: Anybody else?
8 Is there anyone on the committee who
9 thinks that moving forward is not necessarily the
10 way to go? Is there something that we need to
11 discuss, because they are essentially asking us to
12 say, well, yeah, we need to move forward and let's
13 get the results by the end of the year?
14 DR. SINGPURWALLA: Do we have to do this
15 right now?
16 DR. KIBBE: We are not going to decide on
17 which tests to do right now. We are just
18 supporting the concept of having the working group
19 move forward and give us a report.
20 DR. SINGPURWALLA: But one of the things
21 they wanted is recommendations .
22 DR. O'NEILL: No, I don't think so. We
23 are just asking you to endorse the idea of moving
24 forward and having this group, and we will come
25 back to you with a report. If you don't like it,

1 you can say go do more.

2 DR. SINGPURWALLA: I am sorry, you said

3 suggest refinements in your talk, I made a note of

4 it, so do you want the refinements now or later on?

5 DR. O'NEILL: No, we don't.

6 DR. SINGPURWALLA: So, you don't want

7 refinements.

8 DR. O'NEILL: No, it's very high level,

9 not detail oriented feedback that we would like

10 from you right now.

11 DR. SINGPURWALLA: Because I would like to

12 suggest refinements, but not at this minute.

13 DR. O'NEILL: I am sure we would be very

14 interested in your refinements, and, in fact, I

15 would certainly be interested in speaking with you

16 outside of the meeting in terms of getting some

17 additional ideas on this particular test, because

18 again, this is a working group that is under the

19 umbrella of this committee and essentially is

20 coming back to the committee on behalf of the

21 committee saying what do you think, because the

22 committee is the one who is going to give the

23 recommendations to the Agency.

24 So, if you don't like the recommendations,

25 then, it is totally within the committee's

1 responsibilities and rights to say, you know, that
2 is not what we had in mind, or that's not what we
3 think is right.
4 DR. KIBBE: Let me get at some of this a
5 little bit. We have, I think, a tentative schedule
6 to meet in October, and for you, the working group,
7 to have your best shot prepared for us to look at
8 and give you feedback on, right?
9 DR. O'NEILL: Yes, and it's not that we
10 haven't thought this isn't ambitious either, but
11 that's what we are trying to work on.
12 DR. KIBBE: Is it reasonable for a member
13 of this committee to forward suggestions to you in
14 the interim and then have you incorporate them in
15 the working group? If you have some things that
16 you would like to think through and then--
17 DR. SINGPURWALLA: Honestly, I was
18 intrigued by the comment made that we invite
19 suggested refinements, and for me to suggest
20 refinements, I need to have a better appreciation
21 for exactly what is going on.
22 DR. O'NEILL: I hear what you are saying.
23 I guess maybe that was meant in terms of
24 refinements to the process. Part of this is the
25 process, and part of this is the content that the

1 working group will be dealing with, and the working
2 group already has essentially a proposal that they
3 have been reacting to from IPAC-RS that has been in
4 the works for a number of years, and it is that
5 that is trying to be refined, those ideas are
6 trying to be refined in the context of how do we
7 understand what is currently sort of the operating
8 characteristic curve of the current way we do
9 things versus a new proposed way of doing things,
10 and are they achieving where we want to be as a
11 committee.
12 I think that is the sense of the
13 refinements.
14 DR. SINGPURWALLA: So, if the endorsement
15 that you seek is for the process, and not for the
16 inner workings of the process, I have no comments,
17 go ahead, but if it is for the workings, then, I
18 would like to think about it.
19 DR. KIBBE: I believe we are looking for
20 moving ahead on the process right now.
21 DR. O'NEILL: That is what we are seeking
22 from you, yes.
23 DR. KIBBE: What I hear my colleague
24 saying is that he would like to have some input on
25 the actual workings of the committee, with the

1 thought process of the committee, and that if we
2 could find some way to do that, to accommodate that
3 situation within the budget constraints of the FDA,
4 it would be useful.
5 It always is good for a subcommittee or a
6 working group of ours to have somebody from here to
7 carry water for us. You might get yourself into
8 more work than you thought you were going to get
9 into.
10 Anybody else? Jurgen.
11 DR. VENITZ: I am obviously in favor of
12 moving forward, but I would like to give maybe
13 somewhat of an unwanted recommendation, not
14 necessarily a refinement.
15 That is, when I look at the objectives of
16 the working group, they are basically, primarily
17 looking at the statistical properties of the test.
18 I am recommending the group for having
19 information on it, and I would encourage the
20 committee to also, the subgroup, I guess, the
21 working group, to also look at the clinical
22 significance, in other words, in my mind, we talked
23 about that last time, the clinical use is part of
24 what risk-based manufacturing is all about.
25 So, for example, it may be very different

1 whether you are comparing inhaled insulin release
2 to inhaled topical steroids, and I would like for
3 that to be discussed as part of the working group.
4 DR. O'NEILL: I hear you. Maybe I went
5 through this a little too fast. If you look at the
6 constitution of the working group, Dr. Chowdhury is
7 our clinical input on that, so that has been
8 recognized, and that is why he is on the working
9 group, to essentially put, as an overlay, the
10 clinical risk structure on this, recognizing very
11 much it might be product-specific, so that is his
12 role.
13 Lawrence Yu's role is also looking at this
14 from, let's say, the generic drug implication, so I
15 think the working group has been put together
16 primarily to be relatively broad-minded.
17 The statistical component of this is only
18 one of multiple dimensions to this, but it is
19 critical to understanding where we are in terms of
20 the only thing that is not moving right now, which
21 is the test that is on the table.
22 DR. KIBBE: Pat, go ahead.
23 DR. DeLUCA: Since this committee is going
24 to be reporting back to this group, I am just
25 wondering why a member of this group wasn't put on

1 that committee, and it sounds like Nozer could have
2 some real input into it, as well as being a link to
3 this committee. There may be some reason why you
4 didn't do that, but I would certainly consider
5 that.
6 MS. WINKLE: It certainly is an option.
7 The way that this group is set up is basically a
8 fact-finding group for the advisory committee, to
9 give them the facts and the information that they
10 will need to help make a recommendation on this
11 test and how we want to move forward with it, but I
12 think that it would be very helpful to have some
13 input from Nozer.
14 I think that he has some knowledge and
15 some understanding and there is nothing that
16 prohibits us from doing that, but we tried to set
17 it up as an independent fact-finding group for the
18 advisory committee.
19 DR. SINGPURWALLA: By the way, I just want
20 to clarify that I didn't raise the question to
21 thrust myself into this arena. I was honestly
22 asking a question, and since the matter has been
23 raised by my colleague on the clinician, I would
24 like to suggest that a Bayesian be on this
25 particular group.

1 DR. O'NEILL: We will certainly be
2 listening to you. If you want to get into that
3 discussion, we could, but one of the critical
4 discussions we have been having right now is
5 assumptions versus data, and Bayesians are heavy on
6 the assumptions, but you have to have the data to
7 support the assumptions, the game we are in, in the
8 regulatory game we are in, and that is why we are
9 trying to sort of get some sense of what does the
10 waterfront actually look like, because it is very
11 important to the behavior of the characteristics of
12 this test.
13 DR. KIBBE: It is always fun to have
14 statisticians discussing statistics.
15 Do we have any other questions?
16 Seeing no one's hand or little button lit
17 up, I want to thank you very much. We are looking
18 forward to a very informative and useful report in
19 October.
20 My schedule says that we are supposed to
21 be talking until 10:15, and we could either take a
22 break now or if Ajaz promises to get finished in
23 time for a break, we could move forward. What is
24 everyone's pleasure? Naturally, the Bayesian wants
25 to break.

1 [Laughter.]

2 DR. KIBBE: I will give you all 15 minutes

3 and then we will have Dr. Hussain.

4 [Break.]

5 DR. KIBBE: Why don't you go ahead and

6 start, Ajaz.

7 Process Analytical Technology (PAT) - Next Steps

8 DR. HUSSAIN: Thank you.

9 [Slide.]

10 What I would like to do today is to give

11 you a brief progress report on the PAT initiative

12 and have three speakers.

13 [Slide.]

14 I will present a brief history to recap

15 how we got here, current status and next steps.

16 There are three topics that we want to share with

17 you, finalizing PAT guidance, training and

18 certification. Chris Watts will make that

19 presentation.

20 What we are doing with respect to

21 standards development. Ali Afnan will talk about

22 that.

23 A topic that we have discussed twice with

24 you, but we thought we would sort of bring some

25 closure to that, what we have done with rapid

1 microbial methods and how that has been a part of
2 PAT. Bryan Riley will talk to you about that.
3 What we are hoping is, we have not really
4 posed any questions, this is more of a progress
5 report, status report, and we are moving forward,
6 but if there is anything that you think we need to
7 consider, please share this with us.
8 The questions you might want to consider -
9 are we on track? Are there any recommendations for
10 improving how we have approached PAT and how we
11 might want to approach PAT in the future?
12 [Slide.]
13 The aspect that I often share is I think
14 the PAT thought process has been in the Agency for
15 a long time, and, in particular, a focal point for
16 the discussion occurred in October of 1993. I was
17 not at FDA at that time, but Tom Layloff and others
18 in St. Louis had organized a Symposium on
19 Pharmaceutical Process Control and Quality
20 Assurance by Non-traditional Means.
21 The information I have about that is a lot
22 of the focus became on near IR, and a lot of the
23 focus tended to be on endproduct testing although
24 the title was process control, and the discussion
25 that led to sort of a very negative view of near IR

1 and some of this technology came from FDA saying
2 this cannot be USP methods, therefore, cannot be
3 regulatory methods, which is probably more blunt,
4 Tom will correct me if I am wrong.
5 So, I think that was really an unfortunate
6 aspect because from an FDA perspective, a lot of
7 progress did not occur because of that.
8 Tom and I spent a lot of time together
9 thinking about this, and we saw this as an
10 opportunity. It was more of a discussion between
11 an analytical chemist and an industrial pharmacy
12 type, so we were putting our heads together and we
13 made a presentation in the year 2000, the
14 Millennium Conference in San Francisco. I will
15 just share some slides on that with you.
16 Another meeting which was very important
17 in the evolution of this process was the new
18 technology meeting of Royal Pharmaceutical Society
19 entitled Process Measurement and Control. I
20 actually met Ali Afnan and many other people who
21 were then associated with the PAT at that meeting.
22 [Slide.]
23 The aspect I think which was important is
24 this was a presentation that Tom and I did together
25 at FIP meeting. Tom had left FDA and was part of

1 the USP at that time. The title was Advanced
2 Quality Control of Pharmaceuticals: In-line Process
3 Controls.
4 If you look at the outline, what we talked
5 about then was pharmaceutical product development
6 and manufacture: Building Quality In, and sort of
7 design and specifications, how you approach that.
8 We looked at modern in-line controls,
9 potential advantages over traditional controls, a
10 better approach for "building quality in," and
11 talked about the need for accelerating industry and
12 regulatory acceptance of modern in-line controls.
13 That was the thought process before we coined the
14 term "PAT," and so forth.
15 [Slide.]
16 In many sense, if you look at the cartoon
17 there, that was the art of pharmacy manufacturing
18 to the science of pharmaceutical manufacturing is
19 how did we do granulation endpoint. We reach in
20 the bowl, grab a handful of granules, and look how
21 they crumble, and then decided the granulation
22 endpoint was reached, so we wanted to move from the
23 art to more of a science-based approach.
24 Our part of the PAT looked something like
25 this, so if you look at that other cartoon there,

1 that is how we saw it in 2000, this is what PAT
2 might be.
3 [Slide.]
4 I think one of the critical meetings that
5 I attended was a far more technical conclave in
6 North Carolina. I happened to walk into that
7 meeting and G.K. Raju from MIT was talking about
8 it, and that was a chance meeting that really
9 provided us some of the critical information
10 because I think without that, Tom and I could not
11 have made any points in 2001.
12 What the CAMP consortium, the MIT
13 consortium helped us was to really put a value to
14 this thought process, and based on that, we made a
15 presentation to the advisory committee, Vince Lee
16 was the chair then, is to initiate public
17 discussion on application of process analytical
18 chemistry tools in pharmaceutical manufacturing.
19 You gave us strong support to move
20 forward. You recommended that we form a PAT
21 Subcommittee. We also, at that same meeting,
22 related discussion on Rapid Microbial Testing,
23 however, we did not discuss this further at the
24 advisory committee, we had these discussions at the
25 subcommittee, and that is the reason I brought

1 Bryan Riley to come back and share with you that
2 discussion again.
3 [Slide.]
4 But at the same time, I think Helen and
5 Dr. Woodcock, we were discussing this, we felt this
6 was much bigger than just an OPS issue, it had to
7 be an FDA issue, so we took this to the FDA Science
8 Board, and Dr. Woodcock presented that as emerging
9 science issues in pharmaceutical manufacturing.
10 We actually invited--I am not going to go
11 through all the slides, but just to sort of
12 illustrate the key presentations that occurred--one
13 was the opportunity for improving the efficiency
14 from G.K. Raju and then Doug Bean from
15 PriceWaterhouseCooper, and we had industry
16 colleagues from Pfizer who really came and helped
17 us, saying that Pfizer has adopted a "Don't Use"
18 and "Don't Tell" approach.
19 That is the industry approach is to not to
20 use new science and new technology because of
21 regulatory uncertainty, or if it is needed, they
22 will use it, but then they will do something for
23 the regulators to say here, this is what you want,
24 but we will control the process this way.
25 So, we felt that was undesirable from a

1 public health perspective, and we wanted to move
2 forward to facilitate introduction of PAT, and we
3 coined the term PAT. So, we got a very strong and
4 unanimous endorsement from the FDA Science Board to
5 move forward. In fact, the Science Board also said
6 that they would like to talk and give seminars on
7 it, but they have not, but we did give them
8 updates.
9 [Slide.]
10 Taking the recommendations of the advisory
11 committee, this committee's recommendation. we
12 issued a Federal Register Notice to invite people
13 to participate on a PAT Subcommittee.
14 So, we got people to apply. We selected
15 those individuals and we formed a PAT Subcommittee.
16 We brought it back to this advisory committee to
17 see whether the charter for the subcommittee is
18 acceptable.
19 You gave us valuable recommendations. We
20 formed the subcommittee, and we had three meetings
21 - October, June, and February. Tom Layloff served
22 as the acting chair for the subcommittee.
23 [Slide.]
24 The subcommittee moved so rapidly we did
25 not have an opportunity to remove the word "Acting"

1 from these names, so while they were acting, the
2 work was done, so we never finalized their
3 positions.
4 Dr. Kibbe, now the current chair of this
5 committee, took the responsibility for PAT
6 Applications Benefits Working Group. Judy
7 Boehlert, who is the chair for Manufacturing
8 Committee, took the lead for Product and Process
9 Development Working Group.
10 Leon Lachman focused on Validation.
11 Dr. Koch, who is now on the advisory
12 committee, chaired the Working Group on PAT
13 Chemometrics.
14 So, these working groups provided us
15 information, feedback to sort of help create a
16 framework to write this guidance.
17 [Slide.]
18 We also, in parallel, were discussing this
19 further at the FDA Science Board, and the key
20 aspect was the PAT initiative was just a starting
21 point to what was to follow, the 21st Century
22 Initiative, and so forth.
23 So, we took this discussion further to the
24 Science Board, and the second Science Board
25 discussion was very important. There was a topic

1 that Dr. Woodcock herself discussed, and that was
2 actually something similar to what we had the
3 discussion on parametric tolerance interval test,
4 because the current regulatory system and the
5 current pharmacopeial system is such that actually
6 does not promote continuous improvement, it
7 actually penalizes people for doing more testing,
8 and therefore it had to change.
9 So, we had to bring the concept of
10 research and moving away from the current mentality
11 of 75 to 125 type thinking, the market standard
12 type thinking, so we had to build that consensus,
13 and we got strong endorsement from the FDA Science
14 Board to move forward also on that aspect.
15 The other presentation, which is very
16 important to remember, is that of Dr. Ray Sherzer
17 from GlaxoSmithKline speaking on behalf of CAMP,
18 and the thing that he pointed out, that there are
19 many barriers, we need a paradigm shift, and that
20 paradigm shift is necessary because the barriers
21 are cultural, organizational, historical.
22 The challenges are not technical, the
23 technical knowhow exists. The scientists can do
24 this, but the barriers are significant cultural
25 barriers and organizational barriers, and we could

1 relate to that, because we had the same barriers
2 in-house at FDA.
3 [Slide.]
4 As we were building the PAT team process,
5 and you will see a lot of the thought processes
6 that Helen expressed in terms of the desired goal
7 that OPS wants to move in, this becomes a model or
8 the pilot project for a lot of the things we have
9 done.
10 So, we had to build a PAT team for
11 reviewers and inspectors and compliance officers,
12 because this was the engine for success. We had to
13 think very carefully about this because we have a
14 long history of turf issues. We don't talk to the
15 field, the field doesn't talk to us type of
16 mentality, or this is my issue, field keep away
17 type of thing.
18 [Slide.]
19 So, we actually started a team building
20 exercise, so starting with a definition of team, a
21 team is a group of interdependent individuals with
22 complementary skills who are organized and
23 committed to achieving a common purpose, applying a
24 common process, and sharing a common destiny.
25 Now, I think we clearly have worked on No.

1 1 and 2, we haven't really worked on No. 3 yet, but
2 the importance of this is the quality of the
3 results we expect from the regulatory assessment,
4 review, or inspection really depend on the quality
5 of relationship between the reviewer and
6 inspectors, and the quality of the relationship
7 defines quality of thinking, and the quality of
8 thinking defines quality of action that leads back
9 to the quality of results we expect.
10 So, this is really a complex issue and
11 that has to be dealt with very carefully.
12 [Slide.]
13 We started the PAT process with three
14 organizations: our colleagues in Office of
15 Regulatory Affairs, which are the GMP inspectors,
16 Center for Drugs, and Center for Veterinary
17 Medicine.
18 The Center for Biologics chose not to be
19 part of this, and we will discuss that further this
20 afternoon whether they wish to join us or not.
21 So, we formed a PAT Steering Committee,
22 again reflecting all the different organizations.
23 We formed a PAT Review and Inspection Team, and we
24 actually recruited a small group, Raj Uppoor, Chris
25 Watts, Huiquan Wu, and Ali Afnan to come and join

1 OPS, so we had a very successful recruitment
2 process. We actually got Ali to take half the
3 salary to come to work for FDA, and he did.
4 We actually put a PAT Training and
5 Coordination Team, and the training was critical.
6 One of the critical aspects of the PAT Subcommittee
7 was developing a curriculum for training, and then
8 we partnered with three schools: a School of
9 Pharmacy, a School of Engineering, and a School of
10 Chemistry to bring this process together, all three
11 National Science Foundation Centers for Excellence,
12 Center for Process Analytical Chemistry,
13 Measurement Control Engineering Center at
14 Tennessee, and Center for Pharmaceutical Processes
15 at Purdue.
16 So, we brought the groups together and the
17 training occurred, but I do want to share with you
18 the challenges are cultural.
19 [Slide.]
20 If you look at the first picture, if you
21 can see, a perfect team, right, so we wanted to
22 work together, so we did want to talk to each
23 other, it is important, and that is the message I
24 really want to hone in, because the challenges
25 right now we are facing, especially in companies,

1 is this challenge.

2 We have been able to overcome that in a
3 small way within the PAT team, but this has to
4 occur broadly, as Helen pointed out, throughout the
5 Agency.

6 [Slide.]

7 So, I think the challenges are great, and
8 we have to build teams by dancing together, and we
9 did dance together--that is Joe Famulare and Doug
10 Ellsworth dancing, you will never seen them dance
11 anywhere else--and working as a team on smaller
12 projects and building a team. You can see Chris
13 Watts smiling.

14 [Slide.]

15 That led to a team process that paralleled
16 the efforts that we put together to develop a
17 guidance. The guidance is different, it is a very
18 different guidance, it is not a "how to" guidance,
19 it is a guidance developed as a framework, and the
20 guidance simply outlines a framework that reflects
21 analytical chemistry, industrial pharmacy,
22 pharmaceutical engineering principles, but in an
23 integrated way.

24 What it does is it changes quite a bit of
25 things each discipline might think about. The way

1 I like to say that is if you change the way you
2 look at a thing, the thing you are looking at
3 changes, so when Tom and I were discussing, we are
4 discussing as an analytical chemist and a
5 industrial pharmacy type.
6 When we brought engineers in, we got
7 engineering aspect, so now PAT is somewhat
8 different than any of the three views of that.
9 DR. SINGPURWALLA: It is called the
10 Heisenberg principle.
11 DR. HUSSAIN: Yes. So, this is a draft
12 guidance which we are finalizing, and Chris will
13 talk to you about that, but I do want to sort of
14 share some other thoughts.
15 [Slide.]
16 We had very successful workshops. The
17 Arden House conferences this year and last year
18 were very successful, but they were very emotional,
19 especially the one last year was very emotional.
20 The emotions came out first as R&D versus
21 Manufacturing, because they didn't want to talk to
22 each other, and then it come out between
23 pharmacists and engineers, so the engineers came up
24 to me saying these pharmacist types don't know what
25 they are doing, but it was necessary because it

1 forced soul-searching, it forced the thought
2 processes that was needed, and many companies are
3 going through that right now.
4 So, the emotions gave into a lot of
5 rational discussion at Arden House this year, IFPAC
6 meeting, ISPE meeting, PDA meetings. Now we have
7 several proposals, in fact, I expect by the end of
8 this summer or the end of this year, you will see
9 two complete PAT lines, two different companies,
10 from crystallization to endproduct, complete
11 automated manufacturing, so that is how fast two
12 companies have moved, and one we have approved, and
13 Bryan will talk to you about that.
14 The first training session is complete,
15 certification process is ongoing. We have an
16 ongoing interagency agreement with National Science
17 Foundation. We would like to explore ways of
18 expanding this, and one opportunity that has been
19 created is a new initiative called Critical Path,
20 and we will share that with you next time.
21 The Critical Path Initiative focuses on
22 the need for research in three areas: to improve
23 drug development itself. One of those is
24 industrialization, that is where PAT fits in, and
25 we want to use that as a means to sort of highlight

1 the need for public funding for research,
2 especially academic research in this area, and hope
3 to do so in the next several months and years.
4 We had an ongoing CRADA with Pfizer on
5 chemical imaging. Things are looking good there,
6 and we hope to bring some of the results back to
7 you for some sharing of that with you.
8 We have ongoing communication and
9 cooperation with other regulatory agencies. Now,
10 our European colleagues have formed a PAT team very
11 much like ours. They are actually going to meet
12 the end of this month, and they have invited us to
13 participate.
14 Health Canada has met with us and they are
15 very eager to sort of join our training session
16 next year, the next training session that we start.
17 MHLW, the Japanese are looking at it very
18 intently and things are happening on the
19 harmonization front with our trying to harmonize.
20 [Slide.]
21 Now, standards development, it was very
22 important that we have a venue to develop standards
23 that bring in the multifaceted structure, engineers
24 have to talk to pharmacists, have to talk to
25 analytical chemists.

1 The way we thought that will happen is
2 through ASTM, because ASTM has a lot of knowhow
3 already, so we formed a committee called E55,
4 Pharmaceutical Applications of PAT. Ali Afnan will
5 talk to you about that.
6 There is growing external collaboration
7 and emerging support structure. ISPE and PDA are
8 interested in PAT and are actually developing
9 programs to cover a lot of the training needs for
10 the next several years, we have PAT Group in the
11 AAPS, discussion group.
12 We are looking at possible collaboration
13 between AAPS and ISPE to bring the material science
14 and the engineers together to really focus on
15 processing, strong support from IFPAC and the
16 formation of an association for manufacturers. I
17 think they are struggling with some identity
18 crisis. They call it IFPACma, so I suggested they
19 should call it IFPATma.
20 I think this association will be helpful
21 because it will house all the manufacturers of the
22 sensors, the software, and so forth, and give them
23 a voice, a common voice to move forward.
24 When you have an association especially
25 with a nonprofit association, we can partner with

1 them more easily. AICHE has an extensive
2 discussion, and we are building on the vision 20/20
3 of AICHE especially in processing to see how that
4 can be leveraged.
5 A growing number of academic programs that
6 focus on PAT. Several PAT companies and training
7 opportunities have emerged. Pharmacopeias are
8 interested in PAT. Hopefully, they resolve the
9 acceptance criteria first.
10 PAT is now a part of the 21st Century
11 Initiative and FDA's Strategic Plan, so I think
12 that small crystal is starting to crystallize the
13 system.
14 [Slide.]
15 The next step is guidance finalization.
16 We are moving towards a quality system for the PAT
17 process. FDA will participate in the ASTM.
18 This afternoon, we will discuss
19 application of PAT to the Office of Biotechnology
20 Products. I want to sort of make sure I say this
21 in a way that emphasizes the structure.
22 Expand the scope of the guidance to
23 include Office of Biotechnology Products. Since
24 they were not part of the training and
25 certification program, the guidance is not

1 applicable to them.
2 The guidance is a framework guidance. It
3 applies to any manufacturing, whether it's biotech,
4 whether it's automobile, whether it's anything, the
5 concepts apply to any manufacturing, so it will
6 apply to Office of Biotechnology Products.
7 The reason that office is not within the
8 scope is they were not trained and certified on
9 this aspect. So, the question to you would be how
10 would we develop a training program that will meet
11 their needs, and as we go to the second training
12 program, that will have a more biotech focus and
13 then that becomes part of the PAT process.
14 I will stop my presentation and invite
15 Chris to continue. I think in the next two to
16 three years, we want a sunset PAT. What I mean by
17 "sunset PAT," is that becomes a regular part of our
18 CMC and GMP program, so it will merge with the rest
19 of the system.
20 Is two to three years the right time? I
21 think we will see, but the intention is that this
22 is no longer a unique program, it is part of the
23 current system.
24 With that, I will stop. If you have any
25 questions, I will be glad to answer, or we could

1 answer after Chris and others have talked.

2 Finalizing PAT Guidance

3 Training and Certification

4 DR. WATTS: Thank you, Ajaz, and thank the

5 committee for giving me just a few minutes of your

6 time to go over what we have done in terms of

7 training and certification and moving toward

8 finalizing the draft guidance that we put out back

9 in September of 03.

10 [Slide.]

11 I just want to take a step back really

12 quickly and just summarize some of the discussions

13 that took place at this committee and the PAT

14 Subcommittee in terms of defining what PAT is, and

15 that will really give some background on the intent

16 of the training program and what the focus was for

17 the training program.

18 The definition that came from this and

19 subsequently made its way into the guidance was PAT

20 is a system for designing, analyzing, and

21 controlling manufacturing through timely

22 measurements of critical quality and performance

23 attributes of raw and in-process materials and

24 processes.

