

UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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MANUFACTURING SUBCOMMITTEE

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OPEN PUBLIC HEARING

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TUESDAY,
JULY 20, 2004

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The above entitled Meeting was conducted at 8:30 a.m., in the CDER Advisory Committee Conference Room, 5630 Fishers Lane, Rockville, Maryland, Dr. Judy P. Boehlert, Subcommittee Chair, presiding.

PANEL MEMBERS PRESENT:

JUDY P. BOEHLERT, Ph.D., Chair, Manufacturing Subcommittee

HILDA F. SCHAREN, M.S., Executive Secretary, Advisors and Consultants Staff, CDER, FDA

PATRICK P. DeLUCA, Ph.D., Professor, Faculty of Pharmaceutical Science, University of Kentucky

DANIEL GOLD, Ph.D., D.H. Gold Associates

DAVID HOROWITZ, Esq., Director, Office of Compliance, CDER, FDA

AJAZ HUSSAIN, Ph.D., Deputy Director, Office of Pharmaceutical Science, CDER, FDA

PANEL MEMBERS PRESENT:

KENNETH M. MORRIS, Ph.D., Department of Industrial
and Physical Pharmacy, School of Pharmacy,
Purdue University

GARNET PECK, Ph.D., Industrial and Physical
Pharmacy, Purdue University

JOSEPH PHILLIPS, Regulatory Affairs Advisor,
International Society of Pharmaceutical
Engineers

G.K. RAJU, Ph.D., Executive Director, MIT/PHARMI,
MIT Program on the Pharmaceutical Industry,
Massachusetts Institute of Technology

NOZER SINGPURWALLA, Ph.D., Director, Institute for
Reliability and Risk Analysis, Professor of
Statistics, George Washington University

HELEN WINKLE, Director, Office of Pharmaceutical
Science, CDER, FDA

ALSO PRESENT:

JOHN BERRIDGE, Ph.D., Vice President, Pharmaceutical
Sciences, Pfizer, Ltd.

GARY BUEHLER, R.Ph., Director, Office of Generic
Drugs, OPS, CDER, FDA

PAUL FACKLER, Ph.D., Senior Director, Product and
Biopharmaceutics Strategy Development, Global
Generic Research and Development, Teva
Pharmaceuticals

DONALD MARLOWE, FDA Standards Coordinator, Office of
Science and Health Coordination, Office of the
Commissioner, FDA

TOBIAS MASSA, Ph.D., Executive Director, Global
Regulatory Affairs, Operations/Chemistry,
Manufacturing and Controls, Eli Lilly & Co.

MOHEB NASR, Ph.D., Director, Office of New Drug
Chemistry, OPS, CDER, FDA

FREDERICK RAZZAGHI, Director of Technical Affairs,
Consumer Healthcare Products Association

C-O-N-T-E-N-T-S

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

2 (8:32 a.m.)

3 CHAIR BOEHLERT: Good morning. It's 8:30.

4 I call this meeting to order and welcome members of
5 the committee and all other participants that are
6 going to be presenting in this two-day session. We
7 have an interesting program, updates on a lot of
8 topics we've addressed in the past. One that I'm
9 particularly interested in is finally hearing, you
10 know, some discussion on Bayesian statistics. We've
11 touched on it many times in our discussions, so Nozer,
12 I'm looking forward to that. You finally get your
13 chance.

14 DR. SINGPURWALLA: You'll be tested.

15 CHAIR BOEHLERT: That's what I was afraid
16 of. It's not a topic that's in my area of expertise
17 but I expect to learn a lot today. With that, I'd
18 like to turn the meeting over to Hilda for the
19 conflict of interest statement.

20 MS. SCHAREN: The following announcement
21 addresses the issue of conflict of interest with
22 respect to this meeting and is made a part of the

1 record to preclude even the appearance of such at this
2 meeting. Based on the agenda, it has been determined
3 that the topics of today's meetings are issues of
4 broad applicability and there are no products being
5 approved at this meeting. Unlike issues before a
6 committee in which a particular product is discussed,
7 issues of broader applicability involve many
8 industrial sponsors and academic institutions. All
9 special government employees have been screened for
10 their financial interest as they may apply to the
11 general topics at hand. To determine if any conflict
12 of interest existed, the agency has reviewed the
13 agenda and all relevant financial interests have been
14 reported by the meeting participants.

15 The Food and Drug Administration has
16 granted general matters waivers to the special
17 government employees participating in this meeting who
18 meet prior waiver under Title 18 United States Code,
19 Section 208. A copy of the waiver statements may be
20 obtained by submitting a written request to the
21 Agency's Freedom of Information Office, Room 12-A-30
22 of the Parklawn Building. Because general topics

1 impact so many entities, it is not prudent to recite
2 all potential conflicts of interest as they apply to
3 each member and consultant and guest speaker.

4 FDA acknowledges that there may be
5 potential conflicts of interest but because of the
6 general nature of the discussion before the meeting,
7 these potential conflicts are mitigated. With respect
8 to FDA's invited industry representatives, we would
9 like to disclose that Gerald Migliaccio is
10 participating in this meeting as an industry
11 representative acting on behalf of regulated industry.
12 Mr. Migliaccio is employed by Pfizer.

13 Dr. Paul Fackler is participating in this
14 meeting as an acting industry representative. Dr.
15 Fackler is employed by Teva Pharmaceuticals. In the
16 event that the discussions involve any other products
17 or firms not already on the agenda for which FDA
18 participants have a financial interest, the
19 participant's involvement and their exclusion will be
20 noted for the record. With respect to all other
21 participants, we ask in the interest of fairness that
22 they address any current or previous financial

1 involvement with any firm whose product they may wish
2 to comment upon. Thank you.

3 CHAIR BOEHLERT: Thank you, Hilda. To get
4 the meeting started, Ajaz -- if I turn on the mike and
5 you can actually hear me. To get the meeting started,
6 Ajaz will provide an introduction.

7 DR. HUSSAIN: Good morning, and welcome to
8 Rockville. The Manufacturing Subcommittee for the
9 Advisory Committee for Pharmaceutical Science, I think
10 this is the third meeting after the key subcommittee
11 ended and we have discussed many of the developments
12 with this committee and we'd like to sort of use this
13 meeting to bring forward the concepts that have been
14 developed and the challenges that we are overcoming in
15 trying to implement some of the concepts and seek your
16 input in a number of questions that have been posed to
17 you.

18 Just to recapitulate, at the Advisory
19 Committee of Pharmaceutical Science in 2001 July, we
20 had used the CGNP initiative and that was the starting
21 point for discussion on manufacturing in a very
22 focused manner that led to the CGNP initiative for the

1 21st Century and later on we have two other
2 initiatives defined, one on molecular innovation and
3 one on critical path. In some ways I look at all
4 these initiatives as a desire to define a desired
5 state which more efficient, which is more effective in
6 meeting the needs of the customer, that's a patient
7 and so forth. So the desired state that FDA is trying
8 to articulate in a shared manner for the US patient is
9 in many ways very forward and I'll focus many on
10 manufacturing with regards to manufacturing and
11 utilize the six dimensions of our pharmaceutical
12 quality for the 21st Century Initiative as a means to
13 share with you how this meeting agenda was organized.

14 Although we called our initiative CGNP for
15 the 21st Century, we realized that is was probably a
16 mistake to just call it the CGNP initiative, because
17 it is an initiative which is dealing with all aspects
18 of pharmaceutical quality. It applies to CMC Review
19 Process as well as the CGNP inspection. So often we
20 refer to that as the Pharmaceutical Quality for the
21 21st Century initiative instead of just CGNP
22 Initiative.

1 The six dimensions for this initiative are
2 foremost, strong public health protection. We want to
3 maintain that and strengthen that function of FDA. We
4 want to bring an integrated quality systems
5 orientation to our activities and our programs that
6 could simply mean better communication between
7 different organizations within the agencies, the
8 industry and so forth but also a more systematic
9 approach to pharmaceutical quality and more
10 integration and collaboration between different parts
11 of the organizations that deal in pharmaceutical
12 quality.

13 Science based policies and standards, risk
14 based orientation and international cooperation.
15 Those are the five pillars of this initiative. The
16 sixth dimension is time and the time we decided was
17 for two years. We will work on this initiative trying
18 to define the desired state, trying to define the
19 issues to be addressed in the two years. The two
20 years time comes to an end next month, but that
21 doesn't mean the initiative ends. It means that you
22 would now move into a regular routine of trying to

1 implement all these activities.

2 And in September we hope to announce how
3 this process will become a more permanent model within
4 the agency. So the initiative was for two years to
5 define the issues to be addressed and identify issues
6 to be addressed and come up with a way to address
7 those but that doesn't mean that we will have
8 completed all the objectives.

9 If you look at what we have been engaged
10 in, I call those directional vectors, we would like to
11 insure regular review and inspection policies based on
12 state of the art pharmaceutical science and create new
13 technological advances and create risk based
14 approaches that focus both industry and agency
15 attention on critical areas, facilitate modern quality
16 management techniques, including implementation of
17 quality systems from within the agency as well as
18 outside the agency and industry, and have the
19 consistency and coordination of FDA's quality review
20 programs, in part by integrating enhanced systems
21 approaches into the agency's business processes and
22 regulatory policies concerning review and inspection

1 activities.

2 If you look at how we are covering these
3 topics, we can visualize this as a three-dimensional
4 aspect, science, risk and system integration concepts,
5 we started with the PAT initiative. We have a draft
6 guidance. That guidance will be finalized in the next
7 month or so. We took some of these concepts to ICH
8 and now we have a number of topics in ICH and that
9 will be a subject for discussion this morning. We
10 wanted to move to a more flexible approach to post-
11 approval changes and move it from change being bad to
12 change being viewed as an improvement, and we
13 struggled with delegating a compatibility protocol
14 that would be user friendly, useful in many ways.

15 And we're still struggling with that and
16 I think that tomorrow you'll hear some aspects of the
17 struggle with that protocol. Aseptic processing I
18 think is an important guidance that will be finalized
19 soon. Guidance on CFR Part 11, probably this is one
20 of the major accomplishments of this initiative is to
21 address some of the challenges of Part 11, better
22 integration to collaboration and cooperation between

1 inspection and review staff, products specialists and
2 inspection, the PAT model is evolving and this is
3 working nicely and we're trying to expand that beyond
4 the PAT model.

5 Pharmaceutical inspectorate is another
6 major accomplishment. Over the next several years we
7 will have a core group of pharmaceutical inspectorate
8 staff, in ORA who will spend most of their time or 80
9 percent of their time inspecting pharmaceutical plants
10 and they will have a high level of training and
11 certification to accomplish that.

12 Dispute resolution process is also a major
13 aspect of this because in a large system such as our
14 regulatory system, when you start moving towards a
15 different approach for dealing with regulatory
16 aspects, you have to have an efficient dispute
17 resolution process. And clearly pre-approval
18 inspection compliance program was one of those but you
19 will hear tomorrow from David Horowitz and Larry and
20 others a risk based approach to inspection, site
21 selection, where do we inspect, where do we put our
22 resources where the risks are and so forth. So these

1 are some of the activities that sort of cover risk
2 science and system integration approaches that we
3 outlined for us.

4 But quickly, I'd like to summarize why we
5 felt the time was right to move forward here. There
6 was the scientific opportunity. And this was a
7 sensitive document to sort of bring up and simply
8 stated that pharmaceutical development and
9 manufacturing is evolving from an art form that is now
10 based on science and engineering based. Effectively
11 using this model in regulatory decisions when we
12 establish specifications and we evaluate manufacturing
13 processes can substantially improve that efficiency of
14 manufacturing regular processes. That was the
15 initial hypothesis that we started as a basis in 2001
16 and hopefully you'll see that some of the activities
17 that will be discussed at this meeting we can move
18 forward and put a conceptual framework around them.

19 The other dimension was the risk and the
20 risk mitigation and communication opportunity was
21 clearly an opportunity because there are many risk
22 approaches, risk mitigation approaches which have

1 matured, have been utilized within the agency and
2 outside the agency. For example, within the agency,
3 on the food side there is more effective analysis on
4 the devices side have been utilized for a number of
5 years and other industries have utilized some of
6 these. And we sort of brought the concept up and done
7 some designs by quality, by design, again a phrase
8 which is a very old phrase but brought a dimension to
9 this to focus on reliability and risk mitigation and
10 hopefully we can communicate this better, we can find
11 leverages for reducing regulatory but the third
12 dimension of opportunity was the quality systems
13 opportunity. Again, if you look at the evolution of
14 quality, you start with sampling plans, and so forth
15 and GNPs came in there and many of the quality systems
16 are based on other GNPs and what we are hoping to do
17 is to sort of in a jargon free way, adopt the
18 practices in all of these quality systems into our
19 system and we are moving towards a general quality
20 system framework for the agency and hopefully support
21 that for external industry also.

22 So for the two-year journey, which is

1 coming to an end next month, from the perspective of
2 defining the issues and defining the training and
3 conceptual framework, to what is the destination. I
4 often use this slide, the book by John Guaspari, "I
5 know it when I see it", is to me an excellent
6 reflection of the current state. I often say the
7 person in that picture is our CMC reviewer because
8 they often do not have information that they need to
9 make the decisions with respect to risk and so forth.
10 So often the answer is, if you want to change the site
11 of manufacture, I need three batches of separate data.
12 The only decision they can make is when they see the
13 three batches of separate data. So we can move away
14 from that to a vision 20/20, I can see clearly now,
15 which is part of the desired state. And we define the
16 desired state as follows.

17 The part quality and performance is
18 achieved by design of effective and efficient
19 manufacturing processes. Correct specifications based
20 on mechanistic understanding of how formulation and
21 process practicing factor on performance, again,
22 that's missing from the current state. We don't have

1 this information in the submissions. And move towards
2 a continuous assurance of quality. The primary
3 motivation for the third bullet was you achieve that
4 only if you gain a high level of process
5 understanding. You cannot achieve that without that
6 and when you achieve that, that brings a more
7 efficiency continuous manufacturing and so forth.

8 But to facilitate that, our policies, that
9 is regulatory policies need to be tailored to
10 recognize the level of scientific knowledge supporting
11 applications, process qualification and process
12 capability, and we started emphasizing the process
13 capability because product are validated but many are
14 not capable, so there is a missing element.
15 Validation does not insure capability but shows a
16 missing link. So risk base review relates to the
17 level of scientific understanding of how formulation
18 and manufacturing process effect product quality and
19 performance and the capability of process strategies
20 to prevent unmitigated risk of producing a poor
21 quality product. So that was our way of saying, we
22 can facilitate moving toward a desired state by

1 providing regulatory incentives.

2 So this meeting -- the primary objective
3 of this meeting is to seek input and advice from you
4 and from the public on charting the most efficient
5 part of the desired state and the discussion focuses
6 on review assessment of chemistry, manufacturing and
7 control sections of submissions and I deliberately I
8 sort of wrote the CMC as its written in our
9 regulation, chemistry, manufacturing, and controls.
10 The reason for stating it that way, that's as it's
11 written in our CFR, is we often focus only on the
12 chemistry, the manufacturing controls part is --
13 doesn't get the attention it deserves. And that is an
14 opportunity, I think, that Q8 and Q9 sort of bring
15 forward.

16 Risk-based procedure inspections, you will
17 hear a pilot program on selection of manufacturing
18 site inspections. There are elements of risk which
19 says if a process is well, well controlled, there is
20 a way to reduce the risk for those sites and so forth.
21 So you'll hear the discussion tomorrow. You will also
22 hear updates on a number of topics but I just wanted

1 sort of put up the Q8. What do we wish to accomplish
2 with Q8?

3 As an example, we hope that Q8 will
4 facilitate movement towards the desired state that we
5 have articulated. We believe this is important
6 because this will help us better understand the
7 proposed product and process design and its relation
8 to independent review. Improved process of
9 establishing regulatory specifications, this is the
10 heart of the key here. This is the voice of the
11 customer. FDA is the customer defining the voice,
12 making sure the quality is there because the GMPs then
13 have posted so if you don't get the specifications
14 right, the problems linger on.

15 And four, we could identify and understand
16 critical product and process practice, again, this is
17 not well understood today in the part of the type of
18 information we've seen in the submissions. Allow us
19 to do a risk-based approaches and recognize good
20 science and facilitate improvement, improve
21 communication and system thinking and be an advocate
22 for public health, regular and industry.

1 I'll skip this. John Berridge graciously
2 agreed to come and talk to you about how we are
3 approaching Q8, but there is a question that we have
4 posed to you and this is the reason I'm showing this
5 slide. One of the concept that has evolved in a
6 harmonized way to move forward is the concept of
7 continuous improvement and the concept for design
8 space. And this is a part of the question that I
9 think, we have asked you to address. The key factor
10 here or key concept here is that if you have
11 understood the critical formulation basis, the
12 critical process basis and you have charted your
13 design space, within that design space movement is not
14 a change any more and I think that's an important
15 point.

16 So how do we define this design space is
17 a key element. It is a multi-dimensional space that
18 will be defined by critical vector of product in
19 performance. One of the examples of such critical
20 vectors, vectors that define robust manufacturing
21 processes, consistent ability of meeting its
22 specifications, different manufacturing options. Here

1 is a graphical presentation of what this design space
2 might be. Currently, much of this is a black box,
3 especially with respect to raw material properties,
4 processing conditions, and so forth. So we have very
5 limited information about what are the critical
6 factors and so forth.

7 We hope the future will be sharing of
8 pharmaceutical knowledge and that shows us where
9 things are critical and not critical and therefore, be
10 more rational in moving through different things and
11 improving model. We are very confident that many
12 companies already have this information. We have met
13 with several companies. They've come and met with us,
14 shared with us this information and we believe it's
15 already there. So for many companies this is not any
16 additional work. It is simply sharing this
17 information at the right time, in the right way, and
18 for us to move forward.

19 So in many ways you'll see the discussion.
20 We're hoping Q8 brings a level of understanding which
21 is not there today and the key aspect here is the
22 company has its own quality system. We have post-

1 approval changes and the current system says changes
2 is bad because it's uncertain or risky. We don't know
3 what that change might be, that if fact, if that is
4 true, additional testing. Yet you have the CMC
5 regulatory oversight, you have the CGNP regulatory
6 oversight, you have a perceived or real risk out there
7 and all of our activities are focused addressing all
8 of this and aligning this in such a way that we move
9 forward to serve the patients in a more efficient
10 manner.

11 The process of understanding, you align
12 all of this together, you have an opportunity that
13 would say post-approval changes is not bad, it's
14 actually good, it's a continuous improvement and that
15 leads to significant risk reduction on a continuous
16 basis. So that's what you're going to accomplish and
17 I see it Q8, Q9 and the proposed Q10 are graphically
18 in my mind, going together this way and you will hear
19 presentations on this. So the meeting today in many
20 ways, I look at that as moving towards a desired
21 state. We seek your input on how best to do this.
22 Day one, you will hear updates on our current efforts

1 on ICH Q8, Q9 and the proposed Q10. We are moving
2 forward with ASTM in a significant way, especially for
3 the PAT standards and in aspects, which I think ASTM
4 is a paradigm shift because we believe that to do it
5 right, you have to bring this standards and the
6 umbrella of understanding.

7 For example, if you have a chapter in the
8 USP that lacks the process understanding dimension, so
9 that's a live base mentality to those standards.
10 Those standards are not yet useful as when they are
11 within the framework of understanding. So the ASTM
12 model is a basis for moving forward in that direction.
13 I think the awareness topic that we are introducing
14 today is to fill some of the gaps that we think exist
15 even in spite of all the work that we have done and
16 some research planning. Bayesian approaches in
17 chemistry manufacturing control, I think is a
18 significant topic. It's a topic that has been
19 discussed recently at an FDA John Hopkins University
20 co-sponsored workshop but more on the clinical side.
21 We would like to start the discussion on how we can
22 bring some of these concepts to bear on CMC decisions.

1 Professor Nozer is an expert on reliability, Bayesian
2 approaches and so forth, so we requested him to give
3 us a talk. This is simply an awareness topic at this
4 point but I think you want to build on this. There a
5 critical path initiative that we talked to you about
6 but then we move on to some more significant
7 discussion. It's how do we start moving toward
8 implementing the concepts that we have developed in
9 the Office of New Drug Chemistry and Office of Generic
10 Drugs.

11 Moheb Nasr and Gary Buehler can share some
12 of the parts. Our focus mainly has been on Office of
13 New Drug Chemistry right now to bring all of these
14 concepts to bear over time of the Office of Generic
15 Drugs and all of these offices we have will come
16 together in this. But it's going to take some time.
17 But to set the stage for this discussion, what we have
18 is two introductory lectures or presentations. One on
19 the manufacturing science and knowledge. G.K. Raju
20 will do that, and to share some thoughts on quality of
21 design and setting specifications. Then we'll have
22 Moheb Nasr and Gary Buehler share some of their

1 thoughts and then we have invited Ken Morris. Ken
2 Morris has been working with our CMC leadership at the
3 agency in moving towards the question of the CMC
4 review process and we asked him to share some of his
5 thoughts with you after Moheb and Gary have shared
6 their thoughts.

7 Day two will focus on risk based CGNP
8 inspections. You will hear about the study being
9 conducted on industrial practices. Then we'll have a
10 significant discussion on pilot model or selection of
11 manufacturing sites for inspection, how do we identify
12 the risk factors but also I think an important topic
13 which is -- will be a substantial topic, Joe and Moheb
14 will talk about this, CGNPs production IMBs. I think
15 this is going to be a significant topic but mostly a
16 wellness topic. Then I think we'll sort of wrap up
17 this discussion is trying to sort of identify some of
18 the challenges that remain and some of the things that
19 are working well as well as some fascinating
20 continuous improvements and reduction in the need for
21 product food supplements. They use the PAT as an
22 example of how we are bringing the review and

1 inspection people together, the staff together, to
2 make decisions without having to have supplements,
3 compare the quality topic that we discussed and John
4 will also discuss some of his parts on this but
5 they're challenges because some of the concepts are
6 within the old system and some of the concepts are
7 happening with the new system.

8 So with that, sort of that's a broad
9 discussion on the meeting. What we have tried to do
10 is to share with you or ask you some questions. For
11 example, you agree that current activities within ICH
12 and the ASTM has been to move toward the desired
13 state. We also seek your recommendation on how to
14 insure these activities are synergistic and simply on
15 risk basis recommendation in the new paradigm. We
16 have a number of questions. The flexibility for you
17 to address your discussion around these question will
18 help. I'm not sure whether the committee would like
19 to come together to sort of address this in brief
20 summary if they could but the topics that we have for
21 day one, the questions apply to all the topics, so
22 towards the end if you could summarize some of the

1 parts, that would be very useful for us. And you
2 already have this, I won't spend more time on that,
3 with that I'll give it back to you.

4 CHAIR BOEHLERT: Thank you, Ajaz. Is
5 there comments or questions from committee members?
6 Okay, before we go on with the next speaker, there's
7 one thing I neglected this morning and that's to have
8 our committee members introduce themselves. I think
9 this is important for the benefit of committee members
10 who may be new. So we'll start with Dr. Fackler,
11 introduce yourself and your affiliation, please.

12 DR. FACKLER: Paul Fackler with Teva
13 Pharmaceuticals, representing the generic drug
14 industry.

15 MR. MIGLIACCIO: Gerry Migliaccio, with
16 Pfizer representing PhRMA.

17 DR. SINGPURWALLA: Nozer Singpurwalla,
18 George Washington University.

19 MR. PHILLIPS: Joe Phillips, Regulatory
20 Affairs Advisor, International Society of
21 Pharmaceutical Engineers.

22 DR. RAJU: G.K. Raju, MIT Pharmaceutical

1 Manufacturing Industry.

2 DR. DeLUCA: Pat DeLuca, University of
3 Kentucky.

4 DR. MORRIS: Ken Morris, Purdue
5 University.

6 CHAIR BOEHLERT: Judy Boehlert, Consultant
7 to the Pharmaceutical Industry.

8 MS. SCHAREN: Hilda Scharen, FDA.

9 DR. PECK: Garnet Peck, Purdue University.

10 DR. GOLD: I'm Dan Gold, D.H. Gold
11 Associates.

12 DR. HUSSAIN: Ajaz Hussain, Deputy
13 Director Office of Pharmaceutical Science, CDER.

14 MS. WINKLE: Helen Winkle, Director,
15 Office Pharmaceutical Science, CDER.

16 CHAIR BOEHLERT: Okay, thank you,
17 everyone. Our next speaker is going to discuss ICH
18 Q8. Ajax has introduced us to these topics, and John
19 Berridge, Dr. John Berridge, will make the
20 presentation.

21 DR. BERRIDGE: Thank you, Judy. Good
22 morning, ladies and gentlemen and thank you for the

1 opportunity to present to you today on the topic of
2 Q8, Pharmaceutical Development on behalf of the expert
3 working group and some additional thoughts, of course.
4 What I would like to do today is to give you a little
5 bit of background to the topic and address the
6 opportunity for change. Look too, at the progress
7 that we've made so far and then to round off by
8 considering some of the implications, implications for
9 the future as a consequence of this guideline.

10 So at the very highest level, the purpose
11 of the ICH Q8 topic is simply to provide guidance,
12 that is harmonized guidance, on the section P.2 which
13 is entitled "Policy for Development" of the comment
14 technical document format. And its scope is very
15 clearly outlined in the concept paper and it is all
16 the products that are pertinent to the CTD. Of course
17 the CTD is not mandated in the US but I think it's
18 true to say that the majority of applications for new
19 entities are actually using the CTD format today.

20 So that's the very highest purpose but I
21 think it's pertinent to actually look deeper, look
22 underneath and to say what are actually the drivers,

1 why would we really want to do this? So if we go back
2 and think about life as it is now, life before we
3 actually get to the Q8 state. In the United States
4 the amount of information that industry submits in its
5 NDAs is variable partly because some of that
6 information may have been submitted through the IND
7 process. Some companies go to a different extreme and
8 actually submit the report that they would present in
9 Europe.

10 Others, the information is distributed
11 around the new drug application in various places, but
12 even so, there is variable information that is
13 presented and part of is driven by industry concerns.
14 If we provide a lot of information, we get a lot of
15 questions. So there is sometimes reluctance to
16 provide information that would give a full
17 understanding. It's slightly different in Europe
18 where there is the -- there has been traditionally and
19 still is the development of pharmaceuticals concept
20 which describes how formulations are designed and the
21 manufacturing process is put together all in one
22 sanction and the home for that in the CTD is P.2.

1 Japan, there are very limited
2 expectations. So we can see that there is a varying
3 degree of expectation and a varying degree of
4 implementation around the world. Is there anything
5 wrong with that? Well, I think there is because right
6 now there's a lot of focus in an NDA on the future
7 regulatory commitments, a reluctance to describe how
8 the product was truly designed. When you put those
9 things together with the worry about the future and
10 the regulatory commitments, it creates what are called
11 a "check-list" mentality. E go around providing and
12 reviewing submissions in a ticking the box process.
13 Where a development report is written it tends to
14 focus on successful preapproval inspection.

15 And the other major driver, I think, is
16 we've heard in the earlier presentation from Ajaz a
17 desire for international cooperation. So we have
18 disharmony. There is a P.2 section in the CTD but we
19 don't have any guidance on exactly what we would put
20 there. When we look at the regional implications
21 where development of pharmaceuticals is the
22 cornerstone of the European submission, I think there

1 is some missed opportunities. And this all tends to
2 result in the very limited regulator incentive to
3 truly understand how products and processes to
4 describe that understanding and then to move into a
5 process of their optimization.

6 Q8 brings with it an opportunity for a
7 significant change, a change that moves us from simply
8 providing huge amounts of data and what happens when
9 you get huge amounts of data? It tends to get checked
10 and boxes get ticked or they don't get ticked because
11 there's a mistake. So let's move from that, move from
12 these huge boxes of data to a situation of information
13 and knowledge. And we can express that in a different
14 way which is basically a manufacturing sciences based
15 approach to submission and approval.

16 And if we agree to that, then we see the
17 creation of a significant new paradigm. It's a new
18 paradigm for both parties. It's a new paradigm for
19 industry and a new paradigm for the regulators and a
20 significant set of positive opportunities. You've
21 seen this slide almost. The first two points are as
22 age asset. Some people discuss the word

1 "mechanistic". We could substitute the word
2 "scientific", but we're certainly talking about a true
3 understanding of our products and processes. And
4 we're trying, through Q8, with the full support of the
5 expert working group, to get to that state which
6 allows us to effect continuous improvement and opens
7 the door to continuous real time quality assurance.

8 So if we look at the guideline itself and
9 the mechanics, the processes underlying the
10 development of the guideline, the topic was actually
11 adopted back in October 2003 and the expert working
12 group has met three times since then, have produced at
13 the meeting in Washington just a few weeks ago, a
14 third version of the guideline. This is under
15 consideration by the experts themselves with input
16 from their various associations, but we're aiming to
17 get the document out for public consultation, this is
18 ICH Spec 2, after our November 2004 expert working
19 group meeting in Yokohama, in Japan.

20 I think we're cautiously optimistic that
21 that timeline will be met. Q8 itself is a guideline
22 that's being conceived in two parts. Part 1, the core

1 document, describes baseline expectations and optional
2 information. I'll come onto this a little bit more in
3 a moment but describes a concept of regulatory
4 flexibility. Again, I will discuss that a little more
5 in just a moment. And as I've indicated, we hope to
6 get to Step 2 later this year.

7 The second part, which has not been
8 started yet and which is still subject to discussion,
9 relates to annexes of specific dosage forms and the
10 possibility to include in it appropriate examples of
11 risk management. And in that sense, the Q9 guideline
12 that provides a toolbox of risk management examples,
13 provides useful input into the QA guideline. I think
14 we can stick to our intended time line. Then we
15 should be able to start back in November of this year.

16 So I've talked about baseline, other
17 expectations, and it is clear in the guideline that
18 not all the information is mandatory. But the
19 guideline is carefully constructed to insure that this
20 doesn't create any misunderstanding. What it does is
21 describe one system with different levels of focus.
22 And there's a complex phrase here "process

1 understanding and predictive ability" that actually is
2 intended to describe this continuum, not a two state
3 system but a continuum. What we mean is that the more
4 that the process is described and understood, the more
5 one provides for the future regulatory flexibility.

6 The less you give, the more rigid the
7 subsequent approach is. And so it doesn't actually
8 describe a mandated content, it describes an
9 opportunity. So if we look at that in the context of
10 quality by design, which has also been mentioned as a
11 concept today, we're looking at on the left-hand side,
12 understanding that we have a well-characterized
13 product. We understand the process. We've looked at
14 the risk, and taken appropriate mitigating actions and
15 we understand how we're going to monitor our process
16 in the future.