25 So, it is not just focused on any one

1 analytical technique, it is not focused on
2 endproduct only, it is the entire manufacturing
3 process.
4 When you think about PAT, process
5 analytical technology, that term "analytical" more
6 should be thought of as analytical thinking, not
7 just simply analytical chemistry, so we made a
8 point of emphasizing that analytical, when you
9 think about that term, you should include not only
10 chemical, but also physical, microbiological,
11 mathematical, and risk analysis, all those
12 conducted in an integrated manner to come up with a
13 framework for controlling the manufacturing
14 process.
15 [Slide.]
16 So, with that definition, the unmistakable
17 focus of PAT is to really understand the
18 manufacturing process. What we outlined was a
19 process is considered well understood when, number
20 one, all critical sources of variability are
21 identified and explained; number two, the
22 variability is managed by the process, and,
23 finally, product quality attributes can be
24 accurately and reliably predicted.
25 So, with that focus on process

1 understanding, it brings in the concept of really
2 risk management, so we consider that the level of
3 process understanding is inversely proportional to
4 the risk of producing a poor quality product.
5 So, a well understood process then offers
6 less restrictive regulatory approaches to manage
7 change to different approaches to validation.
8 So, if you focus on process understanding,
9 we can facilitate risk-managed regulatory decisions
10 and innovation, not only within the Agency, but
11 within the manufacturing arena and the
12 pharmaceutical industry in general.
13 [Slide.]
14 So, having that background, I want to now
15 talk about this framework that we developed for PAT
16 that came out in the guidance, and it was a
17 framework, as I just mentioned, for innovative
18 pharmaceutical manufacturing and quality assurance.
19 We really set forth some scientific
20 principles, some basic principles and concepts, and
21 described some PAT tools that would support
22 innovation.
23 In my opinion, one of the most important
24 aspects was the regulatory strategy that would
25 accommodate innovation, and that the primary focus

1 there was on the PAT team approach again which Ajaz
2 mentioned briefly, the team approach to review and
3 inspection.
4 Along those lines, we developed a joint
5 training and certification program, so I want to
6 talk to you now about that training and
7 certification program.
8 [Slide.]
9 You have already seen a few slide from
10 Ajaz on the team building aspect, really getting to
11 know one another very well, and again that included
12 people from the Center for Drugs, both reviewers
13 and compliance officers, the field investigators
14 from the Office of Regulatory Affairs, and, of
15 course, the compliance officers and reviewers from
16 the Center of Veterinary Medicine.
17 During this training program, it was
18 important that all 15 individuals who were part of
19 that initial training program, we went through
20 everything together, every didactic session we went
21 as a team, every practicum we went as a team.
22 The team building obviously, everyone was
23 involved there, so there it would really break down
24 the communication barriers, which is really going
25 to be key to ensuring that science-based,

1 risk-based or risk-managed approach to review and
2 inspection.
3 A brief outline of the training program
4 that we had. Two didactic sessions, both of those
5 were conducted here at the FDA, and three practica,
6 again, at the University of Washington, the Center
7 for Process Analytical Chemistry; Purdue
8 University, Center for Pharmaceutical Process
9 Research, and the University of Tennessee, the
10 Measurement and Control Engineering Center.
11 [Slide.]
12 In summary, the first didactic that we had
13 was really just to provide a general overview of
14 some of the pharmaceutical processes, the
15 scientific basis for some of those processes, why
16 they may be necessary, to really give the team a
17 feel for what some of those unit operations
18 specifically may be trying to do to the material
19 and what are some approaches for trying to control
20 that process.
21 Of course, there was some extensive
22 discussion on some of that process analytical
23 techniques, multivariate analysis, an in-depth
24 discussion on the background of where some of the
25 multivariate analysis techniques came from,

1 principal component analysis, partial e-squares,
2 how those can be used in terms of developing a
3 control system for the manufacturing processes, and
4 then finally, a general introduction to true
5 process control from a process control engineer.
6 After that, we went to the University of
7 Washington in Seattle, The Center for Process
8 Analytical Chemistry, and the focus there was
9 really on sensor technology and development. I
10 think CPAC did a wonderful job of tying that in,
11 giving some other industrial examples, and tying
12 that into how some of these sensors may be applied
13 to the pharmaceutical industry.
14 [Slide.]
15 To maintain continuity with the practicum
16 visits, we took some of those, the sensor
17 technology, some of the sensors that were being
18 utilized at CPAC, and put them in the use onto some
19 pharmaceutical processes at Purdue University.
20 There, we really focused on some of the
21 experiments that we conducted were blending, for
22 example, compression, granulation, traditional
23 solids processes, how some techniques were emerging
24 that may be able to allow us to control those
25 processes on line, really understand the impact of

1 those processes on the final product quality and
2 how they relate, not just to consider them
3 independently, but how they relate to the final
4 product quality as a whole.
5 After having done our experiments at the
6 second practicum at Purdue, we then took some data
7 on the granulation process. Then, when we went to
8 the Measurement and Control Engineering Center at
9 the University of Tennessee, we actually analyzed
10 that data.
11 Paul Kemperlein, who is part of MCEC,
12 really walked us through, you know, what are some
13 of the techniques that you maybe use, what are some
14 limitations of these multivariate techniques that
15 you may be want to be keeping in mind when you are
16 going through the review of these applications.
17 [Slide.]
18 Finally, the last didactic, we tried to
19 tie everything together again. We broke up into
20 teams, developed some case studies, so that we
21 could really apply what we had learned throughout
22 the training program, and discussed those as teams,
23 a true team approach, a reviewer, compliance
24 officer and investigator, and really began to
25 discuss what some of the relevant issues were in

1 terms of managing the review and inspection
2 processes.
3 That really ended the initial training
4 portion, but by no means did we think it is
5 complete. I think continuing education is going to
6 be vital to the success of this team, which Ajaz
7 mentioned is really going to drive the success of
8 PAT within the Agency.
9 Along those lines, we have monthly video
10 conferences with the people that are here in
11 Rockville and the investigators that are in the
12 field, and we try to discuss some of the relevant
13 issues that are coming out, for example, some
14 recent publications or some inspections, review
15 issues that may have surfaced, and discussed those
16 as a team, not individually as reviewers or not
17 inspection issues individually as inspectors, but
18 as a team.
19 We also have developed a seminar series to
20 discuss some publications that may be relevant to
21 what we are trying to do within the PAT initiative,
22 and, of course, we are using the Intranet to
23 communicate some of these publications and discuss
24 those on line, really, an easy way of communicating
25 with the entire team.

1 [Slide.]

2 In summary, we have, in terms of the
3 training and certification, we have completed the
4 initial training program. We are now in the
5 process of conducting some lessons learned in terms
6 of what we have accomplished with this, maybe some
7 additional aspects that need to be considered, and
8 some of those will be discussed with this committee
9 this afternoon in terms of expanding the scope of
10 PAT to include biotech products.

11 Again, continuing education and
12 involvement in the next training, I think is going
13 to be critical for this group, so that we maintain
14 links, not only with the team that we currently
15 have, but the team that we intend to build.

16 We can take some of the experience of
17 those reviewers and investigators who have
18 processed and will be processing some applications
19 and who have gone on inspections and really share
20 those with the new group that is coming in and the
21 group that we currently have, so that we can
22 understand maybe what is the best approach for us
23 to go in terms of taking a team to do an
24 inspection.

25 Maybe we don't need to have all three

1 people, maybe one or two should be sufficient, and
2 we can do discussions over the telephone or
3 videoing to handle some issue.
4 Of course, we have involved the entire
5 team in finalizing the guidance. In my opinion, I
6 think it was very important to get a real feel for
7 how the reviewers felt about the guidance, how the
8 compliance officers and how the investigators felt
9 about the policy that was emerging in the guidance,
10 really how that framework was going to be
11 implemented because they are going to be the ones
12 who are really driving things.
13 They are going to be the ones who are
14 enforcing the policy, not really enforcing the
15 policy, but making sure that the process works as
16 it should, so that it is a least burdensome
17 approach to the industry.
18 Within the Office of Testing and Research,
19 you heard Helen mention Dr. Khan is coming on
20 board, I think it is going to be important to
21 maintain a link to the Office of Testing and
22 Research, so that we can support policy development
23 and future training if we develop some in-house
24 expertise and what are some critical issues that we
25 may want to be able to focus on in terms of review

1 and inspection and some of the technologies that
2 may be developed, if we can develop some of that
3 expertise in-house, we can not only bring some of
4 the training in-house, but also have some consults,
5 we have expertise within the Agency that we can
6 consult on a given basis.
7 [Slide.]
8 So, building on a little bit of the
9 guidance finalization, we involved the entire team
10 in the development of the guidance, and, of course,
11 they are going to be involved in finalizing the
12 guidance.
13 The guidance was issued in September of
14 03, and the public comment period extended through
15 November 4th, and those comments are available on
16 the docket. You can see all, I think there were
17 some two dozen companies or individuals that
18 submitted comments to the guidance, and we are in
19 the process of going through those and discussing
20 those and addressing each one of those.
21 We have included the entire team and we
22 have broken the teams down into reviewers again,
23 compliance officers, and investigators, and have
24 those address each of those and see which comments
25 they may think are most relevant and convey that

1 back to the policy team, so that we can move
2 forward in finalizing the guidance.
3 With that, I am going to conclude this
4 portion right here. Again, I think we may have
5 time for some questions afterwards, and I want to
6 turn it over to my colleague, Ali Afnan, who will
7 discuss the standards development process for PAT.
8 Standards Development
9 DR. AFNAN: Thank you very much for giving
10 me the opportunity to be here.
11 [Slide.]
12 I am going to be very quick. The outline
13 of the talk is why we went with ASTM, what is ASTM,
14 what is the history of the committee, where are we
15 going with it, and I will give you some background
16 also as to how, what Chris has just said, links
17 into this process.
18 [Slide.]
19 Having focused on the processing, going
20 away from product testing, which Chris very
21 beautifully put out as PAT being process
22 understanding, we had to come up with new standards
23 and new ways of assessing whether a process was
24 right or wrong.
25 If the process was working well, then, the

1 product would be right, so for that reason, we
2 began to look at alternatives to the current
3 specifications we were working with because
4 effectively, we needed standards, not
5 specifications.
6 We needed a process which included all the
7 interested parties and allowed them to come in for
8 a balanced discussion, definition of balanced
9 discussion being that we would each have one vote,
10 it would have a due process, and, of course, there
11 was the NTTAA Act, the National Technology Transfer
12 Act, which mandates federal departments and
13 agencies to use voluntary consensus standards in
14 place of government standards wherever possible.
15 So, having looked at all of those, we
16 decided to look at ASTM, which had already been in
17 dialog with our other departments in the agency.
18 [Slide.]
19 So, ASTM, which now they call themselves
20 ASTM International, is an ANSI-accredited standards
21 development organization with more than 100 years
22 of experience in standard development.
23 They actually generate standards, best
24 practices, and guides, three different things, but
25 they are all done through a peer review process.

1 Their offices are in West Conshohocken, and they
2 meet regularly. There is a committee which goes
3 around to various places. This year it is in Salt
4 Lake City, and next year it is somewhere in Europe.
5 [Slide.]
6 The history of developing the committee
7 was that through the winter and spring of 2003, FDA
8 met with ASTM re: development of a new committee
9 for Process Analytical Technology.
10 In October of 2003, there was a meeting at
11 ASTM, and then in December, the first
12 organizational meeting was held at which interested
13 parties from academia and industry were present.
14 In January, the nomination and election of
15 committee officers took place. Again, if you are
16 interested in the procedures and the processes of
17 elections or how ASTM functions, the best place to
18 look at is ASTM.org, World Wide Web.
19 In February of this year, we had the first
20 meeting of ASTM E55 Committee, and the next one is
21 in Salt Lake City, 18th through 20th of May.
22 [Slide.]
23 What is the scope of E55? E55 pretty much
24 reflects the FDA PAT draft guidance, but the scope
25 of the committee is that the scope of the committee

1 shall be development of standardized nomenclature
2 and definitions of terms, recommended practices,
3 guides, test methods, specifications, and
4 performance standards for pharmaceutical
5 application of process analytical technology.
6 The committee will encourage research in
7 this field and sponsor symposia, workshops and
8 publications to facilitate the development of such
9 standards. The committee will promote liaison with
10 other ASTM committees and other organizations with
11 mutual interests.
12 What was quite interesting was it took
13 about an afternoon to come up with that, and,
14 really, we thank the industry for taking a very
15 active role in coming up with that scope.
16 [Slide.]
17 Currently, E55 has three subcommittees.
18 One is E55.01, which is PAT Systems Management;
19 E55.02, which is Systems Implementation and
20 Practice. The Executive Subcommittee is 90, and
21 then there is a third one, which is E55.91
22 Terminology.
23 [Slide.]
24 The Chair and the elected officers, which
25 was by ballot effectively, of E55, the Chairman is

1 Don Marlowe from the Office of the Commissioner.
2 The Vice Chair is Ray Scherzer from GSK. The
3 Membership Secretary is James Drennen from Duquesne
4 University, and the Recording Secretary is Gawayne
5 Mahboubian-Jones from Optimal Industrial
6 Automation, Ltd., a system integration company.
7 [Slide.]
8 The Subcommittee officers. E55.01's chair
9 is Ken Leiper, Vice Chair is Gerry, the Secretary
10 is Chris Watts. E55.02 Chair is Ferdinando Aspesi
11 from Aventis. The Vice Chair, from AstraZeneca, is
12 Bob Chisholm. I am the Secretary.
13 E55.91, which is the Terminology
14 Subcommittee, has Larry Hecker, Abbott, as Chair,
15 and Jim Fox, of GSK, as its Secretary.
16 There are also 8 members at large, who
17 serve on the E55 Main Executive Committee, and they
18 are appointed from industry and academia.
19 Thank you.
20 Rapid Microbial Methods
21 DR. RILEY: What I would like to do this
22 morning is give you a brief update on the status of
23 rapid microbiology methods as part of the PAT
24 initiative.
25 [Slide.]

1 As you may know, rapid microbiology
2 methods were not originally part of the PAT
3 initiative. We were sort of looking at rapid micro
4 methods in a parallel track with the development of
5 the PAT initiative, but finally, someone recognized
6 it would make sense to have rapid micro methods as
7 part of PAT, so at the October 2002 PAT
8 Subcommittee meeting, there was an extensive
9 breakout session dealing with rapid microbiological
10 methods.
11 A number of speakers discussed the
12 importance of rapid microbiology methods, how they
13 could fit into PAT and also the best way to look at
14 rapid microbiological methods for the
15 pharmaceutical industry.
16 [Slide.]
17 From that point on, we worked to try to
18 integrate rapid microbiological methods into the
19 PAT initiative because PAT had sort of a headstart
20 on us. So, the first thing we did was looking at a
21 training session for rapid micro. To do that, in
22 July of 2003, here in Rockville, we had a training
23 session.
24 We invited people from CDER, ORA, CBER,
25 and CVM to attend. As an agenda, we had an

1 overview of rapid microbiological method
2 technologies, a very extensive overview. We had
3 two rapid micro method vendors come in and talk
4 about their products and how they can be used.
5 We also had a company come in and talk
6 about their experiences of validating a rapid
7 microbiological method for pharmaceutical use.
8 [Slide.]
9 Since the team approach is very important
10 for PAT, one of the things we had to do was to form
11 a rapid micro method team for PAT. That team
12 consists of Bob Coleman, expert drug investigator
13 from ORA; Dennis Guilfoyle, a pharmaceutical
14 microbiologist from the North East Regional
15 Laboratory at FDA, Brenda Uratani, a microbiologist
16 from the Office of Compliance, CDER, and myself.
17 [Slide.]
18 As we were doing the training and setting
19 up the team, we were also in contact with a large
20 global pharmaceutical manufacturer who was
21 interested in using a rapid microbiology method for
22 their pharmaceutical manufacturing process.
23 We had a number of meetings with them to
24 discuss their use of these rapid micro methods, how
25 they would validate them, how they would submit the

1 information to the Agency, that sort of thing, and
2 these meetings culminated with a formal
3 presubmission meeting with the applicant in 2003,
4 where they discussed what they would submit and how
5 they would submit it.
6 Because what they wanted to do was to use
7 some different rapid micro methods for release
8 testing of a variety of non-sterile drug products,
9 they wanted to use these at multiple manufacturing
10 sites, it was decided that a comparability protocol
11 would probably be the best way for them to submit
12 this information to begin with.
13 A comparability protocol is simply a
14 written formal experimental protocol where, in this
15 case, what they are demonstrating is that their
16 rapid method is equivalent to or superior to the
17 traditional method they have been using, and it
18 talks also about the experiments they will do and
19 also the acceptance criteria that they would want
20 to use to demonstrate that equivalence.
21 So, what they did after this meeting was
22 they submitted two comparability protocols, one for
23 product release testing for several non-sterile
24 drug products, and also testing for pharmaceutical
25 grade waters.

1 After the approval of the comparability
2 protocol for product release testing, they then
3 submitted a changes being affected supplement to
4 implement that rapid micro method for one of their
5 non-sterile drug products.
6 [Slide.]
7 It was decided as part of this application
8 process that an inspection would be done related to
9 the rapid micro method implementation, and because
10 of that, the rapid micro method team had several
11 meetings, one in September of 2003, where we mainly
12 discussed the comparability protocols that were
13 submitted by the company, and then finally, in
14 early February of 2004, we talked about the actual
15 inspection itself, what we would do, how we would
16 do it, that sort of thing.
17 The inspection took place in late February
18 of 2004. It was led by again Bob Coleman from the
19 Office of Regulatory Affairs, and Bob's experience
20 and his leadership in this process was very, very
21 helpful to us especially on the inspection process.
22 It made it go very smoothly.
23 We looked at the rapid micro method
24 itself, how it was validated. We looked at just
25 the general microbiological laboratory aspect of

1 the pharmaceutical manufacturing facility, and also
2 looked at some of the GMPs related to the
3 manufacturing of the product that they would be
4 using the rapid micro method test for.
5 The inspection found no significant
6 problems. There was no 43 issue as a result of
7 that inspection, and we thought everything went
8 well both from our standpoint, as well as the
9 firm's standpoint.
10 [Slide.]
11 What is the future of rapid microbiology
12 methods in the pharmaceutical industry? I think
13 the ultimate goal, the ideal would be real-time
14 testing to provide immediate feedback. I think
15 that would be very, very helpful.
16 Where are we today? The traditional
17 micro methods require several days to several weeks
18 to get results. The current available rapid micro
19 methods that are available today, and can be used
20 today, significantly shorten that time to result.
21 It can be as little as a day or maybe a
22 little bit more than a day, and some of the rapid
23 methods can give you results in as little as a
24 couple of hours.
25 We think even though it is not real-time

1 testing, it still provides much better control,
2 much better understanding of the manufacturing
3 process from a microbiological standpoint and
4 hopefully, can help detect and enable you to
5 correct a potential problem before it becomes a
6 real and serious problem as far as microbiological
7 quality of the drug product is concerned.
8 We are hoping that our experiences that we
9 have had so far with our rapid micro method
10 submission and inspection and approval process will
11 encourage others in industry to also use this PAT
12 regulatory pathway to look at other rapid micro
13 methods and use them to improve their manufacturing
14 process and understanding.
15 I thank you for your attention this
16 morning and I guess we will take questions of any
17 presentations of this session.
18 Committee Discussions and Recommendations
19 DR. MEYER: One question for Ajaz and I
20 guess one for Chris.
21 As the U.S. develops this PAT concept and
22 begins to apply it, it seems like it is better to
23 harmonize as things are being developed than after
24 they are set in stone.
25 Is there an effort with the Japanese, the

1 Europeans, the Canadians to harmonize on the front
2 end?
3 DR. HUSSAIN: Yes, in terms of I think
4 there is quite a significant dialog and discussion,
5 and I think the framework provides a way forward
6 because as a framework, it does not get in how to,
7 and harmonizing how-to guidance is a difficult
8 challenge, so this is the time to do this.
9 That is the reason we felt ASTM also
10 provides a way forward because the devices, the
11 Center for Devices, for example, utilize the ASTM
12 standards, and these are international standards,
13 so many of the members on the ASTM committees are
14 international members right now, Europe and U.S.
15 right now, and we are encouraging people from Japan
16 to join in.
17 So, that would be a way forward, so you
18 are absolutely correct. I mean we are trying to do
19 that as you move along, and the progress has been
20 significant on that. That is what I tried to say
21 is we are harmonizing without trying to harmonize.
22 DR. MEYER: My question to Chris, if I
23 understood you correctly, there is about a
24 15-member team, a variety of disciplines, that were
25 sent through this fairly intensive training

1 program?

2 DR. WATTS: Correct, yes.

3 DR. MEYER: Will that be all there is, or

4 how is this going to grow to be 150 people or will

5 it?

6 DR. WATTS: Well, as Ajaz mentioned, I

7 think within a few years, two to three years, he

8 envisions it being a regular part of the operation

9 within the CMC review and GMP inspection when it

10 comes to this team approach to PAT.

11 We have every intention of expanding the

12 training program to include more members within

13 CDER, the Office of Pharmaceutical Science, Office

14 of New Drug Chemistry, Office of Compliance, but I

15 think the immediate need may be to expand the scope

16 to include the Office of Biotechnology Products,

17 which will be included in the discussion this

18 afternoon.

19 Based on a lot of the comments that we got

20 from the guidance that we issued in September,

21 there were a significant number of comments

22 suggesting that we do expand the scope to include

23 OBP, and as far as an immediate need, I think that

24 may be more urgent in terms of expanding the team

25 concept.

1 DR. COONEY: Another question on the
2 education side, actually, two questions. Could you
3 comment a bit on what do you see as the important
4 metrics that you use in measuring the success of
5 the educational program and then could you also
6 elaborate a bit on what do you see as the major
7 challenges in continuing to evolve and develop the
8 educational program?
9 DR. WATTS: Actually, I think one of the
10 most important aspects was just the team approach.
11 The technical aspects will be actually rather
12 simple to address when it comes to terms of getting
13 some expertise either within academic environment
14 or within industry that have given technical
15 expertise that can convey that to the team.
16 Given the team approach, rather than
17 expecting one member to have all the answers, then,
18 as a team, we think we can have most of the right
19 questions, we can ask most of the right questions,
20 just not having one person have all the right
21 answers.
22 As Ali has said on many occasions, the sum
23 of the team is much more than the individual
24 components, so it is much more than just what each
25 member brings to it.

1 A real metric, again, I think the team
2 approach, that was one of the most important
3 aspects, can they communicate as a team, can they
4 really work as a team, for example, with the rapid
5 micro inspection process.
6 That is relatively a novel concept when it
7 comes to the regulatory environment. Typically,
8 the reviewers are responsible for review only,
9 inspectors are responsible for inspection only.
10 There is little, if any, communication between the
11 two.
12 What we are really treating it as is a
13 two-way street, not just reviewers participating on
14 inspection, but what are some of the key aspects of
15 the manufacturing process that an inspector may be
16 familiar with that they can convey to other members
17 of the team.
18 Really, I think the communication with the
19 team is one of the most important aspects, the
20 technical aspects or the scientific aspects, which
21 will be a little simpler to address, I think, with
22 training.
23 DR. COONEY: Just one more point. In the
24 training exercises, do you present problems of
25 innovation or scenarios where you would not expect

1 previously people to be able to have had all the
2 answers and then ask them to try and synthesize a
3 strategy or an approach?
4 DR. WATTS: Actually, some of the case
5 studies that we developed are along those lines
6 exactly. During the second didactic, it wasn't
7 just this is what one person did. This is the
8 problem, how would you as a team think about
9 solving that problem, not just regulating it, the
10 problem of solving it in general.
11 DR. KOCH: I think the question of
12 developing metrics will become increasing important
13 just in observing the first class that went
14 through, the team building indeed was there. As
15 you go to 150, it is going to be more difficult to
16 dance, there is going to be more variation.
17 The first group was exceptional. If every
18 one of the 150 projected fits that description,
19 it's a wonderful program. I think I have to add,
20 too, the team building exercise that you went
21 through before the training, that was I think
22 replaced by a team building that occurred, say, if
23 I look at the practicum and the didactic, it was
24 quite obvious that the team members were very
25 conscious to make sure that everybody on the team

1 understood the technology to a working level, and
2 it wasn't as if two or three came away with
3 understanding it and didn't bring the others up.
4 It was very obvious that by the end of the
5 program, they were quite excited to move ahead, and
6 that is where the problem I think in the future is
7 going to come, is that as you grow the number in
8 the team, you have to develop more metrics to
9 evaluate how well it is going.
10 A small number is relatively easy, I
11 think, to build the teamwork especially as it is
12 getting off the ground.
13 DR. KAROL: Bryan, I would like to ask you
14 a little bit about the microbial methods. That is
15 very exciting that you are moving to real-time
16 detection.
17 Can you tell us a little bit about the
18 processes that will be involved, what you are
19 thinking of, and are there particular organisms
20 that will be difficult to detect? You know, where
21 are you having your problems in moving in this
22 direction?
23 DR. RILEY: Well, right now I think the
24 methods that we are looking at are fairly simple
25 and straightforward. We are not going to do

1 anything too exotic to begin with. A lot of the
2 methods, even the rapid methods are still growth
3 based, they have an enrichment step, and then an
4 alternate detection method to detect fairly small
5 numbers of microorganisms.
6 But I think as we get into some of the
7 more exotic methods that don't rely on any growth
8 at all, you know, cytometry, that type of thing, I
9 think the issue is going to be again how do you
10 measure, you know, make sure you detect everything,
11 and look at how are we going to validate that, how
12 are we going to make sure that that is possible.
13 DR. KAROL: I wondered if you were moving
14 into DNA technology or any of the molecular biology
15 techniques now.
16 DR. RILEY: It is for some of the
17 identification. What I have talked about mainly
18 has been the enumeration or
19 qualitative/quantitative type tests, but certainly
20 for identification, yes, a lot of people are
21 looking at that using nucleic acid methods,
22 sequencing, PCR, that sort of thing, for detection
23 or identification of organisms, and that I think is
24 becoming much more common, and it is something that
25 I think we are encouraging, as well.

1 DR. KIBBE: Anybody else?
2 DR. HUSSAIN: Why don't we finish with the
3 committee questions before the audience?
4 DR. KIBBE: If we could hold off for a
5 second and see if there is anybody else on the
6 committee.
7 DR. COONEY: I have a question on the
8 rapid microbial. Do you also have an interagency
9 cooperation with Homeland Security, in this area,
10 as well? There seems to be a synergy.
11 DR. RILEY: We don't really have a direct
12 formal connection at this point although one of the
13 team members has been involved in that, so I am
14 hoping that we can work something from that to get
15 more involvement in our aspect of it. But you are
16 right, it does go together, a lot of those types of
17 rapid methods that they would be interested in are
18 things that we could apply, as well.
19 DR. KIBBE: Anybody else on the committee?
20 [No response.]
21 DR. KIBBE: If you could come to the
22 microphone and identify yourself, and then let us
23 know what your question is.
24 DR. CHERNEY: Hi, I am Barry Cherney of
25 the FDA.

1 My question was essentially the same one
2 as was just asked by the committee members, I know
3 the CDC and other federal agencies, DARPA, are very
4 interested in the rapid microbial techniques and
5 have made actually a lot of advancement in that,
6 and I was also wondering what we have done to get
7 involved in those type of efforts as an overall
8 approach for the Federal Government.
9 DR. RILEY; I agree. I think we are
10 starting to do that. Certainly, within FDA, we are
11 looking at some of the different centers to see
12 what they are doing, but you are right, other
13 government agencies have done a lot of work along
14 these lines, and we need to have more of a coherent
15 approach or at least cooperation and information
16 sharing between the different agencies and
17 different groups that are doing that, and I think
18 that will be very helpful for everybody.
19 DR. KIBBE: Ajaz, you had something to
20 say. You leaned forward like you were poised.
21 DR. HUSSAIN: I think what would be useful
22 is if you could share some thoughts in terms of how
23 do you think we have progressed so far, especially
24 Tom and Judy, and folks who were on the
25 subcommittee, what we could have done better or

1 what we should we be looking out for in the future,
2 that would be very helpful.
3 Also, as part of this, I think there are
4 external leverages that really have to come
5 together here, not only in the international arena,
6 but also in terms of academia, in terms of public
7 funding for some of the research that is needed
8 especially in pharmaceutical manufacturing, and so
9 forth, how do you recommend we move forward in many
10 of these areas.
11 DR. KOCH: I guess I would make one
12 suggestion, and that is not to lose the momentum
13 that started with the training of the first group,
14 and I know that the second group hasn't necessarily
15 been put together yet, and there is obviously good
16 reasons for that, but don't lose that momentum
17 because it is a growing area.
18 DR. KIBBE: We have two observers from
19 industry, what does industry think?
20 MR. MIGLIACCIO: I guess I would just
21 comment on the training, that I think one of the
22 frustrations that FDA has is the number of
23 applications and supplements that are coming in
24 from industry.
25 The good news is, I think Chris had a

1 slide that said PAT equals process understanding,
2 and we are 100 percent behind that. What we are
3 doing now is using, in the framework that the
4 guidance has provided, we are using PAT for process
5 understanding, and we are putting all our resources
6 into that, identifying sources of variability and
7 dealing with them, not necessarily moving to
8 primary control of our processes.
9 So, I think there is some frustration that
10 they are not seeing as many supplements. Right now
11 you probably have enough people trained to deal
12 with what you are getting. I think once our
13 resources can move from process understanding and
14 process capability into primary control, then, you
15 will start seeing more supplements coming in and
16 more new drug applications coming in.
17 DR. KIBBE: Anybody else? Comment?
18 DR. BOEHLERT: I was going to make a very
19 similar comment. You know, there was a lot of
20 initial interest. A number of large companies very
21 interested in the techniques involved with PAT
22 making presentations. I am wondering if that is
23 starting to wane, you know, if the FDA has seen a
24 steady influx of companies asking for information
25 or did it start off high and then it is sort of

1 drifting off.

2 The other issue on the microbiology, I

3 think there is probably considerable interest on

4 the part of companies in that technique, but there

5 is some constraints around it right now, and those

6 are compendia tests that are different, and I think

7 there needs to be some interaction with the

8 pharmacopeia on some of these topics because there

9 are different endpoints.

10 Even though you can demonstrate

11 equivalency, the compendia test right now doesn't

12 cover the rapid micro technique.

13 DR. KIBBE: Do you have a response?

14 MR. MIGLIACCIO: Yes. On the is the

15 interest waning, absolutely not. In fact, the good

16 news is if you have seen the transcripts of any of

17 the recent industry meetings and presentations over

18 the last year or so, we have gone from talking

19 about concepts to talking about applications, and

20 there are many more applications out there right

21 now of PAT where people are either solving

22 20-year-old problems or looking at a new way to

23 make a new product.

24 So, it is moving forward. The interest is

25 increasing exponentially right now. It is a matter

1 of once someone introduces in the public an
2 application, others are grabbing onto those
3 applications and bringing them home, so I think it
4 is increasing significantly.
5 Ajaz.
6 DR. HUSSAIN: I totally agree with that,
7 and I think what we have seen is I think the
8 requests we get for presentations have skyrocketed,
9 so we cannot handle most of it, so we are actually
10 refusing--not refusing--we are trying to be very
11 selective in where we speak.
12 I think others have taken up the charge
13 and that is wonderful, and that is the reason why
14 we feel that I think we don't have to keep speaking
15 all the time, and we have other champions that have
16 been created, and the champions are coming from
17 industry, academia, and everywhere.
18 The number of questions being asked of FDA
19 is increasing, and the number of proposals that
20 people are coming forward with is increasing. So,
21 right now, for example, we do not have many, we
22 have seven or eight proposals right now, which will
23 translate into some very focused comparability
24 protocols and other aspects, so at least seven or
25 eight by the end of this year.

1 DR. KIBBE: Tom.
2 DR. LAYLOFF: First of all, I think that
3 the number of people trained is probably more than
4 appropriate for the amount of material coming in.
5 I think the industry is under an
6 imperative to move to just-in-time manufacturing
7 because of the model that Wal-Mart has put out, of
8 essentially maintaining zero inventory at their
9 level, which means that the inventory control has
10 to shift back to the producer, which means that
11 they have to be able to bring things more to
12 just-in-time, and PAT is going to be able to handle
13 that or make it better anyhow, reduce the dwell
14 time, which is going to be critical for maintaining
15 good supply and keeping inventory costs down.
16 I think the initiative has gone very well
17 so far. It has to hatch on its own case, on its
18 own time, otherwise, the momentum will fall apart.
19 So, I think as the industry moves, and you move
20 with it, it will develop and expand.
21 DR. KIBBE: Introduce yourself.
22 DR. RITCHIE: Gary Ritchie. I am with the
23 USP and currently the liaison with the process
24 analytical technology project team that was formed.
25 There were some questions or issues raised

1 directed to the compendia barriers, I suppose, and
2 what I just wanted to do with the committee was
3 just to let them know that the project team is
4 addressing some of those issues, one with respect
5 to rapid micro methods, a second one with respect
6 to I think the content uniformity issue, and,
7 third, I guess in general, other techniques that
8 may be perceived currently as general chapters or
9 proposed that may be barriers, and that there is a
10 work group that will be looking at those areas, and
11 doing what we can do to see if we can improve or
12 remove those barriers.
13 I just wanted to make that comment and let
14 the committee know that it is being actively looked
15 at.
16 DR. KIBBE: Thank you.
17 Tom, did you have something else?
18 DR. LAYLOFF: This is a comment more on
19 compendia issues. The compendia or market
20 standards, the part of the law, and occasionally,
21 you run into unusual circumstances because of
22 incorporation of standards and laws, and probably
23 the most exciting ones I have ever attended was the
24 protein equivalent to nitrogen and the analysis of
25 grain for protein equivalents is a kilodalton

1 determination is done and the nitrogen is
2 determined.
3 There is a number called a PETN, the
4 protein equivalent to nitrogen, the little
5 multiplier. Well, it turns out the multiplier was
6 wrong, and it was a decision to change the number,
7 and the number was off by 2 to 3 percent, something
8 like that.
9 It was one of the most heated meetings I
10 have ever attended because everybody said if you
11 change that number by 2 or 3 percent, you change
12 the value of millions of tons of grain in ships and
13 barges and warehouses everywhere.
14 So, legal standards, even though they may
15 not be correct, cannot be changed in a very
16 cavalier fashion because they involve a lot of
17 work, a lot of impact, and the same is true for the
18 USP, there are many methods that are obsolete, but
19 if you change them immediately, all the firms that
20 have worked away from using those and validated
21 against them, are now in a box of having to
22 revalidate all their processes against the new
23 standards.
24 DR. DeLUCA: Before making my comment, I
25 would just comment I wonder what was the basis for

1 that value in the first place, did it have peer
2 review.
3 With that little comment, you know, what
4 we are talking about here, manufacturing process,
5 for a long time, we have tried to bring science
6 into the manufacturing area, and this is certainly
7 an opportunity to do that. I mean this requires
8 science.
9 I think science requires scholarly work
10 and publications, and it seems that what I have
11 heard today, an awful lot of work has gone into the
12 PAT, but I am not so sure that we have seen
13 publications coming out of this work, and I think
14 this has got to get into the literature.
15 So, I think we need to encourage that.
16 Along those lines, we are. We recognized this I
17 guess a little over a year ago that we wanted to
18 have an actual theme issue devoted to this in Pharm
19 Sci. Tech, and Ajaz is the editor along with Tom
20 Hale of that theme issue.
21 What we are trying to get publications,
22 people who are actually doing research in this
23 area, and it seems with all the presentations that
24 have gone on, some of the conferences and whatnot,
25 that we could solicit from these people, and there

1 is people around this table here who probably could
2 be contributors to this, certainly, we would like
3 to encourage the industry to submit their work in
4 this area.
5 So, I think this is essential to have
6 this, to get this kind of research and science into
7 the literature, the rapid microbiology methods,
8 these would be great publications.
9 I think the important thing about it, that
10 you would have some peer review of these, so you
11 wouldn't maybe make some mistakes about having a
12 value for the nitrogen and protein correlation if
13 you had that kind of critique.
14 DR. KIBBE: Bryan, you had a comment?
15 DR. RILEY: I just wanted to respond to
16 the question about USP and possibly not meeting USP
17 standards if you use a rapid micro method.
18 I don't think it is as big a concern as
19 some people may think it might be because even
20 though some of the rapid methods may use a totally
21 different basis of measurement and give you a very
22 different number than the traditional USP microbial
23 limits test or whatever, I think that you can
24 certain compare, when you are assessing the
25 usability of a rapid method, you can compare it to

1 the results you are getting with the USP method and
2 certainly set your acceptance criteria based on the
3 fact that you are looking at different numbers, and
4 that even though a product can still meet your
5 acceptance criteria with a rapid method, it would
6 still meet the acceptance criteria if you use the
7 USP method even though the numbers may be very
8 different.
9 So, I think that should be taken into
10 account and compared when you are assessing the
11 method itself.
12 DR. BOEHLERT: I agree, I think the issue
13 is around equivalent to or better, which is how USP
14 defines alternate tests.
15 DR. RILEY: Yes, and I think demonstrating
16 equivalence to the USP test should not be that
17 difficult for a lot of the rapid methods.
18 DR. LAYLOFF: With regard to the testing
19 for viable organisms, the rapid tests will
20 frequently give false positives. Do they also give
21 false negatives?
22 DR. RILEY: It can depend on the test and
23 what you are testing. It is something that has to
24 be looked at on a case-by-case basis, if you are
25 looking at a product or you are looking at water,

1 you could have interference, that sort of thing.
2 It really depends on what you are looking at.
3 As I said, there are some growth-based
4 rapid methods, and those would have very
5 similar--if you are looking at growth in the media
6 or not, that is going to be very similar to the
7 growth-based traditional compendia test.
8 Some of the rapid methods that don't
9 require growth, it looks like a viable stain, that
10 type of thing, that is something that we would have
11 to determine experimentally.
12 DR. LAYLOFF: But that would be a false
13 positive rather than a false negative, or do you
14 get false negatives also?
15 DR. RILEY: I think it depends on the
16 method.
17 DR. SINGPURWALLA: You wanted to answer
18 two questions, are we on the right track and any
19 recommendations. Well, I just need a point of
20 clarification. It has much to do with I don't
21 understand what PAT is all about.
22 So, the first question to you is how is it
23 different from process control practiced in
24 automobile industries and manufacturing industries,
25 and if it is the same, I am surprised that the drug

1 industry has not been using it because my sense is
2 that the drug industry has been using it ever since
3 I was a student.
4 MR. MIGLIACCIO: What has happened over
5 the last five, seven years is we have the
6 analytical technology, so the near infrared has
7 been there, and statistical process control has
8 been there.
9 What has been absent is the engineering
10 solution to bring the technology right to the shop
11 floor to marry the analytical technology to the
12 manufacturing equipment. That is what we have now
13 in process analytical technology.
14 So, you are doing real-time process,
15 monitoring, and control versus taking samples,
16 bring them through a laboratory, and then doing SPC
17 on that.
18 So, there is a paradigm shift that we have
19 gone through, that you have real-time monitoring,
20 and not just of a unit dose sample that you have
21 taken out of a blender or 10 tablets that you have
22 taken off a tablet press, but of a very large N.
23 The N has increased substantially our ability to
24 monitor the process.
25 DR. HUSSAIN: I think that is a good

1 point. At the same time, I think the key aspect has
2 been that in the sense some have regarded that the
3 pharmaceuticals would be quite different, I mean if
4 you really look at some of the literature, the
5 thought process had been that pharmaceutical dosage
6 forms are different from making machines, and so
7 forth, so some of those principles might not apply.
8 So, it has been an evolution, it has been
9 a paradigm shift, and in many ways, I have used the
10 phrase testing to document quality to quality by
11 design. We have always talked about quality by
12 design, but our mentality has been testing to
13 document quality, because that is what we could do.
14 I think the pharmacopeial structure, the
15 regulatory structure had sort of reinforced that
16 thought process on that, and Gerry is right in
17 terms of when you bring the analytical tools, the
18 engineers, everybody together, it is a paradigm
19 shift, and it is happening now to a large degree.
20 DR. SINGPURWALLA: So, am I correct in
21 understanding that you are using what the engineers
22 called "control theory" techniques into the
23 pharmaceutical industry, which was not there early
24 on?
25 DR. HUSSAIN: I think "not there" is not

1 probably the correct characterization in the sense
2 different segments have different levels of
3 controls, for example, manufacture of the drug
4 substance material API, which is more closer to
5 chemical synthesis, chemical industry, you have a
6 lot more of that in there.
7 Biotechnology evolved later on, so they
8 have more of that already in place, because process
9 is so critical. So, there are segments, the
10 pharmaceutical dosage forms, you know, tablets,
11 capsules, and so forth, have not received the same
12 level of attention, and that is new for these
13 dosage forms, so it depends on which part of
14 industry you look at.
15 DR. SINGPURWALLA: So, to come back to
16 your original thing, about your question, so when
17 you say PAT, this is a generic thing.
18 DR. HUSSAIN: Yes.
19 DR. SINGPURWALLA: Not specific to the
20 drug industry.
21 DR. HUSSAIN: Well, the framework is
22 generic to manufacturing irrespective of which
23 manufacturing. The language, the vocabulary we
24 have used in the guidance is pertaining to the
25 pharmaceutical industry, and from that perspective,

1 it is somewhat focused on the pharmaceutical
2 situation or scenario.
3 DR. KIBBE: Anybody else? You are doing
4 so well.
5 In light of the fact that we have run out
6 of steam, what I propose we do is break for lunch.
7 We have already checked, I hope we have checked,
8 with our open hearing individuals, and we are going
9 to try to start the open to the public at 12:30
10 instead of at 1 o'clock, so that you are all
11 invited to be back here at 12:30.
12 [Whereupon, at 11:15 a.m., the proceedings
13 were recessed, to be resumed at 12:30 p.m.]

1 A F T E R N O O N P R O C E E D I N G S
2 [12:30 p.m.]
3 Open Public Hearing
4 DR. KIBBE: We have how many people who
5 have asked to speak? We have four. Their
6 presentations, if they have slides, and what have
7 you, will be on the web page by tomorrow, we hope,
8 so that those of you in the public who need copies,
9 and what have you, can get access that way.
10 We have the Regional Director of the CMC
11 Regulatory Affairs from GlaxoSmithKline, Leo
12 Lucisano. We are really lucky to have you here.
13 MR. LUCISANO: I don't have any slides
14 today. Really, my comments are intended to
15 complement Dr. Riley's presentation on rapid micro
16 methods this morning.
17 It wasn't until I saw Dr. Winkle's metrics
18 this morning that I realized that GlaxoSmithKline
19 provides about 10 percent of the annual reports
20 that is reviewed by new drug chemistry and about 5
21 percent of the manufacturing supplements.
22 So, we create a lot of work for the Office
23 of Pharmaceutical Sciences. So, I was delighted
24 when, on February 27th, the PATRIOT team from FDA,
25 the PAT Review and Inspection Team, completed a

1 week-long inspection at our facility in Parma,
2 Italy.
3 It was led by Bob Coleman, as Dr. Riley
4 mentioned. Bob is a national expert based in the
5 Atlanta District Office, and he was accompanied by
6 three microbiologists, one of which was Dr. Riley.
7 The inspection actually was triggered by
8 the submission of a supplemental new drug
9 application in which we sought approval of one of
10 the types of applications for rapid micro methods.
11 That technology was endorsed as PAT technology by
12 this committee back in October of 2002.
13 The inspection was a success and now it
14 enables us to potentially implement this technology
15 across a global supply chain, and it represents the
16 culmination of a 16-month effort between the Office
17 of Pharmaceutical Sciences, the Office of
18 Regulatory Affairs, and industry in addressing the
19 challenges associated with the first PAT
20 application approved as part of FDA's Quality
21 Initiative for the 21st Century.
22 What I wanted to do today was just spend a
23 few minutes talking about the challenges that we
24 had in working with the Agency to reach this
25 milestone. They were really of three types. There

1 was the technical challenges, the regulatory
2 management challenges, and the educational
3 challenges.
4 Just by way of background with respect to
5 microbiological testing in the industry, we use it
6 in a lot of different ways. We may use it to meet
7 the regulatory specifications to release a drug
8 product, we may apply it to the testing of
9 excipients, such as water for injection prior to
10 its use in the drug product, and we may also
11 utilize it to verify that a manufacturing suite is
12 sufficiently clean prior to the next phase of
13 production.
14 So, the conventional methods typically
15 take about four to seven days to complete and
16 oftentimes really represents the rate-limiting step
17 in our decision process associated with batch
18 release or release of a manufacturing area.
19 So, with the availability of commercial
20 instrumentation for rapid micro methods being
21 available and providing results in a matter of
22 hours using technologies, such as ATP
23 bioluminescence and solid phase cytometry, there
24 are tremendous opportunities for us in utilizing
25 rapid micro methods.

1 So, the technical challenges. One of the
2 examples that we had was trying to apply rapid
3 micro methods to regulatory specification for a
4 class of dosage forms, so in working with Dr. Peter
5 Cooney's staff in the Office of Microbiology, we
6 agreed on an approach that adopted a two-stage
7 acceptance criteria, combining the qualitative
8 rapid micro method with the currently approved
9 microbial limit test that used more conventional
10 methods as stated in the USP, so if a batch of drug
11 product tested free of bioburden using the
12 qualitative rapid micro test, that no further
13 testing was required.
14 If the screen indicated the presence of
15 microorganisms, then, the conventional microbial
16 limit test was performed to determine compliance
17 with the regulatory specifications.
18 So, when you think about a high-volume
19 product where the historical data indicates that
20 the product typically is free of bioburden,
21 applying rapid micro methods in this strategy
22 offers very significant advantages with respect to
23 product release and inventory turnover.
24 The foundation for the validation of this
25 methodology was actually provided by the PDA

1 technical report published in 2002. This document
2 addressed the evaluation, validation, and
3 implementation of new microbiological test methods,so,
4 speaking to Dr. DeLuca's comment this morning
5 about the availability of published literature
6 actually facilitating working through some of the
7 issues that we had around process analytical
8 technology and its approval.
9 The second type of challenge that we had
10 was the regulatory management process. We were
11 interested in applying rapid micro methods in a
12 variety of different ways at multiple FDA-approved
13 facilities, so this scope of interest would
14 potentially affect the entire approved product
15 portfolio expanding over 140 approved new drug
16 applications.
17 So, in the conventional regulatory review
18 and approval process, this might require an
19 equivalent number of new drug applications, each
20 containing a data package demonstrating the
21 application of rapid micro methods to the specific
22 product of interest.
23 So, how would we progress rapid micro
24 methods without further overburdening the Office of
25 New Drug Chemistry with additional supplemental new

1 drug applications?

2 Actually, the solution was provided by the

3 Agency with the issuance of the draft guidance on

4 comparability protocols that was published in

5 February of 2003. So, a comparability protocol is

6 essentially a plan that evaluates the effect of

7 changes on an approved product.

8 You don't have to include product-specific

9 data, but describe the analytical procedures that

10 you intend to use and the acceptance criteria that

11 will be achieved to demonstrate that there is no

12 adverse effect on product quality.

13 So, what we agreed upon that we would

14 submit a plan, a comparability protocol to apply

15 this technology, and we do it by a prior approval

16 supplement.

17 Once the Agency approved that plan, we

18 could then implement that technology at any GSK

19 manufacturing site that had a satisfactory CGMP

20 inspection status with the FDA, so that if these

21 conditions were met, any site within the

22 manufacturing network could adopt rapid micro

23 methods according to its own timeline and notify

24 the Agency via a regulatory submission that does

25 not require prior approval, such as an annual

1 report or changes being effected in zero day
2 supplement.
3 This agreement applied regardless of the
4 number of NDA-approved sites or number of
5 NDA-approved products and dosage forms manufactured
6 at a particular facility.
7 So, the process, the end result was a
8 streamlined management process for adopting rapid
9 micro methods or really any process analytical
10 technology, for that matter, across a global supply
11 chain.
12 It offered advantages for the Agency by
13 decreasing the number of prior approval supplements
14 that needed to be reviewed, and also retained the
15 appropriate checks and balances for the Agency to
16 conduct an inspection at its discretion and verify
17 that the manufacturing site has fulfilled the
18 validation requirements approved in a comparability
19 protocol.
20 The last challenge was one of education,
21 and as the discussions evolved between GSK and FDA,
22 we recognized that there was a need for both the
23 Agency and GSK to educate their personnel regarding
24 rapid micro methods, their science, and their
25 regulation. This was achieved in a number of

1 different ways.
2 Dr. Riley mentioned this morning about a
3 day-long seminar that the FDA conducted with a
4 large number of FDA staff, talking about
5 instrumentation, bringing in consultants,
6 discussing their application.
7 We also had a half-day technical meeting
8 between GSK scientists and FDA scientists in May of
9 last year with the objective of that meeting to
10 share the ongoing work that was evolving with rapid
11 micro technology, but there was also a need to
12 educate the global organization within GSK since
13 the regulatory process that was approved for rapid
14 micro methods was very different from the
15 conventional post-approval process for implementing
16 changes.
17 We also had to review our changed
18 management systems to assure that they could
19 accommodate the conditions of approval agreed upon
20 with the agency. The regulatory management process
21 approved for the implementation of rapid micro
22 methods has implications for other process
23 analytical technologies in the future.
24 Consequently, we have functional groups
25 within my organization requesting the Regulatory

1 Affairs Department to educate them under rapid
2 micro experience with FDA, and to guide them with
3 respect to future PAT applications and their
4 approval.
5 Sixteen months from the time that this
6 advisory committee endorsed rapid micro methods as
7 a process analytical technology, we now have an
8 approved regulatory process that can be applied
9 across the company's entire product line at any
10 FDA-approved facility.
11 It required the review and approval of
12 three supplemental new drug applications and an FDA
13 inspection by the PATRIOT team.
14 I would like to thank this advisory
15 committee for really providing the incentive to
16 address the technical, the regulatory management
17 and educational challenges associated with the
18 approval and implementation of a PAT technology
19 platform.
20 The resolution of these challenges
21 required the application of new guidance documents,
22 such as the guidance on comparability protocols,
23 the availability of published scientific
24 literature, such as PDA Report 33, and a new way of
25 conducting business that really required some

1 introspection and some adjustment on both the
2 Agency's part and ours.
3 I know within GSK, we are now motivated by
4 these first approvals and are looking at additional
5 applications of process analytical technologies
6 that may be more expansive in scope and require a
7 somewhat different road map, but I suspect the
8 challenges will still be somewhat the same and
9 require a similar investment of resources, cost,
10 and flexibility to be successful.
11 Thank you.
12 DR. KIBBE: Do you have any questions for
13 our speaker, anybody?
14 [No response.]
15 DR. KIBBE: Well, I will hit you with one.
16 Do you have an estimate of what was saved in
17 man-hours or paperwork on both ends of the street,
18 like for your people and for the FDA people?
19 MR. LUCISANO: With respect to reductions,
20 at the FDA inspection at Parma, we shared with the
21 Agency that for one particular product, we would be
22 saving 160 kiloEuros--it was a European site--per
23 year with the application of rapid micro methods.
24 Certainly, the availability of only
25 submitting or the opportunity to submit only two

1 supplements rather than 140 supplements to gain
2 approval of a technology across approved product
3 line offers significant cost reductions for the
4 Regulatory Affairs Department.
5 DR. KIBBE: Anybody else?
6 [No response.]
7 DR. KIBBE: Thank you.
8 We now have two individuals from
9 Xcellerex, the founder, Parrish M. Galliher, and
10 the Vice President, Quality and Regulatory Affairs,
11 Elizabeth Fowler.
12 MR. GALLIHER: Good afternoon. Thank you
13 to the advisory committee and Keith Webber in
14 particular for the invitation, and Ajaz's support
15 and vote of confidence for our view on PAT for
16 biologics.
17 [Slide.]
18 I want to introduce Beth Fowler, who is
19 our VP of Regulatory and Quality at Xcellerex.
20 The title of our talk is PAT for
21 Biologics, Ensuring Quality of Biologically
22 Produced Drugs.
23 I think I want to focus, what I would like
24 to sort of conduct as sort of a brainstorm view of
25 our opinions on PAT, to focus in on biotech drugs,

1 recombinant proteins produced in mammalian cell
2 systems or bacterial yeast systems, and less on the
3 traditional biologics, such as vaccines.
4 So, before I get going into what we have
5 to say, I would like to mention that PAT, to us, is
6 much broader than the title, the words of PAT. It
7 is not just, in our view, process analytical
8 technology that we are concerned about, it is a
9 broader vision of ensuring product quality across
10 all stages of manufacturing, but also throughout
11 the organization that is responsible for delivering
12 the drug that comes from all parts of the
13 organization as the process is developed, as the
14 process is implemented, and as the product quality
15 is assessed either in-line, at-line, or off-line.
16 We will talk a bit about how, at Xcellerex, we are
17 trying to take this broader view as part of doing
18 business for ourselves and for our customers.
19 We are a contract manufacturing
20 organization for biotech products, so we have the
21 customers' product quality right square in our
22 view, and that drives a lot of what we do in our
23 business, and we find that PAT, in general, in the
24 broader interpretation, is really good business for
25 us and for our customers.

1 I think looking back over the last 25
2 years of the biologics manufacturing business, I
3 think in the eighties, the industry was consumed
4 with the simple task or the herculean task of
5 simply producing these products and the initial
6 ones getting to market, and I think the industry is
7 really consumed with that whole endeavor, which was
8 huge.
9 In the nineties, more and more drugs,
10 biotech drugs, came to the market. We now have
11 approximately 30 individual proteins that have been
12 licensed, so getting to market in the nineties was
13 really where the industry was focusing.
14 However, in the last five years, we have
15 seen the importance of speed getting to the clinic
16 and speed getting to the market as being more and
17 more of a driver in what we hear from our
18 customers, what we have seen in our own lives and
19 biotech companies, rushing drugs to the clinic and
20 to the market, and very much our interpretation
21 today of PAT is focused, not just on quality, but
22 also affording speed without sacrifice of quality
23 or, in fact, improving quality, and I will talk a
24 bit more about that.
25 However, in the next decade, we see the

1 indications and trends in the industry impacting or
2 bringing costs to the forefront of biotechnology
3 and manufacturing through the advent of competition
4 with a number of similar compounds in the market,
5 through the pressures of managed health care, and
6 so we think that PAT will actually be invigorated
7 or stimulated by cost pressure of the industry
8 coming in the next decade.
9 [Slide.]
10 In general, that was our review of PAT,
11 again a broader vision than simply process
12 analytical technology. We are going to talk about
13 the importance of PAT specifically for biologics
14 manufacturing and drill down into the real value
15 and how we are, in several places throughout the
16 organization, in our business, implementing PAT
17 principles at various levels. I will give you
18 specific examples of those, and then wrap up with
19 some conclusions.
20 [Slide.]
21 We view PAT as process knowledge gained
22 through process analytics and statistically
23 designed process optimization studies to begin
24 with. So, in our view, it really begins with
25 understanding the process that is intended to

1 deliver a product of a certain quality.

2 So, we view PAT more as product quality

3 knowledge rather than process analytical

4 technology. The focus is really on product quality

5 wherever it is being produced in the manufacturing

6 process.

7 Again, to begin with, we start in the

8 development laboratory by studying the parameters

9 that affect product quality and yield in a

10 statistically oriented fashion in robustness

11 studies, and I will get into that a little bit.

12 So, the processes are really designed to

13 maintain product quality or to, in fact, improve

14 product quality, and we make real efforts there,

15 and I will give you some examples.

16 We see the advent of continual monitoring

17 to, in fact, further ensure process control to

18 produce a product of a defined quality, and the

19 reason that we think continual monitoring is a

20 benefit is, in fact, that if there are process

21 perturbations during a lengthy step, we can analyze

22 those perturbations more quickly and determine

23 whether or not that product is in jeopardy or

24 whether, in fact, we should invest in further

25 processing to carry it to final form.

1 With regard to then the manufacturing risk
2 of further processing a batch that could be in
3 danger, again, PAT, with the database that is
4 generated through the efforts of PAT, will help us
5 not only assess the risk to product quality, but
6 also from a manufacturing economic side, is it
7 worthwhile investing in a batch that has some sort
8 of perturbation in this processing step.
9 So, it is not just risk to product
10 quality, but in point of fact, from a
11 manufacturer's standpoint, we are also concerned
12 about are we delivering what the customer wants,
13 are we delivering on the contract to produce a
14 certain amount of product of a certain defined
15 quality.
16 [Slide.]
17 Just to talk a little bit about some of
18 the key issues that we see in this business, first
19 of all, just stepping back a bit, there is
20 biological variation in production of the material
21 that we are interested in depending on the system
22 with which you are producing the product.
23 If you are in a transgenic system, there
24 can be animal to animal variation, and in cell
25 culture based processes, whether they be mammalian,

1 bacterial, or yeast or fungi, there is variation in
2 the cell culture step.
3 It is not a surprise, the organisms are
4 very complex, they have a huge number of genes
5 whose function can impact the manufacture of the
6 product, so we expect that in biological systems,
7 there will be inherently more variation that could
8 affect product quality.
9 There can also be unknown pathogens
10 associated with biological systems, and these, of
11 course, are an issue with regard to biological
12 safety of the product, and there can be, in fact,
13 unrelated impurities to the drug with unknown
14 activities that can, in fact, be produced by
15 biological systems at low quantities that may not
16 be measured.
17 So, in general, we see biologics as a
18 highly variable environment within which to make a
19 product, and taking this account, it is to me quite
20 remarkable and wonderful that there are so many
21 approved products on the market today helping so
22 many people who are, in fact, in need.
23 So, we see this background therefore
24 advocating the greater value then of more process
25 analytical technology or more product quality

1 knowledge given the inherent variability. So, that
2 is the general background in which we see the value
3 of PAT.
4 [Slide.]
5 To just talk a bit more about product risk
6 management, this is our present state of affairs.
7 First of all, in today's biologics
8 manufacturing, we generally start with a viewpoint
9 that minimal process change should be attempted or
10 even allowed as the drug moves through the clinic
11 or into the clinic and on to the market, we try to
12 minimize the number of process changes.
13 Two. Process parameters are used, that
14 is, process control parameters are generally used
15 as surrogates for product quality indication or
16 monitoring. That is, we are not really directly
17 monitoring the product quality attributes in every
18 step of the manufacturing process mainly due to
19 limitation in analytical technology and specificity
20 especially in the presence of crude background
21 materials and matrices that interfere with current
22 methodologies.
23 Therefore, we rely on post-production
24 release and some in-process testing again through
25 surrogate markers to ensure product consistency.

1 Again post-facto is the point, post-production is
2 the operative here.
3 Generally, we are faced with processing a
4 batch to completion, which can be an investment of
5 millions of dollars, and then to find out that we
6 have somewhere along the way lost the product
7 quality attributes that we intended to achieve, and
8 that batch no longer can be considered releasable.
9 So, today's business is post-production
10 and there is a huge investment made in the intent
11 of that batch being released, but, in fact, our
12 methodologies are very large, inadequate to ensure
13 that on-line.
14 The future vision that we have is that
15 real-time, on-line or at-line monitoring of product
16 quality can provide increased assurance of process
17 in that product consistency, and that is the vision
18 that we are very interested in.
19 We think it reduces our risk, we think it
20 improves the product quality all along the way. We
21 think the customer ultimately wants to know that
22 anyway, as we do, and at the end of the day, if you
23 add up the dollars, it is cost efficient, and I
24 will give some examples.
25 Secondly, increased process understanding

1 enables risk-adjusted evaluation of process and
2 product data, so that means when we do have a
3 spurious event in manufacturing, which we will
4 have, which everyone does have, and don't believe
5 them if they tell you they are not having them, we
6 can use the product quality analytical methodology
7 on-line to assess the product quality impact at
8 that moment and decide whether or not that batch
9 should be processed or not in order to achieve a
10 certain product quality attribute.
11 [Slide.]
12 So, let's talk about where on-line, or
13 in-line, or at-line technology stands as of today.
14 On this slide on your left, the three
15 major stages of manufacturing include fermentation,
16 purification, and formulation fill finish.
17 In the second column, the purpose of each
18 step certainly is to control product quality in the
19 fermentation and to assure biosafety, that is, the
20 adventitious agents that may impact the
21 fermentation step, purification, again control
22 product quality, impurity removal, ensure
23 biosafety, virus clearance, bioburden clearance, et
24 cetera, and finally, in formulation fill finish,
25 ensure product quality, uniformity, and again

1 safety.