17 If we put those four components together,
18 it drives the framework for continuous improvement.
19 In fact, you can put together the sum, if you like,
20 the product and process knowledge together with
21 appropriate risk management and that can comprise the
22 manufacturing sciences. Well, if we drive towards

1 that framework of continuous improvement with the
2 knowledge as indicated, on top of that, so I should
3 say that the first three are part of the Q8 topic, so
4 the first three are critical elements of the ICH Q8
5 topic. If we put those together, then we can build on
6 top of that this concept of regulatory flexibility.
7 So Q8 is really a major engine driving towards the
8 opportunity for regulatory flexibility. If you look
9 at this in the context of the variable space, you can
10 take a couple of hypothetical vectors and Ajaz earlier
11 talked about what some of those might be.
12 Traditionally, industry has focused on a very narrow
13 understanding or at least described a narrow
14 understanding, even if it knew more, intended to do
15 that three batch validation and any move away from
16 this situation created a post-approval change.

17 What we're saying now is if we consider
18 the overall boundary and we have a good understanding
19 of the impact of these variables on product and
20 process quality, and we can look at elements of risk,
21 that we should be able to move within the space that's
22 described by this rectangle and optimize our processes

1 and this is not a change because it's within a pre-
2 agreed and described variable space. We understand
3 the implications. So we can now move to this new
4 paradigm of continuous improvement. We don't need to
5 keep submitting post-approval supplements.

6 So it creates a kind of if and then
7 process for the future. If industry can provide and
8 regulators agree that there is a appropriate relevant
9 scientific understanding and earlier a couple of
10 concepts were put forward such as stability and
11 availability, if we can show that is understood, if we
12 can show the ability to predict the impact of movement
13 within our defined vector space to predict the impact
14 on quality and performance, if we're confident that we
15 understand the control of product and process critical
16 variables with an ability to be able to assess the
17 impact of change, if we can show a degree of high
18 competence in the value of our specifications and the
19 validity and reliability and reproducibility of our
20 processes, then we get to a new state where first
21 cycle CNC approval is much more likely.

22 We can continue to optimize our processes

1 without seeking prior approval and we can work to
2 improve the dialogue and assist the risk based
3 inspection process because we understand what the
4 critical quality parameters are. Of course, this
5 carries some implications for the future. Both
6 industry and the agency will need to think
7 differently. Industry submissions will need to change
8 and the agency reactions and behaviors for both
9 submissions will also need to change. There are some
10 issues that we need to resolve as we move the
11 guideline forward, of course. Industry, what do we
12 put exactly in P.2. What is the depth of the
13 discussion that we would put? Well, we said it could
14 be a continuum. Looking at it in terms of the agency,
15 how do we construct a consistent review of the
16 section. Because the amount of information is going
17 to vary, it's not in Section P.2 going to be a
18 compliance document. It's an information and
19 understanding document. We want the reaction that
20 gives flexibility and an incentive, not a reaction
21 that is ticking the box.

22 We've said that this document can have

1 utility for both review and inspections, so we need to
2 define exactly what the separation overlap of roles
3 and responsibilities is likely to be. And we need to
4 think about how we might update this document. What
5 would trigger an update to this particular section?
6 Why would we do it, how would it be submitted. Now,
7 if we can get these resolved and I think we can, we
8 get to a future state vision which demands change on
9 both parts. Hopefully with an agency perspective, we
10 get the more open communication about our
11 understanding. We're able to work with the reviewers
12 in an engaged way looking at the science and the
13 agency accepts a change of content of applications
14 which encourages this knowledge sharing and encourages
15 elimination of simply providing data. We would
16 encourage that agency to move to science and risk
17 based evaluations and that will, of course, reduce
18 post-approval change in regulatory matters. The quid
19 pro quo of course is that industry needs to be
20 transparent. It needs to share the information.
21 Sometimes we have the information, sometimes it needs
22 to be generated.

1 We need to understand that our regulatory
2 agencies have needs and we need to provide them with
3 those needs. If the agency is willing to accept a
4 different content, we have to provide a different
5 content, a content which shares the knowledge, a
6 content which focuses on the science and our
7 understanding of products and processes and a content
8 which actually talks about assessment of risk and its
9 mitigation.

10 Putting that all together means that we
11 need to provide an insight into our manufacturing
12 processes if we want to achieve that regulatory
13 flexibility. But I think if we drive Q8 to a
14 successful conclusion, it does, indeed, open that door
15 to the new state and it compliments the other
16 initiatives that have been talked about here today.
17 Thank you for your attention.

18 (Applause)

19 CHAIR BOEHLERT: Thank you, John. Are
20 there any questions or comments from committee
21 members?

22 DR. GOLD: Judy, may I?

1 CHAIR BOEHLERT: Yes, Dan, please.

2 DR. GOLD: First, I'm very much in support
3 of inter-group knowledge in the development of
4 processes. I've long felt that we too often rush our
5 processes because of commercial considerations and do
6 not explore members' base sufficiently, so I'm very
7 much in favor of this, but I am confused about a few
8 issues as explained here. I will get your slide 12,
9 which is parameter space, variable X, variable Y and
10 you show a small explore space in the upper right-hand
11 -- left-hand quadrant showing a rather narrow
12 evaluation of the parameters and then you show a
13 rather large space to the right, parameter space to
14 the right. Is it your thinking that this second
15 parameter space would be explored and defined in the
16 initial filing? And if that were the case, why would
17 we not have enlarged the total allowed parameter space
18 in the initial filing?

19 DR. BERRIDGE: Well, I think each one
20 builds -- it depends on the scale of your
21 understanding because I could have drawn this with a
22 little rectangle around what's in the right-hand area.

1 DR. GOLD: Of course, of course. What I'm
2 really asking is, if you -- in this development, in
3 this enlarged -- am I getting feedback?

4 DR. BERRIDGE: No, it's okay.

5 DR. GOLD: If in this enlarged development
6 of parameter space, you already know the efficiency of
7 the variables and the variables are acceptable to
8 produce a product that will be fit for use, why would
9 you not include it in the original definition of the
10 allowed parameters?

11 DR. BERRIDGE: Well, I think that you
12 would include in your original submission a
13 description of the impact of let's say the extremes of
14 this parameter space. You might not have explored
15 every increment within this parameter space but you
16 will know that moving around the extremes does not
17 have an adverse impact on product quality attributes.
18 You might then move instead of let's say the upper
19 left-hand quadrant, your consent is one where let's
20 take a blending operation as an example. In the upper
21 left-hand quadrant of this picture it really
22 represents a process that says, "Blend for 10

1 minutes". Now, as you move to the future state, you
2 change that time based concept to an -- actually, to
3 a material attribute concept and you talk about blend
4 to uniformity.

5 And you then move within this parameter
6 space, to a blend to uniformity criteria. Now the
7 exact space -- the exact point you're going to be on
8 here is one that you can -- that you monitor and
9 control in real time. And for example, you may
10 include process analysis tools to actually monitor
11 that attribute and you could be moving around in this
12 space on a batch by batch basis, depending upon your
13 material inputs for example.

14 But you can't define exactly where you're
15 going to be at any particular point because you've
16 moved now to a different paradigm, not one that is
17 rigorously controlled, but one which moves within a
18 bounded space that you is not a problem provided you
19 are within it.

20 DR. GOLD: I understand, but then why
21 would you not include that in the additional filing?

22 DR. BERRIDGE: You could include the

1 boundary in the --

2 DR. GOLD: In the initial filing.

3 DR. BERRIDGE: -- initial filing but not
4 necessarily the exact point that you're going to be on
5 a batch by batch basis.

6 DR. GOLD: As a manufacturer won't you be
7 -- won't you have an advantage if you included this
8 larger parameter space in the initial filing --

9 DR. BERRIDGE: Well, as I say --

10 DR. GOLD: Excuse me, and obtain approval
11 for this larger space and use POT to define when an
12 acceptable end point would be reached?

13 DR. BERRIDGE: Exactly. That opportunity
14 is there to describe this boundary absolutely. That's
15 what we're trying to encourage, a description of the
16 boundary and an ability for you to move within that
17 space without having to go to the agency and say I
18 want to move three points to the right because it's
19 actually not a change. It's within the agreed process
20 and product parameters that have been submitted in
21 that original application.

22 DR. GOLD: I'm fully in favor of this but

1 I believe that what you're describing may be a rather
2 trivial example. A more pertinent example, perhaps,
3 would be where you have explored different particle
4 sizes for excipients and have shown that when you have
5 a change in excipient particle size, and that occurs
6 to many of us at various times, you can still achieve
7 a successful blend by modifying the conditions
8 appropriately and upon your knowledge of the particle
9 size and how it interacts with the blending
10 circumstance. Perhaps that's a more significant
11 approach to exploring parameter space in a beneficial
12 way.

13 DR. BERRIDGE: I absolutely agree with
14 you. In the time I was here today, I couldn't give
15 you a set of illustrations of all the things but
16 absolutely. So as I said, you could move within this
17 space and it may be that one of these axes is particle
18 size and excipient dense and another axis could be
19 lubricity of magnesium stearate.

20 DR. GOLD: Correct, correct.

21 DR. BERRIDGE: And then based on the input
22 material attributes, you then as you're monitoring

1 their impact on the process, your actual process
2 itself, the timing or whatever you do with the
3 process, is actually moderated by your assessment of
4 the input attributes and I could have used that as an
5 alternative example.

6 DR. GOLD: Yes. If I may have one more
7 minute, Judy.

8 CHAIR BOEHLERT: Okay, one minute, because
9 we have another question.

10 DR. GOLD: Okay. And that is if we are
11 going to allow enlargement of Section 3 of the CTD,
12 there's no mention in any of this yet of enlargement
13 of the expert report that accompanies the CTD. Is
14 that visualized as part of the extension of Section 3?

15 DR. BERRIDGE: Well, I would have to
16 somewhat disagree with you. We're actually thinking
17 that the body of data of the CTD could change, not
18 necessarily enlarge, but it changes because its focus
19 becomes different. It's information not simply huge
20 amounts of data. In terms of what you call the expert
21 report, there is no longer an expert report. What we
22 do have is a quality overall summary.

1 DR. GOLD: I'm sorry, I'm misusing the
2 term, correct.

3 DR. BERRIDGE: And I think there is an
4 opportunity and FDA itself has been describing the
5 potential for an opportunity to look at how that
6 quality overall summary can act as a good distillation
7 of both manufacturing sciences so it's concisely
8 embodied in that single document. Now, what that
9 looks like has not been discussed within the framework
10 of the CTD group but I think it provides an
11 opportunity that we're beholden to look at.

12 DR. GOLD: And that is one of the
13 objectives that will be coming forth?

14 DR. BERRIDGE: Certainly, it's one of the
15 topics that we should be considering.

16 DR. GOLD: Thank you very much.

17 CHAIR BOEHLERT: Ken, did you have a
18 question or a comment?

19 DR. MORRIS: Yeah, a little of both,
20 actually. Following on Dan's point, I think part of
21 the issue with respect to margining space to use your
22 example, Dan, is the fact that when you're in

1 development, you may not have the range of raw
2 material characteristics in order to define that
3 fully. So you may not have the opportunity to file
4 against the whole range would be one comment.

5 Which certainly leads into the question or
6 to the thought is that one of the things we are always
7 struggling with in the new -- in your new paradigm is
8 now the three batches and out is the rule which we all
9 agree has flaws. How do we define it so that there
10 are criteria that will let industry know when their
11 product is ready to file, I think is the question.
12 I'm not sure. Do we have the answer to that?

13 DR. BERRIDGE: Sure, I want to delve into
14 the answer to that but yes, that's a pertinent
15 question.

16 DR. MORRIS: But I think that's something
17 that we have to discuss as we are discussing, of
18 course, outside this meeting as well, but it's
19 something to be taking an issue, I'm assuming that Q8
20 will --

21 DR. BERRIDGE: I'm not sure that Q8 will
22 actually attempt to define what product set validation

1 should look like.

2 DR. MORRIS: Yeah, I wasn't thinking so
3 much of validation in the strict sense as I was just
4 the scientific basis for a decision. Somebody else
5 may have a comment.

6 CHAIR BOEHLERT: G.K., did you have a
7 comment?

8 DR. RAJU: Sure. I have a question,
9 actually, John, reflecting on Ajaz's comment earlier
10 today on what you're going to put in this section. To
11 what extent is your thought process and maybe all
12 thought ICH about generating new science and data
13 knowledge as opposed to simply taking what you already
14 have and putting it into a submission? To what extent
15 is the about putting what you have in, in a different
16 way or generating a new kind of knowledge, a new kind
17 of understanding?

18 DR. BERRIDGE: Well, I think there will
19 always be elements of both, but I think a good start
20 would be to provide in the initial submission what is
21 already there. I think there could well be more
22 that's available that's not necessarily being

1 encouraged to be shared. I think we need to also, to
2 come back to Dr. Morris' point, think too about the
3 state of knowledge at a particular phase. So I think
4 there will be an amount of knowledge that exists in
5 the initial submission, which is fit the purpose and
6 then as the product moves into the commercial
7 manufacturing phase, a whole new set of information
8 and understanding can then be generated and I think
9 there's an opportunity then to build on the initial
10 R&B knowledge with the knowledge that's acquired
11 through the manufacturing of scale to describe a still
12 greater understanding of the manufacturing sciences
13 and it's probably -- could well be at that second
14 stage that we really get to a more stable situation
15 where we described what we call the band width within
16 which we can truly effect that ongoing continuous
17 improvement.

18 CHAIR BOEHLERT: Okay, Garnet, then Ajaz.

19 DR. PECK: In reflecting through your
20 slides, there is the element of what is done in Europe
21 and the complete understanding of the formulation.
22 What is the objective of a particular product and

1 going back to Slide 12 and flexibility, I still see
2 and I like this, is the material science of the
3 material that we're bringing together into a
4 particular dosage form. That's highly significant and
5 will aid us and we're approaching a better field and
6 you've already mentioned excipients and particle size,
7 that's one element of it.

8 The second part of what's in the
9 flexibility is the understanding of the processing of
10 what we're trying to do and I look at your diagram as
11 an extreme vertices type of thought and you have in
12 the center of the extreme what you want but you do
13 have limits and that guides you and I think we can
14 look towards that kind of guiding rather than just the
15 simple three-batch concept. It gives us space.

16 DR. BERRIDGE: Yes.

17 DR. PECK: And I think you've also
18 emphasized the space part. I think that's important.

19 CHAIR BOEHLERT: Ajaz?

20 DR. HUSSAIN: I think this discussion is
21 very helpful but at the same time the comments
22 consider different ways of defining the space. For

1 example, the aspect of how much information we have on
2 expedients and their functionality at the time of new
3 product development. Some might be limited but you
4 can bring that know how to bear on that because I
5 think we have established a way to say all right, the
6 physics might not be different, so the use of prior
7 knowledge, better use of prior knowledge, I think, is
8 a key opportunity and I think -- so that the company
9 has made 300 different formulations of a drug. The
10 chemistry of the drug might be different but the
11 physics of the powders are not that different. So how
12 can you bring that to leverage an opportunity?

13 CHAIR BOEHLERT: Okay, any last brief
14 comments? If not, John, thank you very much.

15 Our next speaker is Fred Razzaghi, and
16 he's going to provide an update on ICH Q9.

17 MR. RAZZAGHI: Good morning, Dr. Boehlert
18 and good morning, Committee. I'm here to give you an
19 update on the status of the Quality Risk Management
20 Doctrine developed at ICH called Q9. I've been
21 talking to you about what quality risk management is.
22 I'll give you some background. Initial steps in guide

1 development, development of the guideline. The
2 guideline starts off as to the scope, the process and
3 the tools and how it's integrated into operations and
4 what the next steps are.

5 This team is defining progress management
6 as a process in assisting of well defined steps which
7 when taken in sequence support their decision making
8 by contributing to a greater insight into risks and
9 their impacts. And the steps in the process could
10 include identification of risks assessment, education,
11 elimination and communication of risks. There's some
12 understanding in the committee, in the group, that
13 risk is a combination of property of occurrence and
14 severity of the harm that this caused.

15 Here's some background for you. Last
16 October you were presented with three presentations.
17 One, use of management from simple manufacturing, then
18 you provided with a process risk assessment model and
19 then the relationship between risk and knowledge and
20 how to apply them pre and post-approval, e.g. scrutiny
21 and post-approval changes and the variety of GMP
22 areas. IN April at the OPS meeting, one of the

1 objectives that were stated was that OPS will
2 implement a review quality system and procedures that
3 will recognize the level of scientific knowledge,
4 supporting private complications, plus process
5 capability, apply a risk base rate to scrutiny that
6 will relate to level of scientific understanding of
7 how formulations from manufacturing processes factors
8 besides product performance and then the capability of
9 process control strategies to prevent or mitigate risk
10 of poor product performance.

11 Some background in the ICH process to
12 date; there was a meeting in July in Brussels where
13 groups came together to discuss whether or not there
14 were merits to moving ahead. Following that, there
15 was a meeting in Osaka, Japan in November of last year
16 where the concept was developed and approved by the
17 steering committee. In between November and June we
18 snuck another meeting in there in March in London,
19 where we drafted an outline and had a discussion for
20 two or three days about what is the general approach
21 to actually making this happen.

22 And then we had some significant progress

1 made in Washington in June where a first draft of a
2 guideline was issued by the team and it's been
3 distributed to the constituents for review. A few
4 words on the approach here; in July of last year, this
5 statement was agreed upon by all parties, "To develop
6 a harmonized pharmaceutical quality system applicable
7 across the life cycle of the product emphasizing an
8 integrated approach to risk management and science".

9 The ICH process is unique in that it
10 requires consensus by all the parties and it has its
11 own varying process because of that. We also agreed
12 in March that we would keep a few things in mind. We
13 want to approach this with a process oriented thinking
14 in mind. We want to be practical about it. We want
15 to find where we can use available risk tools and
16 apply them appropriately. We want the product that
17 they exercise to give us some predictability. We want
18 to approach it in a flexible manner because we want it
19 to apply to as many places as possible.

20 We expect it to be consistent and
21 integrated. Initially the goal was to come up with a
22 risk based approach here and we sat down and went

1 through a list of why are some of the reasons we need
2 to have a risk based approach here. The document --
3 these are some of the reasons and I won't go through
4 them. I will kind of run down the benefits for you.
5 We thought that enhanced patient confidence in this to
6 assure quality is a benefit. We expect to promote
7 more effective use of regulatory agency and industry
8 resources. Establish a systemic and well-informed
9 thorough method of decision making which leads to
10 greater transparency and predictability. Increased
11 knowledge of exposure to risk, and as Ajaz mentioned,
12 we expect this to foster quality by design,
13 continuance improvement in the technology embracement.

14 The scope of this document is as follows;
15 this provides the framework that may be applied to all
16 aspects of pharmaceutical quality, including GMP and
17 submission of new processes throughout the life cycle.
18 It applies to APIs, drugs, biologics, vaccines and
19 excipients of packaging material. It does not include
20 pharmacovigilance.

21 The process is as follows. First, the
22 process will be initiated, assessed, risk has to be

1 confirmed, communicated and then follow-on review.
2 Some guiding principles here are the evaluation of the
3 risks should ultimately impact on the potential risk
4 to the patient. The extent of the risk management
5 process should be commensurate with the level of risk
6 associated with a decision. The more robust dissent
7 would be to lower a certainty. It is essential to
8 have a clear delineation of the risk question. Risk
9 management should be a iterative process. People who
10 apply risk management should be trained and use it
11 appropriately. A risk management process should be
12 appropriately evaluated and verifiable.

13 Now, once we embark upon starting a
14 process like this, this is some of the thoughts to
15 keep in mind. Define a specific risk management
16 problem or question including the assumptions leading
17 to the question. Assembling background information
18 and data under hazard where human health impact
19 relevant to the assessment. Defining how the
20 assessment information and conclusions will be used by
21 the decision makers. Identify the necessary
22 resources. Members of the team will have the

1 appropriate expertise with a leader clearly
2 identified.

3 The idea here to do a good job of risk
4 assessment you need a team of experts that can bring
5 knowledge and information but there's a need for
6 someone who can exercise a tool, that's aside from the
7 experts on the specific scientific topics. Ask and
8 direct life risk assessment questions. State clearly
9 the assumptions in the risk assessment. Assessing the
10 quality and sufficiency of relevant data and
11 specifically a tie line of deliverables for the risk
12 assessment.

13 Now, I'm going to go through the process.
14 The first is risk assessment and three questions are
15 posed. What can go wrong, what is the likelihood,
16 which links back to the original relationship and what
17 are the consequences? It breaks down into two pieces.
18 Risk analysis is a suspended use of information to
19 identify specific sources of harm and to estimate the
20 risk. Risk evaluation compares the estimated risk
21 against given risk criteria using a quantitative and
22 qualitative scale to determine the significance of the

1 risk.

2 The next step is risk control. It
3 describes the actions of the risk managements
4 decisions. The questions here might be what could be
5 done to mitigate and reduce risk? What options for
6 controlling risks are available? What are the impacts
7 of current risk management decisions on future options
8 risk management? This too breaks down into three
9 steps; risk mitigation focusing on reduction of
10 severity of harm, risk reduction focusing on the
11 reduction of probability and occurrence of harm and
12 detection of harm and risk acceptance is a decision to
13 accept risk, i.e., no additional risk control
14 activities are necessary at the time the decision is
15 made. In other words, once risk control is completed
16 the decision to make the move ahead but the next event
17 you will see allows the opportunity to come back.

18 The next step in the process is to
19 communicate the risk. Risk communication is the
20 exchange or sharing of information about risk and risk
21 management between the decision maker and other
22 stakeholders. Information can relate to the

1 existence, nature, form, probability, severity,
2 acceptability, treatment, detectability and other
3 aspects of risk to quality. The communication of
4 one's stakeholders concerning quality risk management
5 decisions can be made through existing channels. In
6 other words, in each region currently there are ways
7 where industry and regulators communicate on a variety
8 of risk issues.

9 And this is a piece about coming back to
10 the decision. All risk management processes are
11 dynamic or iterative. Quality risk management would
12 apply to benefit from new knowledge with each decision
13 cycle and used to enhance future decisions allowing
14 for continuous improvement. In other words, when the
15 team exercises that process of going through a risk
16 decision, the outcome of that would be something that
17 would be useful next time a risk decision is required.

18 Here is a proposed process flow. I just
19 went through it. There's an initiation step, there's
20 an assessment step, there's a risk control step and
21 then a communication step and then a look back or
22 review. The we've listed some risk management tools

1 and in this section, what the team -- what we tried to
2 do was not to go out and re-invent the wheel, and was
3 to look around for what are some of the best tools out
4 there that are available keeping in mind that a lot of
5 these tools are used in other industries and we need
6 to apply the original criteria for retrofitting it to
7 the particular circumstance that we're dealing with in
8 pharmaceuticals.

9 But one thing that we thought we are going
10 to put on that list is process mapping, which is the
11 orientation of thinking when it comes to risk. Most
12 of the places we're thinking of applying this, we're
13 talking about a process where the knowledge of events
14 prior and following are important to realize. And
15 there's a list of them here and Ajaz mentioned HSSN
16 (phonetic) and FMEA. All of these have a variety of
17 attributes and are used in different places.

18 A complimentary list to that list is the
19 use of statistical tools that give you information
20 that allow you to make a good discussion and there's
21 a list of them here. Design of experiments is
22 something that was mentioned already, so now this part

1 talks about how we take these concepts of risk
2 management and use of the tools and where could they
3 be used and here's a list of them. Risk management or
4 risk assessment could be used in product development,
5 e.g., a discussion of the risks and the limits of
6 knowledge or the specification being set during
7 development. Regulatory authorities can use risk
8 assessment and risk management when they do regulatory
9 pre and post-approval. It could be used as a
10 component of quality system. In other words, in
11 auditing complaints, recalls and changed management,
12 there is always a component that could benefit from
13 the use of risk management.

14 And there's a list of other applications.
15 It could be used in facility management, it could be
16 used in supply chain management, in other words,
17 materials management, assessment of suppliers, that
18 sort of thing. It could be used in production. It
19 could be used in validation. It could be used in
20 laboratory controls, packaging and at the end we put
21 Regulatory Authority Activities which applies to some
22 of the other regions. It is quite active in this

1 committee and they put forth some valuable information
2 to this product -- to this document. David is going
3 to talk about it tomorrow. The risk granting and the
4 process that's proposed comes from that.

5 Our next step is apparently the draft
6 document is out there to the parties that are involved
7 in ICH to review this thing and give their comments
8 back. In September, we plan to get together and try
9 to consolidate those comments and take a Step 2
10 document to Yokohama, Japan for the steering committee
11 to approve. I've listed here for you the
12 organizations that are participating in this working
13 group. As you can see, it's quite diverse and it's a
14 challenge to work the consensus process and it has
15 benefit of leadership from PhRMA, the FDA and from the
16 regulators. And we've gotten very good technical
17 feedback from the European industry. This is the
18 beginning of the list of definitions. This list is
19 expected to grow as we get a little more detailed into
20 the document.

21 And then finally, I have some references
22 for you. Thank you.

1 CHAIR BOEHLERT: Thank you, Fred.

2 (Applause)

3 CHAIR BOEHLERT: Are there questions or
4 comments from the subcommittee members for Fred. Yes.

5 DR. RAJU: Fred, as you look forward, how
6 do you see the Q9 and the Q8 processes in --

7 MR. RAZZAGHI: That's a good point. What
8 we've talked to Q8 about so far is Q9 is basically a
9 tool that needs substance in it. In other words, the
10 real value of risk management is what is the process
11 of working through a decision for example, to come to
12 a decision. But that vehicle would be hollow if it's
13 not filled with information. So the best use of this
14 tool is involvement would be if the relationship
15 between knowledge and lack of knowledge and
16 development can be explored as a risk that using this
17 process will allow us to move to the next phase,
18 continue to make progress and collect more information
19 and --

20 DR. RAJU: And that's something that will
21 take -- is the thinking about connecting the science
22 of this with the science of --

1 MR. RAZZAGHI: Yes.

2 DR. RAJU: -- approaches that would happen
3 after the --

4 MR. RAZZAGHI: Yes, some of these things
5 are working in parallel. Q9 is working to develop the
6 document and we're kind of working closely with Q8 to
7 find out what the synergies are and we'd like to do
8 that same thing. We have in our section about
9 integrating. The real value of this tool is going to
10 be how to be used in a variety of places. So the
11 criteria that we have used for selecting and using
12 would be for it to be flexible and simple but maintain
13 the poignant parts of it.

14 CHAIR BOEHLERT: Other questions? Dan?

15 DR. GOLD: Yes, Judy. Can you explain why
16 you're not developing the severity concepts that are
17 related to all this?

18 MR. RAZZAGHI: That's a good point. We
19 have looked at some models and we haven't quite gotten
20 to the point where we're going to negotiate or discuss
21 how that ranking is going to be done but the
22 preliminary thinking is it is fair to stakeholders to

1 discuss it and come to an agreement as to what the
2 ranking -- what the appropriate ranking should be in
3 the absence of one that's out there that could apply
4 to everybody. There isn't one out there that applies
5 to everybody.

6 In other words, given a certain process,
7 given a certain product, in the context of the science
8 of that product and process, you can discuss and come
9 to an agreement what the appropriate ranking could be
10 or if generally speaking, the risk is low, the person
11 who's using the tool can do a risk ranking on their
12 own and then explain it, you know, in an appropriate
13 setting.

14 DR. GOLD: Have you seen any differences
15 in the three regions in evaluation of severity levels
16 or concerns for severity level differences and
17 viewpoints?

18 MR. RAZZAGHI: Yeah, I think John is a lot
19 more gracious about it than I. I put that bullet in
20 my slide. It's quite a challenge. It's quite a
21 challenge to work with a topic like this in ICH. And
22 there are a variety of -- I mean, risk is understood

1 in a variety of ways by all participants. And work
2 off of a template that says let's look at these
3 principles that we're trying to implement every time
4 you look at a topic, look at a specific issue, it's
5 helping us make progress. And as I said, the
6 regulators especially FDA has come forward with a lot
7 of information and they're really helping to move the
8 process along.

9 PhRMA has done a good job of providing
10 leadership and kind of moving it along. So I would
11 say that the chemistry within the team is working
12 pretty well but we have no illusions about the
13 feedback we're going to get once the document is out
14 for comment.

15 DR. GOLD: Thank you.

16 CHAIR BOEHLERT: Okay, Nozer?

17 DR. SINGPURWALLA: Yeah, I have two
18 comments. On your slide entitled "Risk Assessment",
19 the first comment I'd like to make is that there is a
20 difference between what we mean by probability and
21 what we mean by likelihood and to articulate that
22 difference is going to take me an hour but for the

1 record, I don't think you should use the two words
2 interchangeably.

3 The second comment is that your definition
4 of risk analysis is circular and let me tell you why.
5 You define risk analysis in terms of risk but you've
6 not defined risk. So --

7 MR. RAZZAGHI: No, that's okay. I have
8 the definitions in the back and I kind of flew through
9 it, but --

10 DR. SINGPURWALLA: Okay, and the third
11 comment is your catalog of supporting statistical
12 tools is very incomplete. You can have --

13 MR. RAZZAGHI: It is.

14 DR. SINGPURWALLA: -- a long catalog, but
15 the more important elements that should go into that
16 catalog should be a elicitation of probabilities and
17 elicitation of debilities. That seems to be the very
18 important function that one needs to do a risk
19 analysis. Design of experiments, I'm not going to
20 argue with you but I don't think that it should be an
21 important tool. Control charts, it's accumulated some
22 charts -- it's cumulative some charts, not accumulated

1 some charts. So these are just academic quibbles for
2 the future. You may want to look at these slides more
3 carefully.

4 MR. RAZZAGHI: I would be interested in
5 those two points that you raise because one of the
6 challenges we've issued to the team in I think it was
7 in Osaka, was that in order for this thing to work, we
8 need to go back and do some homework. It's -- you
9 know, we really have to manage the dynamic --

10 DR. SINGPURWALLA: I'm delighted to go to
11 Osaka and tell you what it's all about.

12 (Laughter)

13 MR. RAZZAGHI: You're certainly welcome.

14 CHAIR BOEHLERT: Other questions or
15 comments?

16 If not, thank you, Fred.

17 MR. RAZZAGHI: You're welcome.

18 CHAIR BOEHLERT: Our next speaker is Dr.
19 Tobias Massa and he's going to be talking about an
20 industry proposal for life cycle management for
21 processes and system control.