2 Present day, in the middle column, the
3 third column over, in the fermentation step, we
4 measure cell growth and cell viability, and we
5 measure a number of metabolic parameters that, in
6 part, control whether we use as control of the
7 growth and the viability of the cells with the
8 intent then, and the prevalidated, prospective
9 validated purpose of producing the product of a
10 certain quantity and a certain quality, but we do
11 not measure the product quality directly in the
12 cell culture step.

13 In purification, again we measure process
14 parameters including those listed as surrogate
15 markers of control of product quality. In order to
16 measure product quality, we have to take samples
17 off-line, purify the product, and measure its
18 quality attributes.

19 Finally, in formulation fill finish, we
20 get a chance to really look at the product itself
21 and the environment, the quality in terms of
22 adventitious contamination and volume as an
23 example, fill volume.

24 So, it is not really until we get to the
25 end of the process that we really get a look at the

1 product quality attributes that we are trying to
2 get at.
3 Our view for the future then is that in
4 the cell growth culture step, in the fermentation
5 step, we want to be able to measure on-line,
6 in-line, non-invasively, because we are trying to
7 protect the fermentation from contamination, the
8 content, tbe product concentration in the fermenter
9 and the quality. In fact, it could be a very
10 sensitive attribute of quality. It could be
11 tertiary or quaternary structure. It could be
12 potency, it could be glycosylation.
13 We want to understand the impurity profile
14 and any other adventitious agents that have entered
15 the step. I want to remind you that the background
16 in this step is very dirty, relatively speaking,
17 that is, there are many nutrients added to the
18 fermentation to promote cell growth. These are
19 obviously components that we need to purify away,
20 so there is a complex chemical background against
21 which we are asking to measure the product quality
22 and content.
23 Similarly, downstream in purification, we
24 want to watch quality all the time, the
25 concentration as well, as we are clearing the

1 impurities from the product and clearing any
2 adventitious agents.
3 Lastly, formulation fill finish, I think
4 what we really want to do is as we are formulating
5 our pre-formulation, really make sure we do have
6 the right quality of the product at that point,
7 because at that point in the process, the value of
8 the product is very high, there has been a lot
9 invested in it, and we want to make sure that we
10 are going to go forward, do a fill with active,
11 appropriately folded, biologically active product,
12 if that is the attribute of the product at that
13 stage.
14 So, that gives you a vision of the future
15 of what we are trying to achieve, and we feel there
16 are real values to achieving that.
17 [Slide.]
18 Simply stated, we want to ensure that
19 product quality remains consistent throughout the
20 process from the beginning to the end, not just
21 measuring it after the fact.
22 We want to assess deviations and their
23 impact in real-time, which do occur. Some of them
24 are trivial, some of them are major, nevertheless,
25 the cost invested in a cell culture step is huge.

1 It's about nearly 50 percent of the total
2 manufacturing cost is incurred within the cell
3 culture production step.
4 So, we want to avoid the cost of
5 processing unreleasable batches at that stage. So,
6 this is really cost avoidance, rapid cost
7 avoidance, not just ensuring product quality, we
8 want to kill bad batches fast and early.
9 If we want to continue processing, we have
10 got the data set to justify the batch processing
11 and ultimately, we will be ensured of batch
12 release.
13 Three. Continual process monitoring
14 obviates need for process validation. I think that
15 may be a little bit broad claim, but I think the
16 implication of processing legal technology with
17 regard to its impact on potential, the reductions
18 in process validation is huge.
19 It is huge to us because I can tell you
20 today, in order to validate a process, and I am not
21 just talking about the three qualification lots at
22 scale prior to BLA, I am talking about all the
23 process robustness studies and the assay validation
24 that is done to support those process robustness
25 studies.

1 The industry spends 50 to 100 man-years in
2 studying the impact of process perturbations on
3 product quality and process yield. That is a huge
4 investment at the cost of a quarter of a million
5 dollars per person year. You do the math, it's a
6 gigantic investment.
7 In addition, we validate the assays that
8 support the measurement of the product quality
9 under those conditions. So, there is a huge
10 investment in doing process validation. If we can
11 supplant that by doing real-time process quality
12 assessment and reduce process validation effort,
13 that is a very big implication for the industry.
14 We can reduce testing requirements at the
15 end of the process potentially if we are measuring
16 product quality and content all along the way. I
17 know that makes perfect sense to me as long as
18 those assays are validated.
19 Ultimately, we can increase process
20 knowledge through identification of critical steps
21 and parameters that impact quality, and this helps
22 obviously improve the risk assessment and validity
23 on any particular batch that is in question.
24 [Slide.]
25 The investment risk is substantial. Let's

1 just take on-line bioburden as an example in the
2 cell culture step. The assumptions here are
3 listed. If we are making 20 batches a year, a $20
4 million annual budget, fully loaded, that is $1
5 million per batch, fully loaded, a 90 percent
6 overall success rate facility, that means 18
7 batches a year gets released, that means 2 do not,
8 so the cost of lost batches is $2 million a year.
9 If we had on-line bioburden in the
10 fermenter that could detect the contamination
11 in-line, or at-line, or on-line at the time that it
12 occurred, we wouldn't invest in the processing of
13 that batch downstream. That could save half the
14 manufacturing costs of a batch, that is, the
15 downstream costs, and we would go on with the next,
16 dump that batch, and restart with the next batch.
17 That is good business. It's good business
18 for the customer, it's good business for Xcellerex.
19 [Slide.]
20 We are involved in process analytical
21 technology activities at Xcellerex. It turns out
22 we licensed the technology platform that positioned
23 the company to be in this frame of thinking in the
24 way of doing business, and I have listed here sort
25 of four or five main bullets that we are pursuing

1 at this time under process development.

2 We are using high throughput screening to

3 statistically optimize process parameters.

4 Two. We are using process analytics to

5 look at glycosylation, for instance, and microarray

6 technology, process control via noninvasive sensors

7 which we have developed, including pH and DO2, and

8 we are using on-line environmental monitoring of

9 non-viable particulates in our manufacturing steps

10 in our modular systems.

11 The benefit from optimization of process

12 development, on the right, is certainly to optimize

13 the process from the start, to examine more

14 parameters in less time.

15 So, we are doing very large statistically

16 designed experiments now to screen many more

17 parameters that could affect product quality or

18 yield. We are using automation robotics to do

19 that.

20 In process analytics with these real-time

21 assays, we can assess product quality in complex

22 backgrounds, not in-line, but at-line at this

23 point, and the non-invasive nature of the sensors

24 allows us to avoid contamination of the process

25 stream.

1 Ultimately, on-line will bring us
2 real-time assessment of environmental parameters
3 and control, as I mentioned.
4 [Slide.]
5 So, specifically, in manufacturing--sorry,
6 that was more of a focus on process development
7 analytics--but in the manufacturing, what we have
8 really implemented in automation include electronic
9 batch records, non-invasive sensors, and on-line
10 quality assurance.
11 So, again, this is showing us a broader
12 view of PAT, so at manufacturing level, we are not
13 just talking about on-line sensors and on-line
14 activity, on-line analytics, we are talking about
15 an overall quality attribute or quality program
16 that achieves what we think is a higher level of
17 product quality, and automation is one vehicle to
18 do that.
19 We are using controlled environment
20 modules to separate the operators in the process,
21 and we are using disposables. On the right is
22 listed the benefits of doing business this way.
23 So, this is our sort of approach to
24 process analytical technology, but again thinking
25 on the broader level of product quality knowledge

1 and improvement in the manufacturing.

2 [Slide.]

3 With regard to knowledge management, and

4 data, trending, and archiving, we have put in a

5 system that is getting right at that, and so we are

6 right in line with the PAT philosophy of using

7 process knowledge historically, archiving it,

8 trending it, statistically analyzing it with our

9 eFactory platform.

10 [Slide.]

11 In process optimization, here is another

12 example. We do many multivariate studies with many,

13 many combinations of variables. This is a graph of

14 one experiment in which we have cross-plotted the

15 results of duplicates in one experiment in which we

16 have looked at over 300 different media

17 formulations.

18 Through these methodologies, which give us

19 the statistical data and power, shown in the

20 numbers on the right, lower right, we really get a

21 good look at process robustness and parameters that

22 affect product quality and yield.

23 So, the automation and robotics puts us

24 ahead in terms of understanding more about our

25 process before it goes into manufacturing.

1 [Slide.]

2 Electronic batch records. Here is a
3 picture. This gives us the ability to provide
4 on-line quality assurance, which is again advocated
5 by the PAT guidance. We use electronic batch
6 records to catch compliance issues with the
7 operators, signatures, quantities, process control
8 parameters, so that real-time, we are catching
9 product or process control parameters that are out
10 of spec or out of control.

11 [Slide.]

12 We look at our data historically. Here is
13 a chart of 30 batches or so, and there are four
14 lines on the graph showing the data from different
15 parameters that we are measuring. In fact, this is
16 a composite graph of the step yields of the
17 process, so there are four steps in each graph of
18 data points, is showing the step yield for that
19 particular step in the process.

20 The point here is that we are using
21 statistical process control as advocated in the PAT
22 guidance to learn about the process, to learn more
23 about what affects product quality, product
24 performance, and product yield.

25 [Slide.]

1 A couple of more slides. I would like to
2 just mention the challenges in applying process
3 analytical technology to biologics. Really, I
4 think are three or four key points.
5 First, the investment in bringing
6 analytics on-line is not trivial. We don't see a
7 big driver to do that, and I think that, as I
8 mentioned, cost drivers will, in fact, I believe
9 stimulate more investment in on-line or at-line
10 technology.
11 I think until we have cost pressure in the
12 industry, there will not be a huge driver to do
13 that.
14 Secondly, innovation to develop analytical
15 tools to assess critical attributes really is where
16 it has to start. It has to start back in the lab
17 long before you get to the manufacturing line, you
18 have got to be back in the lab converting the
19 technology to something that is applicable on-line,
20 perfecting that technology, miniaturizing it, and
21 designing it to work in the plant floor.
22 Extensive data has to be accumulated then
23 in order to validate the methodology to identify
24 those critical attributes and appropriate limits
25 for that on-line method.

1 Always, there is a regulatory uncertainty.
2 I think we are always concerned about more data
3 revealing more variation, and why would we want
4 that if, in fact, the variation is out of spec.
5 So, that is always a concern, and I think it is a
6 matter of a lot of the date.
7 Stringency of limits related to the
8 criticality of impact gets to how widely you are
9 going to validate the variance tolerance in your
10 process with your on-line methodologies.
11 [Slide.]
12 Again, the regulatory risk is data, how
13 much data is too much data, what is the collection
14 interval, continuous versus intermittent data
15 collection. How to use that data, speeding release
16 or speeding off-line release post-batch, or
17 real-time release, and how to manage noise.
18 At the end of the day, we do not want to
19 lose product itself, we do not want to lose
20 productivity or lower the plant output. It just
21 leads to higher manufacturing costs and lost
22 product quality for the client.
23 [Slide.]
24 Here is an example of a continuous
25 real-time data set with spurious spikes. This

1 process actually tested the in-control, but, in
2 fact, we had spikes during the continuous
3 monitoring, are those spikes meaningful.
4 The organization needs to have a mechanism
5 by which to analyze spurious spikes due to
6 electronic noise or other things in order to ensure
7 that it is an issue or not an issue.
8 [Slide.]
9 In summary, we think that the impact of
10 PAT is as follows. First, we clearly want to
11 measure the product quality in the process stream,
12 and we support that.
13 Secondly, we want to increase the
14 understanding of the process and the product
15 quality relationship. There is a relationship. It
16 is not just product by process, or process by
17 product. The two go together and understanding
18 more about that is money in the bank.
19 Third, continual process monitoring
20 obviates the need for process validation. We think
21 that is possible within limits.
22 Fourth, we believe that PAT enables
23 science-based decisionmaking real-time in
24 manufacturing where it has a huge value. It can
25 reduce batch release time ultimately at the end of

1 the batch, and can ultimately increase plant
2 capacity. It can overall lower manufacturing risk
3 and, in fact, lower our cost of goods delivered.
4 So, in summary, we think after all those
5 things, PAT technology really can be a very cost
6 effective investment for a manufacturing
7 organization.
8 Thank you.
9 DR. KIBBE: Thank you. Are there any
10 quick questions? Then, we will move on to our next
11 speaker.
12 DR. COONEY: Parrish, do you see any
13 particular needs in the guidance that have been put
14 forward so far on PAT to extend it to biologics?
15 MR. GALLIHER: Yes, we had a discussion
16 actually a week or so ago with Ajaz and team. I
17 think the impact of reduction in process validation
18 is understated in the guidance as written. We
19 would like to explore that further and perhaps
20 expand the interpretation and the understanding of
21 the impact biologics.
22 The cost of process robustness study and
23 the cost of validation is huge, and it may or may
24 not be the right way to go ultimately if we are
25 really thinking about PAT. So, I think that is

1 particularly an area for biologics that I would
2 think about.
3 DR. SINGPURWALLA: I have two comments.
4 One is your control charts. It looks like your
5 step one is out of control, right?
6 MR. GALLIHER: That data does not show any
7 release parameters.
8 DR. SINGPURWALLA: The top one, to me it
9 seems like it is out of control, but that is a
10 minor point. The major point is this, that we have
11 had two talks, one by yourself, one by the previous
12 speaker, and what we have seen is extolling the
13 virtues of PAT into your particular industry.
14 It is my sense that the FDA has taken the
15 initiative and the lead in terms of infusing PAT
16 into the pharmaceutical industry. It has made you
17 more efficient, presumably you saved some money.
18 How much of that money has trickled down to the
19 consumer as a consequence, or is there any estimate
20 of that? Because it is government investment in
21 the end.
22 MR. GALLIHER: I am not sure I can answer
23 that directly. I would say that in biotech
24 manufacturing, cost pressure is not really present,
25 so consumer cost reduction interest in the

1 pharmaceutical, at the end of the day, has not
2 really trickled back to manufacturing organizations
3 as part of biotech pharma companies saying to
4 manufacturing you must lower costs.
5 The game has been to get to market quickly
6 or to the clinic and to produce enough product. We
7 have not seen on a broad scale yet the trickle-down
8 of high cost of drugs, biopharmaceutical drugs to
9 the manufacturing floor. It has not really
10 happened.
11 That is why I said at the beginning of the
12 talk, I think that is in the next decade. As
13 managed care begins to trickle back down through
14 the pharmaceutical value chain to the manufacturing
15 floor, we will begin to see it.
16 DR. SINGPURWALLA: So, what has been the
17 gain then?
18 MR. GALLIHER: The gain for manufacturing,
19 the gain for the organization?
20 DR. SINGPURWALLA: Yes.
21 MR. GALLIHER: The gain for the
22 pharmaceutical organization is to reduce its
23 operating costs and therefore, presumably,
24 hopefully, to increase profits.
25 DR. SINGPURWALLA: Ah, but I want to see

1 some of your profits come to me.

2 [Laughter.]

3 MR. GALLIHER: Well, maybe we should have

4 a talk outside.

5 DR. KIBBE: Anybody else?

6 DR. SELASSIE: I have a broad question on

7 your statistical process control. Are they

8 sequential and are those the overall yields for the

9 whole process?

10 MR. GALLIHER: This is an example of a

11 process development data set, where in process

12 development, again, this is where we are building

13 information about the process, this is not actual

14 manufacturing runs.

15 We are looking at the performance of

16 different steps in the process and the yield. The

17 lines that go through the data points are averages

18 of the data.

19 DR. SELASSIE: I am kind of curious

20 because it looks like as you go from one step to

21 the fourth step, I mean the yields gradually go

22 down. Is that the overall yield or just the yield

23 for each step?

24 MR. GALLIHER: Each line is the step

25 yield. Again, this is listed here as an example.

1 DR. SWADENER: Since this is a sense of an
2 evaluation of the process, I am presuming that some
3 of this is used to determine whether some steps are
4 necessary or not in the monitoring process?
5 MR. GALLIHER: Well, what we do is we look
6 at this, this is the kind of data that we look at
7 to determine whether or not there are trends
8 starting to impact the manufacturing controls, so
9 instead of just looking at a few data points at a
10 time, we look over a number of data points to
11 determine if there is a trend developing in the
12 data.
13 We have shown this graph as a process
14 development data set illustrative of the process of
15 looking at many data points over a long period to
16 determine if there is a trend in the data, in the
17 performance of the process that you wouldn't see if
18 you were just looking at a few batches at a time.
19 DR. SWADENER: Do you sometimes find that
20 some of your data points that you thought were good
21 data points, were not good data points, therefore,
22 you don't need to use them?
23 MR. GALLIHER: No. I mean if we are
24 producing a pharmaceutical drug for intended human
25 use, each batch is tested and has to meet with

1 these criteria before it is ever released.

2 DR. SWADENER: But suppose one data point

3 consistently comes out with the same results all

4 the time, and doesn't tell you much?

5 MR. GALLIHER: Well, each assay is

6 validated to ensure that it is measuring the

7 intended attribute of the product, so we are quite

8 sure that that is not happening.

9 In those particular assays, there are

10 controls that are included in those analytical

11 assays to ensure that the analytical method is, in

12 fact, valid every time it is run.

13 DR. SWADENER: What I am saying is suppose

14 a given data point consistently comes up with the

15 same result, and it is not really adding any new

16 data to the whole process, can you drop that one

17 and move it somewhere else?

18 MR. GALLIHER: Not without going through

19 the program of change control, which is a regulated

20 method of evolving process analytical technology or

21 release assays or process methodologies or

22 controls.

23 DR. KIBBE: I think we need to move on.

24 We are gaining back all the time we saved this

25 morning.

1 Thank you very much.
2 We have a representative from the
3 pharmaceutical segment manager of Siemens Energy &
4 Automation, Troy Logan.
5 MR. LOGAN: Good afternoon. I would like
6 to start by thanking the committee for providing
7 the opportunity to speak here today about some of
8 the experiences that Siemens has had with process
9 analytical technologies.
10 [Slide.]
11 The PAT opportunities that are listed in
12 the PAT draft guidance published by the FDA are
13 that it can help to reduce production time, to have
14 faster production lead time, also right first time
15 quality, which means that the whole quality system
16 is an integral part of the process, and a kind of
17 quality system built in by design.
18 Also, managing variability, trying to
19 reduce the variability of the process to have a
20 more consistent process.
21 Facilitating continuous processing meaning
22 that we can move faster from one unit operation to
23 the next with fewer waiting times, which most of
24 the time are due to laboratory tests.
25 We can increase automation to improve

1 operator safety and reduce human errors, which is
2 more of a risk consideration.
3 Then, the ultimate goal is real-time
4 product release. In fact, to achieve real-time
5 product release, we need to achieve the first steps
6 listed above.
7 [Slide.]
8 Real-time product release means that we
9 can release the product to the market without a
10 final test, so without doing laboratory tests, but
11 just by reviewing process characteristics.
12 [Slide.]
13 If we consider the whole biopharmaceutical
14 process, there are a few steps which are very
15 important and which have a big impact on the
16 quality of the product.
17 For instance, the bioreactor stage is one
18 of the most important steps because it has a large
19 impact on the final quality of the product,
20 compared to separation and purification where the
21 quality cannot be changed very much. We can only
22 isolate the desired product out of the
23 fermentation.
24 So, in fact, the first step where PAT
25 should be applied is in steps where the impact on

1 quality is the highest, and this is the bioreactor
2 stage. Later in the manufacturing process, we see
3 that the biggest impact on final product quality is
4 in the formulation step, so that is why formulation
5 happens to be the first one addressed for PAT for
6 drug manufacturing, also known as secondary
7 manufacturing.
8 All other areas can benefit similarly from
9 PAT. The idea is to start with the areas where it
10 will have the greatest impact and the returns will
11 be the greatest.
12 [Slide.]
13 To achieve real-time product release, we
14 need to bring together many disciplines, and we
15 must carefully consider the capabilities of each as
16 we do. For instance, we have to combine
17 manufacturing execution systems together with
18 advanced control systems, with process modeling,
19 also with process development, with multivariate
20 data analysis or chemometrics, with process
21 understanding and with process analytics, all, of
22 course, inside of a regulatory framework.
23 [Slide.]
24 If we look at the whole concept, there is
25 the process layer on the bottom and the IT

1 infrastructure on the top. There are two aspects
2 of this whole PAT concept, the control aspect on
3 one side and the process monitoring aspect on the
4 other.
5 Looking inside the boxes, we see that the
6 control solution is built out of control modules
7 and equipment modules, brought together to form
8 pharmaceutical modules, a batch management system,
9 and, of course, electronic batch records, which are
10 fed into the MES or IT infrastructure.
11 On the other side are the process
12 analytics which can be applied in two ways.
13 First, for process specification verification and
14 real-time product release, and, second, for
15 collecting information from the process to apply an
16 iterative learning control system that will help to
17 increase our knowledge of the process on the fly as
18 the process runs and, based on that, improve the
19 control strategy.
20 Further on top, as you gain more knowledge
21 about your process, you can begin to optimize that
22 process.
23 [Slide.]
24 We look now to a real world example, that
25 is, control of a bioreactor, which is typically

1 based on monitoring pH, dissolved oxygen and
2 temperature, and apply a closed loop control
3 strategy based on the information from these
4 sensors.
5 If we now also introduce a PAT solution,
6 it can help by providing more information about the
7 process, not just secondary parameters, but also
8 chemical composition and biological performance or
9 biological status of the process. This information
10 can then be used as an input to the control system.
11 Separate from this, there is typically a
12 laboratory that is checking the quality of the
13 product and making decisions about holding or
14 releasing the product to the market.
15 A future strategy can be that decisions
16 are no longer made in the laboratory, but instead,
17 the process control system on the manufacturing
18 floor decides, based on the information obtained
19 from PAT, if product will be held or released to
20 the market.
21 [Slide.]
22 This is an example of where we have
23 applied PAT for fast identification of
24 contaminations or a certain disturbance in a
25 process. This is from a yeast-based fermentation

1 where the major threat to the process is
2 contamination introduced by microorganisms coming
3 in through air that is sparged into the bioreactor
4 or via the substrate before it is transferred into
5 the bioreactor.
6 The conventional laboratory test
7 normally take 8 hours before it is known if this
8 contamination has taken place. With this new way
9 of applying PAT, we are able to quickly, within a
10 few seconds, identify when there is a
11 contamination.
12 [Slide.]
13 What you see here is a representation of
14 this kind of classification. On purpose, we have
15 contaminated the yeast fermentation with 7 of the
16 most common microorganisms that, in the case of
17 this company, caused one-third of their rejected
18 batches, so that means significant economic impact
19 in their business.
20 We intentionally contaminated the
21 fermentation and found that we can classify and
22 identify the outcome into contaminated or not
23 contaminated product, and this chart is the result
24 of that experiment.
25 [Slide.]

1 Here is another example. An in-situ probe
2 was placed inside a bioreactor and is monitoring
3 the process by collecting the spectra from the
4 beginning to the end, and a principal component
5 analysis is being applied. The principal component
6 analysis is used to monitor process change
7 throughout the batch.
8 [Slide.]
9 What you see here is a two principal
10 component plot that represents the major changes of
11 this process. From a process control point of
12 view, we are mainly interested in what is changing
13 in the process, so we would like for everything
14 that is staying constant to be taken out of what is
15 being monitored. That is exactly what a principal
16 component analysis does.
17 The result of this principal component
18 analysis is a plot that is called a process
19 fingerprint. It represents a typical batch track.
20 The next step is to define the ideal track, which
21 is the so-called "golden" track. By following this
22 track, the required endproduct quality can be
23 achieved.
24 The next step is to determine the maximum
25 acceptable tolerance to achieve the required

1 endproduct quality. That is this tunnel, which can
2 be calculated based on good batches. This is a
3 kind of standard deviation that we will allow
4 around the process track.
5 This is a great tool for helping to define
6 if the process is running consistently. Also, if
7 sudden process disturbances occur, it is a fast
8 detection tool that helps to avoid lasting impact
9 of those disturbances.
10 Shown here in the middle of this chart is
11 where we had a disturbance due to an oxygen
12 depletion when an oxygen valve was blocked.
13 [Slide.]
14 Now we have the PAT road map
15 implementation stages for the implementation of
16 PAT. It consists of three major steps. First, is
17 the measuring part including monitoring and process
18 understanding. The second one is the controls, and
19 the third is optimization.
20 Along with these three steps we have some
21 parallel tracks. One is knowledge and change
22 management, another is the validation aspect, and
23 the third, the people and organizational issues.
24 Because the introduction of this PAT solution will
25 cause a lot of changes in the organization, people

1 have to make decisions differently.
2 For example, the decision on holding or
3 releasing product will be made on the manufacturing
4 floor and no longer in the laboratory. This means
5 that the work processes of the organization must be
6 realigned.
7 We start first with risk assessment on
8 product quality and on the process, so to determine
9 the required product quality and assess the process
10 to determine which process parameters are the
11 relevant ones to track.
12 The third part is the analyzer assessment,
13 finding out which analyzer is most appropriate for
14 the type of process and what information is needed
15 from that analyzer. Once all of that information is
16 collected, a multivariate data analysis is
17 conducted. This focuses on finding the
18 relationships between product quality and process
19 parameters.
20 Based on that, you can then begin the
21 design of experiments. The PAT solution will then
22 begin to help to determine which are the good
23 batches and isolate the "golden" batch.
24 The next step is then control. Here, we
25 can modify control parameters if the process goes

1 off track, and we can get an understanding of the
2 ideal process control strategy. When the process
3 is running off track, other techniques can be used
4 to get the process under control again, and we can
5 improve process knowledge with the application of
6 an iterative learning control strategy.
7 During all these different steps, we are
8 collecting a lot of information - process behavior,
9 process capabilities, process quality, et cetera.
10 This data can then be used to further
11 optimize the process meaning we can further
12 optimize the "golden" process track, perhaps the
13 processing time can be shortened, improving
14 efficiency of equipment utilization, or the process
15 can be optimized to use fewer resources and still
16 achieve the required final endproduct quality.
17 In conclusion, the use of these PAT
18 technologies will become part of an ongoing
19 strategy of continuous process improvement.
20 Thank you for your attention.
21 DR. KIBBE: Quick questions, anyone?
22 DR. SINGPURWALLA: Your second slide said
23 something about production release of
24 pharmaceuticals without final tests.
25 MR. LOGAN: Yes.

1 DR. SINGPURWALLA: Are you serious about
2 that?
3 MR. LOGAN: I will have to begin by
4 answering that I am really here as a spokesperson
5 for our technical people, but as I understand it,
6 that is the ultimate end goal that they are
7 attempting to achieve, and they are seriously
8 pursuing it with the end users that we are trying
9 to work with.
10 DR. SINGPURWALLA: Maybe that needs a
11 point of clarification. You don't want to test,
12 you cannot test every product because if you tested
13 it, you couldn't sell it. When I buy a pill, it is
14 presumably not tested, but then you still want to
15 sample even though you use PAT techniques at the
16 end, you do want to sample.
17 Here is an analogy. Suppose you are
18 building an airplane engine, it has got many parts.
19 You test each part. There is no guarantee that when
20 you put it all together, the engine will function.
21 So, you still need to do testing at the end to make
22 sure that nothing has been overlooked. No? Why is
23 that?
24 DR. KIBBE: I will allow your colleague to
25 respond. We will let you off the hook.

1 Anybody else have anything?

2 [No response.]

3 DR. KIBBE: Thank you very much.

4 Our last speaker during the open public

5 hearing is someone from Laboratory Instrumentation

6 Scientist, Foss-NIRSystems, Robert Mattes.

7 MR. MATTES: Thank you. I am Robert

8 Mattes.

9 I would like to talk to you today about

10 near infrared spectroscopy as possibly one of these

11 analytic tools that would help in the toolbox for

12 PAT, and by demonstrating some of our experiences

13 in PAT so far as we have implemented some

14 techniques in the tableting arena.

15 [Slide.]

16 The near infrared, just so everybody

17 knows, is the region between the visible and the

18 mid-IR, and it looks at overtones of the

19 fundamental absorptions in the mid-IR.

20 [Slide.]

21 One of the things that we have done for

22 years using near infrared has been the inspection

23 of incoming raw materials, and we can measure them

24 for identification and qualification of those

25 materials, so that you are making sure that you

1 have the right materials going into a process
2 fermentation cell before starting a reaction.
3 One of the things we also have had a lot
4 of experience in and has been implemented in
5 manufacturing environments is measurement of
6 moisture content and lyophilized product. I am
7 going to show some data from each of those.
8 [Slide.]
9 I have a similar chart to the last speaker
10 here that shows, first of all, the typical types of
11 monitoring that we do real time In a process
12 reactor for temperature, pH, oxygen level, you
13 know, and you are controlling the temperature and
14 sparging and pH level.
15 With the near-infrared probe also
16 introduced directly into the process reactor, we
17 are able to measure analytes, amino acids, glucose
18 levels, feedstock levels in that process reactor
19 real time, which helps the manufacturing people a
20 great deal.
21 We haven't actually installed this in, in
22 research laboratories and plants so far.
23 So, if you are looking at the raw
24 materials that we have now identified and qualified
25 being brought into the bioreactor, then, we are

1 monitoring the analytes and can real-time adjust pH
2 or nutrient levels, and so forth, according to the
3 data that we get.
4 As the product comes out, we can measure
5 the moisture content as the product is being dried
6 and possibly lyophilized. This can also lead to
7 control feedback for process improvement through
8 statistical process control charts, and so forth,
9 as previous people have mentioned.
10 [Slide.]
11 Here are some of the organisms that we
12 have worked with, Escherichia coli, products like
13 you see on the list there, and the biomass also.
14 With one spectrum that you take in the near
15 infrared, you can analyze multiple components
16 instantaneously with the same spectrum.
17 In fact, we are working on one experiment
18 right now where we are looking at 28 different
19 analytes including all the amino acids, glucose,
20 glutamate, lactate, and so forth. Really, your
21 requirements are not limited in that sense.
22 [Slide.]
23 Here is an example of a process, the raw
24 near-infrared spectra of a process as it
25 progresses. As biomass increases the y axis

1 spectra or the absorbance of the spectra increases,
2 as you can see here.
3 [Slide.]
4 You see these two major peaks are the
5 water bands in the near infrared. It is not
6 terribly informative in that form. We usually take
7 the second derivative of the spectra, which
8 enhances the resolution and enhances the peak
9 separations.
10 In the top set of spectra here, we see one
11 analyte progressing with time, and it is increasing
12 in a downward direction because of that second
13 derivative that we have taken. In the lower set of
14 spectra, we see where different analytes are
15 appearing within a process.
16 [Slide.]
17 The colors on the charts are backwards in
18 the overhead here, but I have corrected them in
19 your handout, I am sorry about that, but the
20 biomass should be in red as you will see it
21 increasing with time in the process, and the
22 glycerol content was decreasing there.
23 So, you can see using those spectra, you
24 can predict and measure the levels of different
25 analytes and trend them with time rather than

1 waiting for a week or more sometimes, waiting for
2 the wet chemistry to come back on a process that
3 you are running presently.
4 [Slide.]
5 Here are some of the types of things and
6 the types of error in precision that we have been
7 able to develop. At-line, we are talking about
8 using a peristaltic pump that pumps out of the
9 reactor and back in again. In-line, we are talking
10 about actually having it pulled right in the
11 reactor, which is the type of work I have been
12 working on most recently with some of our
13 customers.
14 [Slide.]
15 One of the things that has been reported
16 recently in biotechnology and bioengineering by a
17 group that worked at Strathclyde University in the
18 UK was CHO cell fermentation, which is a very big
19 topic right now.
20 They used a small, 2-liter bioreactor
21 similar to the one you saw in a previous lecture
22 there, and they were monitoring glucose, glutamine,
23 lactate, and ammonia.
24 [Slide.]
25 This is more like the work that I was

1 doing most presently with about a 100-liter
2 bioreactor with a direct fermenter interface, using
3 standard Ingold port. We are putting our probe
4 right into the sterile environment. The probe can
5 be sterilized right in the environment.
6 As I say, we simultaneously can get
7 results in less than one minute of up to 28
8 analytes. Previously, we have to have developed
9 the model for each one of those. The
10 time-consuming part is upfront on the analysis
11 rather than the real-time usually used in wet
12 chemistry.
13 This then can be turned into monitoring
14 and closed-loop control, adding feed or whatever,
15 changing glucose levels real-time automatically,
16 but certainly in the nearest future, will help the
17 people to know when the levels have changed to a
18 serious level within a reactor real-time.
19 [Slide.]
20 Here is the results of that particular
21 experiment with the CHO cells. You can see the
22 precisions and ranges that were used in that
23 experiment with ammonia, glucose, lactate, and
24 glutamine.
25 [Slide.]

1 Here is an example of monitoring
2 lyophilized product. You mentioned earlier that
3 not every sample can be measured or would be
4 destroyed. In this case, we can, we actually
5 non-invasively, non-destructively measure right
6 through the bottom of the lyophilized bottle, and
7 we can predict the moisture content. So, there is
8 a possibility of 100 percent measurement in this
9 case.
10 You see this band, the largest band there
11 is the water band. Again, it's the second
12 derivative, so it is increasing in downward
13 direction. The driest bottle would be the red line
14 that is up at the top.
15 [Slide.]
16 Some of the benefits for the PAT
17 initiative in the biotech area. It gives a
18 real-time analysis of sterile environments. You
19 don't have to constantly be taking samples out that
20 could lead to problems with sterility and asepsis
21 and also the possibility of closed-loop feedback
22 process control.
23 It is not invasive and can add to the
24 process optimization, as people spoke of earlier,
25 waste reduction, and better understanding of your

1 process, so that they can create safer and
2 improved, more consistent product.
3 Thank you. Are there any questions?
4 DR. KIBBE: Questions?
5 DR. SINGPURWALLA: This is very
6 interesting. So, this is a non-invasive method of
7 looking at some particular unit, but then do you
8 have a template for what would be a normal unit,
9 and how do you compare these templates?
10 Suppose you have a template which says
11 this is what the spectrum of a proper product
12 should be, and then you get a defective, how do you
13 say this is defective?
14 MR. MATTES: What you are talking about is
15 a qualitative analysis before predicting the sample
16 quantitatively? Yes, we can build libraries, and I
17 have done quite a bit of work like this recently.
18 You want to build a library of what
19 qualified good samples of spectra should look like,
20 and if it doesn't conform to those criteria,
21 statistical criteria that you have developed in
22 your library, it gives you some sort of indication,
23 or it will not give you a prediction as such, so
24 you won't be predicting on the wrong type of
25 spectrum.

1 DR. SINGPURWALLA: What you need is a
2 template which measures the spectrum of a good
3 product versus the spectrum of a defective product
4 and the criteria for seeing how diverse those two
5 are, because, you know, a little diversity, you
6 cannot say it's bad or good, but you need proper
7 criteria to say that this is very diverse, and I
8 don't know if you have that, but it is interesting.
9 MR. MATTES: Yes. We use statistical
10 criteria in our library model developments, and we
11 can use bad samples as reject sets, so we can test
12 both positive and negative sets, and it is
13 basically, to use the simplest example, if you had
14 normal distributions of 3-sigma outlier or you
15 choose some number of standard deviations from the
16 mean-centered spectrum of this acceptable
17 population.
18 DR. KIBBE: Anybody else?
19 DR. COONEY: An extension of the previous
20 question. You are using the sensor to measure
21 multiple components in variable and complex
22 systems. To what extent do you have to go back and
23 redevelop the algorithm for each system for the
24 components versus being able to use standard
25 wavelengths or a template, as was asked, that you

1 can apply across different processes?
2 MR. MATTES: Well, each unique process
3 really needs the model development done for that
4 process, so this, as I say, is the upfront
5 time-consuming portion of this model development,
6 but you simultaneously are looking at all the
7 variance caused by all the different constituents
8 or analytes in the matrix of your fermentation.
9 So you need many samples, reference
10 samples, to help you be able to do this, because
11 you are going to have so many degrees of freedom,
12 you need more samples.
13 DR. KIBBE: Thank you. The table at the
14 back end is just references?
15 MR. MATTES: Yes, it is just a
16 bibliography that has some references including the
17 work that Strathclyde University did on the CHO
18 cell mammalian culture.
19 DR. KIBBE: Great. Thank you very much.
20 Now we are back to the PAT Applications
21 for Products in the Office of Biotechnology
22 Products, and we are going to start off with Keith
23 Webber. Keith is here ready to lead the charge.
24 PAT Applications for Products in the
25 Office of Biotechnology Products

1 Overview and Issues
2 DR. WEBBER: Good afternoon. I am Keith
3 Webber and I would like to thank the committee for
4 taking the time today to participate and listen to
5 the issues surrounding our desire to implement PAT
6 technologies for the products in the Office of
7 Biotechnology Products.
8 As Ajaz mentioned this morning, the PAT
9 guidance specifically excluded the biotech
10 products, that are regulated in our office, from
11 its scope.
12 To some extent, this was to expedite the
13 publication of the document and also the training
14 and qualification program for inspectors and
15 reviewers, but as he also said, it is a technology
16 that is certainly amenable to any manufacturing
17 process, so there is not inherently any reason why
18 we couldn't implement it with these products if we
19 have the technologies and the information and
20 understanding available.
21 [Slide.]
22 Now, this afternoon, just to give you a
23 brief overview of the agenda here, I am going to
24 give an overview basically of the biotech products
25 and the manufacturing processes for the products

1 that are regulated in our office, and then Dr.
2 Joneckis from CBER will give a brief overview
3 related to some of the products that are regulated
4 in CBER.
5 After that, two members of the committee,
6 Dr. Cooney and Dr. Koch, will give presentations to
7 describe some of the issues, as well as some of the
8 opportunities available in the area of fermentation
9 and biological manufacturing.
10 That will be followed by Dr. Layloff, who
11 will give a brief overview of the view in this area
12 with regard to the PAT Subcommittee which he
13 chaired when it was active.
14 Afterwards, we will put up some questions
15 to stimulate discussion. I certainly hope that we
16 will get a good amount of discussion from the
17 committee with regard to this exciting area of
18 manufacturing.
19 [Slide.]
20 The biological products as a class include
21 all the products listed here, which were originally
22 regulated in CBER. There was a reorganization back
23 in 2003 that moved the recombinant DNA-derived
24 proteins, or many of them I should say, to the
25 newly formed Office of Biotechnology Products

1 within the Office of Pharmaceutical Sciences in
2 CDER.
3 Essentially, those are the products that I
4 am going to be focusing on today. Dr. Joneckis may
5 have comments on the other products, as well, or
6 the recombinant DNA products that are still
7 remaining in CBER.
8 [Slide.]
9 This is in terms of sort of a review.
10 [Slide.]
11 There are essentially two aspects of
12 process analytical technologies. One requirement
13 is that you have to have the ability to monitor the
14 critical product characteristics that are needed
15 for the product's function, or, if it is an
16 intermediate in manufacturing, you need to be able
17 to know what characteristics are important for
18 being able to move it forward in manufacturing to
19 the next step.
20 Now, alternatively, there may be
21 surrogates as opposed to direct product quality
22 attributes that one can use to make decisions.
23 This monitoring, as has been mentioned a number of
24 times here, will optimally be done on-line, but at
25 this point, I think to a large extent, many of the

1 monitoring is done off-line, so this is something
2 we look for in the future.
3 Secondly, one has to be able to monitor
4 and modulate the critical process parameters to be
5 able to guide the product quality attributes and
6 quality characteristics during the manufacturing
7 process.
8 It is probably worth mentioning two other
9 requirements that may be self-evident, but are
10 certainly not trivial, that is, that you need to
11 know the critical characteristics of the product in
12 the first place that are important for its function
13 or that need to be obtained to get to the next step
14 in manufacturing.
15 You also need to know how these
16 characteristics can be modified and manipulated by
17 the manufacturing process parameters themselves.
18 That is one area that is really dependent upon
19 industry to determine during their period of
20 product development and gaining a thorough
21 understanding of their product and their process.
22 [Slide.]
23 This is really part of a come-down version
24 of process analytical technologies, but I think has
25 most of the important aspects with regard to the

1 manufacturing element itself. One has a process,
2 unit operation, one is monitoring the process
3 characteristics or process parameters, as well as,
4 if possible, the product characteristics during the
5 process.
6 You gather this data, evaluate it, and
7 then make decisions, so that one can adjust the
8 process to ensure that the product that is coming
9 out of that process is going to have the
10 appropriate characteristics that are desirable.
11 [Slide.]
12 This is just a brief overview, which we
13 have seen already in one of the earlier
14 presentations, of the various
15 biotechnology processes that are utilized. This
16 isn't all-inclusive, but are the major ones.
17 You have fermentations, harvesting from
18 the fermenter. You have product capture from that
19 harvest. Concentration is usually a step that goes
20 on after, and may be a part of product capture.
21 There are filtrations that are done often,
22 almost always chromatography of some sort, many
23 times multiple steps. There is formulation
24 process, and if the products are lyophilized
25 products, you then have lyophilization process at

1 the end.

2 I didn't cover filling operations, but

3 those are certainly amenable to PAT, as well.

4 [Slide.]

5 Now, what are the characteristics of the

6 biotech APIs that are generally considered to be

7 critical quality attributes? Certainly, the

8 primary amino acid sequence is critical to the

9 proper functioning of the product, however, this is

10 a characteristic that is relatively invariant, I

11 would say, once you get into the manufacturing

12 area, and it is established at the master cell bank

13 stage or the working cell bank stage, so it is

14 usually not looked at on a lot-to-lot basis.

15 The secondary structure pertains to the

16 local interactions between the amino acid residues

17 to produce a structure, such as the alpha helix,

18 the pink you see in the front, and the beta pleated

19 sheets that you see in the back, in yellow.

20 The secondary structure is really very

21 important to the protein because these are the

22 structures that serve as the building blocks to

23 produce enzymatically active sites or the binding

24 sites for protein.

25 [Slide.]

1 They come together, as I mentioned, to
2 form tertiary structures. This is illustrated here
3 in this figure by a model of an antibody FAV
4 fragment. You can see that this is purely beta
5 pleated sheet, and these tertiary structures form
6 to form the binding sites of the antibody itself.
7 The next level of complexity that is
8 characteristic of some proteins is the assembly of
9 independent protein molecules into multimeric
10 quaternary structures. Such structures assemble
11 post-translationally and they are generally held
12 together by either ionic or hydrophobic
13 interactions between the independent subunits.
14 [Slide.]
15 The last, but not least certainly, of the
16 API characteristics that I am going to talk about
17 today are the post-translational modifications.
18 Glycosylation is probably one of the most common
19 post-translational modifications that is of concern
20 with proteins, particularly those that are made in
21 the eukaryotic cells.
22 It is illustrated in this figure by the
23 sugar chains that are in the center of the Fc
24 fragment of an antibody molecule.
25 Glycosylation patterns and structures are

1 highly variable in proteins from one product to the
2 next, and they can be significantly altered, as
3 mentioned earlier, by the fermentation conditions
4 that occur during cell growth and fermentation.
5 The other modifications that are seen in
6 proteins include the proteolytic cleavages that can
7 either be caused by endoproteinases that chew away
8 at one end of the molecule or exoproteinases--I am
9 sorry, endoproteinases that eat the middle--may be
10 producing the final product as a necessary activity
11 to get the product you want, or the exoproteinases
12 which eat away at the end of the protein and could
13 produce degradation products during the
14 manufacturing process.
15 There also is often or sometimes you see
16 acylations and sulfations, and many other
17 post-translational modifications that I really
18 won't describe here.
19 [Slide.]
20 Now, leaving API on its own and looking at
21 the product characteristics themselves, which
22 really then you get into the whole impurity profile
23 of the product and excipients that may be present.
24 Impurities fall into two categories, the
25 process-related impurities, which are media

1 components coming from the fermentation process,
2 host cell proteins that would come from the
3 expression system, and then leachates, which come
4 from columns or containers that are used to store
5 the product during processing.
6 Then, also, you have product-related
7 impurities, which are perhaps truncations of the
8 molecules or misfolded molecules or aggregates of
9 the product, which can occur during storage or even
10 during manufacturing.
11 [Slide.]
12 Now, I would like to discuss briefly some
13 of the analytical methods that are used currently
14 to look at these factors for biotech products or
15 these characteristics of biotech products.
16 As was mentioned earlier, the primary
17 structure is really something that is not looked on
18 at a lot-to-lot basis unless in particular cases,
19 you might have, as I mentioned, a cleavage of a
20 protein that is part of the manufacturing process.
21 In those cases, then, one generally does look at
22 the primary structure, not necessarily with
23 sequencing, but just to demonstrate that cleavage
24 has occurred appropriately.
25 One area that I also would note here, for

1 products that are patient-specific products, for
2 example, antibodies that are used for treating
3 B-cell lymphomas where each individual patient gets
4 a unique product. There is an area where the
5 primary structure would certainly be critical to
6 look at as an identity test, if nothing else, prior
7 to giving a product to the patients.
8 [Slide.]
9 The secondary structure is somewhat more
10 difficult to evaluate, and that is because there is
11 a limited number of direct techniques. The ones
12 that are primarily used are circular dichroism and
13 NMR at this point.
14 Also, another complicating factor for
15 proteins is that most proteins have multiple
16 secondary structures in them. For antibodies, it
17 is almost all beta-pleated sheet, but other
18 proteins, you have a mixture, so you need to have a
19 method that will be able either to distill out the
20 critical values for that protein or can look at the
21 individual secondary structures separately.
22 One other complicating factor for this
23 with regard to an in-process control, which we
24 hopefully will be able to overcome at some point,
25 is they need relatively pure material to look at

1 secondary structures in a protein.
2 [Slide.]
3 Now, I grouped the tertiary and quaternary
4 structures together because they are both high
5 order structures and are amenable to a similar set
6 of analytical tools.
7 The functional assays, such as in-vitro
8 potency assays, can directly measure the
9 therapeutic--or I shouldn't say the
10 therapeutic--but the activity of the product
11 itself, so it is semi-looked upon as a surrogate,
12 but actually, it is a measure usually of the direct
13 activity, but it requires, of course, the
14 product-specific reagents to do that.
15 This is also true of the immunoassays.
16 You can get a direct picture of the structure of
17 the protein if you have antibodies that will bind
18 to 3-dimensional epitopes that are relevant to the
19 tertiary or quaternary structure, but again you
20 need to have product-specific reagents to do that.
21 Peptide mapping is a valuable method for
22 looking at the disulfide bonds to make sure that
23 they are mapped, that they are forming
24 appropriately.
25 Size-exclusion chromatography is a

1 relatively insensitive method for looking at
2 tertiary structure, but in some cases, you can use
3 it to separate monomeric from multimeric forms of
4 the protein, so that can be a very useful
5 technique.
6 Hydrophobic-interaction chromatography is
7 actually a very good method because it looks at the
8 surface charges and surface characteristics of the
9 protein and can be used to very sensitively detect
10 either misfolded proteins or proteins that are not
11 associated with their other monomers appropriately.
12 [Slide.]
13 For post-translational modifications, this
14 is probably the most variable characteristic of the
15 protein, as I mentioned before, and analyses of
16 these usually requires a highly purified protein
17 and some rather sophisticated methodologies, for
18 example, enzymatic cleavage and analysis of the
19 amino-linked oligosaccharide protein, however,
20 recently, the mass spec and NMR have allowed direct
21 analysis of post-translational modifications in
22 intact proteins, which is an up and coming
23 technique.
24 Peptide mapping can also pinpoint the
25 location of the modification within the protein

1 sequence, which is very useful for characterization
2 of the product.
3 Immunoassays and the functional assays can
4 be used for more impure proteins because they are a
5 little bit more specific for your product, however,
6 the functional assays are often not very sensitive
7 to protein modification itself unless there is a
8 specific modification that is really critical to
9 the activity.
10 [Slide.]
11 So, to summarize, inherent challenges that
12 we see to implementing PAT for biotech products at
13 this point are that the biotech products are
14 generally large and complex pleiotropic molecules.
15 They are composed usually of a mixture of
16 post-translational modifications, they have
17 multiple active sites. Some of those are
18 homologous like two binding sites antibody, or they
19 can be heterologous where you have different active
20 sites doing different functions on the same
21 protein.
22 The activities are dependent upon the
23 complex, folded conformations of a protein, and
24 proteins are also susceptible to multiple
25 degradative events, so you need to look at a lot of

1 different aspects of a protein during
2 manufacturing. As I mentioned before, these
3 include the proteolysis, aggregation, misfolding,
4 oxidation, deamidation, just to name some of those
5 that we know of.
6 [Slide.]
7 Of course, when you are considering the
8 factors involved in protein structure or actually
9 any product, you need to consider the purity,
10 potency, and the strength, of course, but also the
11 impact that those changes or modifications or
12 variabilities to the protein would have on the
13 pharmacokinetics, the pharmacodynamics, and the
14 immunogenicity of the product.
15 That is delving more into the area of the
16 product development stage of pharmaceutical
17 development as opposed to manufacturing itself, but
18 surely, that is one of the early bits of
19 information that one needs to have, we need to
20 gather.
21 [Slide.]
22 Now, I would like to talk briefly about a
23 few of the manufacturing processes that have been
24 touched on before and what the current state of
25 monitor and control are.

1 For fermentation processes, generally, one
2 can monitor and control the agitation rate, the pH,
3 the ionic strength of the media, the temperature,
4 dissolved gases, media components, and by being
5 able to monitor and control those, you can then
6 control the growth rate and the expression rate
7 usually of your product.
8 This is an area where process analytical
9 technology, we will probably see it developed
10 early, because one has that control over some of
11 the aspects of the process.
12 As we have heard before, there are methods
13 now available for detecting or monitoring the
14 biomass and bioburden through using rapid
15 biological methods, rapid microbiological methods
16 for sterility testing. Generally, one monitors the
17 product by light absorbance, for example, protein
18 concentration to A280.
19 [Slide.]
20 Moving on to chromatographic processes,
21 this is again the same format. You can monitor and
22 control your pH of the effluent or the liquid
23 phase, ionic strength, flow rate, temperature, and
24 volume, and of value here, which isn't exactly laid
25 out, though, is that because you can control the

1 volume and monitor the light absorbance, one can
2 then control the composition to some extent of the
3 fractions that you collect out of that, from that
4 column.
5 That is currently being done although it
6 is really looking just at the protein
7 concentration, one usually doesn't know except by
8 doing previous experiments, to know what is in each
9 of the fractions that you collect.
10 [Slide.]
11 Filtration processes. This includes both
12 dead-end filtrations for removal of bacteria and
13 viruses, as well as the ultra-filtration for
14 selectively removing lower and higher molecular
15 species from a product.
16 In most cases, one can monitor and control
17 the temperature and flow rate, the back pressure,
18 and the volume of the filtrate, although you
19 usually can't do all those independently because
20 they are inter-related.
21 Again, we have seen before the protein
22 concentration is monitored by light absorbance and
23 the bioburden is, at this point, generally
24 monitored off-line, but soon could be monitored
25 on-line.

1 Dead-end filtration is usually a
2 flow-through process and that generally allows
3 little control over the product characteristics
4 themselves other than the removal of the material
5 which is filtered out.
6 Ultra-filtration, on the other hand, can
7 be a much more dynamic process, and that may allow
8 more control over the composition of the product.
9 For example, ultra-filtration is often used for
10 formulation of biotech products.
11 [Slide.]
12 It was discussed a little bit earlier, the
13 lyophilization process, and this one may be
14 currently the most close to being a process
15 analytical technology. In the lyophilizer, you can
16 monitor and control the shelf temperature and the
17 product temperature, the chamber pressure, the
18 condenser temperature, the pressure, and time in
19 the lyophilizer.
20 The ability to monitor and control these
21 parameters allows you to control the freezing rate
22 and the drying rate, and the moisture content, all
23 of which directly affect the physical quality of
24 the final product, which really is what we are
25 shooting for in process analytical technologies.

1 Although you have to have a product with
2 an acceptable composition going into the
3 lyophilizer, the physical characteristics of the
4 product that comes out will play an important role
5 in the stability and the activity of the product
6 that goes to the patient.
7 [Slide.]
8 Finally, you will see these questions
9 again at the end of our session, but I just want to
10 introduce them now, because these are points that
11 we would like to initiate discussion with.
12 What technologies are available now to
13 evaluate the characteristics of protein products in
14 real time during manufacturing, or to speed things
15 along with an off-line test which is faster, is
16 valuable to know, as well.
17 What tools would allow us to understand
18 the manufacturing process better?
19 What processes in biological drug
20 manufacturing would benefit the most from
21 implementation of PAT? Essentially, where are we
22 going to get the most bang for our buck, as has
23 been said before.
24 For processes or products that do not
25 currently allow direct product quality monitoring,

1 what other strategies would you, as a committee,
2 recommend for product quality control in addition
3 to control of the in-process parameters?
4 Finally, what additional elements should
5 be incorporated in a training and certification
6 program for reviewers and inspectors of
7 biotechnology PAT applications?
8 Thank you.
9 DR. KIBBE: Does anybody have any
10 questions? It might be a good idea for us to go
11 ahead and get at least the next speaker through the
12 process, and I think it might be useful for the
13 committee to be able to take a break then, so I
14 don't know how that does to your continuity, but it
15 would be helpful for us.
16 DR. JONECKIS: Thank you and good
17 afternoon. I am Chris Joneckis. I am the Senior
18 Adviser for CMC Issues in CBER, Office of the
19 Director.
20 I am just going to briefly describe CBER's
21 perspective on process analytical technologies for
22 the biotechnology and biological products that CBER
23 currently regulates.
24 [Slide.]
25 CBER regulates a wide variety of products,

1 as shown in these slides, the majority of the major
2 product classes shown here. They include a wide
3 variety of biological and biotechnology products,
4 diagnostic and processing devices, cells, and even
5 chemical entities that are clearly derived from a
6 variety of sources and manufactured using a wide
7 variety of techniques.
8 My comments today will predominantly focus
9 on the experience that we have gained with the more
10 traditional biologics and some of the newer
11 recombinant products that are produced from living
12 organisms and are typically extracted and further
13 modified, purified, and, for example, fill for
14 distribution following some of the examples that
15 Keith provided in the manufacturing process.
16 For many of these products, most actually,
17 product contamination with adventitious agents from
18 a variety of sources is of primary concern, and
19 most of these products are again aseptically
20 processed.
21 It is important to point out also that
22 there are recombinant products not just in the
23 blood derivative class for the recombinant
24 analogues that CBER regulates, but also in a
25 variety of other classes including allergenic

1 extracts, prophylactic and therapeutic vaccines.
2 They are also used in the manufacture of various
3 cellular therapies and in some other product
4 classes not shown here.
5 CBER's approach to technology in general
6 is also applicable to other product classes, and
7 many of the comments on PAT that I will make today
8 will be applicable to those.
9 [Slide.]
10 Historically, CBER's approach to
11 controlling the process can clearly be summed up by
12 the mantra, if you will, that, "The process is the
13 product."
14 There has been a long historical emphasis
15 in understanding the product and a long emphasis on
16 understanding and controlling that manufacturing
17 process. This clearly requires, not just an
18 understanding of the process and the product, but
19 the interaction of those two, how the process
20 results in the product.
21 The nature of many of the traditional
22 biologics influenced this approach. Many of these
23 were complex heterogeneous products susceptible to
24 a variety of variability produced almost
25 exclusively from living sources or living sources

1 themselves.

2 The complex mixtures, coupled with

3 insufficient analytical technologies, made it very

4 difficult to detect all the active components or

5 materials, in fact, that can influence the activity

6 of the active components.

7 This necessitated a very strict control of

8 the manufacturing process to reproducibly result in

9 the desired product with the appropriate safety and

10 efficacy profile.

11 Recent advances in analytical technology

12 and enhanced manufacturing processes often result

13 in better defined products, aiding in a greater

14 assurance of producing products with the desired

15 characteristics.

16 Manufacturing is beneficial to implement

17 these newer technologies and improved approaches to

18 better control processes and demonstrate that

19 products can be consistently manufactured. That

20 was clearly shown in many of the recently derived

21 biotechnology and biological products.

22 [Slide.]

23 An overall approach that we have followed

24 at CBER has been that we have always encouraged the

25 application of technologies and concepts to the

1 manufacturing and testing of products.

2 Again, we have lived with developing

3 technologies throughout its history, and have

4 applied those to manufacturing and testing of

5 various products. We are actively involved in the

6 development and application of these new

7 technologies.

8 Again, historically, we have developed and

9 applied technologies appropriate to specific

10 manufacturing and testing issues. We continue to

11 be actively engaged in developing and applying

12 these technologies.

13 For example, the conversion of older

14 technologically-based assays, such as animal-based

15 assays and cell-based assays to newer analytical

16 methods, actively involved again in development and

17 application of proteonomics and genomic

18 technologies to issues, such as product

19 characterization and adventitious agent detection.