22 DR. MASSA: Good morning. What I'm going

1 to talk about now is not formally an expert working
2 group at ICH. It's a proposal made by the three
3 regional industry groups to look at what quality
4 systems need to be in place in order to realize the
5 potential of Q8 and Q9. We are looking at this is how
6 we can utilize science and risk based quality
7 management systems to enable post-approval change and
8 improvement. So we're trying to take what have we
9 learned in Q8, what do we know about the process, how
10 do we apply risk management tools to it and be able to
11 operate in an environment that allows us to make
12 continuous improvement, make post-approval changes,
13 but the important thing is trying to operate within
14 that box that Dr. Berridge described, define what the
15 box is so that we don't have to get into a loop of
16 continually having to make supplements in order to
17 implement that change.

18 So what we want to be able to do is define
19 what are the quality systems that we need to have in
20 place that give both ourselves as well as industry the
21 confidence that we're looking at our manufacturing and
22 control processes appropriately and that based on the

1 knowledge that we gain during development as well as
2 during commercialization, that we are appropriately
3 using all of those tools, collecting all the data
4 appropriately, evaluating all that data appropriately
5 and then implementing change in a controlled manner.
6 What we want to do is put this into -- put this
7 process into a guidance because there are different
8 expectations about how this should be done that vary
9 region by region and inspector by inspector.

10 One of the things that both of the
11 previous speakers talked about was that there is
12 disharmony in what some of these expectations are and
13 the goal here is to try and create a harmonized
14 guidance of how do you apply this tool. What we would
15 like to have in this document is a description of how
16 you monitor your process and controls to identify
17 trends. Now, those trends may tell us you're in
18 control and you don't have to do anything further.
19 You just continue to monitor or they may tell us that
20 we need to do something to get things to an
21 appropriate level of control or improve the process.

22 We also want to have a system that allows

1 us to look at what we've called the undesirable
2 occurrences, the things that we need to react to, such
3 as deviations, product complaints, audit or inspection
4 findings, or the results of our root cause analysis
5 and how do we incorporate those into a technical
6 agenda for the particular product we're talking about?
7 We also want to have a system that allows us to take
8 our proactive activities into account. We know that
9 at the time we go to commercialization, we may not be
10 optimized. In most cases we are not optimized. So we
11 go into commercialization with a knowledgeable
12 technical agenda. How do you -- what quality systems
13 are you going to use to make sure that those are
14 appropriately worked into the quality plan for that
15 particular product?

16 What we hope to do by having this guidance
17 in place -- and it's important that these things need
18 to be linked. What we're talking about needs to be
19 linked to Q8 and Q9, is that we have a standard that
20 allows us to realize the full potential of Q8 and Q9.
21 We have a standard that encourages industry to make
22 changes. I'll show you some slides at the end of my

1 presentation that explains why this industry is
2 discouraged from making changes.

3 We also need to give the regulators
4 confidence that we have the appropriate quality
5 management systems in place to handle this. And as
6 Fred mentioned in his presentation, we want to be able
7 to provide product to the customer and insure that we
8 have a continued source of supply for these valuable
9 products to the customer. One of the things that
10 we've looked at over time or what some of the concerns
11 have been out there relative to our products, and this
12 is a slide that I think Ajaz may have actually
13 presented here at the beginning of our discussions
14 about product quality and GMPs. And one of the key
15 concerns was that we had variability that creates an
16 increased risk. What we don't know about the product
17 and how variability impacts the product creates risk.
18 As a result of that risk, we have more compliance.
19 You have to test more, we get inspected more but
20 that's absolutely the opposite of what we're trying to
21 accomplish.

22 What we want to do is have quality by

1 design; design these things into the process, into the
2 control of the manufacturing process rather than
3 testing to assure quality. And I think this slide
4 kind of gets to what Dr. Peck and Dr. Gold were
5 talking about. In our typical GMP process, we have
6 raw materials coming into a process that's controlled
7 by process variables that lead to some product that
8 meets some determined set of specifications. During
9 development, what we currently do or at least the
10 perception of what we currently do is we concentrate
11 on the process variables and we don't look at the
12 variability of the incoming raw materials. So we
13 concentrate on the process variables and we try to
14 optimize those during the development process and
15 during commercialization, we concentrate on
16 controlling those process variables. But when we get
17 variability in the raw material, to Dr. Peck's point,
18 you know, some of the physical attributes of these
19 materials, we end up with an impact on product.

20 So what we're trying to do is change this
21 paradigm. Now, I'll leave this for you to read but
22 Deming, you know, 50 some odd years ago made a comment

1 about variability in inspections and testing quality
2 in as opposed to designing quality in and the key
3 things to take away from his comments so that you have
4 to understand the process. We were talking about this
5 50 some odd years ago, we still talk about it today.
6 And we want to be able to predict quality from
7 upstream activities and measurements, not on final
8 product quality attributes. And we want to do all of
9 this by working toward reducing variation. Well,
10 that's exactly what quality by design is.

11 Dr. Hussain, today, presented information
12 that was also on a slide that Dr. Nasr gave at a
13 presentation at DIA just last month, talked about
14 FDA's desired state is. Well, I think you can take
15 the FDA off the top of that and put industry's desired
16 state up there as well, because these are exactly the
17 same things we want to achieve. We want to have
18 quality by design. We want to be able to set
19 specifications using mechanistic understanding. We
20 want to be able to have continuous improvement and we
21 want science and risk based regulatory policy that
22 allows us to undergo continuous improvement.

1 These are the same things that we want.
2 This slide has been shown before. It's one that
3 started out in PhRMA and the quality by design paper.
4 It was adopted by the ICH industry groups as we
5 started making our pitch to the regulators about what
6 we were trying to accomplish with Q8, Q9 and Q10 and
7 I think it's been used by I don't know how many people
8 in various presentations. The concept here, quite
9 honestly, is that the more you know about your
10 product, the greater your level of manufacturing
11 science knowledge is, the less risk there is that
12 variability is going to have an adverse impact on your
13 product. So as manufacturing science knowledge
14 increases, and that's not necessarily during
15 development. That can be during commercialization.

16 To the points that have been made before,
17 we've probably learned just as much or more about our
18 process during commercialization than we do during
19 development. So we should take that accumulated
20 knowledge, the risk that associated with that product
21 and processes and controls should decrease over time
22 as that manufacturing science knowledge is obtained.

1 The goal here is to have an appropriate level of
2 regulatory oversight that matches up with the level of
3 manufacturing science and the level of risk that you
4 have. So the more manufacturing science you have, the
5 less regulatory oversight you should need particularly
6 in the area of post-approval changes. The key to that
7 it having the right quality management systems in
8 place that control how you're doing change within your
9 company for that particular product because having
10 that flexibility doesn't decrease the oversight that
11 you have to have as you are implementing change.

12 It's just, what we're trying to talk about
13 here is what's the level of regulatory oversight,
14 what's the level of prior approval that you need in
15 order to implement changes. So how does this come
16 together? How does this work and I'll go through this
17 with words and then show you some diagrams of how we
18 envision this. It starts in development with quality
19 by design, using data rich experiments to identify the
20 critical quality attributes of a product and the
21 process. To the points that have been made before and
22 what Q8 is all about is taking this development data

1 and getting it appropriately into an application for
2 review.

3 The point has been made before that
4 several of us in industry have met with FDA to share
5 what the data base is that we have going into an
6 application and it's, I think, true that we've been
7 reluctant to submit all of the information or more
8 information than what we currently do in an
9 application because all of that is looked at as a
10 regulatory commitment. It's not looked at as here's
11 the data that got us to what the actual regulatory
12 commitments are. How did we identify what the
13 critical process parameters are? How did we identify
14 what the in-process controls and specifications are?
15 It all gets looked at right now as a regulatory
16 commitment. So there needs to be a give and take on
17 both industry's part and the regulator's part what
18 information gets submitted and how those data are
19 reviewed and looked at.

20 All of that data leads us to our
21 validation protocol. What are the critical process
22 parameters that you're actually going to validate and

1 monitor during commercialization? That will lead to
2 your validation report and both of those things, I
3 think, are appropriate to be submitting as part of
4 this piece of data that you're going to be giving the
5 agency. One of the things we haven't talked about,
6 we've talked about setting specifications based on a
7 mechanistic understanding of the process but what we
8 haven't talked about is interim specifications. In
9 other words, what are the specs based on your
10 development data and how might they change as a result
11 of the accumulated commercial data that you get over
12 in your initial manufacturing process.

13 Q6 actually talks about setting interim
14 specifications but it doesn't go into how you go from
15 -- or how you set interim specs and then how you
16 convert those to long term specifications. So that's
17 something that we should be able to think about and
18 work out. Dr. Hussain talked about comparability
19 protocols and hopefully the final document that comes
20 out on comparability protocols will be broad enough to
21 encompass the types of changes we're talking about
22 here. All of this leads to the point of having

1 continuous improvement in supplements without prior
2 approvals. Having the science and the risk management
3 piece of that is one part of doing that. Having
4 quality management systems in place to control that
5 process of continuous improvement is what we're trying
6 to implement with Q10 or propose in Q10. And this is
7 kind of what we, at Lilly kind of call our radiator
8 diagram that depicts what we envision this process to
9 be, starting in development and driving towards a
10 development history report based on the information
11 that's in there, you start to develop an integrated
12 validation master plan.

13 We also have what we call a process flow
14 document which gets very specific about how you make
15 and control the product. It's very specific to what
16 equipment is used, what are the operating parameters,
17 raw material specifications, all of that. Ultimately
18 that leads us from working in the pilot plant to
19 transferring this process to the ultimate site of
20 commercial manufacturing where we undergo
21 qualification and validation using today's parlance.

22 We then get to commercialization, what

1 we're calling execute and monitor, where we're
2 accumulating information and getting ready to make two
3 types of changes; one what we can technical evaluation
4 changes. That's the prospective part. How do we want
5 to optimize the product based on what we've learned
6 during development and what we've learned during
7 commercialization. The reactive part is the GMP or
8 quality evaluation and that's the response to things
9 like out of specs, deviations, product complaints,
10 adverse events. Both of those would go through the
11 same type of risk analysis that Dr. Razzaghi referred
12 to and we would develop a quality plan for that
13 product at that site. And that would cycle back into
14 the process, maybe even going back into further
15 development and then working its way down through the
16 chain again.

17 But in order for that to happen, and what
18 we're showing here are two parallel processes. The
19 top process is really the scientific part. The bottom
20 part of this, the bottom three boxes or the bottom
21 half of this diagram, really refers to having the
22 appropriate quality management systems that allow the

1 science to drive forward. So you can't have one
2 without the other and that's what we're trying to
3 drive through with Q10. So again, coming back to Dr.
4 Gold and Dr. Peck's concerns about how the process
5 should work, if we are concerned about physical
6 attributes, for example, of raw material coming into
7 a process, if we're using PAT to measure those raw
8 material attributes, we can adjust the process
9 variables on a feed forward basis. By the same token,
10 we can look at the product and measure critical
11 quality attributes that are being accumulated for the
12 product and feed back on those process variables. And
13 the combination gives us better control of the product
14 and this is exactly what, I think, we're talking about
15 when we talk about quality by design and operating in
16 that box that Dr. Berridge referred to because making
17 these changes to these operating parameters, these
18 process variables, if you've defined them
19 appropriately in the box are not really manufacturing
20 changes and they're not things that need to --
21 certainly not things that would have to go through a
22 regulatory approval process.

1 What you need to have are the appropriate
2 quality systems that allow you to monitor these things
3 and keep track of how they're occurring and determine
4 what changes need to be made based on that monitoring.
5 Q10 is only part of the solution to post-approval
6 changes. Now, part of the deal here is that if we're
7 identifying the box appropriately that we talked
8 about, we don't have to get into a lot of post-
9 approval changes because they would be considered part
10 of the process. But I still think and I'll make the
11 pitch, that the regulatory process needs to be
12 changed. And the reason we say that is that
13 regulators regulate regionally. Manufacturers
14 commercialize globally. There is definitely -- we
15 talked about disharmonization before. There is
16 definitely a lack of harmonization on the regulations
17 that govern manufacturing changes.

18 Every region has a different set of rules
19 that we operate under and these differences can
20 include the regulatory mechanism for filing the same
21 change, what the review cycles are for the review of
22 the dossier, data requirements and even interpretation

1 of the same data. Over time, this has resulted in
2 this reluctance on industry's part to make changes
3 because the regulatory hurdles are high. And just as
4 an example, if you consider an API in Product A, we
5 start off submitting one CMC dossier for that product.
6 That gets submitted and we'll just talk about four
7 regions right now that result in differences in the
8 specifications, in process control, shelf life and in
9 some cases can even impact how you're actually making
10 the product.

11 One of my colleagues related to me that
12 for the same product they actually have three
13 different manufacturing processes that came out as a
14 result of the review process. So now you've got,
15 instead of having one product, you've got four
16 different bulbs that are regulated differently because
17 of the differences in the review process. If you now
18 start to make process improvement changes, you start
19 getting differences in those products as well or that
20 review process results in different APIs there as
21 well.

22 So now you've got two different processes

1 running three to five different products. It creates
2 an absolute logistical nightmare to do this. Now, if
3 you take that and magnify it even more, saying that
4 you're making a change in an API that effects three
5 different formulations of the same product, you can
6 see that this becomes a real logistical challenge to
7 make change. And just by way of a simple example, we
8 at Lilly had a change which was an extension of an
9 expiration date based on real time data, based on an
10 approved protocol. We had to file over 100
11 supplements or variations and it took over two years
12 to get all of that approved. And that's a simple
13 change that certainly in the United States is an
14 annual report filing, but because of regional
15 differences, we had to go through a rather extensive
16 regulatory process. So I think the combination of
17 what we're trying to do with Q8, Q9 and the proposed
18 Q10 and a change in some of these changed regulations
19 will get us to a point where we have much better use
20 of our resources, much better use of the regulator's
21 resources, and a system that allows us, a quality
22 management system, that allows us to do continuous

1 improvement.

2 Thank you.

3 CHAIR BOEHLERT: Thank you, Dr. Massa.

4 (Applause)

5 CHAIR BOEHLERT: Any comments from the
6 committee? We're using up a lot of time very rapidly.
7 Ajaz?

8 DR. HUSSAIN: Well, I think I wish to
9 thank Toby for coming, especially today's is his
10 wedding anniversary and --

11 DR. MASSA: Thank you. My wife will thank
12 you if the plane gets home on time.

13 CHAIR BOEHLERT: Ken?

14 DR. MORRIS: Just one question, maybe you
15 said this but what's the timeline of this?

16 DR. MASSA: Well, that's an interesting
17 dilemma for us. One of the issues we're running into,
18 particularly with the EU and Japanese regulators, is
19 they have said they don't have the resources to devote
20 to Q8, Q9 and Q10 simultaneously. So we're kind of on
21 hold at this point. The ICH steering committee has
22 given a tentative approval to the Q10 concept but

1 we're not going to be able to form an expert working
2 group until we get to Step 2 for either Q8 or Q9.

3 Now, give credit where credit is due, I
4 think in FDA we're trying to drive this forward
5 independent of the ICH guideline. So we may be able
6 to lead the way here and try and push the EU and
7 Japanese regulators to see the benefit of this.

8 CHAIR BOEHLERT: Other questions or
9 comments? If not, thank you, Dr. Massa. Our last
10 speaker before we take a break this morning is Don
11 Marlowe, who's going to be talking on the ASTM E55
12 committee.

13 MR. MARLOWE: Good morning, Madam Chairman
14 and committee. I appreciate the opportunity to speak
15 to the committee about the development of standards
16 for PAT. What I hope to do this morning is give you
17 a very brief history of where we've been. It's been
18 about a year since we've started doing this and try to
19 give you a feel for the framework that we're operating
20 within and please, as I go along, if there's any
21 questions about where we are, don't hesitate to jump
22 on me here.

1 First of all, I hope to leave you with
2 these four points when we get done and to a later or
3 lesser degree I can do this and get you out in time
4 for your scheduled break. Why use consensus
5 standards, first of all, for PAT? Consensus standards
6 provides an opportunity for all interested parties to
7 participate in the discussion as equal playing
8 partners, so that they members of the regulated
9 industry, academic experts and people from the agency
10 can all come to a non-threatening forum and sit down
11 and talk about the issues and talk about what the
12 important topics are and agree on what approaches
13 should be to accomplishing the objectives that
14 everybody wants to achieve and it's a balanced
15 discussion. If you operate within the voluntary
16 standards community in the United States and
17 particularly if you operate with an ANSI accredited
18 standards developer, you are guaranteed that the
19 process discussion will be a balanced discussion.
20 That means that no sector of the community will have
21 a dominant voice in the discussion and we'll talk
22 about that as we go along this morning, but for

1 example, the FDA is just one partner at the table.
2 The regulated industry and the academics are partners
3 at the table but nobody can dominate the discussion.

4 Due process is an important consideration.
5 The ANSI, American National Standards Institute,
6 basically has an umbrella set of rules within which
7 all standards are developed in the United States and
8 they follow closely to the WTO Code of Practice and
9 the TBT Agreements on the handling of documents
10 within the standards process and one of the key
11 attributes is due process. Everybody has an
12 opportunity to be heard and nobody can summarily
13 dismiss a discussion. It has to be considered and
14 evaluated by all the partners.

15 And finally the NTTAA, the NTTAA is the
16 National Technical -- Technology Transfer and
17 Advancement Act. It was passed about 1995 and has
18 been implemented by the Office of Management and
19 Budget in a guidance document, A-119 which basically
20 tells the federal agencies to use the standards
21 developed through this process, through a voluntary
22 consensus process, wherever possible. So in order to

1 comply with our responsibilities under NTTAA, we are
2 using this standards developed in ASTM as an engine
3 for accomplishing this activity. And ASTM is, as I
4 said before, an ANSI accredited standard developer
5 with all of the baggage and attributes of an
6 accredited developer. They have more than 100 years
7 of experience. They were formulated. They were
8 developed in 1989, specifically at that time to
9 improve fatigue, what we now believe to be the fatigue
10 resistance of steel rails for the railroad industry.

11 But they have many years of experience in
12 all kinds of committees. There's more than 130
13 committees operating within ASTM. The agency works
14 with more than two dozen different ASTM committees and
15 E55 is just the most recent of the committees that FDA
16 has worked with in ASTM to accomplish our
17 standardization objectives.

18 ASTM is a recognized developer of
19 international standards. If you look around the
20 world, more than 44 countries have written ASTM
21 standards into the national codes, so we believe that
22 ASTM is an engine for accomplishing an awful lot of

1 the objectives the previous speaker mentioned. The
2 difficulty with the resources problem in many parts of
3 the world is that the resources are scarce to
4 accomplish the changes that everybody wants to achieve
5 here and with ASTM being a globally recognized
6 developer, we hope that some of these will be eased.

7 Finally, their offices are close. They're
8 up in -- just outside Philadelphia, up between
9 Philadelphia and Valley Forge and it's a speed run up
10 the road. We can be there in about three and a half
11 hours, so it enables us to go up there, consult with
12 the staff managers up there on activities that we need
13 for standards development and also we've held several
14 meetings in their facilities up there and it's a speed
15 run up and down the road for staff.

16 The history of our working with these
17 folks is very brief. It's almost a year that we've
18 been working with ASTM to develop standards for PAT.
19 You can see the calendar here, it really got organized
20 in February of this year and it took about four months
21 to have the first standard published through this
22 consensus process. There's a terminology standard,

1 E2363 and there's more than 70 terms already agreed to
2 by the consensus process in this standard and the
3 standard is being revised as we speak. More terms are
4 being added, terms that their needed discussion in the
5 first cycle of approval for that standard are being
6 revised and added as we speak.

7 The next meeting well be in November here
8 in Washington and it will be part of the standard ASTM
9 committee week. It will be over at the Omni Shorham
10 Hotel over on Calvert Street. And I encourage anybody
11 and everybody who is in the room and wishes to
12 participate in the process to get engaged and I'll
13 have a slide at the end that tells how. This is how
14 the committee is organized. There's really three
15 functional committees; Sub 1 on management, Sub 2 on
16 implementation and practices and Sub 91 on
17 terminology. The Sub 90 committee is just a kind of
18 organizational thing that you need to do to have a
19 committee to keep the train running on time. But the
20 activities of these committees, when we sat down to
21 talk about this, we realized there were a few
22 activities that were easy to talk about, to break out

1 as separate entities, materials, operating equipment,
2 control the environment, people training, analytical
3 equipment and control systems, transport and storage
4 of packaging and package parts and packaged
5 pharmaceuticals as well as the management of the
6 processing and packaging and obviously the systems
7 infra-structure at the bottom, what the plant needs to
8 make it work.

9 I didn't see the second -- the operations
10 and maintenance systems, there's an awful lot of
11 things of that type that can be standardized. The
12 initial work items, you see there on the left-hand
13 margin there is a work effort ongoing. WI is work
14 item. There's a work item to develop some standards
15 for raw materials, another one for manufacturing
16 equipment and finally, a work item on instrumentation.
17 These are the three active work areas. We anticipate
18 that as some of these things are accomplished, that
19 the committee will move onto some of the other
20 activities. So the items that you see there in detail
21 are all managed in E55-02. This was the
22 implementation and practices subcommittee and overall,

1 there's an over-reaching management system being
2 discussed, a management systems standard being
3 discussed in E55-01, the first of the subcommittees
4 that I mentioned and the objective here, obviously, is
5 to have a unified system and E55-01, an umbrella
6 document and a bunch -- several, many E55-02
7 implementation documents to reflect the best
8 practices.

9 Some of the -- the overall effort will be
10 to describe and accomplish a work plan and describe
11 and accomplish and enable the outcomes. As I
12 mentioned before, we would like people to participate.
13 The agency has a pretty heavy commitment to making
14 this work. I am the chairman of E55 and some of my
15 colleagues here in the Center for Drugs are active on
16 the three committees that I mentioned previously, the
17 three subcommittees. Interestingly the senior
18 management of all the other subcommittees are industry
19 people. They are members of the regulated industry
20 and actually have taken their responsibility every
21 seriously about their roles in managing the activities
22 of development of standards for PAT. And contacting

1 Pat Picariello at ASTM is a clean easy way to get into
2 the system. They have a website also, astm.org and
3 E55 has a link in the website, so that if you want to
4 go see what's being done and what the status of things
5 is, it's an easy access to the information. And I'll
6 answer any questions. And I missed by a minute.

7 CHAIR BOEHLERT: Very good, nevertheless.
8 Any questions in E55? G.K.?

9 DR. RAJU: Don, I really value the due
10 process in which you operate and we certainly hope to
11 live up to the expectations in all these meetings. As
12 you look at the rest of our discussion around ICH and
13 you look at the compliment in terms of resources
14 internationally, on one side that's a positive thing.
15 Do you see any duplication possibly in the future in
16 terms of ASTM doing things and ICH doing things given
17 how long it takes for the government. It's tough to
18 look at duplication after the product is over and if
19 there is some, does it get managed with the people
20 more common or is it done structurally with people
21 like you?

22 MR. MARLOWE: It is actually -- I think it

1 is actually done best with the people that are
2 involved. I think that it's unlikely that there would
3 be some kind of a super management system of the whole
4 thing, but I do think that the exercise within ASTM
5 will be a detail exercise, not an overall quality
6 system management discussion. So there will be a
7 discussion on best practices for management of PAT
8 within a manufacturing facility where the regulated
9 industry, the firms, get to share their best practices
10 but the overall impact of that and the overall role
11 that that would play in a quality system management
12 plan for a firm will not be on the table in ASTM.
13 That will be an ICH discussion.

14 CHAIR BOEHLERT: Any other questions or
15 comments?

16 MR. MARLOWE: Thank you, ma'am.

17 CHAIR BOEHLERT: Thank you, Don.

18 MR. MARLOWE: Appreciate it.

19 CHAIR BOEHLERT: And we are right on time
20 so I thank you for your effort on our behalf. We're
21 scheduled for a 15-minute break and we'll reconvene
22 promptly at 10:45.

1 (A brief recess was taken.)

2 CHAIR BOEHLERT: Okay, it looks like we
3 have all members present and accounted for. Now we're
4 going to change directions a little bit and we're
5 going to be educated hopefully, on Bayesian
6 statistics. Nozer, ti's all yours.

7 DR. SINGPURWALLA: Well, thank you for the
8 opportunity or the imposition to give this talk.
9 Let's see, okay, thank you. Well, the good news is
10 that I've given this talk about -- this is the third
11 time I'm giving this talk in the last two weeks which
12 is fortunate because I was asked a few days ago by
13 Sandia Labs to give a talk on Bayesian statistics and
14 things like that. Then I was in Iran giving the same
15 talk and Los Alamos Labs wants me to give this talk
16 again, so I've got a package that I can keep talking
17 and talking and talking about.

18 Now, the motivation why I was invited at
19 Sandia to give this talk is that there is a large
20 group of individuals who are thinking in terms of
21 alternatives to probability. And so they wanted me to
22 talk about this topic and particularly as applied to

1 reliability and fortunately, Ajaz mentioned the word
2 "reliability" so I feel slightly comfortable talking
3 about it but basically the title of this talk is
4 "Reliability for the Analysis of Risk" and it is a
5 Bayesian perspective.

6 So these are my coordinates and this is
7 mostly based on a book that I'm working on for a long
8 time. So first let me start with proper definitions.
9 Everything has to be defined so that there is no
10 confusion of vocabulary. So the first question is,
11 what is reliability and why is reliability relevant to
12 this particular community? It's -- this is some spy
13 is ringing the phone.

14 Okay, so it's the quantification of a
15 certain type of uncertainty associated with the
16 efficacy and safety of a large complex system to
17 include biological systems where it goes under the
18 name of "Survival Analysis". So your drug -- sorry?
19 The drug manufacturing is also a large complex system
20 and it doesn't matter what the complex system is, but
21 basically, reliability is the quantification of
22 uncertainty.

1 The next question is, why do we need
2 reliability, why reliability? Well, it is one of the
3 two necessary ingredients for making logical decisions
4 in the face of uncertainty connected with the efficacy
5 and safety of large systems. So reliability is one of
6 the two ingredients that we really need to make
7 logical decisions no matter what the decision is,
8 whether to administer a certain drug or whether to
9 manufacture a certain drug or how to manufacture the
10 drug, it doesn't matter.

11 What is the other ingredient? The other
12 ingredient is utility and utility is a very difficult
13 concept to essentially make precise but most of the
14 time when we talk about utility, we talked about costs
15 and our rewards that occur as a consequence of any
16 chosen decision. So every time you make a decision,
17 there are going to be consequences and associated with
18 the consequence there is either going to be a risk or
19 -- I'm sorry, I shouldn't use the word "risk". There
20 is either going to be a cost, a penalty, or there's
21 going to be a reward.

22 So the next question comes up, is what do

1 we mean by risk analysis? We've heard this term used
2 repeatedly in this particular audience and I think I
3 would like to see risk analysis as the process
4 assessing reliabilities and utilities and it should
5 include the identification of the consequences. So
6 risk analysis is the process of assessing the
7 reliability and the utility and think of reliability
8 as a probability. Think of reliability as a
9 probability but let's keep it specific.

10 And it should include the identification of all the
11 consequences.

12 The next question comes up why must we
13 quantify uncertainty? Why this business of
14 quantification? Why not just do things? Managers
15 essentially make decisions without quantifying, you
16 know. Generals make big wartime decisions without
17 quantifying. Why not just go ahead and do it based on
18 whim. Well, I'm not saying that by doing things on
19 whim you won't do the right things but essentially
20 formally, by quantification we mean the measurement of
21 uncertainty and by measurement we mean a comparison
22 against a scale. For example, we use feet for

1 distance and pounds for weight, so what we need to do
2 is really we need to come with a scale to measure
3 uncertainty. We are uncertain, we have to have a
4 scale to measure uncertainty because we want to
5 quantify uncertainty.

6 And measurement is a necessary ingredient
7 for invoking the logical method and mathematics is a
8 logical method and I'm sure there may be others but I
9 only know of one. Because without measuring, we
10 cannot talk about it as said very nicely by Lord
11 Kelvin several years ago. So we need to quantify so
12 that we can invoke the logical method and without
13 quantification, we really can't talk about anything
14 systematically. Thus, to quantify uncertainty we need
15 a scale of measurement.

16 So the basis problem is we are uncertain
17 about certain things. We need to quantify it and to
18 quantify we need a scale and so the question comes up
19 what is the scale. What is the scale for measuring,
20 what is the formula (phonetic), what is the weight
21 for measuring uncertainty? So what are the scales for
22 measuring uncertainty? Well, probability is the

1 oldest and perhaps the most commonly used case. There
2 are alternatives to probability that are popping up on
3 the horizon with a lot of passion and with a lot of
4 debate but sometimes without much content. And these
5 alternatives are possibilities and as this community
6 gets more and more into this game, I won't be
7 surprised if 10 years down the line, there will be an
8 Ajaz Hussain standing up and saying, "We should use
9 possibility", so I want to caution you that there is
10 a scale that's lurking on the horizon.

11 There is also another scale, it's called
12 belief. There is another scale called plausibility.
13 There is another scale called fuzzy measures.
14 Confidence limit and point estimate is also a scale,
15 but probability is the oldest and perhaps the most
16 commonly used scale. Well, the questions comes up is
17 if you are advocating probability as a scale, why it
18 should be the scale, what about these other
19 possibilities and beliefs and so on and so forth?
20 Confidence limits, the FDA uses them. Point
21 estimates, the FDA uses them. We think these are
22 alternatives to probability. So what are the

1 strengths of probability?

2 Well, the first strength is it has a
3 foundation that is firmly grounded in coherent
4 behavior -- coherent betting and the axioms of
5 coherent behavior. So there is a foundation behind
6 probability that is firmly grounded in coherent
7 betting. Coherent betting simply means you don't go
8 to Las Vegas purely with the intention of losing
9 money. You're hoping to come out ahead. So any time
10 you gamble, there should be a fair chance of also
11 winning. And axioms of coherent behavior it's a long
12 story but human beings behave in certain ways and the
13 calculus of probability is grounded.

14 But the more important reason,
15 particularly germane to this particular activity, is
16 that it's calculus leads us to a prescription for
17 decision making under uncertainty. Most of you in
18 business and industry are decision makers. So you
19 need to make decisions and you need to make logical
20 good decisions, how you're going to do it. Well, it
21 says that the calculus of probability and I'll tell
22 you what the calculus means, leads you to a

1 prescription for decision making under uncertainty.
2 The others to the best of my knowledge, do not have a
3 similar prescription.

4 So the next question comes up, if that be
5 the case, why are there alternatives to probability?
6 Well, this is a technical issue and I won't go through
7 the details of this but the axiomitization of
8 probability, the legitimization of probability from a
9 mathematical point of view is based on a certain
10 structure which some people find is very rigid and
11 therefore, they propose alternatives to probability,
12 but we won't go into the details but to the best of my
13 knowledge, the alternatives do not have a
14 behavioristic foundation and do not lead to a
15 prescription for making decisions.

16 Also some alternatives lead to answers
17 that are inadmissible. That simply means you get
18 silly answers, answers that fall flat in terms of
19 common sense. But I'd like to make some qualifying
20 comments and slowly we should get to that. As a word
21 of caution, the axioms of coherent behavior upon which
22 probability and its calculus are based are set to be

1 normative. That means they tell us how to behave. In
2 actual individuals may not behave according to the
3 dictates of normative behavior. We have plenty of
4 examples. People do silly things. I like to drink
5 alcohol every day in the evening. I know it's bad for
6 me but I do it. So that's not normative behavior.
7 I'm told not to do it, but I do it and there are other
8 examples. I've done some recent work with my
9 colleague, Jane Booker, who is at Los Alamos Labs, and
10 we have been able to overcome some of these
11 objections. Again, I won't go through the details.

12 All right, so that much for some
13 background. And now the main question, what is
14 Bayesian inference which is what you all want to learn
15 or those of you who know about it simply find all of
16 this very trivial. Those of you who don't know,
17 wonder why all this is happening. So what is Bayesian
18 inference? Well, the answer is very simple, Judy,
19 extremely simple. And the answer is this; when the
20 quantification of uncertainty is solely based on
21 probability and its calculus, inference is said to be
22 Bayesian. So to be a Bayesian simply means following

1 probability and the rules of probability. And of
2 course, it's not easy to understand the rules and it's
3 not easy to work with it, but as a general statement,
4 if you are purely going to describe uncertainty, and
5 measure uncertainty using the calculus of probability,
6 you are a Bayesian. Any time you violate from that,
7 you're not a Bayesian.

8 In other words, a Bayesian is strict in
9 his or her adherence to the rules of probability.
10 That's it. It's not very hard to be a Bayesian.
11 Well, of course, within the class of Bayesians there
12 are categories and I'm just putting this down. One
13 are called Objectivists and the other are called
14 Subject Matter Specialists. The Objectivists, the
15 spokespersons for that particular school were
16 Jeffreys, a British astronomer, mathematician,
17 philosopher. Jaynes was a an American physicist,
18 passed away recently and LaPlace, you all know who he
19 was.

20 So they wanted everything to be objective
21 and they simply said, "We should quantify uncertainty
22 using probability but we should not have any personal

1 opinions coming into the picture and what we need are
2 standards by which we can work". Of course, this
3 particular school was criticized. In fact, La Place
4 was severely criticized for doing this and essentially
5 La Place suffered a tarnishing of his reputation.
6 Then there are the subject matter specialists and the
7 biggest proponents of that school are De Finetti,
8 Savage and Lindley, who happens to be my co-author and
9 friend. They basically are of the opinion that to
10 quantify uncertainty you really have to understand the
11 subject; drug manufacturing, engineering, economics,
12 physics, whatever have you. You have to really get
13 into the guts of the subject in order to be a good
14 Bayesian. That was basically the idea.

15 There is a long debate about it and a long
16 -- so, what is non-Bayesian inference? Well, it's the
17 opposite of Bayesian inference; any process of
18 uncertainty quantification that does not fully
19 subscribe to the calculus of probabilities so labeled.
20 Well, of these, Frequentist Inference is the most
21 prevalent. In the FDA and in NIH and in government,
22 Frequentist Inference is the most prevalent. All your

1 military standards; 404, 105D, a lot of your control
2 charts, quality control procedures, the old ones, the
3 Shohart (phonetic) chart, Quinsome (phonetic) charts,
4 they all Frequentist and a Bayesian would reject them,
5 including Deming, who at some times rejected them not
6 because he was a Bayesian but he was using his common
7 sense.

8 Now, why is there Frequentist Inference?
9 Frequentists, while subscribing to the notion of
10 probability as a metric for quantifying uncertainty,
11 interpret probability in such a way that sometimes
12 they have to forsake probability as the sole basis for
13 quantifying uncertainty. Well, I just mentioned
14 probability but there are many ways to interpret
15 probability and if I had the whole day, I would go
16 into all those particular issues but I've been given
17 only 45 minutes. Fortunately, they are during the
18 morning. I was scheduled to speak in the evening when
19 all of you would be either gone or asleep or if you
20 were awake, you would fall asleep. But we've been
21 moved up and there is a long reason why all this
22 happens.

1 So I'm just going to put up one little
2 picture as a schemata of what's going on. So here we
3 have the quantification of uncertainty and we
4 basically have two groups. One group says probability
5 is the metric. Then there is another group that has
6 possibility, belief, confidence intervals, and all as
7 metrics for confine uncertainty. Within this
8 particular group, you have the objective Bayesians, we
9 have the subject matter Bayesians and then we have the
10 Frequentists or Sample Theoretic people and it's a
11 kind of a strange box here because this box has an
12 arrow here and also an arrow here. This particular
13 proponents of this, most statisticians that I know and
14 I was trained as a Frequentist, essentially use
15 probability as a metric but the interpretation of
16 probability at some point in time drives us into this
17 particular box. So that's the schemata.

18 Well, that's an overview and that's a
19 general statement. Well, the best way I can
20 illustrate all this is by a very simple example and in
21 the course of the example I will define what I mean by
22 risk and I will also define what I mean by utility and

1 this is what you would call risk based decision making
2 or whatever verbiage you use. The simple example that
3 I will use is the simple example that I've always been
4 successful using for the general audience because
5 everybody flies, takes an airplane, including myself
6 and you're faced with a decision. And what brought
7 this to my attention is I was on a committee of the
8 National Academy of Engineering or Science or whatever
9 on certification of aircraft and I was dealing with a
10 lot of people who manufactured huge, big, powerful
11 engines which take this plane up and the particular
12 individual who was on this committee was a very fine
13 gentleman from Boeing who was responsible for putting
14 two engines on the Boeing 777. So that was a big
15 decision why they built this plane with only two
16 engines when the classical jumbo jets had four
17 engines, so how did they make this decision to use two
18 engines?

19 Well, they didn't use decision theory to
20 be quite honest with you. They didn't use what I'm
21 prescribing but I had to talk to him and tell him this
22 is how I would go about doing it. So I'm going to

1 give you that example. So the example here is should
2 we outfit a newly designed airplane with one engine or
3 with two engines? Now, when you're manufacturing
4 drugs at Pfizer or wherever have you, I'm sure you
5 have a lot of decisions to make. You can translate
6 this into your own particular problem. So how should
7 we go about looking at this particular problem?

8 Well, I'm not going to put numbers because
9 I'm very uncomfortable with numbers, so let's C_1 be
10 the cost of acquiring and installing an engine. Risk
11 analysis is the most important thing are two
12 ingredients, probabilities and utilities. Utilities
13 are costs. Probabilities are probabilities no matter
14 how you interpret them, those two things are the most
15 important elements of making risk informed decision
16 making or whatever verbiage you use. So C_1 is the
17 cost of acquiring and installing an engine. This is
18 slightly loose. C_2 is the loss incurred due to an
19 aircraft failure. So if the airplane fails because
20 you don't have enough engines, you're going to suffer
21 a big loss, I just called it C_2 and I call this C_1 .

22 And I'm assuming that C_2 is much bigger

1 than C1 because a loss, if an airplane goes down, is
2 going to be much more than cost of putting an engine.
3 You know, it keeps running and running and running.
4 Let C1 be the reward received upon successful flight.
5 So every time you carry passengers from Tehran to
6 London, which is what I flew and then back from London
7 here, they collect effort from. So this is -- just
8 measures the air flow. All right, now comes the next
9 component and again, it's all laid out in notation, P1
10 is the probability of failure of an engine during its
11 mission. There's a probability that the engine will
12 fail and I do fault analysis, failure modes on
13 effects analysis. I do all kinds of things, collect
14 data, collect expert judgment, talk to the fellows who
15 design these engines, blah, blah, blah, and come up
16 with a number P1 as the probability that a single
17 engine will fail. Well, I have two engines so P2 is
18 the probability of failure of both engines. So you
19 know, one engine can fail and there is a certain
20 probability, and P2 is the probability that both
21 engines fail and when both engines fail, we have a bit
22 of a problem. How do we calculate P2? It's a big

1 complicated question. I have simply multiplied P1 by
2 P2 which is what old-fashioned individuals in the
3 industry were doing.

4 They were assuming that the chances of
5 failure -- that the failure of one engine doesn't
6 increase the chance of failure of the second engine.
7 So they were just multiplying it and they got into
8 ridiculous problems doing this. But I've just put P2.
9 Now, the next question is, so this is a part of risk
10 analysis, getting this P1 and P2 and C1, C2 and C is
11 all a part of risk analysis. But also a part of risk
12 analysis is the consequences to each decision. What
13 is the consequence in this simple example? Either we
14 succeed, which is S, or we fail which is F. So there
15 are two consequences. It again, illustrative. There
16 are other ways to look at this in much more detail but
17 I'm just giving you a general sense of what needs to
18 be done. If you want to move forward in this
19 business, these are the kind of thinking that should
20 come into play.

21 So we start by constructing a decision
22 tree. Again, there is fancy vocabulary here used by

1 different people. The last meeting we had they used
2 some other term which was more acceptable to others
3 but basically you had a constructive decision tree.
4 So let's look at the decision tree. And this is the
5 guts of everything. We have to make a decision and
6 that's called a decision node, D. The decision maker,
7 the engine designer, the airplane designer has to make
8 a decision. So she has two choices. She uses a
9 single engine, which is decision D1 or she uses two
10 engines which is decision D2. So those are the only
11 choices she's allowed.

12 Now, as soon as she makes her choice,
13 nature comes into play, that's called R1 to denote the
14 random node. What is nature going to do? Either it's
15 going to result in a success or it's going to result
16 in a failure. This is not a game because you're
17 making a decision against a benevolent nature. In a
18 game, when you want to use this in the context of
19 strategic issues, you have an opponent who is kind of
20 active, but this is a passive opponent. So you either
21 result in a success S, or an a failure, F. Then you
22 have to outline your utilities. The utility of a

1 success when you make decision D1 is USD1. The
2 utility of a failure when you make Decision D1 is
3 UFD1. P1 is the probability of failure, remember I
4 did that before and one minus P1 is the probability of
5 success.

6 Again the rules of probability say that if
7 this is P1, this should be one minus P1, so you have
8 the utilities here. Similarly, you do this at this
9 node, the second node, that is you have chosen two
10 engines and then at least one engine survives. We
11 assume that with one engine the airplane can fly and
12 we assume that with both engines failing the airplane
13 comes down. In actuality, it doesn't, it glides down,
14 but we just assume that it's a failure and then there
15 is a utility associated with those two. So any risk
16 informed decision making you want to make, if you're
17 not going to come up with a good decision tree, then
18 you're just doing it in a haphazard way. This is the
19 important step that you have to go through and the
20 important step involves a lot of important sub-steps.

21 You have to calculate your probabilities.
22 You have to calculate your utilities and you have to

1 outline what the consequences are. Here I have only
2 two consequences, S and P1. Well, the rest of it is
3 all mechanical calculations but I'll illustrate what
4 the calculations are. At this random note, R1 we
5 compute the expected utility of decision D1. This
6 expected utility is called, by definition, the risk.
7 This is the risk of decision D1. It's the expected
8 utility. What do we mean by that? It's the -- the
9 following calculation is the utility of success when
10 you choose decision D1 multiplied by the probability
11 of the success plus the utility of the failure when
12 you use Decision D1 multiplied by the probability of
13 failure.

14 So this expected utility is calculated by
15 R1 and I, of course, should also write here saying
16 that this is what is called the risk of decision D1.
17 This is the definition of risk, expected utility. And
18 that's why I made a comment to the previous -- one of
19 the previous speakers what it means. Well, these are
20 just numbers. You don't have to worry about it but
21 these utilities I have set down in terms of costs.
22 Of course, discomfort to a passenger also is a form of

1 utility and we need to quantify that and that's going
2 to be very important especially in the drug business
3 where you can take some kind of a medicine and have
4 side effects. It cures your disease, but you feel
5 lousy. How do you put a value to it?

6 Well, that's the more difficult part but
7 somehow you had to come up with a value and I have
8 simply used dollars and cents to encapsulate this.
9 Similarly, you do this at R2. You do exactly the same
10 at R2 and you compute the expected utility at the
11 second node. And again, I have these numbers. You
12 don't need to go through the details but you have to
13 compute the expected utility at this node and at this
14 node. Then the beauty of all this is this principle
15 of maximization of expected utility, MEU. It says,
16 use decision D2, namely two engines if the expected
17 utility, that is the cost multiplied by the
18 probability, added over the two consequences, exceeds
19 the one for decision D1. Otherwise choose decision D1
20 which is a single engine. So all you have to do is
21 construct the tree, not easy but this is where you
22 have to work with the correct scientists and the

1 correct people, elicit probabilities, which is where
2 most statisticians would play a role, elicit utilities
3 which is where economists, managers, marketers and
4 others would play a role and compute expected
5 utilities and choose that decision for which the
6 expected utility is the highest.

7 Well, these are some notes because the
8 audience I was talking to was engineers who always
9 like to dabble with numbers and always like to pull
10 out their calculators and punch a few digits, seven
11 digits off to the decimal point and brag about it. We
12 don't want to do this here. So here's a commentary.
13 The role of probabilities and utilities in making
14 decisions is clear. The more important point is this;
15 that it is the calculus of probability that leads us
16 to the maximization of expected utility as a
17 prescription for taking action. So there is
18 probability and there are rules of probability which
19 would be the next topic if I were continuing this talk
20 but just so that you may know that it's the rules of
21 probability that lead you to the maximization of
22 expected utility.

1 The alternatives to probability need to
2 provide a similar prescription. I don't think they
3 have one and they need to come up with one before the
4 alternatives could be. Okay, the above plus the fact
5 that the calculus of probability has an axiomatic
6 foundation that is grounded in coherent betting and
7 behavioristic rules is the strongest argument in favor
8 of the Bayesian paradigm so why should we be a
9 Bayesian? Because it's the calculus of probability
10 that leads you to a prescription for making decisions
11 and that the calculus of probability and probability
12 as a metric for measuring uncertainty had a foundation
13 that is grounded in so many other things.

14 Now, a lot of people like to be Bayesians.
15 The fact that the Bayesian recipe can address problems
16 like one of a kind system. Suppose you've designed a
17 new airplane where there has been not trial runs, do
18 you make a decision to fly it or if you want to send
19 a spaceship to the moon, you have not sent spaceships
20 before, should you decide it or not, that's a one of
21 a kind system.

22 Information fusion, the Bayesian -- the

1 calculus of probability allows you to fuse information
2 systematically, rather than doing it in an ad hoc way,
3 the ability to make predictions. Savings on sample
4 size are simply desirable by-products. There are a
5 lot of by-products that are very desirable but the key
6 argument for advocating a Bayesian point of view is
7 philosophical and mathematical. The key reason is to
8 have a sound philosophy and sound mathematics. The
9 fact that there are some nice by-products should not
10 be the driving argument. That's just something which
11 is desirable.

12 But there are some issues and what are
13 those? But this philosophic disposition also entails
14 a price to be paid. It takes the form of two issues.
15 So you want to be philosophically clean and clear but
16 you have to pay a price. And what is the price? The
17 actual behavior of humans is not always normative. We
18 don't do things which we are supposed to do always.
19 We get more pleasure doing things that we are not
20 supposed to do and maybe pleasure is a part of our
21 utility but we -- there is a specification of the
22 prior that comes into this business, posses

1 difficulties and my previous meetings here at the FDA
2 and other places the big flag raised against the
3 Bayesians is the prior. You'll hear the word, "But
4 the prior, where do we get the prior for". Because to
5 get the prior you need to understand the underlying
6 science and engineering or the economic theory so
7 statisticians don't like to get involved, at least
8 some of them, don't like to get involved in physics or
9 chemistry or pharmacy or economics. They just want to
10 do what they're trained to do.

11 But this particular paradigm requires that
12 you start talking to your scientific colleagues in
13 other disciplines and that becomes an issue. The
14 other more important issue is that the priors may not
15 be unique. My prior and your prior may not agree and,
16 again, it's a big topic of discussion. Why it is so,
17 we won't go into it but the Bayesians have an answer
18 to this and what is the answer of the Bayesians?
19 Well, the answers are the following. The first answer
20 is that the behavioristic axioms dictate how one ought
21 to behavior. They're a prescription for rational
22 behavior. The Bayesian says, "This is how you should

1 behave. The fact that you don't shouldn't be a
2 criticism of the paradigm".

3 The second more harsh reaction is that one
4 has no business working on a problem that one does not
5 understand, thus studying the underlying science and
6 engineering is a desirable thing. And the basic
7 argument is whether you're testing an engineering unit
8 for success or failure should not be viewed in the
9 same vein as studying the sex of newborn babies,
10 whether they are male or female. There has been
11 studies, you know, what proportion of newborns are
12 males or females and there is also this same similar
13 issue of testing for success or failure. You
14 shouldn't look at those, both those problems in the
15 same vein. One has genetics and biology; the other
16 one has physics and other things going into it.

17 Non-Bayesian methods lead to inferences
18 that are inadmissible and this is a heavy price to
19 pay. And here are some examples of non -- of
20 inadmissible answers. You can get estimates of
21 failure rates and densities that are negative. You're
22 estimating something which by definition is a positive

1 quantity and you can produce estimates that are
2 negative and engineers will simply reject that answer.
3 Well, you get confidence limits that are silly. I
4 won't go through the details, and you can also get
5 into this trap. Perhaps more important for the FDA,
6 you are testing some kind of a drug for acceptance or
7 rejection, approval or non-approval. A capricious
8 individual, a capricious organization, can manipulate
9 the process in such a way that you will accept bad
10 things.

11 So in the context of military standard
12 781(c), sequential live testing, there is a nice
13 example where a manufacturer of bad products can sell
14 the government the bad product by completely following
15 the rules but by behaving in a certain capricious
16 manner. I won't go through the details but just as an
17 example.

18 Thus, as a matter of principle, some do
19 not use procedures that could lead to a trap, even if
20 the alternative procedures demand more of the user
21 such as specifying a prior. And the other point I
22 want to make is there's no known situation wherein the

1 use of a Bayesian approach has resulted in an
2 inadmissible solution or an inconsistent estimate. In
3 other words, the Bayesian solution is a safe bet once
4 a prior has been agreed upon. And the main important
5 problem is eliciting priors which seems to be the main
6 job of a statistician; namely, you elicit priors to
7 estimate probabilities and of course, it's a big
8 enterprise which is what we need to work on and I have
9 -- this talk goes on for the whole day but I'm not
10 going to punish you, nor am I going to give you a test
11 which is what I promised Helen, so I'm going to spare
12 you in the hopes that -- okay.

13 I have all this on a disk which the people
14 at Sandia were kind enough to transcribe to a disk, so
15 I'm not going to give you all the 80 slides. I can
16 provide 19 slides but this is just a casual
17 conversational overview. There is a lot behind this
18 and there is a lot that needs to be done but my only
19 advice to you, Ajaz, is unless you take a specific
20 problem, simple as it is, and work it through, you
21 cannot lead the way. We are simply otherwise talking
22 about what needs to be done. Sit down, take a problem

1 and work it step by step perhaps in collaboration with
2 industry, get the whole group together, just to see
3 how this needs to be done, thank you. Bye.

4 (Applause)

5 CHAIR BOEHLERT: Thank you very much,
6 Nozer. Are there any questions or comments? Yes,
7 G.K.

8 DR. SINGPURWALLA: G.K., yes.

9 DR. RAJU: Nozer, have you seen people at
10 Boeing or -- ever use this successfully?

11 DR. SINGPURWALLA: Oh, yeah.

12 DR. RAJU: And what is the benefits, what
13 has been their experience?

14 DR. SINGPURWALLA: Well, since you asked
15 the question, the subject of reliability was invented
16 at Boeing. They invented the idea of fault trees.
17 Well, it's part of the game.

18 DR. RAJU: Is it strictly Bayesian
19 influence, Bayesian decision?

20 DR. SINGPURWALLA: Well, I'll tell you
21 what, Boeing Laboratories closed about 20 years ago.
22 So I can't talk about Boeing any more. I can only say

1 one thing, that they invented the Bayesian -- I'm
2 sorry, they invented the fault trees, failure modes
3 and reliability. They contributed fantastically to
4 it. Where I see this happening mostly is right now at
5 the labs, at the national labs, there is a lot of
6 passion one way or the other, for this and there is a
7 lot of activity going on in this.

8 Of course, people in business have used it
9 quite a bit. People in oil exploration have used it,
10 you know. There are pockets of resistance but I think
11 the pockets of resistance are losing the battle.

12 DR. RAJU: The arguments from the purists
13 is the traditional --

14 DR. SINGPURWALLA: No, no, we are the
15 purists. The argument from the impurist, okay. As
16 long as we get it right.

17 DR. RAJU: The FMEA that the aerospace
18 industry started are not truly Bayesian and you can't
19 really multiply them because they haven't really been
20 formulated as probabilities. I mean, this is --

21 DR. SINGPURWALLA: FEMA?

22 DR. RAJU: FMEA.

1 DR. SINGPURWALLA: Failure modes and
2 effects analysis is a strictly engineering function.
3 What they do is they say that the airplane has failed,
4 why did it fail? Was it the engine or was it the
5 pilot? If it was the pilot, why did the pilot fail?
6 Did he have an alcoholic drink or was he upset and if
7 it's the engine, was it the wings? You know, they go
8 through and trace the whole process. So that's the
9 failure modes and effects analysis.

10 Now, when you design a new airplane, you
11 want to calculate the probability that it will be
12 successful, so you have to first lay out the whole
13 scenario, that's the failure mode and effects
14 analysis, then work your way up calculating the
15 probabilities. Now, people make mistakes. What's the
16 biggest mistake they make? They multiply
17 probabilities when, in fact, they shouldn't. So
18 here's a classic example. Take the Boeing 777, the
19 Boeing 747. It's got zillions of parts. Each part
20 had a probability of failure. If you multiply all
21 those probabilities, then the probability of success
22 of the airplane goes down to zero, yet the airplane

1 flies. So immediately the reaction was something is
2 wrong with our calculations. So the big criticism is
3 not Bayesian methods and don't confuse Bayesian
4 methods with calculating probabilities, you know.

5 If you don't calculate your probabilities
6 correctly, you are going to get silly answers. So I
7 think the big question is, how to do it correctly.
8 It's very difficult, time consuming and demanding, but
9 there are certain rules which have been -- obvious
10 rules which have been violated and that is the biggest
11 problem.

12 Any other comments? Ajaz?

13 DR. HUSSAIN: No, I think if I recall the
14 discussions we had at one of the previous meetings,
15 probably the main advisory committee meeting where we
16 discussed the zero tolerance and we discussed the
17 traditional confidence and --

18 DR. SINGPURWALLA: That's right, that's
19 right.

20 DR. HUSSAIN: -- confidence and criteria
21 for bio-equivalence and so forth.

22 DR. SINGPURWALLA: And we changed?

1 DR. HUSSAIN: Right, and I think could you
2 put this in that framework? What are the advantages
3 of moving away from that type of approach to something
4 that uses a Bayesian type of approach?

5 DR. SINGPURWALLA: Well, let me give you
6 an example of why you shouldn't use confidence limits,
7 okay? And this is going to be a quiz, Ajaz because
8 that's how you're going to learn. I have -- X is the
9 height of all men in this room. And suppose X is
10 distributed normally with some mean -- don't even
11 worry about normal, there is some mean μ_1 . Y is the
12 height of all women in this room and they're also
13 normally distributed like us, thank God, otherwise
14 we'd be accused of sexism, and their mean is μ_2 .
15 Okay, the height of men is μ_1 , the height of women is
16 μ_2 .

17 And for some reason, some crazy
18 statistician wants to estimate the ratio of μ_1 over
19 μ_2 , the height of men over the average height. And
20 he calls that R_0 and he computes confidence limits on
21 R_0 . Does all his calculations nicely, computes
22 confidence limits and he comes and says the following.

1 "I've computed the confidence limits. They are minus
2 infinity to plus infinity and the probability of
3 coverage is 99 percent". Will you buy that? No, it
4 has to be one. That's the kind of answer you'll
5 produce. So there are certain traps that you can fall
6 into. Now, it doesn't mean that you'll always fall
7 into a trap. Sometimes you'll fall into a trap but
8 once you fall into a trap, you have to be careful
9 because you don't know where the next trap is.

10 There's another reason. The meaning of
11 confidence limits is itself a convoluted idea. A
12 confidence limit when you calculate, doesn't tell you
13 anything about the particular scenario. It says, if
14 you repeated this process over and over and over
15 again, 95 percent of the time you'll get what you
16 want, whereas the Bayesian response is, "Well, I'm not
17 interested in the, you know, 99 other scenarios that
18 I have not seen. I'm more interested in this
19 particular scenario". That's why you should get away
20 from them. But they are very strongly ingrained into
21 our culture and that's the reason why we have this.
22 So the particular meeting that we had, we advocated a

1 decision -- they used another language, but basically
2 this is what they were doing. Thank you. Any other
3 comments?

4 DR. HUSSAIN: Just one more, one of the
5 other aspects, we had a two-day workshop on this, at
6 FDA at Johns Hopkins University.

7 DR. SINGPURWALLA: I'm familiar with that.
8 I mean, I'm familiar with the characters that go to
9 the workshop.

10 DR. HUSSAIN: Right, and our sister center
11 CDRH has been using Bayesian approaches.

12 DR. SINGPURWALLA: For equipment only.

13 DR. HUSSAIN: Right. In the context of
14 what we are talking about ICH Q8, Q9 and so forth, I
15 think one of the attraction that leads me to seek more
16 information and probably more research in this area
17 for myself and for FDA is use of priors because prior
18 knowledge and use of prior information to make better
19 decisions is the opportunity, I think, I see of --

20 DR. SINGPURWALLA: That's right.

21 DR. HUSSAIN: How can -- can you share
22 some more thoughts on that?

1 DR. SINGPURWALLA: Yeah. First is, I want
2 to criticize you with no prejudice, of course. You
3 should not be a Bayesian because you could use prior
4 information, no, no. You should be a Bayesian because
5 it's logically closed and coherent. Now, the fact
6 that it allows you to use prior information is
7 certainly a big advantage because you're going to save
8 on the amount of testing and so on and so forth. The
9 danger is bad prior information could also lead you
10 astray. So getting an honest and honorable period is
11 going to be an activity and there are methods by which
12 you elicit prior information from people who are
13 subject matter specialists and experts and codify it
14 very carefully.

15 There are methods and there is a large
16 body of literature to do it. There is also a
17 philosophic position and that is the following. That
18 any Bayesian analysis is the analysis done by either
19 an individual or as a group of individuals -- as a
20 group acting as a whole and it's their best judgment.
21 So it's completely possible that given the same data,
22 and given the same information, one group can come up

1 with a certain conclusion and another group can come
2 up with a different conclusion because they have
3 different prior knowledge and different priors.

4 That people find objectionable. They want
5 one answer to run across the board. So that is a
6 criticism. So I don't know if I've answered your
7 question but getting prior information is an essential
8 step and there have been efforts to get away from this
9 ever since the days of La Place and right now there is
10 a large body of Bayesians in this country actively
11 growing, who are trying to get away from the prior
12 information and come up with canned priors.

13 Most of the pure Bayesians reject them as,
14 you know, not being to the spirit of what is intended
15 here. So there is a big activity but there are
16 methods by which you can elicit and quote prior
17 information and that's where the research effort
18 should be going. The prior information plus the data
19 gives you the probabilities. Utilities is another big
20 very important subject, particularly in the drug
21 context because there are side effects which are
22 uncomfortable. The drug industry has a very serious

1 problem in terms of utilities. It's not just dollars
2 and cents. It's more than that, so I think those two
3 are the key important steps. Another question?

4 DR. MORRIS: Yeah, so if I understand
5 correctly then, so if your risk is the weighted
6 average of the utilities weighted by the probabilities
7 --

8 DR. SINGPURWALLA: That's right.

9 DR. MORRIS: -- and if we don't really
10 have priors, as you say, if there's an absence of
11 priors or in some cases maybe the data that have been
12 collected aren't really critical attributes and don't
13 really reflect the utility or -- so you can't really
14 calculate a probability I guess, then are you
15 basically saying that that's -- you can't really apply
16 the Bayesian methods until that's the case?

17 DR. SINGPURWALLA: No, thank you.

18 DR. MORRIS: So --

19 DR. SINGPURWALLA: Okay, I got the gist of
20 your question.

21 DR. MORRIS: Okay.

22 DR. SINGPURWALLA: And it's because I just

1 didn't make one thing clear. It is true that you have
2 to calculate the weighted average, utility multiplied
3 by probability. How do you get the probability?
4 There are two schools of thought, the Bayesian and the
5 non-Bayesian. Okay? The Bayesian says you must have
6 a prior to calculate the probability. The non-
7 Bayesian says well, the priors could be subject, non-
8 unique and therefore, we should only have data to
9 calculate it. The Bayesian said, you need the prior
10 and the data to calculate the probability. The non-
11 Bayesian simply says, you only need the data and no
12 prior, okay?

13 But once you've calculated the
14 probability, both the Bayesian and the non-Bayesian
15 will use the same prescription. The only flaw here is
16 that the non-Bayesian, in using the prescription,
17 essentially uses the calculus of probability and the
18 calculus of probability demands that you have a prior.
19 It's slightly, you know, elaborate to explain but both
20 will do the same thing.

21 Decision theory has been practiced even by
22 non-Bayesians, okay, but the foundation for it comes

1 from the Bayesian thought process. Simply being a
2 Bayesian means following the rules of probability.

3 CHAIR BOEHLERT: Okay, any other questions
4 or comments? Nozer, thanks very much.

5 DR. SINGPURWALLA: Sure.

6 CHAIR BOEHLERT: Our last speaker before
7 lunch is Dr. Ajaz Hussain.

8 DR. HUSSAIN: I wanted this to be sort of
9 filling the gap to some degree but I think it's an
10 important topic. It's again, an awareness topic that
11 we wanted to sort of put on your radar screen. We
12 probably will discuss this in detail at a subsequent
13 meeting but I do want to sort of bring an awareness of
14 this initiative to you as a critical path initiative
15 and I'll focus on the industrialization dimension.