20 This large laboratory component assists us

21 in maintaining our knowledge base for discussions

22 in applying these new technologies.

23 We clearly partner with manufacturers in

24 developing and implementing new technologies and

25 concepts. As I have indicated, we have had to live

1 with developing technology throughout history.
2 It is through these interactions with the
3 manufacturers in both development and in
4 post-approval phases that allowed the advancement
5 and development and introduction of new
6 technologies or appropriate manufacturing
7 processes.
8 Issues are addressed, validation issues,
9 for example, and other types of issues about
10 understanding this new technology are addressed
11 throughout the development process, the
12 post-approval process, on review and inspection, as
13 well as in review of applications.
14 [Slide.]
15 The approach to process control that CBER
16 has emphasized is best described as a comprehensive
17 life-cycle approach to validate this process and
18 spans the life cycle of that product.
19 This approach relies on developing an
20 understanding of the process and product. Use of
21 knowledge gained can be applied throughout the life
22 cycle and typically is.
23 In addition to CBER's perspective, this
24 comprehensive approach was largely influenced
25 through interactions with manufacturers of

1 biologics and biotechnology products, incorporated
2 concepts and approaches often used in manufacturing
3 industries.
4 It emphasizes identification and control
5 of critical unit operations and process variables
6 to product intermediates, resulting in a product
7 with acceptable quality attributes.
8 Some of the elements are shown here. They
9 are familiar I am sure to many of you. They also,
10 I should point out, overlap with many of the
11 fundamental underlying principles necessary to
12 implement many of the PAT applications.
13 [Slide.]
14 As a result, over time, there have been
15 many PAT-like applications of technology to
16 manufacturing and testing. For example, as Keith
17 had indicated, there are many examples of continual
18 on-line monitoring of critical process attributes
19 often with real-time feedback mechanisms that may
20 be computer assisted.
21 Within the defined parameters from the
22 validation studies and such there is also some
23 flexible control within those parameters, so one is
24 not necessarily fixed to certain endpoints if the
25 appropriate validation characteristics support a

1 range within which one can operate.

2 We have been involved with application of

3 on-line analysis of various intermediates and

4 product attributes, as well as facility systems.

5 Some examples are indicated here.

6 We have approved several years ago an

7 on-line measure of a critical physical-chemical

8 quality intermediate for a naturally-derived

9 product. We have entertained discussions, again

10 several years ago, on measuring through a

11 non-destructive method the moisture content of

12 final filled containers. We have approved

13 appropriate physical property for changing

14 lyophilization conditions in lyophilizers.

15 CBER regulates and reviews major facility

16 changes. We approve numerous supplements that

17 described on-line applications of water systems

18 when conductivity measurements were substituted for

19 the wet chemistry measurements in water systems.

20 Most importantly, we have recently

21 approved microbial methods for two applications.

22 Rapid microbial methods are very concerned

23 especially to or for our cellular products, and for

24 those products where they cannot be held or stored

25 prior to the release of the sterility testing

1 results, so implementing methods that have allowed
2 for a rapid turnaround to determine whether the
3 products are sterile or not has provided great
4 increase in the assurance of the quality of that
5 product.
6 I should point out that that last method
7 is not an on-line method, but is an off-line
8 method.
9 [Slide.]
10 There are clearly potential applications
11 for new manufacturing and testing technologies that
12 have been discussed. Many of those advantages for
13 PAT have been described and are probably known much
14 better to you all than to me.
15 I think some of the best applications
16 would be if one could use those in terms of
17 defining product or intermediate quality
18 characteristics. Unfortunately, that provides the
19 most challenge and at present, I think there are
20 some great limitations to doing that in an on-line
21 fashion.
22 Immediate applications I think may be more
23 likely in terms of drug product manufacturing,
24 measuring of more single types of process or other
25 very select quality attributes.

1 Some of the challenges I think that we
2 face at CBER is that we still have, in contrast to
3 some of the more purified and defined recombinant
4 products, a large amount of complex and
5 heterogeneous products. All of the issues that
6 Keith discussed about the identity, purity, and
7 composition of these products is in many cases
8 magnified when one has a complex and heterogeneous
9 product.
10 Again, I think that leads to the ability
11 that it may be difficult to know from a multifactor
12 analysis the heterogeneous mixture, what actually
13 that relationship is.
14 Again, manufacturing unit operations in
15 biological and biotechnology products often perform
16 multiple functions. Again, the ability to measure
17 all important product quality characteristics in a
18 continuous mode from any of those functions, I
19 think is going to be very challenging.
20 For CBER, we have the development of new
21 products, not just products within a class, but
22 again completely new products, gene therapy,
23 therapeutic vaccines, as well as cellular products.
24 [Slide.]
25 Just in summary, I think it is still

1 important at CBER that we understand and emphasize,
2 understanding both the product and the process,
3 clearly integral to the development and manufacture
4 of biotechnology and biological products.
5 The comprehensive, life-cycle approach to
6 process validation remains integral to the
7 consistent manufacture of these products.
8 Validation is still a regulatory requirement and
9 when conducted in a comprehensive life-cycle
10 manner, has provided great assurance that the
11 process will consistently produce that desired
12 product.
13 That has been most readily seen at CBER
14 when products that were approved prior to
15 validation being a regulatory requirement,
16 validated their process. They had potential
17 savings both from economic and public health
18 perspectives.
19 We see PAT more as an extension of the
20 existing process understanding the manufacturing
21 control paradigm. I think clearly, PAT has
22 potential applications for biotechnology and
23 biological manufacturing processes especially if it
24 can monitor again intermediate quality attributes
25 and provide greater assurance of that product

1 quality.
2 We will continue to partner with
3 manufacturers of existing and new products to
4 facilitate implementing any type of new technology
5 and concepts, including those that can enhance the
6 knowledge and control of the manufacturing process.
7 Thank you.
8 DR. KIBBE: Does anybody have any
9 questions for Chris? Go ahead.
10 DR. COONEY: One of the particular
11 challenges for the class of products you are
12 dealing with are viruses, viral contamination.
13 How do you see some of the issues of
14 detection and validation of viral removal being
15 advanced by PAT?
16 DR. JONECKIS: That is an interesting
17 question. Currently, I guess, for the committee's
18 benefit, most people do challenge or clearance
19 studies, usually small scale, representative of the
20 larger scale manufacturing process.
21 In terms of detection, again, as I
22 mentioned earlier, there are efforts underway to do
23 genomic and proteomic screenings for potential
24 contaminants within products at various appropriate
25 stages in addition to the current various levels of

1 safety that are provided.

2 I suppose theoretically if one could with

3 the increased sensitivity of certain methods, one

4 may be able to do more on-line monitoring, if you

5 would, again at early or appropriate stages to

6 actually see if there is any type of potential

7 viral materials present.

8 One could potentially in theory, depending

9 upon how much is present, again, sensitivity of

10 your methods, actually measure on-line for the

11 various steps, present of type C retroviral

12 particles, CHO-derived products, and things of that

13 nature.

14 Similarly, you know, it has been done for

15 measuring DNA and other types of materials when it

16 is there in a large amount in early purification

17 steps, given the sensitivity of the assay, one can

18 measure those on-line in addition to whatever model

19 studies are done to provide additional assurance

20 that your model truly reflects what is occurring.

21 DR. KIBBE: Anyone else?

22 Seeing none, I am going to take the

23 prerogative of the Chair and declare a 15-minute

24 break, which means we should be back in our seats

25 and ready to go at approximately 2:35.

1 [Break.]

2 DR. KIBBE: I have been assured by experts
3 in the field that Tom has all the answers in his
4 presentation, so when we get to them, we will be
5 done for the day.

6 Charles Cooney is on the podium.

7 DR. COONEY: Thank you very much.

8 I am pleased to have an opportunity to
9 share some thoughts this afternoon on the question
10 that Keith Webber put before us, and that is the
11 extension of PAT to biological processes.

12 In preparing for any talk, one obsesses
13 over a number of things, one of which is the color
14 of your tie, of course, but another is the title of
15 the talk. I obsessed over a complex title and a
16 simple title, and I resolved that dilemma by having
17 both.

18 [Slide.]

19 PET for PAT? The message that I am trying
20 to convey in my title as a place to begin is that
21 when we think about PAT and all of its virtues and
22 aspects that have been dealt with earlier today,
23 process analytical technologies applied to
24 processes and products, it is a very important
25 fundamental concept, and it means a lot.

1 When you think about it in terms of the
2 process, it occurred to me that we really need to
3 think about analyzing the process, as well as
4 analyzing parts of the process and the product
5 itself.
6 So, the emphasis here is to think about
7 process evaluation tools as a component of process
8 analytical technologies, and I think that the broad
9 definition that has been used for PAT very much
10 embraces that idea.
11 [Slide.]
12 In putting together my comments for this
13 afternoon, I have identified more questions than I
14 have answers, and the reason for this is that as we
15 think about going forward with the extension of PAT
16 to biological products, there are a number of
17 issues and questions, and I would like to try to
18 put at least a few of these into some context.
19 The first set of questions I have
20 summarized here as Some Issues. What are the
21 issues, what is the context as we look forward, one
22 of which is the pipeline of new products, what will
23 that look like going forward in the next 10 to 20
24 years.
25 I think there is no doubt that it is going

1 to be expansive, there is going to be increased
2 complexity in the nature of the products, and it is
3 going to be a very vibrant pipeline simply based
4 upon what we see in discovery and what we see in
5 clinical trials today.
6 If we think about the increase in the
7 number of BLAs and NDAs that will be coming through
8 for biological products, it puts a real future
9 stress on the Agency because as we look at the
10 number of these products, they are increasing
11 exponentially, and I don't think that the number of
12 people in the FDA is increasing exponentially.
13 Just a guess, but I think it's true.
14 So, what that means is that the pressure,
15 in order to be more efficient, and to focus on a
16 risk-based strategy and understand where and when
17 to look, at what, is really very, very timely to be
18 in this process right now.
19 Then, of course, there is the question of
20 follow-on biologics that are beginning to--I will
21 come back to this in a moment--but are beginning to
22 come forward, and I think are going to be an
23 increasing issue.
24 Both of these issues raise the question
25 how do biological products respond to the physical

1 process changes that occur when you develop a
2 process, scale the process, move it, change its
3 location, and the like.
4 We have some understanding of this, and,
5 of course, this is fundamental to understanding how
6 biological products, particularly the complex one,
7 respond to the complex processes used to make them.
8 Underlying all this, do we have the
9 adequate analytics to address the uncertainties
10 associated with manufacturing in this industry, and
11 I am struck by looking at the presentations we had
12 earlier today, and, of course, they all focused on
13 where we have the analytics in place.
14 In fact, do we have the necessary
15 analytics? No, I don't think we do.
16 Are efforts underway to develop them?
17 Well, we are going to hear in the next presentation
18 that there are some very exciting efforts that are
19 underway, and I think the future looks bright, but
20 it is only going to come with a lot of diligence
21 and a lot of innovation in order to measure the
22 kinds of things that we really need to be looking
23 at.
24 Then, ultimately, how do we bring this
25 together to assure robustness in design and

1 operation of these processes.

2 [Slide.]

3 I tried to address where we are going.

4 Keith Webber already identified a number, in fact,

5 the previous two speakers identified the range of

6 products that are out there today and the ones that

7 are likely to be out there tomorrow, and we can

8 expect that there are going to be a lot more

9 antibodies, replacement proteins, designer

10 proteins, vaccines, not just for therapeutic use,

11 but for prophylactic use, cellular and gene

12 therapies are being developed quite aggressively.

13 One of the other observations I would like

14 to make, though, when we look at the range of

15 products that are there today and that are going to

16 be there tomorrow, is that this question of

17 follow-on biologics is on the minds of many people

18 and we need to take stock of where we are today,

19 because we really have follow-on biologics today,

20 we have multiple processes for the same products,

21 multiple manufacturers for human growth hormone,

22 multiple manufacturers by very diverse technologies

23 for human insulin.

24 How we have managed them is perhaps not

25 the same way that we wish to manage them in the

1 future, but these are realities today, these are
2 not things that are looming out there for the
3 future.
4 [Slide.]
5 When we look at the processes that are
6 going to be used, we have very diverse recombinant
7 protein production processes. Why are there so
8 many? Why isn't there a single technology that has
9 emerged?
10 The answer is very simple, not all
11 processes are suitable for all products.
12 Furthermore, the intellectual property landscape is
13 such that it dictates complexity in the processes
14 that are used simply to work your way through the
15 minefield of intellectual property that is out
16 there.
17 Is that going to get simpler as we look
18 forward? No, the processes are going to become more
19 complex, driven in part by innovation, and driven
20 in part by the nature of the products, tissue
21 products, multicellular products, and certainly the
22 potential future for transgenic plants and animals.
23 So, as we look at the array of complex
24 processes for these complex products, I do not see
25 that landscape getting simpler. I see it remaining

1 complex and as a consequence, we need to be able to
2 have the analytics in place and the ways of
3 handling the data and the ways of understanding
4 these processes that is better in the future than
5 it is today.
6 So, this leads us to a series of
7 challenges, and I have tried to organize these
8 challenges in a way that represents where we are
9 coming from and where we are going to go.
10 There is the continuing challenge of
11 rapid, cost effective development and scale-up. We
12 need to shorten the timelines, the timelines for
13 developing the processes, and if we develop better
14 processes, that should lead to improved timelines
15 for approval of those processes, and we need to be
16 able to have more flexibility, so that the process
17 of development and scale-up could be a lot more
18 nimble and lean than it is today.
19 But then once we have processes in place,
20 I think the industry has done an increasingly good
21 job in the drug space of continuous improvement,
22 and most recently, and we have heard examples of
23 that today, PAT is a major contributor to how that
24 is going to go forward in the future. That is very
25 positive.

1 We need to understand how to better
2 achieve continuous improvement in process change in
3 the biological space, and that is the challenge
4 that we are focusing on in this particular session.
5 What the tools that we need to do that?
6 What are the methodologies? Where is the
7 uncertainty, and, of course, how do we understand
8 that risk, and risk is implicit in all of this.
9 Follow-on biologics present their own
10 challenges, and then when we get into complex
11 biologicals, cellular therapies, and tissue
12 engineering, there are a wide variety of unknowns
13 and we need to understand quickly what are the
14 parameters, what are the biomarkers, what are the
15 surrogate markers, what are the direct methods that
16 we can apply in order to get a grasp of these
17 processes and how they will define the products
18 that we make.
19 Furthermore, as we look at these
20 challenges, there is a constant tension between the
21 safety and the economic agenda, and where is the
22 proper balance in terms of how much risk we seek to
23 minimize and how much risk we seek to embrace and
24 manage and take forward.
25 [Slide.]

1 Well, when you look at the broad issue of
2 the relationship between the process and the
3 product, one has to look at what goes in and what
4 comes out. We have raw materials and environmental
5 conditions that are variables going in. We are
6 trying to control a number of the parameters in
7 this space.
8 Some of those parameters are suitable for
9 control in a closed loop fashion. Again, we heard
10 a number of examples of how that is increasingly
11 important today. A number of those parameters we
12 don't control in a closed loop manner, but we need
13 to control them nonetheless.
14 I think the challenge in looking at this
15 very microscopic view of a process is the
16 information flow. We know how to do process
17 control. We are going to get better at
18 implementing new analytics on these processes.
19 There is a long history of applying statistical
20 process control and a wide variety of other
21 methodologies of process control.
22 We are going to get better at doing that,
23 and that is all going to be incremental. What is
24 not going to be incremental is the more systems
25 view of understanding to do it better. I think

1 there we will have some big jumps, but where I
2 think we are doing a terrible job is on the
3 information flow.
4 The information is quite an asset, a lot
5 of money goes into generating that information, and
6 do we adequately understand and mine it, and the
7 answer is no, we don't. In fact, it's a very
8 poorly utilized asset, and in some cases, the
9 reason is, well, if I don't look at it, I don't
10 have to worry about the variance in it. That is
11 one way to control variance.
12 Another way is to say, well, let me
13 embrace that variance, let me learn from it, let me
14 capture that information, and feed that back and
15 learn, and that is an area where I think we are
16 getting better, but, frankly, I think if I look
17 back over the past decade or two, even looking at
18 work that I have done, I think we have done a
19 pretty bad job.
20 Now, what I would like to do is to stay in
21 the frame of raising questions rather than
22 providing answers, but I can't go through a
23 presentation like this without showing some data
24 and without taking an example to illustrate where I
25 think there are some opportunities and some of the

1 kind of learning that represents work-in-progress.
2 In biological processes, one of the main
3 issues we deal with is the oxygen dilemma.
4 [Slide.]
5 We all know that in most biological
6 processes, there is a requirement for oxygen for
7 efficient growth, and in this particular case,
8 recombinant protein expression. That is a given.
9 By the way, there is some interesting data
10 to suggest that that is not necessarily true, but
11 we won't go there now. But that is a general
12 methodological given, and let's assume that it's
13 true for the moment.
14 But on the negative side, there is the
15 potential that if a little bit of oxygen is good,
16 is a lot of oxygen better, and the answer is not
17 necessarily, because there is potential for both in
18 vivo and in vitro protein oxidation of methionine,
19 cysteines, for instance, and as we scale-up and as
20 we change the amount of oxygen, as we use enriched
21 oxygen in processes, is this going to be a hazard,
22 is it going to be a problem?
23 We wanted to explore that, and we also
24 know that oxygen can induce stress. Actually,
25 oxygen too high or too low can induce stress. One

1 of my hobbies is high altitude mountaineering, and
2 I decided what would it be like to operate under 35
3 percent partial pressure of oxygen. Well, I don't
4 recommend going there on a regular basis.
5 [Slide.]
6 But when we look at processes today, we
7 are looking at scale. Traditionally, what we have
8 done is to do a lot of our optimization of a
9 process at a shake flask scale, 100-milliliter,
10 perhaps to a 10-liter scale, and then go to 10 or
11 100 cubic meter scale.
12 The benefits of doing research at the
13 homogeneous milliliter or liter scale is that we
14 can make the assumption that it is almost
15 homogeneous, and the work we have done over the
16 years is to better resolve events in time, so we
17 have taken analytics, like some of the probes, and
18 so on, that have been discussed earlier, and we
19 have learned to evolve events in time and
20 understand how the time space is critical.
21 At the fermentation scale, we might do 200
22 to 300 experiments in order to get what we think is
23 an optimum, but we really know it is not, in order
24 to scale to the 10 to 100 cubic meter scale, but
25 all we do is get to a place that allows us to

1 economically be in the business, and then,
2 hopefully, we will be allowed to undergo continuous
3 improvement following that.
4 What I want to suggest is that what we
5 really need to think about is how we look at this
6 process development and scale-up paradigm very
7 differently.
8 That is, if we scale down, and, for
9 instance, one approach is to use reactors that are
10 100 microliters, and they indeed are homogeneous,
11 or somewhere in that small space, and do large
12 numbers of experiments, and not just resolve events
13 in time, but do the kind of things that were
14 described earlier, create large experimental
15 design, so that we can now not just look at our
16 experimental space, but we can look at the
17 interdependencies between the independent variables
18 in a much more effective way, reduce the
19 uncertainty associated with how the process
20 responds to the environment, as well as changes
21 with time, and reduce the uncertainty of scale-up,
22 and presumably reduce the variance as we do so.
23 That is not to say that we shouldn't also,
24 at scale, resolve events that take place in time.
25 There is going to be variance in a biological

1 process. We can learn a lot from that, and that
2 allows us to manage the risk associated with these
3 processes, and that goes on, as well, but we are
4 doing a better job with that than we are simply
5 going to the large-scale experimental design.
6 [Slide.]
7 A model system that we happened to choose
8 is alpha-1 antitrypsin. It is a human recombinant
9 protein. It is an interesting model because you
10 notice that methionine 358 and the one at 351, it
11 sticks up like a sore thumb and is sensitive to
12 oxygen. So, we reasoned it would be useful as a
13 molecular probe in order to determine if oxidation
14 was a problem.
15 This molecule also actually has 10
16 methionines, several of which are partially or
17 completely exposed, and 1 unpaired cysteine that is
18 partially exposed, but with models such as this,
19 this might be the product where its structure is
20 well known, you can begin to do microscale
21 experiments that you can then project to the larger
22 scale and ask, well, what is the effect of oxygen
23 on the molecule.
24 [Slide.]
25 In this particular case, we observed that

1 there was an oxygen-dependent proteolytic cleavage,
2 and as you look at these three lines, the green
3 line is for the expression, transient expression
4 under air. The top line is transient expression
5 under anaerobic conditions, which turns out to be
6 not so bad. But the bottom line is expression
7 under pure oxygen, so there is this oxygen
8 dependency of the proteolytic cleavage.
9 [Slide.]
10 How do we resolve that? Well, one
11 approach is the very hypothesis-driven problem,
12 and, of course, when you have a problem, and a
13 complex problem, and as you can see by the photo on
14 the left, if you don't get the ropes right, you
15 could be in serious trouble, so you have got to
16 know where the problem is if you want to be in the
17 position on the right.
18 [Slide.]
19 So, how do we resolve that? Well, we have
20 a hypothesis. In this case, we tried many
21 hypotheses. I am only going to tell you about the
22 one that is right. That way you will remember that
23 I got it right the first time. Wrong, but
24 nonetheless, we speculated that it was the protease
25 ClpP that was responsible.

1 [Slide.]

2 It is a complex protease that involves
3 ATP. You do the hypothesis-driven experiments, you
4 knock it out, and as you can see by the figure on
5 the righthand side, you eliminate the
6 oxygen-dependent proteolytic cleavage, not all the
7 cleavage, but that hypothesis, which was one of
8 about a dozen that we explored, in fact, worked.

9 [Slide.]

10 Are there other ways to think about these
11 kind of problems? Do we have analytical techniques
12 that allow us to probe much more broadly the global
13 cell response?

14 [Slide.]

15 Of course, the answer is yes, and the
16 technology of using DNA microarrays to do
17 transcriptional profiling is one kind of tool that
18 can be used in identifying where the problem is,
19 and, after all, isn't that what PAT is about.

20 It is about getting at the underlying
21 science to understand what the issue is, and then
22 focus on the right issue, not necessarily measuring
23 everything that you possibly can measure.

24 E. coli is very convenient. It only has
25 about 4,000 genes, but fortunately, those genes are

1 set up in pathways, and rather than think about
2 4,000, I don't like big numbers, I would rather
3 think about, well, there are about 170 pathways.
4 [Slide.]
5 So, if we look at the response in terms of
6 pathways, we can begin to say, well, are there
7 pathways that are up or down-regulated, and,
8 indeed, this is an example in the case of the
9 experiments I showed you a moment ago.
10 What you see on the lefthand side is the
11 regulon associated with the peroxide response for
12 E. coli to high oxygen--excuse me--on the lefthand
13 side to the superoxide response, the righthand side
14 is the peroxide response.
15 What you can see by the elevated levels of
16 the genes in the superoxide response, that E. coli
17 reacts with the operon, superoxide dismutase and
18 some other enzymes, and the peroxide response is
19 transient, if anything at all.
20 This tells us where the problem is. The
21 problem is associated with the small amount of
22 superoxide radical that is being made.
23 [Slide.]
24 When we look at clusters of genes, one can
25 see that the green ones are up-regulated in the

1 presence of oxygen, and when they are red, they are
2 down-regulated, which happens in the case of
3 nitrogen, and you see green dots with superoxide,
4 but one of the other strange things is that you see
5 proteins that have iron/sulfur in them
6 up-regulated.
7 Why would any self-respecting E. coli
8 up-regulate genes associated with iron/sulfur
9 proteins when you are making a recombinant protein?
10 This didn't make sense, and, in fact, it has
11 nothing to do with the production of alpha-1
12 antitrypsin, but rather has to do with the fact
13 that a small amount of superoxide, that free
14 radical, knocks out the iron/sulfur clusters.
15 There are about 100 proteins in E. coli
16 that have them. Those proteins are not functional,
17 so how does the cell respond? It up-regulates
18 pathways in order to compensate.
19 [Slide.]
20 So, within these global techniques, you
21 can begin to understand where the problem is and
22 think about the strategies to better design the
23 process, and basically, it is about taking the next
24 step.
25 Where is the appropriate next step? I

1 will leave it to your imagination whose feet they
2 are.
3 [Slide.]
4 A little quick self-assessment. When we
5 introduce a process to make a biotherapeutic
6 product, do we know the optimum conditions for
7 quality and quantity of the product today?
8 No, and as a consequence, once the process
9 is in place, we see very substantial process and
10 product improvement during the course of operation,
11 and that is good because it means that we have
12 recognized that there is going to be variance and
13 that we have recognized that we can manage that
14 variance, we can learn from it, and collectively
15 benefit. That is the reality.
16 So, there are lessons learned there. The
17 variance that is going to occur is not something to
18 be avoided, it is something to embrace and learn
19 how to manage, and it is getting the right balance
20 of managing that risk.
21 So, during routine manufacturing, do we
22 improve the product in the process? Absolutely.
23 [Slide.]
24 What is the way forward? Well, is there a
25 better way than incremental adjustments to optimize

1 and scale a process? Sure, and I think the idea of
2 taking these complex processes and learning how to
3 operate large numbers to capture design of
4 experiments and to capture what happens in that
5 space, and learn how to assess the
6 interdependencies of the parameters is a very
7 exciting opportunity.
8 The technologies that allow us to do it,
9 both from a process side, from an analytical side,
10 from a data analysis side are really important to
11 bring together, and we are not there, but we can be
12 there.
13 We need to live with variance and take an
14 adequate opportunity to learn from that variance.
15 Listen to the data, don't ignore it, listen to it.
16 In doing that, we can again grasp much
17 more experimental space both in variables, as well
18 as time. So, this issue of embracing that
19 variance, learning what it is about, learning where
20 the problem is, and then using that to come back
21 and develop a robust process, this is the kind of
22 mind-set that PAT is about, and biological
23 processes are very much in need of being thought
24 about and treated and respected in this way.
25 [Slide.]

1 In closing, the last slide is to look at
2 what are some of the process evaluation tools.
3 This is not all-inclusive, but it is meant to
4 reinforce just a couple of points that I have made.
5 One is the leverage analytical technology
6 on process and products, what does this really
7 mean? This is PAT, and this is leading us to a
8 process understanding and a process evaluation.
9 That is very much what it means, that we
10 need to be able to look at the process globally,
11 and not just locally. It fits exactly in with the
12 guidance that has been laid out for PAT.
13 We need to explore the biological space
14 and the parameter variance. We need to understand
15 how this variance propagates through a process.
16 It is very interesting, if you take
17 process simulation tools, and we can do a very nice
18 process simulation on any of these processes, and
19 then you do things like Monte Carlo simulation
20 where you have variance in the process, you can
21 begin to understand how that variability at
22 multiple steps is going to propagate through very
23 complex processes.
24 As a consequence, when you do that, you
25 then are not surprised by how a little bit of

1 variance here, a little bit of variance there,
2 propagates to give you what the end result is going
3 to look like. So, with simulation and these tools,
4 you can avoid some surprises.
5 We need to better interrogate the cell at
6 the molecular scale, and then be able to do the
7 multi-scale analysis to scale up. So, part of what
8 I think PAT is about, is multi-scale analysis,
9 driving down to understand the science, so we can
10 understand where the problem is, and then driving
11 back up with appropriate solutions to eliminate the
12 right problem, in the right way, at the right time.
13 A lot of this about understanding these
14 interdependencies in what is a very large
15 experimental space.
16 Lastly, understanding this connection
17 between the molecular processes, process
18 performance, and product quality. We are doing I
19 think an exciting job with drug substances in this
20 regard, and we are perfectly capable of carrying
21 that over, with work, to biological products, as
22 well.
23 I will stop there and I hope that I have
24 generated more questions than providing answers,
25 because that is what I started out to do.