16 The key aspects here I think, I hope you
17 had an opportunity to at least look at the executive
18 summary of this initiative document or the White Paper
19 that we issued recently. The key focus area is
20 innovational stagnation. I think we are trying to
21 examine this and challenges and opportunities on the
22 critical path to new medical products. The finding

1 that I think as a nation both private and public
2 funding for research and biomedical research has been
3 growing quite significantly over the years but the
4 translation of all that basic research to products for
5 the patients seems to be not in sync and that's what
6 we were trying to examine and at the same time the
7 cost of new drug development seems to keep
8 skyrocketing.

9 And there are different figures out there,
10 800 to \$1.7 billion and so forth. So from a
11 regulatory perspective, I think what we feel is the
12 critical path which is from the prototype design to
13 the approval of that, is not receiving adequate
14 attention from the research community and even from
15 the academic community and this could become or is
16 becoming a bottleneck to new drug development. So the
17 critical path that we have identified and defined is
18 an area which has not been receiving the attention
19 with respect to new methodologies, more efficient
20 methodologies, and research in development of drug
21 products and medical products.

22 So if you really look at it from a new

1 drug development improving efficiency of drug
2 development and review, new development is a high risk
3 and highly costly enterprise and it's often due to the
4 high failure rate that we see. And can we do better?
5 And I think we must do better is the theme that we are
6 trying to move forward. There is a plan to issue a
7 list of projects that we think are the high priority
8 projects in both safety efficacy and
9 industrialization. And the feeling is strong that the
10 current process is not sustainable if you want to
11 maintain a robust pharmaceutical industry to meet the
12 public health needs of the U.S.

13 With that in mind, I want to focus on the
14 three dimensions of the critical path initiative, the
15 one on industrialization which goes from the physical
16 design of the prototype to characterization small
17 scale production, manufacturing, scale up and mass
18 production. If you really look at the challenges we
19 face today in conventional materials and dosage forms,
20 tablets, capsules and so forth, the functionality of
21 exigence, the availability of exigence, the
22 characterization is still a big gap, we don't

1 understand all of those things, but as we move forward
2 to its nanotechnology, nanomaterials, the physics
3 becomes more and more important and we are not able to
4 address physics adequately for our conventional
5 materials, so a challenge in the complexity is going
6 to be much greater.

7 So how does -- this is simply to sort of
8 remind us what the current state is. Research and
9 training needs from both the national perspective as
10 well as the perspective of FDA, I think, is clearly a
11 topic for discussion that we want to sort of bring
12 forward and have it in a public forum. The question
13 I have is our nation's education and research
14 infrastructure, is it adequate to meet the critical
15 path challenges? To me that answer is a clearly
16 sounding no. And I say that from two perspectives.

17 One is before coming to the agency, I came
18 -- spent nine years in teaching so very familiar with
19 the academic situation in the U.S. The society
20 essentially has decided that the role of pharmacy from
21 pharmacists in the U.S. is going to be of a drug
22 information, patient care. So the schools of pharmacy

1 which used to have a program and the rigors of
2 physical and analytical sciences in those programs has
3 completely be gone. So schools of pharmacy, the
4 pharmacy graduates coming out of schools of pharmacy
5 in the U.S. actually often do not qualify to fund the
6 PhD program. In fact, I would prefer not to use them
7 because they don't have the physical grounding
8 necessary.

9 So schools of pharmacy, the industrial
10 pharmacy programs in the U.S. are really incapable of
11 meeting the needs of this nation. And I've said that.
12 Some people have disagreed with that but I think
13 that's -- I strongly feel about that. And I think
14 there is a need to focus or take our focus on more of
15 a pharmaceutical engineering type of curriculum and
16 there is a need for center for excellence in
17 pharmaceutical engineering, education and research.

18 Now, how do we sort of promote that?
19 Several schools have contacted us, schools of pharmacy
20 and in collaboration with schools of engineering have
21 contacted FDA that they would like FDA to work with
22 them in developing such a center. And I think we have

1 a strong interest in that and we will meet and we are
2 meeting with these schools to see how we can support
3 this. But clearly, the critical path initiative
4 document was intended to bring this issue at a level
5 for public discussion, debate, so the society can
6 decide how well to fund this area because a lot of
7 this information, a lot of the science and a lot of
8 the knowledge that needs to be created has to be a
9 public data base. It cannot be a private enterprise.

10 So I think I would like you to sort of
11 think about and if you have towards the end or right
12 after my talk how should FDA support the case for a
13 focused effort on pharmaceutical engineering? We have
14 met with ISPE, International Society for
15 Pharmaceutical Engineers, and politely I said, there's
16 not much pharmaceutical engineering there. So we need
17 to bring more pharmaceutical engineering in that and
18 actually have a workshop on the topic of
19 pharmaceutical engineering and the national need for
20 this focus. So please think about this and please
21 share your thoughts on how we should proceed.

22 We will be meeting with schools of

1 pharmacy and engineering who have interest in this and
2 try to explore this possibility. I think clearly from
3 an internal FDA perspective, I think next several
4 months we will have to put a research agenda together.
5 We are right now focused on the Office of
6 Pharmaceutical Science on the industrialization
7 dimension, so what are the research and training needs
8 of FDA?

9 I think from a research perspective, we
10 have been sort of collecting a set of topics,
11 projects, or topic areas for research and realignment
12 of our research programs and clearly the PAT research
13 program that we have initiated, some internally, some
14 on collaboration, for example, the collaboration with
15 Pfizer, we are exploring other collaborations with
16 other companies, too, that will be part of this
17 critical path initiative but we are, as I speak, have
18 a group of people meeting with NCI, National Cancer
19 Institute, on looking at collaboration on physical
20 characterization of nanomaterials and physical and
21 biological characterization, so we're moving in that
22 area of physical characterization of nanomaterials.

1 Clearly we have an interest in
2 computational methodologies. Office of
3 Pharmaceutical Science has a wonderful group of
4 bioinformatics with respect to toxicology. We have
5 done some work with respect to use of prior
6 information and use of export systems in terms of
7 formulation but that has been limited. There's an
8 opportunity for that. There's an opportunity --
9 actually, we are putting together a very strong
10 chemometrics group. We already have a few people.
11 We're hiring a few more to include computational fluid
12 dynamix (phonetic) and include all elements that I
13 think would be needed to bring a sound computational
14 basis for CMC aspects. I think our other aspect is
15 support for generic drugs, efficient methods for
16 bioequivalence (phonetic) is clearly one of the
17 aspect, but I think as we move forward in the critical
18 path, I see blurring or actually increasing the
19 challenge of what is pharmaceutical equivalence and
20 how do you define bioequivalence, so our focus will be
21 on that and in fact, we will have to probably take up
22 the topic of what is pharmaceutical equivalence soon

1 because I think there is an opportunity to align that
2 and to streamline that and to actually make it more
3 simpler because today a tablet is not pharmaceutically
4 equal to a capsule but if you put a tablet inside a
5 capsule, it's pharmaceutically equal. So we have
6 logical ways of defining this. I think we need to
7 sort of pick that up.

8 So all of this sort of comes together as
9 a research program that we have Mon Surhan (phonetic)
10 in the room. We just hired him from the University of
11 Texas and I think he and Cindy Busey (phonetic) are
12 focusing on the industrialization dimension. So this
13 year's program planning for research, I think, we will
14 really focus on this. Jerry Collins and others are
15 clearly focused on the clinical side of it. So here's
16 an opportunity but you also have a chance to sort of
17 give us your thoughts, what are the project topics
18 that we really should consider, these are the broad
19 areas that we are working on and developing a research
20 program to meet these needs.

21 Clearly, the training needs are equally
22 important, the pharmaceutical inspector training

1 program, the critical elements development that we
2 start next month, the training program, but also
3 training of the CMC review staff that Moheb will talk
4 to you about. And I think we will have to have a
5 systematic way of doing that, especially if you have
6 to alleviate some of the concerns John Berridge raised
7 and how do you address these things.

8 So just I'll stop here and put these two
9 questions on your radar screen. Anytime you have
10 suggestions and so forth, please send these to us.
11 Thank you.

12 (Applause)

13 CHAIR BOEHLERT: Thank you, Ajaz. Any
14 questions or comments for Ajaz? Ken?

15 DR. MORRIS: Yeah, just a comment and this
16 is not news to Ajaz. I'll apologize in advance for
17 repeating it but to get it as part of the record, I
18 think one of the historical issues has been separate
19 from FDA or industry and that is that NIH and NSF just
20 don't view the kind of research that we're talking
21 about as fundamental enough to be treated by them and
22 they expect the pharmaceutical industry to shoulder

1 the burden of that and that's historically, I think,
2 why the departments, particularly at the graduate
3 level, have had to abandon the sort of research so
4 that they could maintain funding in other areas.

5 So I think that's -- not to just express
6 regrets but to say that in the future if we can bring
7 pressure to bear as I know you guys have already
8 talked to -- Helen and Ajaz both have already talked
9 to folks in the other agencies, but if we can bring
10 pressure to bear so that they understand that
11 significance of this both financially and in terms of
12 public health, can only help.

13 CHAIR BOEHLERT: Any other questions or
14 comments?

15 DR. SINGPURWALLA: Yeah, I was just going
16 to pursue the point that was raised by my colleague
17 here. I'm just curious. Work that needs to be done
18 which is of interest to the FDA, why should the NSF
19 put money into it? Am I correct in articulating that?

20 DR. MORRIS: Well, I guess what I would
21 say is that the disconnect hasn't been that it's work
22 that's needed by the FDA. The disconnect has been

1 their recognition of this as a relatively fundamental
2 set of research topics that need to be addressed in
3 general. I think, just as we draw largely on material
4 science and biology and the other disciplines to bring
5 into pharmaceuticals, there are specific aspects of --
6 in my particular case, of course, I'm narrowed by the
7 scope of my research. For instance, if you look at
8 material science literature, very little of it deals
9 with small molecular organic molecules.

10 So it's not like you can go to the book
11 and grab the fundamental theories to be able to be
12 used on these sorts of compounds necessarily. And
13 they've just not historically recognized the value of
14 this and the broad significance of scientific
15 endeavor.

16 CHAIR BOEHLERT: Any other questions or
17 comments?

18 DR. PECK: Yes.

19 CHAIR BOEHLERT: Yes, Garnet?

20 DR. PECK: Well, that's not what I was
21 going to talk about but I'll say it anyway. Several
22 years ago we applied to NSF a rather, what we thought

1 a rather good grant proposal to study the fundamentals
2 of corn starch. And the only way that that grant was
3 eliminated was the fact that corn starch is not a
4 uniform material. We were trying to find out why it
5 wasn't uniform and what kind of physical properties we
6 could measure and we had a methodology that was
7 proposed but they couldn't fathom why we would look at
8 this very variable material, how important was it to
9 our particular endeavors and at the time that was the
10 major disintegrating agent in most of our
11 pharmaceutical tablets.

12 We simply wanted to understand it more.
13 So NSF turned us down and we did something else.
14 Concerning what Ajaz said, I have to be very careful,
15 Ajaz. You may know of my feelings and some of them
16 are historical. I'm not convinced that our solution
17 is in pharmaceutical engineering. If we consider
18 basic engineering programs, at least the ones I'm
19 aware of, the amount of biological education that is
20 provided those individuals is very limited. You hit
21 on something that has to do with pharmaceuticals and the
22 fundamentals of pharmaceuticals which gave us those

1 tools to bring along new drug delivery systems for the
2 patient.

3 But it was aided by this sensitivity to
4 where the products were going. I'm having trouble
5 right now coping with pharmaceutical engineering
6 programs. There are so many excuses why we cannot
7 open up the programs and that's going to be a major,
8 major hurdle with doing what is needed. As you have
9 noted, we have to change in our fundamental programs,
10 in our graduate programs. So you have identified the
11 needs and that's great, but some of those that have
12 control over what we can do have to loosen up. That
13 is a concern that I have.

14 DR. HUSSAIN: I think your point is well-
15 made and well-taken that just an engineering approach
16 is inadequate and not sufficient. I totally agree
17 with that. And therefore, I think the pharmaceutical
18 engineering curriculum itself will have to sort of
19 bring together the key elements and not looking at
20 that as a purely engineering discipline. It has to
21 bring the fundamentals of chemistry, biology, and
22 engineering all together and that's something which is

1 not present in our curriculums in the U.S.

2 But if I start looking outside the U.S.,
3 you see a very strong push for these comprehensive
4 programs, especially in China, and more so in Japan
5 coming through quite vigorously in a sense. So I
6 think the challenge here is this; the community, the
7 pharmaceutical community is a very small community.
8 If you look at the American Institute of Chemical
9 Engineers, it's a huge community. If you look at
10 American Association of Chemists, it's very huge, but
11 the subset that is interested in the pharmaceutical
12 industry is often small. So you need to maintain that
13 identity. The industrial pharmacy programs and the
14 pharmacy school programs were successful in sort of
15 meeting those needs, but now the societal needs and
16 the societal demands, supply and demand is such that
17 look at BS degrees that you have either in chemistry
18 or even pharmacy BS degrees that Purdue has, you
19 create a scenario where the professional pharmacist
20 and their salary structure is so dramatically
21 different so it's not sustainable from attracting the
22 strongest candidates to your program.

1 The pharmaceutical engineering as a team
2 provides a means to create that identity, provides a
3 means to create that resource structure and attraction
4 for students then focus on that. So we will have to
5 develop the curriculum that is needed to meet the
6 needs. So your point is well-taken, Garnet.

7 CHAIR BOEHLERT: Any other questions or
8 comments? If not, I'd like to thank all of this
9 morning's speakers. We are right on time. We will
10 break for lunch and reconvene again at 1:00 p.m. I'd
11 just mention, members of the committee, we've made
12 arrangements for lunch and Bob King will be escorting
13 us, right, to the place, our destination.

14 (Whereupon at 12:01 p.m. a luncheon recess
15 was taken.)

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1 So you'll see different levels of
2 activities while they're trying to manage the day-to-
3 day activities, how do we move towards the "desired
4 state".

5 And following that discussion, I've
6 invited Ken Morris to come and speak to you about his
7 experience in helping us think about this and helping
8 us move towards what I would like to call a question-
9 based review process.

10 And I like that term because it helps us
11 to hopefully focus on asking the right question.
12 Question-based review process is actually in place in
13 our Office of Clinical Pharmacology and
14 Biopharmaceutics. And I actually like it quite a bit
15 where you simply, clearly identify what are the
16 questions to be addressed; and then focus your review
17 around those questions.

18 And I think we have an opportunity in the
19 CMC world to do the same. And so Ken has been working
20 at it with the CMC leadership within the Office of
21 Pharmaceutical Science, debating, discussing. So he,
22 I think, is the right person to share some of his

1 thoughts with you before you get into your
2 deliberations and discussions.

3 So that's the agenda for this afternoon.

4 After listening to the discussions this
5 morning, especially with respect to some of the
6 discussions with the design space and some of the
7 opportunities, for example, Dan, you raised the issue
8 if you have understood this range of conditions work
9 fine, why don't you sort of take advantage of that?

10 And I think that's what we are trying to
11 do in Q8. I see as Q8, from my perspective, is trying
12 to harmonize different regulations in Europe, U.S.,
13 and Japan with respect to changes or variations by
14 changing what is -- how we define change.

15 For example, if you have a range of
16 studies done, and you understand the range is not
17 critical, so why not redefine that as not being a
18 change? So that's, I think, what we're trying to
19 achieve.

20 So keeping that in mind, I'll share with
21 you some of my thoughts on specifications. Some
22 challenges and opportunities in the enhancement of CMC

1 sections of NDA's quality by design is how to set
2 specifications.

3 And I was planning to speak after G.K.
4 Raju but I think listening to this might help you
5 because I think G.K. is going to talk to you about the
6 wonderful opportunity we have from the knowledge-
7 sharing perspective.

8 So with that in mind, I'd like to sort of
9 again repeat that I think the opportunity is therefore
10 companies that acquire extensive understanding about
11 the product and manufacturing processes and share this
12 with the regulators, that helps us to be -- enhance
13 our science and risk-based regulatory quality
14 assessment in setting specifications, reduction in
15 volume of data to be submitted replaced by more
16 knowledge-based submissions, and flexible plus
17 continuous improvement.

18 In fact, I think our goal is to move
19 towards the state where you have one cycle review, CMC
20 review, and essentially everything is banished in the
21 GMP inspection site in the continuous improvement.

22 And I think this is the desired state that

1 is possible. And I think Dr. Woodcock's presentation,
2 which is in your handout, she has continued to think
3 about this. And her latest presentation on quality by
4 design I think is quite telling in the sense this is
5 a proactive approach on how you approach the
6 development and how you approach specification
7 settings.

8 Quality by design stipulates or postulates
9 key performance parameters early in the development
10 process. Now this is based on what we know at that
11 point plus your prior information. And then you
12 design product and processes to be robust around for
13 these parameters.

14 But the challenge today, as John Berridge
15 discussed some of this in his presentation, without
16 adequate product and process development and/or
17 knowledge sharing, you have high levels of uncertainty
18 with respect to critical attributes, what is critical
19 and what is not critical.

20 And when you have that high level of
21 uncertainty, we often have to make decisions
22 conservatively. If you don't know, everything is

1 critical then.

2 And also I think the questions that we
3 struggle with is is the sample size representative, in
4 representative disc samples and adequacy of risk
5 coverage? Example, compendial discs to assure batch
6 quality.

7 So those are the regulatory risks or
8 concerns that our reviewers are trying to minimize
9 through their approach to specification setting. In
10 absence of extensive understanding of product or
11 process factors, you have to make a conservative
12 decision.

13 I think reduced concerned risk by covering
14 all apparent attributes with acceptance criteria based
15 on capability of test methods and/or manufacturing
16 process plus very inflexible SOP that sort of follow
17 from that. So that's the current way of sort of doing
18 business of current regulatory risk mitigation
19 strategy.

20 But I think I wanted to illustrate some of
21 this using a current situation on distribution
22 attribute. Now there are many, many guidances that

1 sort of you have to look at to glean this information
2 but I won't be able to do all of that for you today.

3 But I just wanted to sort of share with
4 the ICH Q6A decision tree and how it sort of addresses
5 the resolution and why I think the current state tends
6 to be testing to document quality. And in ICH Q8,
7 we're moving toward the desired state where we are
8 trying to get to a quality by design.

9 The biopharmaceutics classification
10 system, the BA/BE guidance, the SUPAC guidance, and
11 the dissolution guidance itself are sort of
12 interconnected. Unfortunately we don't have the time
13 to share with you all of those connections that I have
14 sort of worked out.

15 But let me start with the Q6A decision
16 tree. The first question that we asked in this
17 decision tree does the dissolution significantly
18 effect bioviability? If the answer is yes, we develop
19 test conditions and acceptance criteria to distinguish
20 batches with unacceptable bioviability.

21 If the answer is no, we go down this
22 decision tree to say do changes in formulation or

1 manufacturing variables effect dissolution? If the
2 answer is no, we go down to adopt appropriate test
3 conditions and acceptance criteria without regard to
4 discriminating power to pass all clinically acceptable
5 batches.

6 But if the answer was yes, are these
7 changes controlled by another procedure and acceptance
8 criteria? If the answer is yes, we come back to the
9 previous result. If the answer was no, adopt test
10 conditions and acceptance criteria which can
11 distinguish these changes. Generally, single point
12 acceptance criteria acceptable.

13 Now, I have inserted some questions. How?
14 How do we know dissolution significantly effects
15 bioviability? Okay? There are wonderful studies that
16 are done in Phase I, Phase II which actually show you
17 so much information.

18 For example, one typical that is carried
19 out is a related bioviability study solution was
20 established. We actually do not use that effectively
21 in our decision-making. Often you will see a solution
22 perfectly superimposable to a solid dilution

1 essentially saying dissolution is not great limiting.
2 Okay? So we know that that happens in many cases but
3 not in all cases.

4 But then the solubility, the particle
5 size, dissolution rate, all can give you the signal.
6 We don't utilize that information today.

7 So often our answer is yes, dissolution is
8 an important attribute. It is an important attribute
9 and we have to control it using a dissolution test.

10 And the many questions that how, what,
11 why, and so forth that you see on this chart are not
12 fully addressed but not only the information is
13 scattered throughout the NDA submission but also I
14 think we often don't have time to pull all this
15 together in a concise way to answer these questions.

16 And, therefore, we often set
17 specifications because that is the tradition.

18 Suppose I go down this route, dissolution
19 does not significantly effect bioviability. Should we
20 be asking the question do changes in formulation or
21 manufacturing variables effect dissolution?

22 Why would we ask that question?

1 The answer is for over shelf life, over
2 the period of shelf life, there might be change which
3 might not be apparent in the release.

4 All right. But then we establish a
5 dissolution criteria using a dissolution test. So
6 that's the current situation.

7 And here are three examples, more recent
8 examples of how we set specifications. Now these are
9 three very recent examples. And here are the reviewer
10 comments, three different ideas.

11 Without adequate product development
12 and/or knowledge sharing, we debate frequently. So
13 one of the last decisions we might do is this is your
14 specification to the end of the NDA review cycle, this
15 is what our decision might be. And you often have no
16 choice but to accept it.

17 So here is the first comment. The
18 reviewer recommends tighter dissolution specification.
19 Q of 80 percent in 30 minutes. And in this case, it
20 was based on, you know, what the clinical batches
21 were.

22 And if you go down the list, they say the

1 sponsor-recommended dissolution specification method
2 was unacceptable. We simply say the sponsor's Q of 70
3 percent is too low. The direct product that releases
4 only 70% is likely to be bioequaled -- is less likely
5 to be bioequaled than a product that releases 100
6 percent.

7 Therefore, we recommend a Q of 80 percent.
8 Sometimes that Q of 80 percent may not be actually a
9 profile point in this, the total example. Therefore,
10 we propose the sponsor's specification of Q of 80
11 percent at 60 minutes should be changed to
12 specification of Q of 80 percent in 30 minutes.

13 Much of this discussion is based on three,
14 four, five batches that we see in the new drug
15 development. We do not bring the systematic thinking
16 with respect to the physical, chemical properties of
17 the drug, the formulation, the disintegration
18 mechanism of any of them. That's not really fully
19 utilized today.

20 And then what I say here is we have cGMP
21 problems. Here is a warning letter. An inspection of
22 your drug facility, blah, blah, blah, there is no

1 assurance that written production and process control
2 procedure established for coating are sufficient to
3 produce a product that has the quality it purports or
4 represents to possess.

5 The duration of coating cycle as
6 determined by the pan operators is based on a visual
7 determination that coating solutions are even
8 distributed before proceeding to the next step.

9 It should be noted that it was hundreds of
10 batches. So the numbers are not small here. A number
11 of batches made in `97 or `98 were rejected due to in-
12 process distribution failures.

13 And then you go on to the partial release
14 of various products even though there was not data to
15 invalidate all the specification results. And so
16 forth, and so forth. This is catastrophic. And this
17 is not a small company. This is one of the major
18 companies.

19 So what happens is, I think, every aspect
20 of our regulatory is interconnected. And G.K. Raju,
21 his data has always shown us in the sense that, you
22 know, all the specification results are a significant

1 -- they contribute a significant increase in cycle
2 times and so forth.

3 And here is a couple of examples that I
4 took from his slides. But here also many of these are
5 physical attributes, dissolution. And what I would
6 argue is many of these are physical attributes that --
7 where we have struggled with.

8 Dissolution is not the worse case
9 scenario. I would say when it comes to particle size,
10 gasket compacture, and others, you have significant
11 measurement variability that you have to deal with.

12 But let's look at this. Testing to
13 document quality clearly requires a less variable test
14 method. Here is the data from our lab in St. Louis.
15 The current USP 10 milligram Prednisone caliber
16 tablets exhibit slow dissolution over time. It's not
17 a stable caliber. It keeps changing.

18 So if the acceptable test equipment
19 calibration limit is 28 to 54, and if you often live
20 with our F2 criteria, which is an average of six, and
21 then you compare the two average profiles, and that
22 average profile should not be more than ten percent

1 different between the pre-change and post-change, what
2 do we see?

3 The calibration limit far exceeds that but
4 that's what we have been practicing for years. So
5 what can we say about the use of F2 criteria where the
6 mean profile difference that we accept is ten percent
7 or less as a way to document and change quality?

8 And if you look at the table there, the
9 table from two different data sets, the shift in the
10 stability of this calibrate, so if I look at
11 calibration as a means to say this is my target,
12 that's giving me a target value, even the mean
13 estimate, the point estimate is questionable with this
14 method.

15 And just to summarize the dissolution
16 experience at the FDA's Division of Pharmaceutical
17 Analysis, dissolution testing with USB Apparatus 1 and
18 2 requires diligent attention to details, both
19 mechanical and chemical, dual response can respond
20 differently to small variation in apparatus setup or
21 degassing, large difference in dissolution results are
22 possible unless all parameters are carefully

1 controlled.

2 The experience at Division of
3 Pharmaceutical Analysis, FDS St. Louis indicates that
4 differences in reproducibility can often be traced to
5 improper mechanical calibration and/or degassing.

6 And we have a situation where we often
7 have to reject, recall batches, because of minor
8 dissolution failures. And we have no good means of
9 getting out of that trap that I think we are in.

10 And this is not new. Our Canadian
11 colleagues, Health Canada, has been talking about this
12 for years. And this is from 1992. We often see false
13 positives and false negatives in some of our
14 measurement systems.

15 And here is just one example. I'm not
16 going to explain that but Ian Miggelri, and he used to
17 be at Health Canada, published this some time ago.

18 Now, just to continue the thought
19 processes that are so entrenched in testing to
20 document quality, and we often ignore all the prior
21 information and we focus on the test results, is a
22 reason for thinking -- of major thinking.

1 Here is another example from the Q6A
2 decision tree. I just want to illustrate two points
3 from this. Now the question I want to illustrate from
4 this is do we always need a dissolution test for every
5 solid dosage form? The answer is yes currently.

6 But I think Q6A opened the door to say not
7 necessarily. Although I'm not too pleased what Q6A
8 recommends, a disintegration test instead of
9 dissolution, which is probably far worse than that.
10 I think there is a better way to deal with this.

11 In Decision 3, No. 71, it says the product
12 is not modified release, the drug has high solubility,
13 the product has rapid dissolution, then you ask the
14 question has a relationship been established between
15 disintegration and dissolution?

16 If so, then you might want to go to a
17 disintegration test instead of a dissolution test.
18 Now in Europe, this is acceptable. I don't think we
19 have approved a single one in the U.S.

20 But the point I want to make here is just
21 pay attention to that. We're focused not on
22 understanding the product, not on understanding the

1 process. We are trying to create comparison between
2 two different tests, a disintegration test and a
3 dissolution test.

4 And the reality is this. If you are
5 familiar with the disintegration test, you have a cube
6 with a 10 mesh screen which goes up and down. So you
7 put a tablet and that goes up and down. And you just
8 look at the time when all the tablet fragments have
9 passed through the sieve.

10 So in this case, the table is
11 disintegrating into larger chunks to small chunks at
12 a point where you stop and say the tablet has
13 disintegrated. The total dissolution of that is
14 throughout the surface, larger particles, smallest
15 particles and so forth. So dissolution can continue
16 after disintegration is over.

17 Now the point to illustrate here is this,
18 they're twofold. One, we are comparing apparatus --
19 dissolution apparatus to that of a disintegration
20 apparatus. The hydrodynamics are different and the
21 medium might be different. That's not a true
22 comparison. That's not a quality comparison per se.

1 But that's fine.

2 The other aspect here is, I think, the
3 hesitation that we often have is now, yes, there is a
4 risk associated here by moving to a disintegration
5 test because dissolution continues even after the
6 disintegration time is over. The reason a risk could
7 be polymorphic transitions. You may see polymorphic
8 transitions and a disintegration test might not ever
9 pick it up, correct?

10 So these are sort of the questions that I
11 think with good science, what we have talked about in
12 Q8, we can address some of these questions in a
13 submission. But not today because we don't have all
14 this information to really make a rational decision.

15 Testing to document quality, the face has
16 many dimensions. It is applied as in process and end
17 product release and stability testing. So the
18 reliability of specification is a key question
19 because, I think, we look at that in absence of
20 process understanding.

21 Managing post-approval change and
22 continuous improvement is a challenge. And I showed

1 you just one aspect of the F2 metric and what
2 challenges it poses. Product and process knowledge
3 acquisition and generalization is also challenged
4 because now you are relying on a traditional wet test
5 to -- and if you're trying to do a design of
6 experiment, that's a humongous resource commitment in
7 the time it takes to do these tests.

8 So how can pharmaceutical development
9 knowledge help? How can we demonstrate quality was
10 designed in, specifications based on mechanistic
11 understanding, continuous "real time" assurance of
12 quality, and flexible continuous improvement.

13 I think the Q8, the Q9, and the overall
14 Q10 are all trying to move in this direction to answer
15 these questions. What I would hope to see, and this
16 is for debate, discussion, and so forth.

17 This is the same decision tree that I
18 showed you earlier from Q6A but now, from a design --
19 quality by design perspective, dissolution
20 significantly effect bioviability, that's a design
21 question.

22 You postulate that based on the

1 characterization of your API or drug substance. You
2 know the solubility and you know the pKa, you know so
3 you have a knowledge based on how this molecule might
4 behave. And so you postulate.

5 And then throughout your development
6 program, you confirm based on mechanisms and/or
7 empirically. So that product design applies to those
8 two decision trees that you have.

9 At the same time, from a risk perspective,
10 if we understand the PKPD of this, we will have a
11 better focus maybe towards the end of the drug
12 development process, not at Phase I, Phase II, but
13 towards the end of the NDA submission process, what is
14 acceptable? What is not acceptable bioviability?

15 Today, the answer is anything outside of
16 80 to 125 is, by virtue, an acceptable bioviability.
17 And that's a wonderful clinical pharmacology question
18 of what that question is.

19 So once you have that, you start answering
20 this question, design for manufacturing and controls
21 or design of manufacturing and controls and how
22 reliable are these because the second decision diamond

1 that you have, do changes in formulation or
2 manufacturing variables effect dissolution? Right?

3 If the answer is yes currently, are these
4 changes controlled by another procedure or acceptance
5 criteria? If the answer is yes, you still go back to
6 the dissolution test step. My answer to that question
7 would be is that really necessary? With this
8 scientific knowledge base and so forth, can we do
9 better?

10 So those questions can be brought to bear
11 on this. An overall, risk-based CMC, why can be
12 asked. I think a reviewer should ask why do need
13 this? Why do you need redundant system? What is the
14 value of this? And so forth.