1 DR. KIBBE: Thank you. If there anybody
2 who has any quick questions you want to take care
3 of now before I go on, any point of understanding?
4 [No response.]
5 DR. KIBBE: In that case, Dr. Koch.
6 DR. KOCH: I have had the benefit today of
7 a number of speakers who were leading up to the
8 type of things that I wanted to say. I left out
9 some things, and those of you who have paged
10 through the slides probably can't believe that.
11 There is a lot of slides there, it is going to be a
12 little bit like a fire hose here for a while. I am
13 going to try to stick to things that are more of a
14 miniature nature or micro-analytical rather than
15 hitting the broad base of all analytical.
16 Let me move into it and I think I will tie
17 in with some of the previous speakers.
18 [Slide.]
19 PAT. We have heard a number of
20 definitions of it, but again it is looking at all
21 aspects from the chemistry tools through the
22 control strategies and into the data handling
23 aspects. The goal again, process understanding.
24 [Slide.]
25 The origin of PAT goes back, oh, 50 years

1 at least, and we have got a few examples that go
2 back to the mid-forties with some of the German
3 chemical companies applying it, so it is not as if
4 the approach is new.
5 We can go into all of the reasons why it
6 is relatively new in the pharma industry, but that
7 is mostly psychological. It started within the
8 analytical chemistry labs where tools used for
9 specifications, et cetera, as coming from the areas
10 listed here, were then made portable for running in
11 the process or close to where the process was, and
12 adopting the term "real time analysis."
13 [Slide.]
14 That real-time data resulted in a number
15 of things, in fact, almost every time one went into
16 a process, and this is borrowing from the
17 petrochemical experience, almost every time a
18 sample was taken to a chemical analysis lab, we
19 found out that the results were different if we did
20 it in real time, taking and watching things that
21 you could see fleeting intermediates or a number of
22 things that were indicating both safety and
23 environmental problems.
24 It also was a very good scoping tool for
25 understanding what type of issues and what places

1 in a process could be monitored, process
2 understanding results from doing this.
3 [Slide.]
4 What is appropriate for PAT? It really
5 comes down to a very broad statement, and that
6 anything that gives you data that you are presently
7 not measuring, certainly want to look at cheaper
8 and more reliable, and then we are entering into
9 something here where we are going to get more data
10 than we ever wanted, but we are going to want
11 additional data points in order to build better
12 models from which to control from.
13 This is probably going to be the crack in
14 the wall for Bayesian type approaches where you
15 have to make assumptions because you finally get
16 too much data that you can't possibly study all of
17 it.
18 It is also going to allow us to depart
19 from traditional analytical science technologies,
20 that list that showed up before as coming out of
21 the analytical laboratories, have to move away from
22 that.
23 [Slide.]
24 We are going to have to look at fully
25 integrated analyzer systems. Historically,

1 analysis is detection. The thing that people have
2 avoided forever is the problem with sampling, I
3 think taking inadequate representative sample to be
4 analyzed.
5 Then, the other thing that often was
6 slipped over because of expense and capability had
7 to do with collecting the data and making sense out
8 of it, and eventual information and knowledge.
9 That has to be all integrated into a system.
10 The next point has to do with inferential
11 analysis, and we have heard that referred to a
12 couple of times, and that is where you can project
13 to the desired product properties by doing some
14 measurement during the process, and it doesn't have
15 to be the property itself, but you have enough data
16 that you can extrapolate to that point.
17 [Slide.]
18 Then, you have to revisit some of these
19 underutilized, but not revolutionary techniques.
20 The few that I mention here are technologies that
21 were discovered in the early 1900s, but not used
22 forever, largely because of instability of optics
23 or computer possibilities back when it was first
24 looked at.
25 [Slide.]

1 I want to mention a couple of these. One
2 is in the optical low coherence reflectometry, that
3 when you do that type of measurement, the result
4 you get depends on things like on the column on the
5 left, the thickness, the particle size,
6 concentration, shape, and some of these other
7 morphological things all affect the measurement.
8 As a result, if you can interpret the
9 signal that you get from the measurement, you can
10 then use it to monitor a number of things. There
11 are examples there, that are largely from a
12 chemical and materials point of view, but
13 eventually, you get down to being able to monitor
14 tablet coating.
15 The technique started in measuring coating
16 of airplane wings, and we found that that could be
17 extrapolated quickly to other measurements that is
18 being used now for tablet coating, as I mentioned,
19 and we are finding that there is variations during
20 a fermentation or a biological process that can be
21 monitored, and it is a technique that operates at
22 high concentration, in slurries of 70 to 80 percent
23 as a technique for particle size versus the
24 historical need for dilution.
25 [Slide.]

1 A couple of examples. You can look at a
2 multi-layer film. Here is an example of a drug
3 delivery patch. I think you can see some of the
4 peaks there on the bottom.
5 Very interestingly, what happens in this
6 process, it looks like a chromatogram with various
7 peaks, however, it is the bounce back of the
8 photons at each layer, and you measure the time
9 that it takes to come back and project into
10 distance.
11 Each one of those peaks is a layer. It is
12 a layer from the barrier layer on the outside and
13 the back, and then the intermediate layer is
14 between active ingredients, so it becomes a way to
15 measure how much active ingredient one has placed,
16 so the baseline is basically the thickness of the
17 active ingredient.
18 The scattered material example is one
19 where you have a total reflection of the photon and
20 the path in which it travels indicates the
21 complexity of the mixture, and you can extrapolate
22 then into things like particle size, shape, and
23 waveguide formation, et cetera.
24 [Slide.]
25 An example of being able to look at

1 consistency, there is one curve here that shows at
2 one concentration, you can see quite a range of
3 small particles from basically 20 to 90 nanometers,
4 or you can take one size, in the lower example, of
5 308 nanometers, and get a concentration difference.
6 So, it has proven to be quite valuable in that
7 regard.
8 [Slide.]
9 Moving on to Raman, certainly, everyone
10 has heard the terminology, but as you look at some
11 of the potential advantages now that the stability
12 of the lasers have improved in some of the data
13 handling, and as databases grow, you can look at
14 non-invasive or non-destructive technology.
15 You can work in aqueous systems. You can
16 do multiplex of your instrument using fiber optics
17 that can go hundreds of meters, and you can also
18 then look at chemical structure and fingerprinting
19 of both inorganic and organic materials.
20 [Slide.]
21 Then, with effective probes, in fact, this
22 particular probe that is demonstrated here, was the
23 one that we used in the practicum and moved between
24 the various centers to study some milling and
25 mixing operations, but we have done a number of

1 things in composition, as well as, at the bottom
2 right, putting it in a protein mixture in terms of
3 determining aspects of that material.
4 [Slide.]
5 The fringing electric field or
6 dielectrometry sensor is pretty simple, one that
7 was developed for detecting mines, and it has to do
8 with the ability to set your electrical fields with
9 the various sensors in setting the distance and the
10 intensity, and you can get a disturbance of that
11 electrical field based on the properties of the
12 sample.
13 You can measure things like density,
14 distance from the sensor, texture, and moisture,
15 and moisture not only in concentration, but
16 distribution, so you will start to look at filter
17 cakes or other aspect of various processes. You
18 have another relatively unused method that can be
19 applied.
20 [Slide.]
21 To date, a number of things happening in
22 the paper pulp industry, pharmaceutical products,
23 and we have got a few companies, pharma-based, that
24 are using it for mixing consistency, a lot of food
25 applications including some of the baking companies

1 to monitor the moisture distribution in cookies and
2 cakes and things, and that turns out to be pretty
3 important for them, composites, plastics, et
4 cetera.
5 [Slide.]
6 Going on to surface plasmon resonance, a
7 number of things, primarily in miniaturization and
8 sensitivity have occurred here, and plugging some
9 disciplines together from electrical engineering
10 and genetic, have come up with some real-time
11 biosensors that are operating at a very fast mode.
12 [Slide.]
13 Work sponsored by the Department of
14 Defense, again that tie in with some of the things
15 we heard earlier on homeland security.
16 You can start to look at high throughput
17 screening, automated protein purification, and
18 number of toxins, food-related activities, and we
19 are actually moving quite rapidly into response in
20 the food industry for safety, security, nutrition
21 in the food and related water chains.
22 [Slide.]
23 One example, this has been demonstrated in
24 a protein purification system, would be a way in
25 which after the broth is separated and some

1 chromatography applied using biosensors, one can
2 determine when to change columns or monitor the
3 process, which brings us to biosensors and the need
4 in the bioprocess in general.
5 [Slide.]
6 I have been in discussions with Harry Lam
7 of Genentech, to get a feel for what type of things
8 the industry is looking at, and certainly to
9 maintain a consistent product performance or
10 process performance with the development cycle from
11 early stage through manufacturing.
12 [Slide.]
13 Measurement is needed in order to look at
14 the underlying functional relationships that occur
15 in the process, as well as some of these
16 interactions of the organisms with their
17 environments.
18 [Slide.]
19 We need to improve the capabilities for
20 process control, and the type of measurements are
21 going to be broad based, biological, chemical,
22 physical.
23 [Slide.]
24 Much of this has been touched on today -
25 biological with this whole range of things that are

1 of a cellular nature.

2 [Slide.]

3 Chemical, we have got a number of things

4 in the media that need to be addressed, that have

5 to do with the nutrients and the additives, et

6 cetera.

7 [Slide.]

8 It continues on when you start to

9 characterize the product, the by-products, the

10 environment, as well as the off-gas.

11 [Slide.]

12 Physical. We have heard much of this in

13 terms of the type of things that need to be looked

14 at.

15 [Slide.]

16 What can we look at today? Much of this

17 was mentioned here in the last couple of

18 presentations, of things that are being used to

19 monitor, but that leaves a number of the issues on

20 the table yet to be addressed and solved.

21 [Slide.]

22 Also, the industry is looking at the

23 various requirements that are going to be

24 necessary, and it is a lot more than just having a

25 measurement tool, but to get into the things that

1 have to do with sterilization, interference, and
2 the fouling, low maintenance, and the small size.
3 We have heard several assumptions today
4 that if it's smaller, it could be better.
5 [Slide.]
6 That gets us into what has been driving
7 the improvements in measurement over the last, say,
8 20 years, and it has been the advances in
9 miniaturization. Much of this has been driven by
10 technologies in the computing industry and the
11 ability to make things smaller and use microfluidic
12 technologies, et cetera.
13 Certainly, new materials, the optic
14 advances, and computing have helped, but
15 miniaturization is really a big one.
16 [Slide.]
17 It has been focus of the center where I am
18 located in Washington. It has been a
19 multi-industry, and I have implied that a few
20 times. A number of industry come together and
21 discuss advance in real-time measurement, and we
22 are now beginning to apply those things to the
23 food, pharma, biotech industry.
24 [Slide.]
25 Multidisciplinary. There are many

1 examples where bringing different disciplines
2 together results in some very interesting sparks
3 coming from that smoke, presently supporting 20
4 different research projects at 5 universities, and
5 involved with some international collaboration.
6 [Slide.]
7 The initiatives, and we will see the
8 importance of this growing, is sampling and
9 sensors. That is one that we try to act as a forum
10 across industry. Trying to also compile analytical
11 and chemometric methods, what to use in terms of
12 interpreting the data.
13 A couple of things that are used just
14 inside for the members, are to look at
15 micro-instrumentation for the high throughput
16 experimentation, the CombiChem, and some of the
17 process optimization tools, and then a fermentation
18 platform, and I will mention some of the things
19 there.
20 [Slide.]
21 When we look at this response to high
22 throughput experimentation, we get into the
23 micro-instrumentation world, but also the
24 micro-reactor world. I have to agree with that
25 Charles mentioned, the petrochemical industry is

1 finding huge benefits in scaling down before you
2 scale up, and going down to molecular interactions
3 in a number of data-gathering aspects at the small
4 scale to understand how to then move on from that
5 to macro scales.
6 [Slide.]
7 We also have a number of techniques that
8 are being miniaturized largely due to advances. As
9 I mentioned before, most of the analytical
10 technologies, we only have a few that have not been
11 miniaturized yet or taken on-line, and some of
12 those are microscopy-based, but we actually have
13 some breakthroughs now in bifringes and other
14 things that could help in this respect.
15 [Slide.]
16 I will give you a couple of examples. In
17 micro-LC, we have got a small 100-micron flow
18 channel where you mix a sample at a mobile phase
19 and then detect the deflection in your laser beam
20 with a position-sensitive detector.
21 [Slide.]
22 We have since found, after starting into
23 this project, that low molecular weight material
24 diffuses much faster than the higher molecular
25 weight material.

1 [Slide.]

2 So, why not put two sensors in-line and

3 then begin to calculate the difference between

4 those distances in terms of a particular molecule.

5 [Slide.]

6 What has resulted is an in-line molecular

7 mass sensor where we are able, in this case, to

8 look at polyethylene glycols from a very low

9 molecular weight. Actually, it has now been taken

10 to over 100,000 molecular weight in terms of a

11 standard curve.

12 [Slide.]

13 This has resulted in other things now, in

14 some biological testing where we can see peptide

15 synthesis, we can look at polysaccharide synthesis

16 and be able to see differences as chains are

17 building, and also be able to see differences in

18 diffusion in following trends in that way.

19 [Slide.]

20 Developments at Sandia, again, homeland

21 security basis, have resulted in a micro chem lab.

22 This is a very interesting thing, obviously, the

23 size of a dime is quite impressive, but when you

24 look at the SAW ray detector you have go a 1-meter

25 column, and your sample pre-absorption.

1 [Slide.]

2 You put all that into a hand-held unit,
3 this is a now a hand-held GC, but the end there
4 indicates it is also an LC, so that has all been
5 incorporated into taking today's lab technology
6 down to a very small size.

7 [Slide.]

8 Some work that we have been involved with
9 recently is when you go to use of nanoparticles in
10 your column, you can increase the speed. We are
11 now talking of these compounds being separated in
12 two seconds.

13 Normally, you are looking at 40-minute
14 type turnarounds on a lot of these GC analysis
15 things that have been improving, and I can't really
16 talk about it, but we now have a similar separation
17 in 500 milliseconds, that things are really flying
18 in that way, so it has become a real-time
19 analytical technology.

20 [Slide.]

21 A small mass spec has been developed.
22 There is three or four examples of taking mass spec
23 down to these small sizes.

24 [Slide.]

25 We are also involved with development at

1 UC/Davis with the micro labs, the electrical and
2 computing and the food science areas, to develop a
3 NMR.
4 [Slide.]
5 This is an NMR now that early signal is
6 shown on the bottom left, which showed water, a lot
7 of excitement by the food group because they could
8 monitor a number of things in real time. It has
9 since been refined to the bottom right there, and
10 it has been taken from a protein signal, we have
11 now seen carbon and phosphorus, so we are talking
12 about a hand-held NMR that is going to be
13 multinuclear and have a cost of probably under
14 $20,000.
15 [Slide.]
16 So, all these advances in sensors and
17 controls again highlight the need, how do you get
18 the right sample to these technologies.
19 [Slide.]
20 The chemical industry has come to us, and
21 we have been a forum for discussions on how to
22 create new sampling and standardized technologies
23 in that arena.
24 [Slide.]
25 The typical sampling in a petrochemical

1 plant is a large, often covering a wall, quarter of
2 a million dollars worth of instrumentation just to
3 interface the process with the analyzer.
4 [Slide.]
5 That has now shrunk down to an inch and a
6 half by an inch and a half modules, a standard set
7 by the ISA, and this platform now houses the valves
8 and filters and regulators to interface again the
9 process with the analyzer.
10 [Slide.]
11 What has been evolving here, this concept
12 started in late 2000, and it has now generated to
13 point where we are beginning to think of how we
14 could make this Smart and how to utilize advances
15 in micro-analytical.
16 [Slide.]
17 So, the base here has been defined. We
18 now have a standard sampling interface that can be
19 heated or cooled, or whatever, and the flow
20 patterns all defined, and in the next couple of
21 months, we are standardizing a connectivity.
22 This is getting into some control
23 engineering terminology of how do you move the
24 signals from that platform to distributor control
25 systems and other fields of how do you use that.

1 [Slide.]

2 Then, what has happened is you can now
3 drop your pressure regulators, your valves, and
4 your filter onto that platform and be able to
5 monitor what they are doing.

6 A very interesting story happened at again
7 interfacing the process with the analyzer. The
8 first year of use of these devices caused the
9 engineers to say why does the analyzer have to be a
10 refrigerator size, when the sampling system has
11 come off the wall to this fairly small
12 compartmentalized unit.

13 So, this platform has now become the base
14 for micro-analytical, so it has become a standard
15 platform for the development of micro devices.

16 Three or four years ago, if somebody had
17 come in with a small GC and say wow, isn't this
18 neat, and we would say that is really nice, but how
19 do we use it, how do we go to this big,
20 wall-mounted sampling system and put this little GC
21 at the end of it.

22 That has changed, people are now putting
23 on a fair amount of suction for the development of
24 these devices.

25 [Slide.]

1 So, we predict, and it is beginning to
2 happen, that the NeSSI platform will become the
3 base for a micro-analytical lab. Already we have
4 oxygen and pH and moisture, mass flow controllers,
5 little mass specs, all of the techniques that are
6 listed there have the plan to be mounted on this
7 particular platform.
8 [Slide.]
9 And then we have been devising different
10 interfaces. Our Raman sensor now will fit on the
11 NeSSI platform.
12 [Slide.]
13 The surface plasmon resonance, this is the
14 one that does the very fast biological detection,
15 is now down to the size where the flow channels
16 will interface with the surface and provide almost
17 real-time biological detection in the NeSSI
18 platform.
19 [Slide.]
20 And we have taken something that basically
21 used to be flow injection analysis, it migrated to
22 be called sequential injection analysis, now it is
23 micro sequential injection analysis, where you can
24 put wet chemistry on a multi-functional,
25 multi-position valve, so you can scale down wet

1 chemistry and titrations and things, and do things
2 like glucose, nitrogen, nutrients, and inorganic
3 detection, and this is now on the NeSSI platform.
4 [Slide.]
5 So, there is almost nothing right now that
6 we don't have that couldn't possibly fit on here,
7 and we see it, not only for the process control,
8 but all kinds of optimization studies that could
9 interface with lab-based fermentation and with the
10 micro-reactor systems for the chemical world.
11 [Slide.]
12 The last thing I will mention is our
13 Fermentation Initiative.
14 [Slide.]
15 We are trying to apply the known
16 techniques and compare them with things that are
17 evolving and have applications in other fields. We
18 want to provide training and understanding the
19 implication of some of these measurements.
20 [Slide.]
21 We have set up some platforms that are now
22 outfitted with this array of instrumentation, and
23 you can see things like dielectric spectroscopy,
24 the surface tension, light reflective spectroscopy,
25 et cetera, that are not traditionally being used in

1 the fermentations, but we are gathering data and
2 finding then ways to extrapolate to which
3 fermentation areas they will best influence, and
4 then looking at sampling.
5 Sampling and fermentation is a big
6 problem. Go back to some of the things that we put
7 together that Genentech summarized.
8 [Slide.]
9 They are very concerned about how to
10 achieve these type of considerations, and then you
11 get into some of the sterile requirements and how
12 do you design your sampling system, so it will meet
13 these requirements.
14 [Slide.]
15 So, what we have is a plan to continue to
16 scope out activities from an analytical point of
17 view, but to implement and evaluate this NeSSI
18 platform for not only sampling, but sensor and
19 process control interfaces, so we have a platform
20 now that is being put in to work with sampling the
21 broth and another one with head space.
22 We are looking at chemometric tools to
23 model this batch variability and look at various
24 data fusion approaches. We need to do this to
25 begin to develop these automated tools to evaluate

1 production data and implement chemometrics as much
2 as possible for quantifying process performance and
3 applying these PCA approaches to performing
4 automated pattern recognition.
5 [Slide.]
6 To borrow a little bit from Helen's
7 earlier slide, it is going to be an exciting time.
8 We have got a lot of things in front of us, but to
9 take the advances in PAT from the other industries,
10 through the pharmaceutical on to the biological, I
11 think is going to be very rewarding.
12 DR. KIBBE: Thank you.
13 Are there any quick questions?
14 DR. SINGPURWALLA: I have a comment.
15 You have this nice chart on
16 multidisciplinary, page 16, and you also had CPAC
17 initiatives. Just from a parochial point of view,
18 I noticed the absence of a statistician, yet, you
19 are discussing the sampling, which is really a
20 statistical issue.
21 DR. KOCH: You are right. In fact, that
22 list is not complete. What that list is, is the
23 present principal investigators involved with our
24 programs. We have just finished a project with the
25 chairman of our Statistics Department where we were

1 funding things just for what you are saying.
2 So, really, that list is project
3 dependent. I could probably add as many as six
4 other areas, like physics was on there, and a few
5 others in the past year, so we rotate projects in
6 and out. Chemometrics is probably based in
7 statistics. They don't like to admit it.
8 DR. KIBBE: Anything else? Ajaz doesn't
9 want to comment? Okay.
10 Tom, wrap us up.
11 DR. LAYLOFF: Much of what I wanted to say
12 has been said already, so I will speed through my
13 slides, and I have a few comments at the end that
14 are not in the slides.
15 [Slide.]
16 First of all, PAT, with the subcommittee
17 to this committee, advisory committee, we had a
18 series of charges which were given to us.
19 [Slide.]
20 We had meetings lasting through 2002,
21 three meetings. We covered applications and
22 benefits, process and analytical validation,
23 chemometrics, process-product development, process
24 and analytical validation, a proposed PAT training
25 and certification program, which I think was one of

1 the highlights of the activities.

2 Computer systems validation, 21 CFR 11,

3 and Joe out there tackled that one, PAT case

4 studies, and rapid microbiological testing was

5 tacked on near the end there.

6 [Slide.]

7 We reported that back to this committee

8 back in October. There was a definition of process

9 analytical technology. I am not going to read that

10 to you again, you have already seen it.

11 [Slide.]

12 Again, more statements on PAT

13 applications.

14 [Slide.]

15 Now, this was not included. Historically,

16 there has never been anything to stop people from

17 using new technologies. As a matter of fact, in

18 the 1978 preamble to the CGMPs, there is no

19 prohibition in the regulations against the

20 manufacturing of drug products using better, more

21 efficient, and innovative methods.

22 It is a big box, and it has been there

23 since 1978.

24 The USP also allows alternative methods

25 for assessments.

1 [Slide.]

2 The committee proceeded by coming up with
3 a general guidance through Raj Uppoor and the OPS
4 staff to generate a guidance, which defined a
5 regulatory position for the process and added some
6 incentives. Then, the FDA PAT team, which came
7 through the training program you have heard about
8 earlier.

9 [Slide.]

10 Of course, the Agency's perspectives. One
11 of the things that I think is very interesting,
12 coming from many years of service in the Agency,
13 was the Agency's use of existing knowledge,
14 experience, and guidances from other FDA
15 components, and NIST, ASTM, and ANSI.

16 The FDA tended over the period of my
17 tenure to be very introspective, if it wasn't NIH,
18 not invented here in FDA, we had very little use
19 for it. Going to ASTM and NIST was more of an
20 engineering approach, and we tended to hang with
21 the pharmacists in the USP.

22 The USP, of course, was established by
23 practitioners as a book of recipes to assure
24 quality, and we hung with that, with the
25 practitioners rather than with the engineering.

1 ASTM was established by engineers and
2 chemists to deal with defective rails in the
3 railroad, so they tended to be very
4 engineering-oriented, and it was quite interesting
5 that when FDA-CDRH went out looking for standards,
6 they went to the engineering standard type area
7 rather than practitioners of pharmaceuticals.
8 Now, the switch in OPS of looking at ASTM
9 standards is very interesting because it moves
10 process analytical technologies into an arena where
11 there are engineers and chemists, scientists rather
12 than practitioners. It's a switch in philosophy.
13 Also, the ANSI and ISO fit in that also.
14 They established a framework for manufacturers with
15 flexibility needed to develop new designs.
16 [Slide.]
17 Future issues. Validation data and
18 retention. We have heard some about retention of
19 data, and I don't think that has been addressed
20 well, but the process analytical technology is
21 going to deluge with information, and there is
22 going to have to be some way of defining what is
23 essential and should be retained, and what is not
24 essential.
25 The definition of in-process endpoint

1 detection, data acquisition and storage. In a
2 process of PAT, you have to have some component in
3 the process which is measurable and defines an
4 endpoint. You have to have analytics, but you have
5 to have something that you are looking for.
6 The documentation of the data acquired and
7 electronic signature closures of decision points
8 are going to be an issue, and the incoming material
9 stream consistency and robustness assessments are
10 going to be critical for supporting PAT also.
11 [Slide.]
12 Regulatory incentives, we have gone over
13 those already, not a requirement.
14 [Slide.]
15 How to move forward, try and do it by
16 evolution rather than revolution. Don't bring it
17 all up at once.
18 [Slide.]
19 And the guidance which came out in
20 September, just a few items from it.
21 [Slide.]
22 The guidance is intended to describe a
23 regulatory framework that will encourage the
24 voluntary development and implementation of
25 innovative pharmaceutical manufacturing and quality

1 assurance--manufacturing and quality assurance,
2 voluntary, innovative. Those are key terms.
3 [Slide.]
4 The scientific risk-based framework
5 outline in the guidance should help manufacturers
6 develop and implement new and efficient tools for
7 use during pharmaceutical development,
8 manufacturing, and quality assurance while
9 maintaining or improving the current level of
10 product quality assurance.
11 The framework we have developed has two
12 components: a set of scientific principles and
13 tools supporting innovation, and a strategy for
14 regulatory implementation that will accommodate
15 innovation-keys.
16 [Slide.]
17 Among other things, the regulatory
18 implementation strategy includes creation of a PAT
19 team approach to the CMC review and CGMP
20 inspections and joint training and certification of
21 PAT review and inspection staff.
22 The Agency is encouraging manufacturers to
23 use the PAT framework described here to develop and
24 implement new pharmaceutical manufacturing and
25 quality assurance technologies.

1 [Slide.]

2 The guidance is written for a broad
3 industry audience in different organizational units
4 and scientific disciplines.

5 To a large extent, the guidance discusses
6 principles with the goal of highlighting
7 technological opportunities and developing
8 regulatory processes that encourage innovation.

9 [Slide.]

10 Biologics and PAT. The umbrella guidance
11 covers biological production within the scope.
12 Presentations before our committee included
13 individuals that were using, or companies that were
14 using, process analytical technology to monitor
15 fermentation and purification of biological
16 materials, so it fits if you can define those kinds
17 of controls.

18 However, the process differences that
19 occur in biologics may require or likely will
20 require additional skills and an expansion of the
21 training and certification program.

22 So, that PAT concept, the training of
23 reviewers and inspectors will probably need to be
24 expanded with training in biologics type PAT
25 applications. The standard chemical stuff is not

1 going to work, you are going to have to expand it
2 beyond that.
3 But I think the concept that came out of
4 our committee of having a training program and a
5 certification of competencies is very useful for
6 building teams to get around some of the silos that
7 we have in FDA, that have been there, because those
8 silos contribute to poor science and poor
9 regulation, some of them, and that needs to be
10 straightened out, and this is a good attempt at
11 beginning to do that.
12 [Slide.]
13 Acknowledgments. Ajaz has done a great
14 job, I am a great fan of his efforts in taking this
15 and driving it forward because he has really done a
16 great job of pulling it.
17 Raj for doing the guidance. My former
18 colleagues at the DPA, DPQR, colleagues that
19 presented at the PAT Committee, and those reports
20 are at that web site.
21 It has been a lot of fun for me to work on
22 the PAT Subcommittee. As Ajaz said, it was a
23 project that we started about 11 years ago, and to
24 see it come to fruition now has really been great.
25 I think the industry has got to do more,

1 they are going to do more as they reduce their
2 inventories and move to just-in-time manufacture,
3 which will reduce cost, and, very importantly, help
4 bring the vision of health to all closer.
5 That's it. Any questions?
6 DR. KIBBE: Any questions for Tom? Now,
7 we understood that you had answers to all of these
8 questions from Keith Webber.
9 DR. LAYLOFF: I do, I do.
10 DR. KIBBE: If you could just tell us what
11 the answers are, we could all go to--Happy Hour,
12 right.
13 No questions? Perhaps, Keith, you would
14 like to lead us through these questions and try to
15 get at least some of our collective wisdom on some
16 of them.
17 Committee Discussion and Recommendations
18 DR. KIBBE: What technologies are
19 available now to evaluate the characteristics of
20 protein products in real time during manufacturing?
21 Who has an answer?
22 Dr. Koch.
23 DR. KOCH: I don't know if I could answer
24 that directly, but there are a number of monitoring
25 methods that are being used by those manufacturing

1 protein products today, and it probably might be
2 best to pool some kind of a compilation from those
3 who are presently in that product arena.
4 Often from the place where I am sitting, I
5 have a difficult time judging what measurement
6 techniques that we develop, and we have been
7 involved with technologies that have made it into
8 commercialization, but when we ask one of our
9 members is it working or how well is it working,
10 and their processes, we can normally tell just by
11 the smile or lack of it.
12 So, we are in a situation where we are
13 developing tools for a toolbox, and we are never
14 quite sure how well they are being applied.
15 I don't know, Gerry, you are probably in a
16 position, or Rick, I saw earlier.
17 MR. MIGLIACCIO: My background is on the
18 small molecule side, so I wouldn't want to leap
19 into this.
20 DR. LAYLOFF: I have a question on what
21 does it mean evaluate the characteristics, because
22 the sequence is pretty well clean on proteins. Are
23 you talking about secondary, tertiary, quaternary
24 structures?
25 DR. WEBBER: I am talking about more the

1 overall structure, say, tertiary, and in those
2 cases where it is applicable, quaternary
3 structures, but also the post-translational
4 modifications structure of the product, which is
5 one of the I think most variable in terms of what
6 we see to change during, say, fermentation, or it
7 can be selected out during purification.
8 You can get various species of product get
9 selected or rejected during purification, so that
10 is really what I was looking at there.
11 DR. LAYLOFF: So, it is not a process
12 closure, it is actually an assessment of the
13 product coming out of the process.
14 DR. WEBBER: In this particular question,
15 yes, it is the product which is not necessarily
16 coming out, but the product during manufacturing.
17 One of the areas that I have seen reported is the
18 ability to use--and I discussed it a little
19 bit--immunological techniques or lectins to look at
20 structures.
21 For example, carbohydrates on products, I
22 haven't seen that in practice yet as a PAT, but
23 that is something that may be coming down the line.
24 DR. KIBBE: Dr. Cooney.
25 DR. COONEY: First of all, this is a very

1 important question because this is a question that
2 relates what you make to its therapeutic safety and
3 efficacy, on the one hand, so part of addressing
4 this question is to understand the relationship
5 between particularly post-translational
6 modification, glycosylation, acetylation,
7 phosphorylation, and so on, and its therapeutic
8 efficacy.
9 It is also important because a lot of
10 those properties are known to vary with the
11 process, so whatever you use at this point for an
12 assay or an analytical technology, links you back
13 to the process, on one hand, presumably you will
14 understand that linkage, and links you forward to
15 the patient, on the other hand.
16 I think the advances in mass spec that
17 have evolved with proteins and, in particular, with
18 proteins that are modified, is quite substantial.
19 Quite recently, I saw ultra-high pressure
20 chromatography, which takes advantage of a number
21 of innovations in chromatography by being able to
22 go to very small particles with a very high amount
23 of surface area at very high pressures, and by
24 doing that, you can very quickly get a very high
25 resolution of complex mixtures.