15 But also I think we need to find ways to
16 answer the question so what. Now if the virtue of, I
17 think, what I have learned from a quality system is
18 you have to focus on the voice of the customer. Now
19 if dissolution does not significantly effect
20 bioviability, if a drug is highly soluble, and this is
21 a rapidly disintegrating drug, is that a critical
22 variable?

1 I think today we'll answer always yes.
2 Dissolution is an important attribute, no doubt about
3 that. But a test? Is that important? I think we
4 have to start thinking about so what? And the so what
5 has many, many connections. What is acceptable? And
6 so forth.

7 I think overall CMC systems approach that
8 Moheb will talk to you about, I think he's starting to
9 think about this as a quality systems assessment
10 program. And it's to sort of bring the connections
11 and the Q8 offers that opportunity to link the morpnic
12 form particle size stability failure mechanisms to ask
13 those questions why and then how.

14 So based on quality of pharmaceutical
15 development knowledge, can we not evaluate overall CMC
16 systems approach, that is link to morpnic form
17 particle size stability failure mechanisms and address
18 the concerns and risks? Is dissolution specification
19 needed? Instead of wet dissolution test can we use
20 disintegration test?

21 I don't like that personally but that's a
22 valid question. Real time release and stability based

1 on process controls and say NIR tests, capsules and so
2 forth.

3 The key is, I think, we all understand
4 that not all information is mandatory. We are okay
5 with this. And we are work in the ICH to avoid a two
6 different system model. Instead we are moving towards
7 one system with different levels of quality by design.

8 And you'll see that, I think, in different
9 offices you'll have different levels of process
10 understanding. And so forth.

11 The challenges we face. Common approach
12 to a more clear articulation of not all information is
13 mandatory. We seek your help on that, I think, in the
14 questions we have posed.

15 Improved process understanding and control
16 technologies may afford reduction in regulatory
17 requirements. That's the design space concept that
18 that's coming about.

19 And I think the key is and in most
20 relationships it is expected between effectiveness of
21 the quality by design and risk to patient being
22 exposed to product that is not fit for use. That's

1 something that will need to evolve.

2 And I think what we are moving forward is
3 hopefully ensuring continuous improvement and a
4 process for continuous learning and updating of this
5 knowledge base.

6 So with that, I'll stop. And I have --
7 invite G.K. to share his thoughts on it.

8 CHAIR BOEHLERT: Are there any questions
9 or comments for Ajaz?

10 Yes, Nozer?

11 MEMBER SINGPURWALLA: Ajaz, I'd like to
12 make a comment.

13 MEMBER HUSSAIN: Yes?

14 MEMBER SINGPURWALLA: Just to keep the
15 notation and the language clearer and clean. What you
16 have is not a decision tree. What you have is an
17 event tree. A decision tree is one where you make a
18 decision. What you have is a flow of event as they
19 occur.

20 So just so that we don't, in the future,
21 confuse, you should really call it an event tree.

22 MEMBER HUSSAIN: Unfortunately, I can't

1 change the ICH.

2 (Laughter.)

3 MEMBER SINGPURWALLA: Change it.

4 CHAIR BOEHLERT: Any other questions or
5 comments?

6 (No response.)

7 CHAIR BOEHLERT: Okay, before we begin
8 with G.K., I would just like to note for the record
9 that there is no open hearing this afternoon because,
10 indeed, there were no people that requested time.

11 So having said that, G.K., it's all yours.

12 MEMBER RAJU: Thanks, Judy. And thanks,
13 Ajaz, for the opportunity to present today.

14 I'm going to try to talk about
15 manufacturing science and knowledge and in some ways
16 build on what I presented before in this general
17 audience. And I think in many ways compliment the
18 presentations of here today.

19 The outline for my talk, I'm going to
20 frame manufacturing and science within a broader
21 social context. Once I have a frame, I'll define some
22 vocabulary. Hopefully, Nozer will approve of the

1 vocabulary. And use that vocabulary to then describe
2 the desired --

3 CHAIR BOEHLERT: G.K., G.K., you may need
4 to get closer to the mike.

5 MEMBER RAJU: Sure, okay.

6 Once I've defined the current and the
7 desired state, I then use that vocabulary to define
8 leverages to go from here to there. Implications of
9 those leverages, possible next steps given those
10 implications for the leverages and, of course,
11 acknowledgments because we stand on broad shoulders.

12 The frame that I'm going to use for the
13 rest of my talk is to say that pharmaceutical
14 manufacturing is not really something you do inside a
15 plant in a company. It really is a social capability
16 that has resulted from a set of choices that we have
17 made, all of us as patients.

18 So all of us here are patients. But all
19 of us as patients have made decisions about risk, what
20 is a good release? How does it work? And how much
21 are we going to pay for it?

22 The government, who has decided to fund

1 certain kind of research, and if Ken wasn't happy that
2 they didn't fund other kinds of research, the
3 pharmaceutical industry that has decided to focus on
4 product innovation and in doing so has made a tradeoff
5 about process innovation. And academia, who has
6 decided to have all their tenured professors to focus
7 on everything except pharmaceutical engineering.

8 (Laughter.)

9 MEMBER RAJU: And so all of us are
10 stakeholders in this broader society as if we could go
11 with what Ken said. And in the end, inside that
12 plant, in the broader social structure, somebody is
13 making these drugs that we consume.

14 So I'm going to try to frame it in that
15 sense and now let's look deeper with that frame.
16 Given that frame, let's define a vocabulary. The
17 first set of vocabulary is around science. It was the
18 first thing that Ajaz wanted to include in my talk.

19 And interestingly science is both a noun
20 and a process, in some ways something active and it's
21 doing. And there is the process of scientific
22 inquiry. And there is an extent of science which is

1 what you know at any point in time.

2 Given that, and we've defined
3 manufacturing science in the past, you can then go to
4 the next word in your definition and say once you have
5 science down, how about the word system. A system is
6 a set of processes and broader systems, including
7 people, with a common material and information flow.

8 The way I define system, the manufacturing
9 system is very much connected with the quality system.
10 They're not two different things. They're almost the
11 same thing although there are reasons to be different
12 in that particular industry. So the second piece of
13 vocabulary is now in place.

14 Here is a set of manufacturing systems
15 that you could have. I'm going to call them A, B, C,
16 D, and E. That's pretty obvious. That's how I
17 learned the alphabet. And given these classes of
18 manufacturing systems, let's look at what our
19 manufacturing system looks like as we go to the rest
20 of the talk and move forward.

21 The third piece of vocabulary is the word
22 capability. I'm going to define given the frame that

1 pharmaceuticals is a social capability to have
2 manufacturing capability to be defined consistent with
3 that frame. Manufacturing capability is the ratio of
4 the voice of the customer to the voice of the process.

5 And we, as a society, have focused on how
6 much, what is important to us in terms of one, the
7 patient who says what is important to him is safety,
8 efficacy, and availability, the regulator who we as a
9 society decided that their role is to assure that
10 safety, efficacy, and availability, the head of that
11 operation who only wants to do better because that's
12 how his job is really about, the CEO who focuses on
13 not only the effectiveness, that is he wants all of
14 these customers to get what they want but he also
15 wants to do that with an efficient allocation of
16 resources, and the scientist in all of us, not just
17 the academic who simply wants to understand because
18 that's just the reason why he exists.

19 And so we have a hierarchy of customers,
20 each of which has a voice. And we as a society
21 decides which of these voices will be heard and we
22 invest. And we make the investment.

1 What shows up after many, many years, is
2 the voice of the process. That simply said, this is
3 what you've invested. This is what the society is
4 giving you back in terms of its inherent variability
5 of its process.

6 That then is the manufacturing capability
7 in the world, in the United States, in our group of
8 industries, in our segments of industries.

9 With those three pieces of vocabulary,
10 which is manufacturing science, manufacturing system,
11 and manufacturing capability, let's now define where
12 you want to be in the context of this desired state
13 that we heard five or six times on the previous slides
14 earlier today.

15 What did we say the desired state was? We
16 saw the FDA desired state. And we had the industry
17 come up and say you can put industry here. We want
18 the same thing. What is that same thing? That same
19 thing is that we give the customer what he wants with
20 a deep amount of understanding in our designs to make
21 sure he always gets it. So we're not even worried
22 about him any more at the bottom of the pyramid.

1 It says we understand the mechanistic
2 basis why something happens and we try to understand
3 the first principles of that knowledge. You can argue
4 that this is an unreachable state. We're still trying
5 to find out first principles. We believed in Newton,
6 in Isaac Newton. Here comes all of these new things
7 with nanotechnology that says maybe Newton misled us.
8 But at least he took us so far.

9 So this is an evolving thing. It's about
10 a domain. It's about a set of questions. This is the
11 first principles for pharmaceutical manufacturing as
12 we know it.

13 The desired state is dynamic. That is we
14 want to be at that level in society but we get to that
15 level one product at a time based on the product we're
16 making now. And that's the development process and
17 that's the continuous improvement process.

18 Strategically, you'd like to have society
19 have laid the foundation of that knowledge so that you
20 already start with the generic mechanistic
21 understanding, understand the basic causal variables.
22 You adapt it to your own new drug.

1 You're already starting so high and then
2 you do a little bit of development here and then
3 you're at that level. You should have no supplements
4 to file. That's the design space that you saw in the
5 earlier presentation from Ajaz.

6 The other alternative is to say society
7 has laid all of that foundation great but I'm not
8 going to invest in going too high too far ahead of
9 time because this is enough to ensure safety and
10 efficacy.

11 I am going to work with my commercial
12 plant and I'm going to continue to improve. Because
13 the basic foundations are in place, I may or may not
14 have to make any submissions even in this case because
15 the foundation of mechanistic knowledge is available
16 in the greater social structure.

17 That's where we'd like to be. If you
18 translate that's where we'd like to be from a
19 knowledge point of view into what do we want our
20 manufacturing system to be, I'd like to argue that
21 we'd like to have much simpler processes.

22 Today, much of our processes look like

1 System B. What we'd like is processes that have few
2 steps. They have a lot of automated control. And
3 maybe we won't even have to do the final product
4 release testing if we've laid the foundation of
5 knowledge that has been institutionalized into our
6 system and shows up in our capability.

7 The current state, however, seems to
8 reflect -- at some point this is personal opinion, of
9 course, that the level of our knowledge in
10 pharmaceutical engineering is at a basically
11 correlative and descriptive level.

12 It's a consequence of the broader social
13 investment in it that shows up in academia and,
14 therefore, in research, and a greater industrial
15 investment and a customer prioritization about what he
16 wants in a pharmaceutical and its regulation and what
17 he thinks the FDA should do if it needs to exist in
18 the first place.

19 Given this is where we are from a
20 knowledge point of view, what is the dynamics of that
21 knowledge? The dynamics of that knowledge is we stay
22 at that level of knowledge and we stay at that level

1 of knowledge from the beginning to the end. So this
2 is what I call a social structure that has a learning
3 disability.

4 And we need to overcome this learning
5 disability by saying from a system point of view, this
6 is what our system looks like. We have a system where
7 the causes are far away from the effects. And we
8 can't correlate them. And so we can't get to
9 causality and so we can't climb this family of
10 manufacturing systems.

11 We spend 25 days testing here. And we
12 have a cause organization that is separate from it.
13 We need to transform this system which is the result
14 of social decisions made in the past.

15 What is that transformation about? It's
16 about two choices which really are about when you do
17 that transformation. You could do that transformation
18 in development, which is the strategic leverage, which
19 is learning before doing. You do all this
20 improvement, change your manufacturing system to be E
21 or D during development.

22 Or simply the other alternative is to do

1 that during commercial manufacturing if we've laid a
2 body of knowledge already in place, you might still be
3 able to do that.

4 But what shall we do today when we haven't
5 laid that body of knowledge in place? And our
6 processes look like this. And we all agree on the
7 desired state that we want to look like this. What
8 are the leverages that make us go from this
9 unsatisfactory position to here? And you saw Ajaz
10 present the benefits of getting to this higher state.

11 That is how are we going to all work
12 together during manufacturing or during development
13 given this body of knowledge to climb up this
14 portfolio of manufacturing systems? Why is it
15 important to do? One of the leverages -- and I'll
16 take one leverage.

17 In this case, I'm going to choose the
18 tactical leverage instead of the strategic leverage,
19 which, I think, you've heard a lot about in the
20 morning. Let me talk about the tactical leverage.

21 That is let's climb this set of
22 manufacturing systems during manufacturing if we can.

1 Why is this important? A number of pharmaceutical
2 companies have warning letters. And what is the most
3 cited component of these warning letters over the last
4 few years? It's about the quality. It's about
5 investigations of the broader quality system.

6 Let's think about an investigation around
7 some real data. Here is the solution. And as a
8 broader social structure, you have to first ask the
9 question is this a critical quality variable? If we
10 had asked this question and socially invested in the
11 answering of this question, I would have either had
12 yes here for this graph or I wouldn't have a graph
13 because we wouldn't have this variable.

14 But because we didn't answer this question
15 over the last 25 years, I have this graph. And I have
16 this question on the graph. First question.

17 Second, because I'm not even sure about
18 this, the next question that remains, what is its
19 specification? If this and this had been laid in
20 place ahead of time, I wouldn't even have to show them
21 on this graph. So let's put them out because they are
22 strategic leverage questions.

1 Let's ask the tactical leverage question.
2 The tactical leverage to climb up the pyramid, not the
3 question that's about releasing a batch. I'm not
4 asking the question should you release a batch. The
5 answer to that in today's vocabulary is easy.

6 I'm asking the question if we are going to
7 use knowledge as a basis for changing the way
8 regulation is done in our social structure because we
9 can't pay the price for it, we've got to climb up the
10 knowledge pyramid and here are the questions we have
11 to answer for ourselves to be able to climb that
12 knowledge pyramid.

13 First, are these data representative of
14 the underlying reality? Is this the solution really
15 the dissolution of the one million capsules it's meant
16 to represent?

17 As part of that, there's a sampling
18 question but it's also a measurement question that
19 Ajaz talked about. Is that measurement an appropriate
20 measurement of dissolution and the way it was done?
21 So this is a sampling and testing measurement.

22 Two, have I seen this before? Learning

1 disability is about seeing the same thing and giving
2 the same reaction and not able to separate that you
3 haven't understood and prevented it. That's a
4 knowledge management question. That's about have I
5 seen it before? Can I go back to a past answer?

6 What is this variation? Is this somehow
7 inherently different from all of this variation? Or
8 is this simply a little bit of variation put together
9 showing up in a general pattern that regresses that?
10 Is this a special cause? Or is this just natural or
11 common cause or normal cause?

12 This is the whole basis of SPC and
13 Shewhart's theory where he spent many, many decades of
14 his life teaching us about how to answer these
15 questions and how to ask these questions.

16 Is this process capable? Capable of
17 meeting which customer's needs? The patient's needs?
18 The regulator's needs? The head of manufacturing who
19 simply want to do better? The scientist's needs who
20 want to understand why?

21 And then have we put in a place an
22 effective, corrective, and preventative action here so

1 that this doesn't happen here?

2 If we're going to use a knowledge-based
3 and science-based approach to manufacturing in the
4 future, then answering each of these questions should
5 be a piece of science just list each of the clinical
6 trials and their publications are pieces of science.
7 That is if we are to climb that pyramid, it should be
8 based on building blocks that have significant
9 scientific quality.

10 Small scientific studies about sampling
11 and testing not for release but for process
12 understanding. How much you sample and what should be
13 your measurement technology to climb that pyramid?
14 And you are going to come up with very different
15 questions when you're asking the climb the pyramid
16 question versus release question.

17 How do I know? What is the body of
18 knowledge? What is the scientific study that I have
19 to put in place to say this is special cause
20 variability versus common cause variability?

21 What is the basic building block of
22 science in this overall pyramid that allows me to put

1 in place effective, corrective, and preventative
2 action that makes me climb up to System E so I don't
3 see that again.

4 And the bigger questions that I put in a
5 different color are how do we answer and put pieces of
6 science ahead of time in the development context?
7 Investigations, small leverage in manufacturing. And
8 that's 90 percent of our products today. We must
9 focus on the strategic leverage one part at a time.

10 But the opportunity in manufacturing is to
11 build these blocks of science around investigations,
12 around technology transfer, around process
13 characterization. And this is the basis on which we
14 get regulatory relief. But beyond that, satisfy the
15 higher customers in our overall social capability
16 structure.

17 This is one way of climbing up this family
18 of manufacturing systems and reaching one that is much
19 more independent of the broader social structure, much
20 more independent of the operators as this is highly
21 automated.

22 And that is the basis for completely

1 eliminating any of those warning letters or even
2 having to see the investigator because no one want to
3 really see him.

4 Implications of the vocabulary and the
5 leverages are first the vocabulary provides a positive
6 position. It doesn't matter what word you use but if
7 you use the word science, the customer likes it, the
8 regulator likes it, the patient loves it, the
9 government likes it, maybe NSF doesn't like it in some
10 cases. They all like it. It's a positive word. And
11 so is capability.

12 It's an enabling vocabulary because it's
13 something that's so general. And we all like good
14 science. And it's all about a broader community of
15 understanding that I think it is the basis of
16 collaboration among all these four stakeholders. To
17 work together for this broader social structure of
18 understanding.

19 Three, it's a basis for a very different
20 relationship with the regulators. If you think about
21 academia as saying let me start with some general
22 glass beads instead of reality and try to understand

1 if I can explain reality that is starting with first
2 principles and trying to see if they explain any data
3 and really industry that starts with today's data and
4 try to understand it better.

5 Causal knowledge in the middle is the
6 middle of the top down and the bottom up strategy that
7 says let's look at using some of these research
8 exemptions and these safe harbors that are put in
9 place in the PAT guidance to really work together
10 between the regulator and the regulated to truly
11 understand the root causes in these investigations
12 including bringing in new measurements to do that.

13 In doing so, that would lay the foundation
14 to climbing up the pyramid and making of the regulator
15 quite irrelevant. But while doing so, this is the
16 opportunity and the guidance is an opportunity to
17 start going deeper than today's root causes.

18 And guess what? That fits perfectly, that
19 vocabulary fits perfectly with the current momentum
20 around the FDA, cGMP in the 21st century. The
21 critical path takes it further as well.

22 Not only is this one of the components of

1 their four-pronged components for the 21st century,
2 but it is the fundamental basis for risk. Risk
3 analysis is a scientific process. It is a fundamental
4 process through manufacturing system for modern
5 quality management techniques and science.

6 And you heard the Q8 and the Q9
7 discussion. What did they say? They said we can get
8 this a lot more harmonized. This is a lot more
9 difficult to harmonize.

10 Remember what Fred said? Science is the
11 underlying theme that is also going to be the more
12 powerful framework in which to harmonize because of
13 the very reason that everybody has a positive,
14 enabling view about it. And this is a very powerful
15 foundation that the FDA has laid.

16 Five, science is a basis for the
17 collaboration among competitors. It's very difficult
18 to climb that pyramid in development when you are in
19 a hurry to push out a product. You are always going
20 to hear every company say that.

21 What is missing in that conclusion is the
22 presumption that you can't learn from all your past

1 products and you can't learn from all the other
2 companies that do the same set of things again and
3 again. That is can you learn through science and
4 publications about excipients that are more than 50
5 percent of your products that you all share?

6 Could you learn from the fact that you've
7 been doing this for 12 years in a row? And can you
8 capture that knowledge which is your priors?

9 Science to collect to your past and to
10 collect with your competitors to get out of that
11 dysfunction that says I only have a year so I can't
12 move up the pyramid. You only have a year in the
13 boundary that you've drawn for yourself.

14 And finally, science is about going into
15 the very process that gives us all the rewards that we
16 want as regulators. It is the benefit. It is the
17 fastest way to generate the products that we need. It
18 is the basis for true process understanding, for the
19 academics, for the regulators, and the broader CEO to
20 ultimately get back his economic rewards as well.

21 Those economic rewards lay the foundation
22 for enhanced manufacturing capability that allows all

1 of the different stakeholders to achieve all their
2 needs, that is the voices of the different customers,
3 and lays the foundation as a social structure for a
4 complete reversal of where we spend resources.

5 If you go back to the last 25 years and
6 you look at where we, as a society, are spending
7 resources in terms of QC and QA and regulatory people,
8 and the FDA, and the investigators, you could say
9 maybe the qualitative direction is clear. Maybe the
10 units are tough to figure out. This is clearly on the
11 wrong track.

12 And when we design it then, which is
13 quality by design, let's spend the next 25 years
14 reversing back, go back to the same basic level so
15 that all these resources, including the industry, can
16 focus on bringing in new products.

17 The next steps for the next 25 years,
18 given that the cGMP initiative is coming to its two-
19 year cycle and an end in a month that is based on many
20 years of history before that, first is to broaden the
21 shared vision. We saw the FDA put us a vision. We
22 had the industry come back and say I agree with that

1 vision.

2 We can now connect this vision to the
3 CEOs. If this is a social capability, how are we
4 going to bring them into this? With the government,
5 which might impact decisions about funding, for
6 example, a long-term social map.

7 At this time, we have good intentions.
8 We're beginning to have a common vocabulary. The PAT
9 guidance is a guidance but we need much more of a map
10 into the future. A lot more of science and knowledge
11 has to be characterized. And the implications are
12 there in terms of benefits, rewards.

13 And what do I do next has to be clarified
14 over the next few years in the real economic case.
15 And I believe that could be the basis to broaden the
16 shared vision and maybe get funding at a social level
17 for some of this research that is badly needed and has
18 been for a while.

19 Something that came up earlier today, we
20 need some real case studies. In terms of the PAT
21 submissions that are coming, they're still let me just
22 test the waters, in my opinion, however little I know

1 about it. Let's do something real now that we've
2 trusted each other and we've learned to trust so that
3 we can really turn things around in the next 25 years.

4 Besides case studies of real data and the
5 fact that I presented those slides to you shows that
6 I'm willing to go as far as I can but I'm not somebody
7 who generates these data and they can go further than
8 me.

9 Pilot the future. Just like you have a
10 new Medicare, a Medicaid program that's piloted in a
11 state before you push it out to a broader society,
12 pilot something about this science-based
13 manufacturing, knowledge-based manufacturing into the
14 future where nobody loses. It's a fish bowl for the
15 broader society.

16 And I know a number of academics who would
17 probably play a lead role in that. And I've thought
18 about it as well.

19 Acknowledgments, of course, I must start
20 by acknowledging the Consortium for the Advancement of
21 Manufacturing that has funded a lot of my research.
22 MIT and Purdue, Ken Morris is here. I stand on big

1 shoulders which Charlie and Steve as well. And Janet,
2 Helen, and Ajaz, who have been an unbelievable help
3 for society. And I've really benefitted from all.

4 And if you just look at this list, you can
5 see that it has got industry, academia, and
6 regulatory. You can't do it without all four of those
7 -- did I count -- I missed one. I didn't work enough
8 with the customers, I think, because I am one.

9 Bottom line, to end, I introduced a frame
10 that said it's a social capability. And what we see
11 today is the result of the social choices, of all of
12 us together equally responsible for the good and bad.

13 I said science, system, and vocabulary are
14 three words that we can all share to describe the
15 desired state and the current state. Given that we
16 seem to agree on the desired state and we seem to
17 agree that the current state is not satisfactory, we
18 had to then talk about leverages to go from here to
19 there.

20 I took one case, a very tactical case, and
21 a strategic case would be actually a much more
22 powerful story, and let's say investigations is one of

1 them. And you could take technology, transport, you
2 could take characterization. Let's build a body of
3 science around it, science of processes to climb up
4 the pyramid.

5 What are the implications? And what are
6 the next steps? And, of course, thank you to all
7 those who have helped me along the way.

8 That's my talk.

9 (Applause.)

10 CHAIR BOEHLERT: Thank you, G.K.

11 Are there any questions or comments from
12 members of the Committee? Yes, Kenneth?

13 MEMBER MORRIS: G.K., as the sort of
14 keeper of the statistics in general, are there any
15 estimates of the number of non-value-added tests, real
16 or perceived, that we do in the course of releasing
17 material?

18 MEMBER RAJU: First, tests are non-value
19 added.

20 MEMBER MORRIS: Right.

21 MEMBER RAJU: If they're designed in, you
22 don't have to do the tests. So that's the amazing

1 part. Even if you count the tests as value added, by
2 most computations in the literature, about five
3 percent on a time basis is value added in our
4 industry. Ninety-five percent is non-value added in
5 all the paperwork and all the waiting time because we
6 haven't designed in the quality. And that's because
7 of our social investment or the lack of it.

8 There would be a time when the number
9 would grow if you include testing but let's not even
10 go there. Let's go over the body of knowledge that we
11 have to put in place. And we deal with the
12 consequences but maybe we said I'd rather fund
13 genomics than this. And we deal with the consequences
14 of making that choice.

15 CHAIR BOEHLERT: Any other comments?
16 Questions?

17 (No response.)

18 CHAIR BOEHLERT: If not, thanks, G.K. for
19 a job well done.

20 MEMBER RAJU: Sure.

21 (Applause.)

22 CHAIR BOEHLERT: We have a speaker with

1 two ovations so I don't know what that means.

2 (Laughter.)

3 CHAIR BOEHLERT: You know the next topic
4 is risk-based CMC review and we're going to look at it
5 from two perspectives, the Office of new Drug
6 Chemistry and the Office of Generic Drugs. And first
7 Moheb Nasr will be speaking on the ONDC perspective.

8 DR. NASR: Good afternoon. Can you hear
9 me okay? Can you hear me now?

10 (Laughter.)

11 DR. NASR: I don't know why I'm hear.

12 (Laughter.)

13 DR. NASR: I think we'll find out
14 collectively. I think many presentations were made
15 this morning that very much convey why we are here.
16 I think we talked about the principles behind Q8 and
17 Q9. Ajaz articulated his vision of the desired state.

18 And G.K. did his always wonderful job even
19 though he did something I asked him not to do and that
20 is his insistence in using pyramids. I think being an
21 Egyptian, I'm entitled to use of pyramids but G.K.
22 always uses pyramids.

1 What I would like to do today is to share
2 with you where we are and where we are heading. What
3 I'm sharing with you is a roadmap into the future.
4 Without any exaggeration, I think we are changing the
5 paradigm of how to assist quality of pharmaceuticals
6 in the U.S. and in the world.

7 I'm going to share with you where we are,
8 why we are changing, some of the high-level thoughts,
9 and by the end of my presentation and Gary Buehler's
10 presentation, our combined effort, hopefully we'll
11 illustrate to you where the Agency is heading. And
12 then we can open the floor for discussion and seek
13 your input.

14 I will appreciate hearing from you all
15 after my presentation because we are working at a very
16 fast pace in order to make this change happen. And we
17 would like to make this happen in a matter of weeks
18 and months, not years and so forth.

19 These are the topics that I will try to
20 cover within 25 minutes but Gary and I have an hour so
21 I may use a little more time, Gary.

22 I would like to share with you where we

1 are. I would like to update you on what we had
2 before, which we called the CMC risk-based approach or
3 initiative. I want to tell you that we are changing
4 from chemistry review into a new quality assessment
5 paradigm and describe to you what I mean by that.

6 I would like to summarize in a few slides
7 the difference that I see between chemistry review and
8 the quality assessment. And I would like to share
9 with you some of our pilot programs and supplement
10 review and so forth.

11 CMC review, as we all know, is intended to
12 assure the identity, purity, quality, and strength, an
13 potency as related to safety and efficacy for drugs
14 throughout their life cycle from IND to NDA, most of
15 all through the ANDA process.

16 This is an organization chart of ONDC.
17 You see how simple it is. We have about 130, 135
18 review chemists and scientists spread out through 19
19 chemistry teams co-located in 15 clinical divisions.
20 It's very difficult to manage such an organization.
21 We are not managing well.

22 I hope in the future when I come next

1 time, if Ajaz invites me, to share with you our new
2 organization and how it will not only compliment the
3 future product assessment but manage the losses within
4 the agencies much better than it's being managed
5 today.

6 This illustrates how much work we do in
7 the office. The in the last fiscal year, we reviewed
8 159 NDAs. We had close to 1,000 INDs. We had about
9 2,000 supplements. That's a lot of work. And if
10 continuing in that direction, we are going through a
11 viscous cycle for when every time we approve a drug,
12 the number of the supplements increase, our workload
13 increases, and we create a problem not only for
14 ourselves but for efficacy in the public as well. And
15 there is a crying need for a change.

16 To summarize our current CMC review
17 practices, when it comes to the application that we
18 receive, the quality of this application varies
19 considerably. Some are much better than others.

20 The applicants don't always seek
21 consultation and meetings through the review process
22 or follow some of the recommendations that we make and

1 agreements we make during the review process and
2 during the submission.

3 And sometimes they have, sometimes they
4 don't have, but in many cases they do not provide
5 enough pharmaceutical development information that I
6 consider to be essential in order for us to do what we
7 call risk-based CMC review.

8 What about our review? We evaluate all
9 CMC information and data that comes in the application
10 without doing too much as far as differentiating
11 between what is critical and what is less critical.

12 We evaluate all the information that comes
13 to us. And that evaluation does not necessarily
14 utilize the vested training and background of our
15 reviewers. Basically we have one CMC reviewer, for
16 most part a chemist, who conduct the entire
17 evaluation.

18 And if you don't have enough knowledge,
19 they try to do the best they can. They are trained
20 while they are doing the review. And there is good
21 mentorship throughout the process. It's a value list-
22 based review. I think someone today called it a

1 check-list review. It's not really a check-list but
2 it's a value list-based review.

3 We don't do enough in-depth review of
4 process information and that's in part not totally
5 because of the center field agreement. We have tight
6 specification, I have to admit to that. But the
7 specifications are set based on the limited data we
8 receive.

9 This is the information we get, and based
10 on that information, we set the specification with our
11 goal is to assure that consistency of manufacturing
12 process. So basically the specification is a way to
13 control the manufacturing process.

14 Often we have late and voluminous CMC
15 amendments that lead to delay in review. And as you
16 all know, we have problems with the cycle of review
17 and approval.

18 The decisions are made based on submitted
19 data and the individual experience. There is a lack
20 of critical information pharmaceutical development.
21 Guidances, for the most part, are established to
22 provide regulatory relief but at times create an

1 increased number of supplements and that creates
2 problems for us at the agency and for industry as
3 well.

4 What are the problems with the current
5 system? For us at the agency, it is very resource
6 intensive. You have seen our organization chart and
7 you see the workload. We have to deal with recalls
8 and drug shortages at times.

9 For you all in the industry, there's a
10 perception that because of the existing regulatory
11 system, it discourages continuous improvement.
12 Regulatory burden, what's the value of all the
13 supplements and all the review we do? And what is the
14 consequences of being out of specification that
15 require investigation, recalls, 483s, warning letters,
16 and so forth.

17 What about the public? High cost drugs
18 maybe and delay in drug approval at times.

19 In the middle of this, with all what we
20 are doing, with all the problems, we are facing some
21 major challenges. In trying to outline these
22 challenges in this slide here, we have the GMP

1 initiative which, I think, many of us agree is really
2 a product quality initiative for the 21st century.

3 How can we fit the existing regulatory
4 system into the new way? How can we do that? There
5 is a conflict. How to deal with first cycle approval?
6 The heavy workload. How can we address the
7 consistency issues and problems and difficulties that
8 exist among the 19 chemistry teams in 15 clinical
9 divisions?

10 We are attempting to do that through the
11 guidance process. It helped some but created
12 different kind of problems.

13 We have problems with the guidance and
14 policy development. There is a lack of expertise in
15 many critical CMC areas, many sites of pharmaceutical
16 development. We are dealing with novel, new delivery
17 systems, combination drug products, new technologies.

18 Because of all these, what we have done
19 before and attempted to do it with some success is
20 react rather than have a proactive proposal of how to
21 deal with issues in the future.

22 I want to spend a couple of minutes

1 talking to you about the standards of the risk-based
2 CMC initiative that started in the year 2000 and went
3 on until last year when I came here to this shop.
4 That initiative was evolved over many years.

5 It's multi-tiered. If you look at the
6 initiative, it was outlined as a three-tiered process.
7 When everything was said and done, it was a five- or
8 six-tiered because every tier split into two sub-
9 tiers. We would start with Tier 1A and talk about
10 three years. So if you go through the five-tier
11 process, it would have taken us many, many years.
12 That's okay.

13 The whole initiative was product specific.
14 It addresses and deals only with what we are very
15 comfortable with and that's mainly synthetic drug
16 substances. Characterization must be done using
17 traditional analytical techniques that you can clearly
18 see. It applies only to very specific products such
19 as immediate release or dosage and so forth.

20 That initiative was intended to provide
21 regulatory relief by incorporating science-based and
22 risk-based assessment in CMC review. But one thing

1 that became obvious with the GMP initiative is the
2 relevance of that initiative with our new product.

3 This is something that we have to deal
4 with only for a small class of drugs and in very
5 special cases or if there is some merits for better
6 utilization of science- and risk-based to apply that
7 for everything we do, from that pre-marketing into the
8 post-marketing.

9 So now we are dealing with more
10 progressive and expanded initiative that was focus on
11 the totality of quality assessment. The risk-based
12 quality assessment has a variety of advantages. And
13 what I have done in these two slides is summarize some
14 of the excellent findings that were obtained after the
15 PQRI Conference about a year ago. The PQRI Conference
16 that Toby Massa co-chaired.

17 The benefits of the policy assessment risk
18 is the quality assessment for the patient for the
19 increased availability, faster approval, and the
20 patient will continue to receive our quality products.
21 So we are not going to sacrifice the product by --
22 that may result from a reduction of regulatory

1 oversight. It's basically more focused on our
2 regulatory process rather than reducing regulatory
3 focus.

4 For us at the Agency, there will be more
5 product and process knowledge that is shared by
6 industry, more efficient resource allocation,
7 increased trust and better communication. And for
8 industry, there will be more efficient science-based
9 inspection, faster -- and you will hear more about
10 that. I think David Horowitz will talk to you all
11 tomorrow about the new paradigm in GMP inspection.

12 There will be faster, more consistent
13 review, a potential for reduced regulatory burden,
14 ability for you to manage the changes without very
15 strict regulatory oversight from the Agency, focus our
16 resources on critical issues, flexibility to focus on
17 what should be done not what can be done, improved
18 communication with the Agency.

19 And I think that the striking element of
20 what we are trying to do today is if you look in the
21 past, the Agency changes regulation. The industry we
22 had. The industry raises the bar because of new

1 delivery system and newer technology. The Agency
2 react. But in this new paradigm, we are working
3 together in order to head in the right direction.

4 When we talk about the new quality
5 assessment paradigm, I would like to make clear to
6 everyone here today that this is not a single
7 initiative to address one dimension of a multi-
8 dimensional, often complex quality assessment process.
9 This is not a streamlining effort.

10 It's a new paradigm of quality assessment
11 for new drug applications. And Gary will share with
12 you his thoughts about generic drug applications as
13 well. But that covers for the new drugs the entire or
14 the totality of quality assessment from pre- to post-
15 marketing activities.

16 With that we have to change our vision and
17 our mission. And that is part of where we are heading
18 with our new organization. I'm going to focus here on
19 a couple of things because I think -- I do believe
20 that the vision and the mission should clearly
21 indicate to us, to our staff and to the public, where
22 we are heading.

1 Our new vision indicates very clearly that
2 this is a scientific organization that services the
3 center, the Agency, and the public through leadership
4 and innovation and international collaboration. I do
5 believe in international collaboration. I do realize
6 that we are dealing with global industry. And our
7 efforts here have to be done under the umbrella of
8 harmonization with other international agencies.

9 As far as our mission, we no longer
10 continue to do chemistry. What we will be doing is
11 for our office to assist the critical quality
12 attributes of manufacturing processes for new drugs,
13 establish what is the standards to assure safety and
14 efficacy and -- and that's very critical here and
15 that's why we need to work together to be a partner to
16 facilitate drug development.

17 Some of the future elements that we need
18 to work on and we started working on our assessment
19 will start with a comprehensive quality overall
20 summary. And I think you had some questions and some
21 comments about that this morning. And that is
22 something that we need to work on.

1 Review practices should be based on good
2 scientific principles. There will be considerable
3 increase in emphasis on manufacturing science. The
4 CMC review and the quality assessment functions we do
5 will be critically reviewed by our colleagues and
6 staff and scientists at the Agency. And we must
7 integrate our review functions with the inspection.
8 And that goes under the umbrella of Q8, !9, and
9 potentially Q10.

10 When it comes to CMC's specification and
11 there will be another time for a larger group for
12 another discussion about how we set the specification
13 and why we set it and how it should be set but the
14 main principles are specification has to be risk-based
15 -- based on risk-based assessment, clinical relevance,
16 safety considerations, process capability, knowledge
17 gained from pharmaceutical development reports, and
18 better utilization of modern statistical
19 methodologies.

20 There is such a thing as regulatory
21 relief. Such relief will be provided based on the
22 following three criteria.

1 One is process understanding and control.
2 And that what you can share with us through the
3 pharmaceutical development reports, assessment
4 throughout the manufacturing process, and your
5 ability, because of your understanding of your
6 process, and your plans to continue to improve the
7 process. So these are three criteria that has to be
8 there in combination in order to provide an assurance
9 of your ability to continue to improve the process.
10 One of these elements by itself is insufficient.

11 Pharmaceutical development reports may
12 facilitate meeting for a cycle approval, science-based
13 specifications, risk-based GMP inspection and
14 regulatory relief from post-approval activities.

15 What we do at the Agency is done by
16 people, not by machines and computers only. And
17 that's why it's very important that we invest in our
18 staff and provide the correct work environment and
19 resources to support our staff. So it's very
20 important for us to provide better work environment to
21 our staff to facilitate superior performance and job
22 satisfaction.

1 During the CMC restructure, we are in the
2 process of reorganizing the office. The
3 reorganization is intended to facilitate the
4 implementation of the new quality assessment paradigm.
5 What I'm saying is we are not moving 15 or 19 offices
6 from one place and put them in another place. The
7 organization will be there for one purpose and that is
8 to facilitate the new paradigm and to facilitate the
9 implementation of the new quality assessment.

10 I may come back to you later on on this
11 one but I just want to give you heads up. We are
12 considering establishing a CMC Scientific Advisory
13 Board and some of the functions of this Board would be
14 to provide scientific consultation when needed.

15 There is no way we will have enough
16 expertise in house to address every regulatory or
17 scientific issue we deal with. The Board will oversee
18 the ONDC regulatory research program, restructure and
19 modernize the ONDC training program, and also develop
20 regulatory science seminars.

21 We are in the process of recruiting and
22 hiring and training pharmaceutical quality assessors

1 with expertise in drug discovery, analytical
2 chemistry, pharmaceutical development formulation, and
3 pharmaceutical engineering. I think there are so many
4 people here in this room, if you know of anyone whose
5 is looking for a challenging opportunity, I'm all
6 ears.

7 (Laughter.)

8 DR. NASR: We have several vacancies both
9 in the review side, on the technical side, and in
10 management as well. And I'm serious of inviting you
11 to help us help yourself by sharing some of the talent
12 that is out there that we need in the Agency.

13 ONDC is building a strong and independent
14 scientific organization to better serve the public and
15 our internal stakeholders. And if you see where we
16 are today, we are co-located with the 15 clinical
17 divisions.

18 Linkage with clinical division is very
19 important but it is one of many linkages that must be
20 there in order to assure appropriate quality
21 assessment. So we will maintain the linkage with our
22 clinical colleagues but we will have to work closely

1 with our colleagues in the Office of Compliance and
2 the Office of Generic Drug as well. And with industry
3 and other scientific organizations.

4 Our re-engineering effort is intended to
5 work on problems that have been identified in order to
6 meet expectations and to establish a modern equality
7 with appropriate metrics to measure the quality of CMC
8 review and performance.

9 This is very important here and we are
10 working very hard to do that. It's very easy to have
11 metrics to count beans, how many reviews, how many
12 supplements, how long it takes you to do that. But we
13 need to identify the appropriate metrics to measure
14 the quality of the work we do and that input of our
15 review into drug development. This is something we
16 need to work on.

17 Before I go to these two slides, I'd like
18 to remind you all that we have a very large quota of
19 competent, dedicated, hard-working scientists. But
20 what I'm sharing with you today does not necessarily
21 indicate in a negative way that our organization is
22 not functioning well. But we are shifting our

1 paradigm.

2 So I want to describe to you where we are
3 today and where we are heading. And I think I can
4 best describe that in these two slides.

5 Here is what we do today. What we do is
6 chemistry review. This is not something -- I've used
7 a term that I intended that everyone is using that
8 term around the agency. The review is conducted by
9 chemists. There is extensive data analysis in order
10 to generate the necessary knowledge and summary
11 reports of CMC issues. That's what we do.

12 We get a lot of raw data, stability data,
13 validation data. We use -- we review everything that
14 is submitted to us. And generate summaries in order
15 to be able to have a story to tell about the product
16 itself.

17 One would question is it us who should be
18 developing this story or is it the industry or the
19 sponsor who developed the product that they can come
20 and tell us their story?

21 It's a guidance-based review. There is
22 more focus on chemistry and specification issues and

1 there is less focus on process and manufacturing.
2 There is no clear emphasis on what we consider to be
3 critical CMC issues. We do not have a peer review
4 process to evaluate the quality of the work we do at
5 the center or in the office.

6 Quality assessment is a very different
7 thing, assessments conducted by interdisciplinary
8 scientists, chemists, pharmacists, engineers, and
9 others as needed. There is more reliance on knowledge
10 provided by advocates and that includes pharmaceutical
11 development report and comprehensive quality overall
12 summary.

13 It's a risk-based assessment. It's not
14 everything. Focus on critical quality attributes and
15 developments to safety and efficacy and these are some
16 of the critical attributes that we must focus on.
17 It's a question-based review and there is a greater
18 utilization of peer review process.

19 I want to spend the next two slides to
20 briefly summarize where we are with some of these
21 changes we are making. You will hear tomorrow from
22 Steve Moore, a team leader in our office, talking

1 about comparability protocol.

2 I think comparability protocol can serve
3 as a bridge or linkage between the existing system and
4 the new quality assessment paradigm. And that's why
5 it's taken us more time in reviewing the comparability
6 protocol guidance before we put it out because when we
7 put it out, we want to make it more useful and more
8 meaningful and to facilitate the changes that we are
9 all trying to achieve.

10 Comparability protocol utilizes and
11 applies quality by design principles. It should
12 facilitate continuous improvement with risk regulatory
13 oversight from the Agency. It provides scientific
14 basis for expecting, understanding, managing, and
15 addressing changes.

16 It brings more focus of what is critical
17 and what is less critical. It has a great potential
18 for down-regulating CMC supplements. The bottom line
19 is with the workload that I described to you earlier
20 in the first few slides, we can no longer continue to
21 have a quality review of the large volume and that
22 application information we get within the existing

1 system we have.

2 We are exploring ways not only to down-
3 regulate but potentially eliminate certain types of
4 CMC supplements that have many potential to adversary
5 effect on identity, quality, purity, safety, strength,
6 and potency as they relate to safety and efficacy. So
7 we are looking why do we have supplement? What role
8 they serve?

9 ONDC is developing in our new organization
10 ways to manage the supplement review more efficiently
11 to facilitate continuous post-marketing product
12 improvement and to provide more resources for new NDA
13 review. I think if we understand what you are doing
14 and you share with us your understanding, and we'll do
15 that at the pre-marketing stage, we have great
16 confidence in your ability to manage your own change.

17 You can go ahead and manage that. That
18 will provide more resources for us to be more of a
19 partner during drug development.

20 We have a pilot program for resubmitting
21 the NDAs because we have to find ways to reduce the
22 resources and put the resources where they are the

1 most needed where a single CMC reviewer perform
2 initial assessment. Initial assessment is being done
3 in two weeks. And relevant material are requested.

4 An assessment protocol is developed and
5 then assigned to a primary reviewer. A primary
6 reviewer will perform an in-depth assessment as always
7 done.

8 Streamlining of resubmission will provide
9 more resources for our original NDA review. Where I'm
10 coming from is this, if from direct resources and have
11 enough and correct and enhance the level of
12 communication with the sponsors, that may lead to
13 first cycle approval and potentially a decrease of the
14 number of resubmissions.

15 And this slide here, this is my summary
16 slide, this is my last slide, what I have here on the
17 left are some truths. These are truths. We are
18 working on re-engineering supplement review,
19 streamlining our review of resubmissions, talking
20 about quality by design for pharmaceutical development
21 reports, comprehensive quality overall summary.

22 The re-engineering of the supplement will

1 provide less regulatory oversight for post-marketing
2 approval changes and that may lead to more incentives
3 for continuous improvement. The same thing with the
4 other tools. They will provide more resources. They
5 will enable us to do risk-based assessment. And there
6 will be less review time.

7 And all this will lead or may lead to
8 first cycle approval of new drugs. And putting all
9 these things together, what we will end up having is
10 at the end better product available at maybe less
11 cost.

12 I think I missed one slide. My last slide
13 that you didn't see, I would like to acknowledge Dr.
14 Janet Woodcock and the Steering Committee for
15 providing a lot of insight, Helen, Ajaz, Chi-Wan, and
16 Guirag Poochikian for providing considerable input in
17 this presentation.

18 Thank you.

19 (Applause.)

20 CHAIR BOEHLERT: Thank you, Moheb. You
21 have some very ambitious endeavors.

22 Are there any questions or comments?

1 Gerry?

2 MR. MIGLIACCIO: Well, I want to go back
3 to your CMC specifications to be based on, Slide 18.
4 You say clinical relevance and safety considerations,
5 which obviously we all agree on. Then you follow that
6 with process capabilities. Can you elaborate? Those
7 could be mutually exclusive.

8 DR. NASR: I can elaborate but I think
9 there is time that will have to happen very soon,
10 Gerry, where we will need to get together. By we, I
11 mean the Agency, the sponsors, and others as well, to
12 look at the ways we are setting specification.

13 The way that specification are being set
14 now is at times because of process capability, that
15 means if you can produce a product with a certain
16 level of impurity, that would be in the spec --

17 MR. MIGLIACCIO: Right.

18 DR. NASR: -- whether this is justified or
19 not. And even if that's not the spec, what is the
20 detection ability of a particular analytical
21 instrument? We set specification at times because of
22 safety concerns for certain kinds of impurities

1 because of some compendium requirements.

2 What I'm saying or suggesting in this
3 slide that we have to exam all of these things
4 together in order to see how can we set
5 specifications.

6 And what we will end up having at the end
7 of the day in my mind, and this is just me and not the
8 Agency speaking now, so I'm going to take off my FDA
9 hat, is a combination of all this. And it would be
10 more on a product by product basis rather than the
11 more generic level of setting a specification for all
12 products, one size fits all.

13 So, again, I did not answer your question.
14 But I think yes, many of these things are conflicting.
15 And I think that's what you are saying. But we will
16 have to look at all this -- two weeks together and all
17 these issues together to see how we can set
18 specifications in the future.

19 MR. MIGLIACCIO: Well, just a follow on,
20 I mean conflicting yes but a highly capable process
21 has generally very little clinical relevance to slight
22 changes in that process. And that's what the concern

1 is is setting specifications based on process
2 capability. There is no clinical relevance to that.

3 Secondly, at the time that we're setting
4 specifications, you have preliminary process
5 capability. The knowledge base will increase
6 significantly in the first three to six months after
7 commercialization. And so to base anything on
8 preliminary process capability is a concern.

9 DR. NASR: I agree with you. And I'm not
10 talking about specification the way we do it now after
11 the initial review of the NDAs. I think Toby talked
12 this morning about interim specification which, by the
13 way, is something that we do now. It's not that novel
14 of a concept.

15 But what I'm trying to say in this slide
16 that there is a crying need for us to have a handle on
17 setting specification. And to have a specification
18 that are most relevant for that particular product and
19 not use a specification as a tool to control the
20 manufacturing process.

21 I think what we have done before because
22 we didn't know -- we don't know in many cases how you

1 are developing your manufacturing process and you know
2 that, Gerry, you know, the level of information vary
3 from sponsor to sponsor.

4 We try to have an assurance because we
5 have our responsibility to the public that the product
6 that you will produce in the future have the same
7 critical attributes to the product that was used in
8 the clinical trial. And that is by making sure that
9 the level of impurities, for example, are the same.
10 And even if they can be tighter, we tighten that so to
11 make sure that you continue to -- you have better
12 control over your process.

13 Is this the best way to do it? I don't
14 think so. But we will have to put our thoughts
15 together to see how can we set that in the future
16 because what is happening now in some cases is the
17 specifications are too tight and they may not be that
18 relevant to clinical issues to start with.

19 And that may result in disruption of the
20 manufacturing, recalls, need for investigations, and
21 so forth.

22 MR. MIGLIACCIO: Thanks.

1 CHAIR BOEHLERT: It sounds to me like this
2 is a subject we might need to have some continuing
3 discussions on because this whole issue of
4 manufacturing capability versus safety and efficacy is
5 one I think that drives industry a little nuts from
6 time to time.

7 And if you want to reduce the number of
8 supplements, this may be an area that we can take a
9 look at because -- and you mentioned impurities. And
10 it happens to be a subject that is near and dear to my
11 heart.

12 And very often safety has been
13 demonstrated at very much higher levels than are
14 approved as specifications. And if something changes
15 down the road, you shouldn't have to file a supplement
16 if it's well within those limits that have been
17 established as safe as effective.

18 And so I think it's a topic for a
19 continuing discussion and an area we may be able to
20 relieve the regulatory burden.

21 DR. NASR: That's a very good point, Judy.
22 Without stealing the thunder from future events that

1 will be taking place, we are currently working on
2 having a public workshop between the industry, the
3 Agency, academia, and so forth, to focus only on
4 setting specifications.

5 And all the issues I outlined on this
6 slide what comes from analytical methodology, from
7 safety and efficacy, from clinical relevance, from
8 manufacturing, all these things will be raised because
9 I think we need -- if we are talking about the future
10 paradigm and specifications that are more relevant and
11 not one size fits all, there is a need to do that.

12 And we started the elementary discussions
13 to get there.

14 CHAIR BOEHLERT: Okay.

15 Ken?

16 MEMBER MORRIS: Thanks. You know, Moheb,
17 it hadn't occurred to me until I saw it on your slide
18 even though we've talked in general terms about this,
19 but in terms of metrics for determining the quality of
20 the review process in the future, do you have any
21 ideas of what that is going to look like?

22 I hadn't thought of it before you

1 mentioned it but I can see whereas now you can sort of
2 count submissions or something like that, it's going
3 to change in the new system.

4 DR. NASR: I think we started already,
5 Ken. Question-based review, the peer review process
6 that we instituted already. And also we are looking
7 in instituting a quality management system throughout
8 our new organization. Quality assurance program and
9 I also, as I indicated in one of my slides, am
10 considering the establishment of a Scientific Advisory
11 Board.

12 So I think we have several elements but
13 what really needs to be done is to see are these
14 sufficient metrics? Are they quantitative enough? Do
15 we have a map here where we can connect all these dots
16 to have an overall system?

17 Once concept that I've seen that's been
18 used by other regulatory agencies, if you wish, is
19 sharing the review with the sponsor. I mean if we are
20 talking about scientific organization and dialogue
21 between industry and the Agency, how about if we share
22 our assessment, if you wish, and see how we can learn

1 rather than judging the in-depth of the quality, how
2 can we learn from this to do a better job in the
3 future?

4 CHAIR BOEHLERT: Okay.

5 Dan?

6 MEMBER GOLD: Thank you for a very
7 interesting talk. I think you're making a lot of
8 progress.

9 I have a question related to an issue that
10 came up during the last meeting of this Committee
11 where a representative pointed out that in Europe the
12 quality summary is -- it's a top-down approach to the
13 review of the application. And they were pointing out
14 that they thought that in the U.S. it's a bottom-up
15 review. And that your reviewers are really not
16 looking at the quality overall summary.

17 Can you comment on that please?

18 DR. NASR: Yes, I can.

19 I think, as you can see, that's one of the
20 major elements in our future review practices.
21 Because of that, I spent about two and a half weeks in
22 Europe in April because what I've decided to do is to

1 expand my area of knowledge about other regulatory
2 processes that proved to be successful. And I went to
3 visit several national authorities and I participated
4 in advisory Committee discussions and so forth.

5 If you are talking about the expert report
6 which was used in the old system versus quality
7 overall summary which is currently part of the common
8 technical document, I can share with you the
9 following. What I'm talking about goes beyond the
10 existing quality overall summary, which has a very
11 narrow scope.

12 I think we are talking about more expanded
13 quality overall summary that has more pharmaceutical
14 development component into it. That's number one.

15 Such a summary can serve as a summary
16 because part of what we do now in our review is
17 creating the summary. So why don't we have you, as a
18 sponsor, as the one who developed the drug, provide us
19 with such summary?

20 And then the focus of what we do is to be
21 -- is to assist the critical areas that in the
22 application itself.

1 Number three, such a summary will not be
2 the only thing we review but it can be a starting
3 point to highlight what could be critical CMC issues
4 that we expect to see in that particular application.

5 And then we will focus our efforts on
6 critical issues but also since we have the entire
7 submission, we will go and be as detailed as we need
8 to in order to have complete understanding of some of
9 these issues.

10 MEMBER GOLD: So do I understand --

11 DR. NASR: I forgot to add one thing if
12 you allow me. That also may require us revisiting
13 under ICH or under another way of how the submission
14 is put together.

15 MEMBER GOLD: Do I understand you then to
16 say that if we put into -- if we submit a very good
17 quality summary, this is going to accelerate the
18 review of the application and the more rapid approval
19 of the application?

20 DR. NASR: Yes.

21 MEMBER GOLD: All right. One second
22 question if I could? I realize that the initiatives

1 that we're talking about are very new for the Agency.
2 Do you have any metrics that indicate the improvement
3 using these techniques that you have seen so far in
4 terms of reducing application review time?

5 DR. NASR: I have some metrics and I'm
6 doing some experiments. As a scientist we have to
7 continue to do experiments. Some of the knowledge I
8 have is based on my experience talking to our European
9 colleagues. And when I talked to them about
10 utilization of quality overall summary and expert
11 report, it does reduce the review time. That's number
12 one.

13 Number two, we are currently experimenting
14 with resubmission of NDAs in some of the critical CMC
15 review teams within some clinical divisions. And what
16 we are trying to do is to start the assessment
17 process, as I indicated on one of my slides, by a
18 high-level evaluation of the application itself, and
19 development of an assessment protocol in order to --
20 before the assignment is made in order to facilitate
21 the review.

22 That's much better than the current

1 practice where you have the many folders, as you know,
2 Dan, and you go through the entire review before you
3 develop the entire story.

4 I think having a quality overall summary
5 will facilitate the development of the initial
6 assessment protocol, if you wish.

7 MEMBER GOLD: Thank you.

8 CHAIR BOEHLERT: Any other questions or
9 comments?

10 (No response.)

11 CHAIR BOEHLERT: If not, Moheb, thank you.

12 DR. NASR: Thank you.

13 CHAIR BOEHLERT: From the Office of
14 Generic Drugs perspective, we have Gary Buehler.

15 DR. BUEHLER: Thank you, Judy.

16 First I'd like to thank Ken. Usually I'm
17 last to speak at just about everything I go to and
18 somehow I don't know what you did to someone, Ken, but
19 thank you very much.

20 (Laughter.)

21 DR. BUEHLER: It's really nice to not be
22 last. I was last at the GPHA meeting in the

1 wintertime. And I was right before the golf
2 tournament.

3 And I started to speak and I heard all
4 these cleats outside and everything. People were
5 banging their bags around and everything. So it's
6 very nice to have a nice quiet group here.

7 I'd like to acknowledge Dr. Berridge's
8 presentation. I have to say, Dr. Berridge, that was
9 the clearest explanation of this paradigm I've ever
10 seen. I mean it was -- your slides were great.

11 And actually I may be calling you for some
12 of them. After you see my slides, you'll understand
13 but it was really a very clear explanation of what
14 we're trying to tell people today.

15 And I have to admit there is a fair amount
16 of repetition here. And I'm not going to be an
17 exception.

18 Also I have to say your English accent is
19 great. You know I am from Philadelphia. I'm a
20 Colonist. I haven't lived there for 30 years but
21 people still say I talk like a Philadelphian. And
22 it's just so authoritarian. I'm hoping to be able to

1 do this in that way.

2 Acknowledgments, I have to say that a lot
3 of my talk was furnished by Frank Holcombe and Vilayt
4 Sayeed. They're in the audience today so if I say
5 anything wrong, there they are.

6 Our mission is really very simple. It is
7 to provide quality, safe, effective generic drug
8 products to the American public. I'm a nuts and bolts
9 guy. This is what I have to do. And it basically is
10 we have to review and approve applications.

11 We almost approved 400 applications last
12 year. That's what I do. And, you know, this is a
13 vision. This is a vision for the future. And believe
14 me we are fully supportive of this vision in trying to
15 make the quality of all drug products, generic and
16 innovator, better and the process much easier and much
17 better for both the industry and FDA.

18 But, again, as you can see, my workload is
19 increasing. And it has increased dramatically over
20 the past two years. In 2003, we received 449
21 applications. In 2004, we expect to receive 566 full,
22 original ANDAs.

1 You don't -- I have about -- it's
2 somewhere over 50 review chemists. It maybe 52 or 53.
3 You don't need Bayesian statistics to figure out that
4 that is about 11 original applications per reviewer
5 per year.

6 MEMBER SINGPURWALLA: You'll get a better
7 estimate if you use that.

8 DR. BUEHLER: Okay, thank you, thank you.

9 (Laughter.)

10 DR. BUEHLER: That's a lot of work. We
11 have a tremendous amount of work. It's increasing.
12 It's increasing much faster than I can hire people to
13 review these applications.

14 So we are looking for better ways to
15 review these applications. We recently had an office-
16 wide retreat for the entire office to look at ways
17 that we can cut down on our workload, become more
18 efficient. If we're looking at something we don't
19 have to look at, we don't want to look at it anymore.
20 We're trying to identify anything we can to have a
21 more efficient operation.

22 Along with our originals, and Moheb

1 brought out the point that every time we approve an
2 original, we're looking at more supplements. And if
3 you approve 300 or 400 a year, you're looking at a lot
4 more supplements. So anything we can do to reduce the
5 supplement load, we're also very interested in.

6 Quality -- and this -- I mean these
7 posters you may see on buses. If you go to Los
8 Angeles or Chicago, we've actually had our posters on
9 buses. The waiting rooms in Eckerd's and I believe
10 Giant had then in waiting rooms. So we are very proud
11 of the quality of the generic products that are on the
12 market today.

13 We believe your generic drug is safe,
14 effective, and bioequivalent. We believe people
15 should be able to take them with full confidence.

16 So the products out there today are not
17 bad. I mean they're good, safe, effective products.
18 We're just looking at better ways to make them, more
19 efficient ways to make them so that the industry and
20 the FDA will have a less burden in reviewing the
21 applications.

22 And it gets to the definition of quality.

1 And Helen asked me, she said your quality slide is
2 blank. And there are a lot of definitions of quality.
3 I know David will probably give you one tomorrow. I
4 think Janet Woodcock has one.

5 And to me quality is pretty much, you
6 know, in the eyes of the beholder. You know when
7 something is inferior in quality. I had a 1976 Dasher
8 a few years ago. And it was the worst car I ever
9 owned. It wouldn't start. The air conditioner
10 wouldn't work. And clearly my decision, based on the
11 quality of that car, was I never bought another
12 Volkswagen.

13 And all of you out there have stories
14 about appliances, or electronics that you've had, that
15 really did not perform the way you thought they would.
16 And your judgment on those were that they were poor
17 quality. And you probably never bought that
18 particular brand again. That's your right to not do
19 that.

20 Quality with drug products is a different
21 thing, though. Sometimes we can tell. If you have a
22 patch that doesn't stick right, that falls off when

1 you take a bath, or if you have a bottle of pills that
2 are broken when you open then, you can make a sort of
3 a consumer-based assessment of quality there.

4 But for the most part, you don't know if
5 they're within specification. You open that pill
6 bottle every day and you take a pill with full
7 confidence that it is going to make your cholesterol
8 go down or your blood pressure go down. It's going to
9 relieve your pain because you trust the FDA, you trust
10 the drug industry that what they say is in that pill
11 is in that pill. And what they say that pill will do,
12 they'll do it.

13 So that's where we come to play in. The
14 FDA has to be the person that helps to assure this
15 quality. That's what we've been doing in reviewing
16 the applications to date and that's what we want to
17 continue to do.

18 Now the slide I showed previously, this
19 one, our challenge with generic drugs is that many
20 people relate quality to cost. And that's not a far
21 stretch. A Lexus costs ten times more than a Daewoo.
22 And they don't sell Daewoos anymore, yes. I mean but

1 that's an extreme example.

2 I actually rented a Daewoo once. It was
3 a horrible a car really. I see why they're not around
4 any more. But really that's -- I mean that's a clear
5 judgment people have. You'd always rather drive a
6 Lexus than a Daewoo.

7 But with respect to generic drugs what we
8 tell people is it doesn't matter that they cost half
9 as much. You should take them with confidence, that
10 they're made under the same quality conditions that
11 the innovator drug products are and you should be able
12 to take them with confidence.