1 So, a combination of size, shape methods
2 plus mass spectrometry and being able to work with
3 large molecules and very small amounts of material,
4 that seems to be where things are going, and
5 provides a very powerful armamentarium of PATs.
6 DR. KIBBE: Tom has another comment?
7 DR. LAYLOFF: I was wondering, on
8 chromatographic procedure, whether or not you could
9 have subsequent post-translational modification of
10 the proteins themselves. Denaturation would be one,
11 but reactions with the supports themselves at
12 15,000 psi are reactive with solvents catalyzed on
13 the supports.
14 I don't know how you validate the
15 separation tools at 15,000 psi.
16 DR. COONEY: You raise a very good point.
17 The work on ultra-high pressure chromatography is
18 very new and solvents and dissolved gases and
19 solvents are very reactive at those pressures.
20 That needs to be sorted out. It's the right
21 question, and I think one can design the
22 experiments to get the answer.
23 DR. KIBBE: I feel like we are doing 1 and
24 2 a little bit. What tools would allow us to
25 understand the manufacturing process better? The

1 tools that will allow us to understand the product
2 will also allow us to go back and look at the
3 process.
4 Is there anything specifically that
5 anybody would like to add on that?
6 DR. LAYLOFF: I was going to say one of
7 the things that comes up, of course, in near
8 infrared, in applications, is that you don't have
9 to separate anything, you just look at it, and you
10 define your endpoints on a polyvariate system.
11 It may be also possible to do something
12 like looking at a mass spec fingerprint without
13 separating anything, just look at the mass spec,
14 just hammer it and see what it looks like during
15 the course of a process, just hammer it at
16 intervals and just see what it looks like until you
17 define an endpoint by another source, and then use
18 that as an endpoint indicator.
19 DR. KIBBE: Anything else you need?
20 DR. WEBBER: Just one follow-up question
21 with regard to No. 1 from the presentation that Dr.
22 Koch did.
23 You had shown LC and NMR technologies that
24 were miniaturized, and we like to think smaller is
25 better and more PAT-like. Would those

1 technologies, as they are now, be amenable to
2 biotech products or do smaller molecules, would
3 they be useful for looking at, say, fermentation
4 components, and things like that?
5 DR. KOCH: We plan to have all those
6 techniques tied in with the fermentation project,
7 so there are early reasons to believe that we will
8 be getting data from them.
9 I think one of the important things to
10 point out, when we even talk about DNIR or Raman or
11 some of the others, I think we will find with time
12 an array of technologies with a multivariate
13 evaluation of the data is going to prove in the end
14 to be quite valuable, so that you can look at, and
15 see, the variations that are coming from batch to
16 batch or system to system.
17 DR. WEBBER: Thank you.
18 We had completed Item No. 2 or not, you
19 sort of led into that, but are there any other
20 comments with regard to what tools would be
21 available to allow us to better understand biotech
22 processes?
23 DR. KOCH: Maybe just a comment on that
24 one. It seems like at the top of most
25 manufacturers' list is bioviability, and that takes

1 on all kinds of definitions based on what product
2 one is working with.
3 The more tools that are developed to
4 determine the health of the organism, the maturity
5 of the system, or measurement or metrics to
6 determine when is the best time to harvest, there
7 is a number of things I believe are going to be
8 advancing there, both direct and indirect methods.
9 DR. LAYLOFF: Then, there is also going to
10 probably be indirect methods, like on flowing
11 stream systems, where you actually take the
12 fermentation broth, react it on to other species,
13 which could serve as a surrogate to where the
14 process is located.
15 DR. COONEY: One of the things that will
16 surely happen in the diagnostics field is improve
17 proteomic techniques. The genomic techniques are
18 not so bad, the proteomics are still early stage,
19 but as we develop better proteomic techniques, as
20 you develop better immuno-based panels that are
21 important in diagnosis of disease, there is going
22 to be a spillover benefit to the application of
23 these to the processes themselves.
24 So, this not a static, obviously a static
25 situation, and I expect that the main driver for

1 some of the new analytical techniques will not be
2 process understanding, but rather will be
3 understanding the biology, and that it is up to us
4 to take those same techniques and those same
5 methodologies and begin to apply them to the
6 processes.
7 The other piece of this, to emphasize a
8 point I made earlier, by being able to do a lot of
9 measurements on a small scale, one can take
10 advantage of experimental design and look at your
11 experimental space, so these techniques that allow
12 you to do that are important.
13 Another area, I mentioned doing
14 large-scale fermentation type of experimental
15 programs, but you need to do this for downstream,
16 as well, and there is a fair amount of work, there
17 is a modest, well, there is a little bit of work
18 being done to miniaturize the downstream processes
19 that hopefully should have the benefit of also
20 being able to do design of experiments on a larger
21 amount of downstream space at the same time, so
22 there is yet another area of development
23 particularly in the microfluidic space.
24 DR. KIBBE: Just a quick follow-up
25 question of our experts over here. One of the

1 things I have noticed whenever we discuss PAT, is
2 we deal with a tremendous amount of data influx, we
3 get lots of data, and then we have to sort out the
4 data that is really valuable to us.
5 Is there a role to play for the
6 ever-increasing power of the computational machine
7 that sits next to the instrument?
8 DR. COONEY: Absolutely yes, not only in
9 working your way through large data sets, but also
10 learning how to do simulation both at the molecular
11 scale and upwards.
12 There is very interesting work being done
13 with modeling of small molecule-protein
14 interactions that is useful from a design point of
15 view, but it is also useful to explain some of the
16 phenomena that you see in a process.
17 So, having large computational capacity is
18 very important both from the passive data mining,
19 as well as the proactive process simulation role.
20 DR. KOCH: I have to more than second
21 that. The number of sensors being developed, and
22 that is just begging for a number sensor mining and
23 then into the data mining, and then on into how do
24 you handle the monstrous amounts of data.
25 DR. KIBBE: Just a personal opinion about

1 accepting monstrous amounts of data is I sincerely
2 hope that the companies analyze it, pick out what
3 is important, and the FDA accepts only those things
4 that are worth looking at, and doesn't demand every
5 ton that comes through the door.
6 DR. SINGPURWALLA: Well, I have to
7 disagree. I am suspicious of data mining because
8 you are looking at patterns. You may look at
9 patterns that are purely imaginary. There is a
10 classic example of consumption of alcohol and
11 professor's salaries. You know, there are dubious
12 correlations that can come about.
13 Now, having said that, I think when you
14 are exploring any data--and I think you asked a
15 very good question, and I am not sure if the
16 question has been addressed--with a lot of data, we
17 are collecting a lot of data, by itself, may not
18 contain the knowledge of the information that you
19 are really looking for.
20 You may collect a lot of data which
21 provides information which is not really relevant
22 to what it is that you are interested in. So, the
23 whole idea is when you are doing a data analysis
24 rather than data mining, what you have to do is
25 have some kind of a hypothesis in mind, have some

1 kind of a model in mind, and the model is never
2 suggested by the data, the model is always
3 suggested by the science that you are looking at
4 and let the data then give you the unknowns of the
5 particular model or help you change your model or
6 help you update your model.
7 So, I think your question is very nice and
8 very important, and I think it goes back to why
9 collect the data. You should have a purpose for
10 collecting the data. You should have an
11 experimental design in mind when you collect the
12 data, and the design itself should be driven by a
13 certain hypothesis. So, this is more of a
14 philosophical comment.
15 DR. KIBBE: Off-line, we will talk about
16 the philosophy of making observations about your
17 surroundings and then developing the thesis and
18 hypothesis versus having an hypothesis and making
19 your observations fit it.
20 Shall we go on to the next question?
21 DR. COONEY: I can't let this point go
22 unnoticed. I think that you are absolutely right,
23 and I like your hypothesis, and I think the
24 experiment that has to be done to confirm it is to
25 increase the salaries of professors.

1 [Laughter.]
2 DR. KIBBE: What processes in biological
3 manufacturing would benefit the most from
4 implementation of PAT? I think we are dealing with
5 fermentation here, and the alcohol is just
6 naturally connected somehow. Go ahead.
7 DR. COONEY: I would address this question
8 in two ways. One is if you look at which
9 particular products might benefit by early
10 implementation, and I would suggest that the
11 simpler the better, better to walk rather than run,
12 taking very complex biological products made by
13 very complex processes would be a very perhaps
14 difficult place to begin, so that I think one needs
15 to think about what are the logical targets.
16 But then within the process, it is
17 important to think about it, as well, because it's
18 in the fermentation that you define the initial
19 product that is being made, but a lot of the
20 concerns about process variance occur once you have
21 made the product and it is then subsequently being
22 processed.
23 So, that suggests that you need to
24 methodically think through your entire process as
25 you do for a drug substance, but because there are

1 more steps, there is more complexity, obviously,
2 there is more to do.
3 But one of the characteristics of
4 biologicals is that it is important to get the
5 synthesis right, and then it is important to treat
6 it right once it has been made.
7 DR. DeLUCA: Let me just add to that, I
8 think it's a good follow-on, and I guess we have
9 heard a lot about the biological process in
10 fermentation, purification, and certainly we have a
11 sensor technology in the Smart systems today to be
12 able to handle that.
13 I guess I wanted to move to the fill and
14 finish end of it, and I guess I have a lot of
15 questions. You know, do you apply PAT to current
16 products? What properties can vary from unit to
17 unit? What does the variation mean in the
18 pharmacological sense? These are the types of
19 questions.
20 But with regards to the biological, it
21 seems in the fill and finish that most of these
22 freeze dried, so they are going to be lyophilized,
23 and I think in lyophilization, this is not a
24 trivial situation here, and I think you think that
25 you put 10,000 vials into a chamber and you get out

1 10,000 vials with little variation.
2 You have to look at processing, and most
3 products are processed and then filled in the
4 containers. In freeze drying, the processing takes
5 place in an individual container.
6 Each little container is processed after
7 it's filled, and the heat that goes to that
8 container is such that each vial doesn't see the
9 same temperature, you like to have a small
10 variation across the shelves in the type of flow,
11 and the heating element, the fluid that goes
12 through it to heat and freeze, but it isn't.
13 So, you end up with, you could have
14 product that has a variation in moisture, you can
15 have products that vary in meltback collapse, so
16 this can occur, so I think it is important that
17 when we are looking at PAT and looking at the fill
18 and finish, that moisture becomes very, very
19 important in these lyophilized products and these
20 biologicals, and I think applying things like NIR
21 to that, I think makes this a very doable thing, to
22 be able to do that with every product. It's a
23 non-invasive procedure, and I think that is
24 critical.
25 So, you have to bring in robustness in

1 here. What can the product chemically tolerate in
2 the way of moisture? I mean it is being freeze
3 dried because obviously, it can't be put into a
4 solution form, so moisture is going to have an
5 effect.
6 But what moisture content, can it tolerate
7 5 percent or maybe it only can tolerate a half
8 percent, or maybe there is an optimum moisture
9 content that is good, because you are going to get
10 into changes in tertiary and quaternary structure,
11 aggregation, and whatnot with regards to moisture.
12 So, I think that is an area that really
13 lends itself to PAT, I think is in actually
14 determining the moisture of these products, and
15 again knowing where, you know, what kind of
16 variation it can tolerate, and you have to somehow
17 try to have some idea of the pharmacological effect
18 of this, whatever the effect is of the moisture,
19 does it really translate into a pharmacological
20 effect, but I think that is an area that needs to
21 be looked at.
22 DR. KOCH: I would certainly agree with
23 that, but one other part of the biological drug
24 manufacture, particularly fermentation, that I
25 think needs to be addressed is just the

1 fermentation itself in terms of reaction
2 engineering.
3 If you look at today's fermenters, they
4 don't look that much different than they did 50, 60
5 years ago. Aeration is very important, as it
6 nutrient and contact, so maybe the most effective
7 fermentation is where you optimize those
8 parameters, and huge vessels are not necessarily
9 the way to do that.
10 I think we are in a sunk capital situation
11 where industry probably can't afford to redesign
12 the approach, but there are some very interesting
13 approaches, that if you could number up from the
14 micro scale that Charles indicated, you might have
15 a far more effective control of the material and
16 far less of impurities that are being generated.
17 DR. COONEY: I would like to add another
18 point to what Pat said. When one is doing a
19 de-bottlenecking exercise on a manufacturing
20 process to try and improve the throughput, you
21 begin that exercise from the end of the process and
22 you work your way from the end forward.
23 One very logical way of thinking about the
24 application of the strategy, of PAT strategy, it is
25 due to exactly the same thing, that if you

1 understand, if you really understand the product
2 and then you work your way back down the process,
3 that makes it easier to de-bottleneck and design
4 going forward.
5 DR. KIBBE: Since we started at the front,
6 then, moving towards the back with the questions,
7 we will keep going towards the back.
8 The next question is for processes or
9 products that do not currently allow direct product
10 quality monitoring, what other strategies do you
11 recommend for product quality control in addition
12 to control of in-process parameters?
13 DR. SINGPURWALLA: I like this question.
14 DR. KIBBE: He likes this question. It's
15 a Bayesian question.
16 DR. SINGPURWALLA: Exactly. I am really
17 impressed with your insight and intuition.
18 There is a technology, and there is a
19 technology called information fusion. Sometimes it
20 is called information integration. The basic idea
21 is this. The analogy here is like investigating a
22 crime. Some crime has been committed. You don't
23 know who has committed the crime. You are gathering
24 all kinds of evidence, and then you are pooling
25 that evidence in a very systematic way to make a

1 probabilistic judgment about the crime. You cannot
2 make a judgment with certainty, because the only
3 way to make a judgment to certainty is to see
4 something.
5 So, you have a similar situation here, and
6 the problem you mention is common in other
7 scenarios where you cannot directly observe the
8 product.
9 You are not allowed to either observe the
10 product or test the product for whatever reason you
11 have, but you have evidential information. You
12 have information on degradation, you have
13 information on other kind of attributes, and how do
14 you systematically integrate that information is a
15 well-developed technology, and I think that would
16 be germane here to the kind of question that you
17 are raising.
18 You have a process, you cannot directly
19 observe it, but you presumably can observe other
20 things related to it. So, the question is how do
21 you systematically pool that information, and there
22 is a methodology, and, of course, it is Bayesian,
23 as our chairman so wisely suggested, and it is
24 available.
25 DR. KIBBE: Do you have a different

1 method?

2 DR. LAYLOFF: No, I like Bayesian, but I

3 was thinking that the monitoring and control, the

4 in-process parameters may be polyvariate with

5 respect to the quality of product.

6 It may be a series of interactions on

7 product quality, so the thing has to be linked

8 together, so the evidentiary procedure may be many,

9 many different mixtures of it to relate to the

10 product quality.

11 DR. SINGPURWALLA: Just to add to that,

12 you used the word polyvariate?

13 DR. LAYLOFF: No, I didn't.

14 [Laughter.]

15 DR. SINGPURWALLA: It's multivariate.

16 DR. LAYLOFF: I know I did something

17 wrong.

18 DR. SINGPURWALLA: The thing you want to

19 be careful about is this multivariate information

20 may be interdependent because the same phenomena

21 can appear under two guises, so you don't want to

22 add up, you know, the basic information should not

23 be added up. You have got to recognize the

24 interdependence when there is a multivariate case,

25 and therefore the technology, the mathematical

1 technology that you need has to be nicely refined
2 and carefully thought out, but the technology is
3 what I am suggesting is purely an analytical
4 technology, it is not a physical technology.
5 DR. WEBBER: Thank you.
6 This question was mostly--I think that's a
7 great answer, but we are looking at sort of, as Dr.
8 Cooney pointed out, the oxygenation issues with
9 fermentation, how that affects product. If you can
10 understand those, what sort of surrogates can you
11 use to monitor or have a comfort level with the
12 product quality based on looking at secondary
13 parameters, but I think the answer you have given
14 is one that we have to consider, as well, the
15 analytical methods used to ensure that those aren't
16 interfering with one another.
17 DR. COONEY: There is a fundamental
18 problem with surrogates, and that is that many of
19 them come from correlative observation, and the
20 point was made quite appropriately earlier that
21 when you take the data, develop a correlation, that
22 may work within a certain amount of space with a
23 certain set of assumptions, but it indeed is a
24 correlation.
25 I think the challenge that we have is to

1 take that correlative knowledge and then create an
2 hypothesis that, in fact, can be tested by one or
3 more of the many techniques that we are talking
4 about.
5 I think what we are really talking about
6 in this initiative is a change in the mind-set and
7 the way that we think about developing and
8 exploring and validating our processes, so there is
9 going to be a lot of these iterations of learning,
10 many of which will come from the surrogate
11 procedures and correlative observations, but we
12 need to drill down and understand that we are
13 solving the right problem at the right time in the
14 right way.
15 DR. KIBBE: Ajaz.
16 DR. HUSSAIN: I think the points are well
17 made. As we were putting the guidance together,
18 one of the key aspects that we did say that in some
19 cases, correlations would not be sufficient from a
20 regulatory perspective, and we would look for
21 causality as a means for making judgments, and so
22 forth, and we sort of leaned that way, risk in a
23 systems way, because keeping in mind, you are
24 looking at a constrained space once it's in
25 manufacturing.

1 So, there are opportunities to utilize
2 correlations in some low-risk areas, but also when
3 there is a risk associated, you might prefer it to
4 be causal rather than correlative. That is how we
5 sort of structured the guidance.
6 DR. KOCH: I guess this supports the
7 Bayesian approach, as well, we will find out in a
8 second, but rather than the crime analogy, I would
9 like to think of something that is more like going
10 to have a physical with a physician, where you are
11 actually trying, in our product quality
12 specifications, you know, assuming that is the
13 perfect health you are looking for, but then
14 develop a number of tests that would be analogous
15 to doing body fluids or x-rays or a bunch of
16 technologies, and then looking at the results that
17 are coming back like in the physician's office, all
18 of the tests are not going to be judged equally,
19 but if you have a blood pressure and a lipid and an
20 EKG, that is out of a predefined specification, you
21 will start to spend your time at that first in
22 order to see how the process is working.
23 So, you will have a lot of data to work
24 from, but you will have to make some assumptions
25 early on in terms of what type of data relate more

1 quickly to the final health of the product in this
2 case.
3 DR. KIBBE: Jurgen, do you have any
4 opinions so far?
5 DR. VENITZ: To respond I think to the top
6 four or five questions in terms of how do you link
7 all of this to the in-vitro potency, I think
8 Patrick alluded to that a little bit when he talked
9 about the fill stage, the late stage. You are
10 measuring attributes. You may or may not know what
11 they actually are other than they depend on some of
12 your process variables.
13 My question, as a pharmacologist, is
14 always so, why should I care about that. It is
15 driven by your ability to measure, not necessarily
16 by your ability to understand the consequences.
17 You do know it is affected by your process, but you
18 don't know whether it has any pharmacological
19 consequences that I should care about.
20 So, whenever you are looking at those
21 steps, there has to be a linkage between whatever
22 attributes you have to the ultimate pharmacological
23 activity of the product.
24 So, maybe that is my comment.
25 DR. KIBBE: Thank you, Jurgen.

1 DR. WEBBER: I certainly agree with that
2 completely. I think one can measure all sorts of
3 things, but you have to look at what the critical
4 product characteristics are, and that is something
5 that has to be determined during the clinical
6 development stage and product development stages.
7 DR. VENITZ: It goes beyond that. I mean
8 when I listen to the gentleman talk about what
9 process analytical technology does, the way I
10 understand, it is basically a statistical way of
11 relating process variables and their impact, their
12 criticality in terms of other attributes that you
13 measure using some of those sensors that we heard
14 about, but that doesn't tell me whether I should
15 care about any of this, because you are really then
16 changing your variables to affect your attributes
17 in a way that you think it should be.
18 But my question is, so what is your
19 template, how do you know that that is the way your
20 attributes should be, unless it is relevant to the
21 pharmacologic activity of your product?
22 If it is not relevant, then, yes, you
23 might be improving your process, but it is
24 cosmetic, it is not of any particular relevance for
25 me to care about. So, as part of this in the

1 development stage, maybe not in manufacturing, the
2 ultimate manufacturing stage, there has to be a
3 linkage to the pharmacologic activity.
4 DR. KIBBE: Go ahead, Pat.
5 DR. DeLUCA: Just to add, I think it is
6 critical that we have good control, I mean with
7 regards to the fermentation before it gets to the
8 fill and finish. I think that is essential. I
9 think when the product gets to the point where it
10 is going to be formulated and put into final dosage
11 form, you want to have good control over that,
12 because in that finishing, there could be a lot of
13 variation.
14 I just mentioned moisture before, but when
15 you are freezing, you are freezing an amorphous
16 form, and then when you are drying, you get a lot
17 of conversion into the crystalline states, and
18 there could be variation in the distribution of
19 crystalline and amorphous form in the finished
20 product, and that is going to affect the water
21 content and the effects, so there is a lot of
22 variation that can occur in that stage, that I
23 think there needs to be control over.
24 I support that there needs to be great
25 control in the upstream processing, as you

1 mentioned.
2 DR. KIBBE: Anybody else on the first
3 four?
4 That brings us to: What additional
5 elements should be incorporated in a training and
6 certification program for reviewers and inspectors
7 of biotechnology PAT?
8 I am going to take the prerogative of the
9 Chair to speak first, and then you all will tell me
10 what mistakes I have made.
11 I have been involved with educating
12 college level students for years, and one of the
13 things that I find is that they learn something in
14 a specific incidence or example, but they don't
15 learn things in the generalities, and one of the
16 most powerful tools we have to handle all of this
17 is a true and real understanding of the scientific
18 method and the application of the scientific method
19 to the problem in front of you, and not just
20 learning how to do it in one situation, but
21 learning how that works in any situation.
22 I don't know whether you can get that into
23 a training session, with a process that hasn't been
24 well developed and isn't templated, when you look
25 at the data you have in front of you and can use

1 that.

2 The second is critical thinking. Often,

3 students really don't know the difference between

4 facts and opinions, because they have been trained

5 over their life to accept someone who stands in

6 front of them in a lecture hall and says something

7 as if they were saying facts, when, in fact, most

8 of the time we who lecture give opinions about

9 everything and very little real facts.

10 They also have a hard time differentiating

11 results from conclusions. They look at the result

12 and immediately leap to a conclusion that isn't

13 necessarily supported by the facts, and if we could

14 add anything to anybody's training who are going to

15 be involved in reviewing data or doing inspections,

16 it is that level of sophistication that would be

17 very helpful.

18 DR. SINGPURWALLA: I agree with you on

19 that point certainly. I really also think that

20 there should be some kind of education and training

21 on basically uncertainty, what is the meaning of

22 uncertainty, how to quantify uncertainty, what are

23 the different ways of quantifying uncertainty, what

24 is the difference between variability and

25 uncertainty, is there a difference, and basically,

1 not statistics or statistical technology, but just
2 the background of what it is all about, I think
3 that would be very valuable because that seems to
4 be running through completely all the way here.
5 So, that is what I would like to add,
6 "parochial."
7 DR. LAYLOFF: I think also it would be
8 useful to turn to the biotechnology industry, to
9 the people working in CMC, to try and help define
10 what attributes reviewers and inspectors should
11 have to properly evaluate, because those guys live
12 with that stuff on a daily basis, and I am sure
13 they would be willing to help.
14 DR. KIBBE: Judy.
15 DR. BOEHLERT: Finally, I am going to make
16 a comment. My background is in small molecules, so
17 I am sorry, but it would seem to me with the
18 complexity of these processes, that you might want
19 to go to industry and sort of talk with them, and I
20 think you know, as well, about what are the issues
21 that can occur, because things go wrong in these
22 processes that don't go wrong in conventional
23 processes.
24 You have adventitious contamination and
25 things that don't happen elsewhere, so

1 investigators, reviewers need to learn to ask the
2 right questions and go beyond what they see to say,
3 well, what about this, what about that, could this
4 happen here, did this happen here, and that you
5 need to train people to ask the right questions,
6 because it's a whole different ball game when you
7 get into these products.
8 DR. KIBBE: Anybody else? Do we have
9 anybody who hasn't spoken? Would you like to
10 comment on our discussion?
11 DR. SELASSIE: I think I will pass.
12 DR. KIBBE: What I am going to do now,
13 unless Keith has something specific he needs us to
14 do, is I am going to summarize.
15 DR. WEBBER: I didn't have anything
16 specific for you to do now. Maybe before you
17 summarize, I would like to thank the committee
18 certainly for getting together and addressing the
19 issues and the questions that we have, giving
20 presentations, and giving us your input on this
21 difficult issue that we have ahead of us.
22 DR. KIBBE: You had five things that you
23 wanted us to help you with and some of them we can
24 help you with and sometime we will help you with.
25 Starting with the first one, technology

1 changes at an ever-increasing rate since the
2 beginning of civilization, each breakthrough in
3 technology is taking shorter and shorter periods of
4 time. if you wait two weeks, there will be a new
5 technology to measure something.
6 The question is what do you need to know,
7 what good questions have you asked, and that is the
8 core of the quality of scientific endeavor, so make
9 sure you ask good questions, and there will be
10 someone out there will develop a way of getting you
11 an answer.
12 No. 2, data collection is important. I
13 think there is fun in data mining, I enjoy it. I go
14 looking for patterns and try to develop patterns,
15 but the question really is are these patterns of
16 correlation of cause and effect, how do you know
17 the cause and effect, and this boils down to being
18 able to think critically about the analytical data
19 in front of you.
20 No. 3, variability control seems to be the
21 key. If we know how much variation we can allow in
22 any critical step in order to still maintain a good
23 product, then, that is the variation we should
24 allow, and we should really look at variability on
25 each critical step in the process.

1 If we know our critical steps, which is
2 always an assumption that we make, and we hope we
3 do, and we know the variability that will throw our
4 process out of control, then, we know where we need
5 to limit ourselves, and making intelligent choices
6 about those limits are really important.
7 Related observations. I know my friend
8 likes, under No. 4, Bayesian approach. It all
9 boils down to critical thinking about the things
10 that you can measure and the things that you need
11 to measure, just because you can measure it doesn't
12 mean you need to know about it. If it is something
13 critical you need to measure, you need to find a
14 way to measure it.
15 This brings us to No. 5, which I think
16 boils down to training people to think critically
17 and to apply the scientific method appropriately.
18 The quality of good science is the quality of the
19 questions.
20 The difference between a normal researcher
21 and Albert Einstein is that the way he posed the
22 questions allowed him to get breakthroughs and
23 answers. The other thing that he had that most of
24 us don't have, and I won't say any one of you
25 doesn't, is that he was never satisfied with the

1 quality of the answer, and he always kept looking
2 for better and better answers.
3 Twain said that what we don't know doesn't
4 get us in trouble. It is what we know that ain't
5 so.
6 So, we have to be very careful to avoid
7 thinking we know something about our process just
8 because we made a measurement, and it really isn't
9 something that describes the process, but it is
10 just a convenient measurement.
11 We find in clinical realm that often a
12 technique comes along looking for a disease to
13 diagnose, so don't look for a technique that
14 diagnoses a disease you don't have or wouldn't even
15 get. Just look for the ones that help you get the
16 answers.
17 On that note, I will end whatever
18 soliloquy I have.
19 Helen, do you have a comment? I saw you
20 getting closer to the microphone.
21 MS. WINKLE: No.
22 DR. KIBBE: We are going to be back here
23 at 8:30 tomorrow morning.
24 [Whereupon, the meeting was recessed at
25 4:30 p.m., to reconvene at 8:30 a.m., Wednesday,

1 April 14, 2004.]

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