13 That's our challenge. And that's why
14 Congress actually asked us to start this campaign to
15 make consumers aware of the quality of generic drugs.
16 And believe me with the number of applications
17 escalating that I'm getting, that's of primary
18 importance to me is to continue the quality of generic
19 drugs.

20 Now our current paradigm, and this is what
21 we do today when we get an application, we look at the
22 quality standards. We make sure that the standards

1 are comparable to the reference-listed drug. We do
2 look at the specifications of the reference-listed
3 drug established by Moheb's people in the CMC review
4 in the innovator products.

5 We make sure the product is manufactured
6 in compliance with good GMPs. And the process and
7 specifications are conditions of approval that require
8 approval for any subsequent changes. Basically we
9 lock in the specifications. If you want to change it,
10 you've got to submit a supplement to us.

11 That's what we do now and we will probably
12 continue to do that for a little while longer.

13 Now in original ANDAs, there's extensive
14 negotiations over specifications. And we did an
15 internal study in our office recently where 40 percent
16 of the original applications, the comments on the
17 first review cycle were all related to tightening
18 specifications.

19 And basically I don't blame the generic
20 companies. They come in, they base their
21 specifications on the batch that they made, that they
22 submitted to us, and they don't know what the

1 specifications of the RLD are. It's a mystery. It's
2 kind of a guessing game for them.

3 And so they submit specifications based on
4 their biobatch. And they try to, you know, make them
5 as wide as they think we'll accept because these are
6 the specifications that is going to lock them into
7 their manufacturing processes for the next who knows
8 how many years.

9 And we try to crunch them down a little
10 bit according to, again, the references to drug and
11 what we think they can do.

12 And, unfortunately, this takes time. And
13 our average review time for an ANDA right now is about
14 18 months. And we would like that to get down.
15 Congress would like that to get down. And we're doing
16 all we can to try to reduce that number.

17 It also necessitates a high number of
18 supplements because once we lock in these
19 specifications, any time that the company wants to
20 change one of these specifications, they have to
21 submit a supplement.

22 Now in the new approach and, again, I

1 harken to Dr. Berridge's presentation. You know, I
2 feel like I should be like Mickey Mantle and Casey
3 Stengel when they went down to Congress and they were
4 testifying on the reserve clause in Congress and they
5 asked Casey to give an explanation of the reserve
6 clause.

7 And he went into this long explanation
8 that, you know, went all around and around and
9 whatever. And actually the Congress was kind of
10 laughing at the end of it. And then they went and
11 asked Mickey Mantle if he could give his comments.

12 And he said I agree with Casey.

13 (Laughter.)

14 DR. BUEHLER: So basically in this, I
15 agree with Dr. Berridge. The extent of product
16 knowledge is key. It drives the range of risk-based
17 decisions based on supportive data to assure a quality
18 product. And that is a product with established
19 quality attributes, purity, potency and strength,
20 identity, bioviability and delivery, labeling,
21 packaging, and physical performance.

22 So, again, very general terms. You know

1 where is the specifics? And I said to myself if I had
2 to make a talk on the quality initiative, I want to be
3 able to provide good examples to the industry because
4 the industry asks me what do you want us to do?

5 And I was hoping to be able to kind of
6 have a slide where one side is this is what you do now
7 and the next slide is this is what we want you to do.
8 And then the next slide will be like this is what
9 you'll get out of it, you know. This is what you
10 won't have to do because you've done the second part.

11 I'm still not able to do that. We're
12 still working on that. And I will throw some
13 challenges out to you at the end of this presentation
14 to try to help us to get to that point because I
15 believe we have to get to that point.

16 You out there have to know what's in it
17 for you. You're a business. You're a business to
18 make money and the generic drug industry especially is
19 a very competitive business. And they want to know,
20 you know, how it can effect the way they manufacture
21 drugs. And we have to be able to tell them that.

22 This is voluntary. And I want to

1 emphasize that. I know that there are some companies
2 that are not ready for this. And these companies are
3 the companies that are submitting my 500-plus
4 applications to the Office of Generic Drugs.

5 We will work with you. We will be glad to
6 work with you. We want to work with you through your
7 trade organization, the GPHA. We will try to organize
8 webcast presentations so that you can begin to
9 understand what we want from you.

10 It will be a phase-in process probably.
11 We hope that certain parts of your application can use
12 this paradigm if not the entire application. And,
13 hopefully, you can do that through comparability
14 protocols.

15 We want to be able to move the generic
16 industry into this paradigm but we know it won't
17 happen overnight.

18 We don't want to unnecessarily impede
19 optimization of manufacturing processes and that's
20 what people are accusing us of right now. They're
21 saying that FDA is in the way of the, you know,
22 movement forward of the generic industry. And we

1 realize many firms won't be able to do this.

2 Gerry, I'm going to pin you down. Do you
3 make Viagra 24 hours a day?

4 MR. MIGLIACCIO: No.

5 DR. BUEHLER: No? Do you have a dedicated
6 facility for -- is that because of the competition?
7 Did you make Viagra 24 hours a day?

8 MR. MIGLIACCIO: No.

9 DR. BUEHLER: No? Okay. I thought those
10 bathtub guys were giving you some competition.

11 MR. MIGLIACCIO: They are.

12 DR. BUEHLER: They are? Okay. How do
13 they get those bathtubs on the side of the mountain?
14 Have you ever seen that commercial for the bathtubs
15 sitting on the side of the mountain?

16 (Laughter.)

17 DR. BUEHLER: How do they put the water
18 in?

19 But, I mean obviously for a product like
20 Viagra or Norvasc or some of your big guys, I mean you
21 are making -- you don't ever shut those lines down,
22 correct?

1 MR. MIGLIACCIO: Sure we do.

2 DR. BUEHLER: I mean -- but I mean to just
3 do some maintenance on them but not to make another
4 product.

5 MR. MIGLIACCIO: Sure we do.

6 DR. BUEHLER: Yes? Okay. Really?

7 (Laughter.)

8 DR. BUEHLER: I'm amazed. Okay. I
9 thought you just -- 24 hours a day. No? Okay. All
10 right.

11 MR. MIGLIACCIO: Let's stop with this.

12 DR. BUEHLER: Okay, I should. I should.
13 Well, all right. The innovators are always beating me
14 up. So I thought I would pick on Gerry a little bit
15 but he's got the answers so I can say for sure generic
16 companies don't make products 24 hours a day. And
17 they don't even make products probably week after week
18 after week.

19 Some very isolated products perhaps but
20 most of your generic companies make numerous products
21 and they are breaking down their equipment and
22 starting to make new products, you know, weekly or

1 monthly. So it becomes more of a challenge for the
2 generic company to implement these process
3 initiatives.

4 And that's why I'm committed to work with
5 the generic industry to try to phase these processes
6 in to how they make their products.

7 We want to get a review completed in one
8 cycle within the statutory time frame. We'd like to
9 get an approval out within one cycle. That's pretty
10 rare right now but we are working to that.

11 We'd like regulations based on knowledge
12 and science that provide flexibility in approval
13 conditions. And we'd like the need for supplements
14 based on knowledge in the risk of changes effecting
15 the quality of the product, again, Dr. Berridge.

16 Now we have made internal changes to
17 enhance approvals. We're changing work assignments to
18 optimize review resources.

19 Right now we have a system where we are
20 assigning teams of reviewers to batched applications
21 or actually applications of -- we often get
22 applications from different sponsors for the same drug

1 product.

2 And so we are assigning actual review
3 teams to those applications because we found that many
4 times the reviews kind of run along the same line.
5 They use the same DMFs. And so it's much more
6 efficient to actually review the applications that
7 way.

8 We want to improve communications with the
9 DMF holders. We actually want to work with GPHA to
10 try to do that. Many times the DMFs that we have are
11 deficient when we first review them. We would like to
12 remedy that because the DMF review is very critical to
13 our review process.

14 We are incorporating the aspects of the
15 CMC risk-based initiative. We want to identify CB
16 supplements suitable for expedited approvals. And
17 what we want to do here is when CB supplements come in
18 to our office, we want to triage them through the team
19 leader. And we want to issue an immediate approval if
20 we can, if the team leader can make the assessment on
21 the spot that the supplement can be approved.

22 We expect to deal with comparability

1 protocols. We expect that the generic industry will
2 phase into this paradigm and that we hope that they
3 will do this through the comparability protocol
4 pathway.

5 And we want to utilize in-house knowledge
6 for specific drug products to identify new elements
7 critical to product quality and to provide prior
8 approval supplement relief.

9 Now, for the industry, formulation and
10 process design based on inherent mechanistic
11 understanding of drug and its impact on product
12 quality and performance. We need to have this
13 information from you. Sometimes we get some.
14 Sometimes we don't get much at all. But that's what
15 we're going to be looking for.

16 And I know, again, you're out there asking
17 what are you going to do with it when you get it?
18 Well, I guess you're going to have to trust us. We
19 want to see it. We want to try to work within this
20 paradigm but we can't do it unless we have the
21 information.

22 We want specifications determined by the

1 knowledge of the process or the product. We want a
2 clear rationale for selection. And we have to confess
3 that we don't have that clear rationale right now.
4 Our rationale right now is based on the data we
5 receive.

6 Process understanding to mitigate risk
7 associated with drug substance properties, we want
8 continuous process improvement. We want to identify
9 the parameters critical for product manufacture and
10 product shelf life for stability.

11 And, again, we have to get together to do
12 this because I know that you're not going to send us
13 a submission where you are going to try to guess at
14 what we want because that's too much of a risk for
15 you.

16 So we have to get together. And you have
17 to know what we want. And we have to realize what
18 we've asked for so that when we get these
19 applications, we will be able to review them
20 efficiently.

21 Our staff will follow guidances in current
22 scientific literature. And the staff in OGD is very

1 dependent upon guidances. We don't have the one on
2 one interaction with the drug industry, with the
3 generic drug industry, that they have in new drugs.

4 We don't have the end of Phase II meeting,
5 the pre-NDA meeting, the little fireside chats every
6 once in a while when they have an issue. We just
7 don't do that. With 550 applications we can't do
8 that. And so we have to work within guidances and
9 formal guidances to the industry.

10 We have to train our staff and we have to
11 train regulated industry in what this process is and
12 what we expect. And we have to get to the specifics.

13 This represents a fundamental change in
14 our thinking, in our culture of accepting applications
15 and reviewing applications. And we have to be able to
16 get away from this culture and into this new paradigm.

17 We need a review based on knowledge of the
18 product and what manufacturing changes will make a
19 difference.

20 Why should you do this? And this is the
21 big question that many of you have. Greater
22 flexibility in optimizing your manufacturing process.

1 This is a good thing. This should be able to help
2 you. And this should be able to help the industry as
3 a whole.

4 Lessened post-marketing supplement burden.
5 You saw my slide where, you know, we're getting, you
6 know, almost 3,000 supplements this year. We have to
7 be able to find some way to lessen this burden for my
8 office and for your industry.

9 And reducing no assignable cause, results,
10 and investigations. These are when you get your 483s
11 and they don't know why but something failed in your
12 process. And there is no cause assigned.

13 Now my ICH slides, I think I'm just going
14 to blast through because actually Mr. Razzaghi and Dr.
15 Berridge have done a very good job in explaining how
16 ICH fits together with this particular paradigm and
17 mine are just little summary slides.

18 Dr. McClellan, our former Commissioner,
19 stated that other high-tech industries have achieved
20 enormous productivity gains and we should expect
21 nothing less from the pharmaceutical industry. Yet
22 the Wall Street Journal said FDA regulations leave

1 drug manufacturing processes virtually frozen in time.

2 It's true that regulations designed to
3 protect the public's health make this a very special
4 industry. And they promote a conservative risk-
5 adverse mentality. And FDA counters that the drug
6 companies resistance to change is also partly to
7 blame.

8 You don't want to risk changing. And we
9 have to admit that we're a pretty conservative bunch,
10 too. And we sort of, you know, go with the flow and
11 we don't like to rock the boat too much.

12 But here we've made the first step. We
13 want to encourage the use of equipment and protocols
14 for continuous monitoring of manufacturing processes,
15 PAT. We want to encourage moving to risk-based cGMPs
16 to free the industry from rules that do little or
17 nothing to ensure quality. And we're willing to
18 facilitate initiatives as long as they improve the
19 quality and reduce the risk.

20 We acknowledge the generic industry as
21 experts in manufacturing. You manufacture hundreds of
22 drug products. And we know that you know how to do

1 this. And we know that you are aware of the many
2 processes, the many new processes that are available.

3 You can identify and articulate the
4 financial impact both for changing and for the losses
5 with current technology. And I said before, I am
6 sympathetic. I realize you are a business. You do
7 make money. And the economic aspects of this are
8 important.

9 We have to avoid the perception of a two-
10 tiered quality product system once we get into this.
11 We don't want to have, you know, the sort of, you
12 know, the Level A quality people and the Level B
13 quality people. And I don't believe we're going to
14 get that. But we have to make sure that that isn't a
15 perception.

16 And the partnership assumes product
17 quality is about providing flexible regulatory impact
18 based on product understanding.

19 Because this system includes a continuing
20 of information, how this flexibility is applied needs
21 to be well understood to ensure even treatment and
22 outcomes. That's what I'm saying. We have to be able

1 to provide details to you about how this will work.

2 FDA is not in the business of
3 manufacturing. We don't manufacture. And your
4 question to us is what do we need to do? And our
5 question to you industry is what do you think needs to
6 be done?

7 We invite you to come to us either
8 individually -- we know that sometimes you will have
9 issues where you want the entire industry to be
10 present when you are presenting your issues to us.
11 You can ask for a meeting on this and we will grant
12 the meeting to discuss how you can move forward.

13 We also want to work with GPHA and my
14 friend Gordon is in the back. We hope to be able to
15 set up something with GPHA so that we can talk about
16 general principles and, hopefully, again, because we
17 have talked about general principles an awful lot.
18 Hopefully we can get into the specifics of how to do
19 this problem, what we want you to do, and what we
20 expect to see, and what the effect will be upon you
21 long term.

22 I just have to finish with another slide,

1 another bus slide. But I am very proud of the generic
2 industry. I'm proud of what we've been able to do to
3 alleviate the high drug costs in America today.

4 I am a bit overwhelmed by the number of
5 applications that we have in our office right now but
6 I'm also very pleased that the generic industry is
7 sending them to us. And we will happily review and
8 approve them hopefully.

9 Thank you.

10 (Applause.)

11 CHAIR BOEHLERT: Gary, thank you. Also
12 some very ambitious initiatives.

13 Nozer?

14 MEMBER SINGPURWALLA: Yes. I have a lot
15 of questions and comments.

16 First is I'm not sure whether you were
17 addressing your talk to the Committee or to the
18 generic drug industry. I got the impression that you
19 were talking to the generic drug industry.

20 DR. BUEHLER: There's a few of them here.

21 MEMBER SINGPURWALLA: There's a few.
22 Okay.

1 Well, I would like to ask you a few
2 questions and then I'd like to make some comments.

3 First is do you have any example wherein
4 a generic drug is of better quality than its non-
5 generic counterpart?

6 DR. BUEHLER: Better quality?

7 MEMBER SINGPURWALLA: Yes.

8 DR. BUEHLER: No.

9 MEMBER SINGPURWALLA: So all --

10 DR. BUEHLER: We say they're equivalent
11 quality.

12 MEMBER SINGPURWALLA: Oh, equivalent. But
13 there is never a counter example where a generic drug
14 is of better and more effective quality than a non-
15 generic?

16 DR. BUEHLER: Well, you know, it depends
17 on how you define quality.

18 MEMBER SINGPURWALLA: Whatever way you
19 want to define it.

20 DR. BUEHLER: Okay. Well, I mean --

21 MEMBER SINGPURWALLA: Just yes or no.

22 DR. BUEHLER: Yes.

1 MEMBER SINGPURWALLA: There is?

2 DR. BUEHLER: Yes.

3 MEMBER SINGPURWALLA: Okay. Second, the
4 approval time for a generic drug you said is about 18
5 months?

6 DR. BUEHLER: Yes.

7 MEMBER SINGPURWALLA: How much is it for
8 a non-generic counterpart?

9 DR. BUEHLER: Probably I think it's 12 to
10 14, something like that.

11 MEMBER SINGPURWALLA: So a generic drug
12 takes a longer time to be approved than a non-generic
13 drug?

14 DR. BUEHLER: Yes.

15 MEMBER SINGPURWALLA: Well, I propose that
16 if you use Bayesian methods --

17 (Laughter.)

18 MEMBER SINGPURWALLA: -- you will cut down
19 on both the generic and the non-generic approval time
20 because if a generic drug -- if a non-generic drug has
21 been approved, there is prior knowledge there --

22 DR. BUEHLER: That's absolutely correct.

1 MEMBER SINGPURWALLA: -- and that should
2 be translated to the non-generic -- to the generic
3 counterpart and you should save on --

4 DR. BUEHLER: Well, Congress has made this
5 similar argument that you're making.

6 MEMBER SINGPURWALLA: Well, Congress
7 sometimes is wise.

8 DR. BUEHLER: Yes, sometimes.

9 (Laughter.)

10 MEMBER SINGPURWALLA: Now, on your Slide
11 23, you cited two examples. One is by Dr. McClellan
12 and the other one is the Wall Street Journal, and you
13 said that that was kind of a contradiction but I don't
14 see it as a contradiction.

15 One was talking about productivity. That
16 is manufacturing. The other was talking about the
17 process of approval. They're two different things.
18 You know to approve a drug, you have to look at its
19 chemistry and all kinds of, you know, biological
20 features.

21 To manufacture, it's a different process.
22 So I can see the two -- I don't see the two as being

1 in conflict. I can see the two as being true because
2 productivity gain means how quickly you can
3 manufacture, how efficiently you can manufacture.
4 Approval is a different process.

5 DR. BUEHLER: Well, I think the point
6 being Dr. McClellan said that the drug industry should
7 do better but at the same time the Wall Street Journal
8 said that we, the FDA, were holding back the drug
9 industry.

10 MEMBER SINGPURWALLA: Possibly true but on
11 a different matter.

12 DR. BUEHLER: Okay.

13 MEMBER SINGPURWALLA: And you say FDA is
14 not in the business of manufacturing. I agree. But
15 there are two comments. You monitor the manufacturing
16 and secondly this is the Subcommittee of the
17 manufacturing. So you do monitor the manufacturing
18 process.

19 DR. BUEHLER: But we don't manufacture.

20 MEMBER SINGPURWALLA: Of course not. But
21 you don't design the drug either.

22 DR. BUEHLER: We monitor manufacturing.

1 MEMBER SINGPURWALLA: You're just
2 monitoring. And anyway, my comment to you is I think
3 if you were to use Bayesian methods, you would save on
4 time --

5 (Laughter.)

6 MEMBER SINGPURWALLA: -- and you'd
7 probably have more time on your hands so that you can
8 give more talks.

9 (Laughter.)

10 DR. BUEHLER: Are the copies of your
11 slides available. I should be able to get those.

12 MEMBER SINGPURWALLA: Yes, but my slides
13 are not going to help you.

14 DR. BUEHLER: I see.

15 MEMBER SINGPURWALLA: They are just -- my
16 slides are not going to help anyone. They're just
17 going to tell you what it is all about.

18 To really -- to be effective, you really
19 have to go, take a specific example, work it through
20 very carefully, and make the case that this is what
21 can be done.

22 DR. BUEHLER: I agree. I absolutely

1 agree. We need some examples to get through our
2 system and to be able to illustrate to everyone the
3 economics of this and the efficiency of this. And the
4 fact that there is benefits for the drug industry in
5 doing this. I absolutely agree.

6 MEMBER SINGPURWALLA: I'm done.

7 CHAIR BOEHLERT: Ken, then G.K.

8 MEMBER MORRIS: So, Gary, after you've
9 instituted the Bayesian analysis --

10 DR. BUEHLER: Yes.

11 MEMBER MORRIS: -- when you're talking
12 about not being able to have the same sort of end of
13 Phase II meetings but in the face of the extended,
14 relatively extended review time, is there a
15 possibility, because it does actually in many cases,
16 I know the direct contact really does speed up the
17 process by resolving issues that are quickly resolved
18 when talking scientist to regulator, et cetera, is
19 there any chance at least for like teleconference --

20 DR. BUEHLER: Yes.

21 MEMBER MORRIS: -- meetings and --

22 DR. BUEHLER: We've actually instituted --

1 we had -- believe it or not, you know, in past years,
2 we had a system where we didn't talk to anyone during
3 the first cycle on the telephone.

4 MEMBER MORRIS: Yes.

5 DR. BUEHLER: And we are revising that
6 policy. And that was a policy that instituted as the
7 result of the generic drug scandal and trying to sort
8 of mandate this level of consistency across the entire
9 office with respect to review.

10 And we have sort of broken away from those
11 shackles and we are encouraging our reviewers to talk,
12 especially at the end of the first cycle. And to be
13 able to discuss the deficiencies of the first cycle.

14 One thing that I did mention that we are
15 trying to address are the DMF deficiencies. We're
16 highly dependent upon, obviously, the DMF for the
17 active pharmaceutical ingredient. And we are trying
18 to do something where we can either get those reviews
19 done in an earlier time frame so that the deficiencies
20 can be set ahead of time and that they can be back in
21 time for when the application is reviewed.

22 Because clearly we get many applications

1 that could go out on the first cycle except for the
2 DMF deficiencies.

3 Yes, G.K.?

4 MEMBER RAJU: Coming back to -- you said
5 you like John Berridge's presentation from the
6 morning. In his presentation he talked about the ICH
7 Q8 and Module 3 about pharmaceutical development.

8 DR. BUEHLER: Yes.

9 MEMBER RAJU: To what extent does that
10 directly translate? Is it different for the generic
11 industry, the importance of pharmaceutical development
12 and what you want submitted in terms of the whole ICH
13 process and Q8 and what they're putting into that
14 section? Do you want something from the generics?
15 The same? More or less?

16 DR. BUEHLER: Well, it sort of probably
17 will have a different focus. I mean and -- and Paul
18 can maybe address this better than I but to me a
19 generic firm in their development report, the big part
20 of their development is they want to develop a
21 bioequivalent formulation to the RLD. That's sort of
22 the big target.

1 And how they do that with respect to, you
2 know, if there is a patent that is in their way and
3 how they design around the patent, how they choose the
4 inactives for the particular formulation. And then,
5 you know, the development aspects of all of the
6 formulating of that product, we would be very
7 interested in seeing.

8 And so I think to us that would be our,
9 you know, the development information that we would
10 want to see and all that was attendant to that.

11 MEMBER RAJU: But the paradigm in which
12 you evaluate quality is bioequivalence. Then your
13 desired state in terms of mechanistic understanding is
14 based on the innovator's understanding? Or is it
15 based on getting a special -- a mechanistic
16 understanding for the generic all over again?

17 DR. BUEHLER: Well, many times the
18 manufacturing processes are vastly different from the
19 generic and the innovator. So if we want to
20 understand the mechanistic, you know, the
21 manufacturing process from, you know, A to Z or
22 whatever, it could be totally different than the

1 innovator's.

2 We certainly refer to the innovator
3 applications for, you know, referencing and actually
4 looking at what they do and what problems they had.
5 But with respect to the generic, we have to look at
6 their process and, you know, they would have to define
7 the critical parameters in their process.

8 MEMBER RAJU: Okay. So as far as the
9 product is concerned, it's pharmacokinetics and
10 dynamics. You take that from the innovator because
11 it's already out there. But in terms of the generic,
12 not only bioequivalence but you'd also look for some
13 mechanistic understanding of their formulation --

14 DR. BUEHLER: Yes.

15 MEMBER RAJU: -- to give them a
16 specification release.

17 DR. BUEHLER: Yes. I mean some products
18 are -- I mean like extended release products have
19 vastly different ways of manufacturing and mechanisms.
20 So --

21 CHAIR BOEHLERT: Okay. Nozer, did you
22 have another comment?

1 MEMBER SINGPURWALLA: Yes, I'm sorry to
2 come back. I'm curious. Why does a generic drug take
3 18 months for approval whereas a non-generic one takes
4 12? Why less? Why more in the other way?

5 DR. BUEHLER: There we have almost 600
6 pending applications in our office right now.

7 MEMBER SINGPURWALLA: Oh, so the cause of
8 it is you are overloaded?

9 DR. BUEHLER: Yes, it's a queue system.

10 MEMBER SINGPURWALLA: But it's kind of
11 unfortunate and unfair to the generic manufacturers
12 that since the FDA is overloaded, they have to wait,
13 right?

14 DR. BUEHLER: Well, yes and --

15 MEMBER SINGPURWALLA: I don't own shares
16 in a generic drug.

17 DR. BUEHLER: Well, well, no.

18 MEMBER SINGPURWALLA: I just want you to
19 clarify.

20 DR. BUEHLER: And that's an average, too.
21 And we do approve many applications in eight months,
22 nine months, ten months.

1 MEMBER SINGPURWALLA: Oh.

2 DR. BUEHLER: And they depend upon the
3 quality of the submission, whether it is a
4 controversial drug or not, whether we have patents to
5 deal with, whether we've been sued on the particular
6 product.

7 Sometimes when we're sued, well, Gerry,
8 sorry, but Gabapentin, I mean there's still no
9 Gabapentin on the market. The patent went out four or
10 five years ago. We have products in our office that
11 have been pending for seven or eight years. Now what
12 do you think they do to a mean?

13 MEMBER SINGPURWALLA: Okay. So the bottom
14 line is that it's not for scientific reasons that you
15 are taking a longer time --

16 DR. BUEHLER: No.

17 MEMBER SINGPURWALLA: -- to approve.

18 DR. BUEHLER: I mean it's a -- we had a
19 generic drug scandal in 1990. So part of that scandal
20 was taking products out of order, taking preferential
21 treatment to certain companies. And so we have a
22 rigorous queue system in our office where we take

1 things, you know, first in, first reviewed. Not
2 necessarily first approved because it depends upon the
3 quality of the submission.

4 And they are stacked up in line. Each
5 chemist has a queue that goes down. Our
6 bioequivalents division has a queue of applications
7 like, you know, 30 pages long.

8 MEMBER SINGPURWALLA: I got the message.
9 I thought it was for scientific reasons. And if that
10 was the case, then I'd be a bit surprised because you
11 already have knowledge from the poor non-generic drug
12 manufacturer who has done all the investing, you know,
13 and done all the work. You should be able to exploit
14 that.

15 DR. BUEHLER: No, we acknowledge that.
16 No, they do a good job.

17 MEMBER DeLUCA: Along those lines, Gary,
18 do you want to comment on the future? Because this is
19 going to get worse as far as workload with the drugs,
20 the biotech drugs that are going to be coming off
21 patents in 2005. You're going to have a very
22 increased workload in the generic area.

1 DR. BUEHLER: Well, I probably won't
2 comment on the biotech drugs because that's a bit up
3 in the air as to just who will be doing those. But,
4 no, from this slide, obviously the trend is more work.

5 Moheb, actually his slide, I think he said
6 he had about 100 and some new NDAs, 115 new NDAs. We
7 got 102 last December, 102 ANDAs in December, in one
8 month. So the trend clearly is going up.

9 Like I said, we did have an office-wide
10 retreat about a month ago where we looked at just
11 about every one of our processes to try to determine
12 where we could do a better job in looking at fewer
13 aspects of the application. And trying to identify
14 really the critical parts of the application that have
15 to be reviewed.

16 And at the same time, we're hiring people.
17 I mean every, you know, every couple weeks a new
18 person comes on board. And we are trying to get to
19 the point where we have 60 review chemists, where we
20 have three divisions of four teams each, five chemists
21 in each team. And we believe that that will give us
22 a good base to be able to address this workload.

1 CHAIR BOEHLERT: Paul first, then we'll go
2 Garnet, and then Dan.

3 DR. FACKLER: I just want to make a couple
4 of quick comments. One about the pharmaceutical
5 development reports. They're admittedly different for
6 generic drug development than they would be for the
7 innovator's product. We have only a couple of targets
8 that we need to hit.

9 We're looking to have pharmaceutical
10 equivalents. And then we're looking to have
11 dissolution comparability and bioequivalents. So the
12 development reports for a generic product are focused,
13 you know, certainly more tightly focused than you'd
14 have for the comparable brand product.

15 The question about quality. Are there
16 ever generic products with better quality than
17 innovator products? It depends on how you assess
18 quality. We sometimes have a problem reducing
19 bioavailability on oral products to match an
20 innovator. And you could argue that a better quality
21 product would have better bioavailability.

22 But then we'd be coming out with a 15

1 milligram tablet to go against a 25 milligram table
2 innovator. It's not an equivalent. We have to back
3 off that kind of a formulation.

4 And the other kind of quality comparison
5 is the variability that you see in the bioequivalents
6 study. And there is an inherent variability in a drug
7 substance but there's also a variability associated
8 with a drug product.

9 And it's sometimes difficult to engineer
10 -- for us using different release mechanisms, it's
11 sometimes difficult to engineer the same variability
12 see in an innovator product.

13 And the last point I wanted to make was
14 really a question about the review time. We
15 understand that reviews should be -- or the first
16 review should be completed in, I think, 180 days. And
17 recognizing with the large number of applications and
18 the limited resources, we sometimes don't receive
19 those within 180 days.

20 My guess is that the review time is very
21 short compared to new drug applications if you
22 discount the time that an application sits in the

1 queue, if you will.

2 DR. BUEHLER: Yes. And that time also
3 reflects the time with the firm. So if we send
4 deficiencies to the firm and the firm decides that
5 this isn't a high priority application to respond to
6 and they have three others on their table that, you
7 know, the patent is going to go out in a month, they
8 want to respond to, they will let the application sit.
9 And so that time counts against us, too.

10 DR. FACKLER: The other time that counts
11 against it is the 30-month stay.

12 DR. BUEHLER: Yes.

13 DR. FACKLER: So that if we've made an
14 application, we can't legally market a product for 30
15 months whether or not FDA has approved our
16 application.

17 MEMBER SINGPURWALLA: An unfortunate
18 system of rules I should say.

19 (Laughter.)

20 DR. BUEHLER: Well, it's a heavily legal
21 influenced system.

22 CHAIR BOEHLERT: Garnet?

1 MEMBER PECK: I do believe that you
2 mentioned something to this effect that you will have
3 an API that has an ANDA submitted by multiple
4 companies.

5 DR. BUEHLER: Yes.

6 MEMBER PECK: Yes. Just --

7 DR. BUEHLER: Many times.

8 MEMBER PECK: -- recently there were seven
9 companies got approval about the same day so are you
10 trying to work those as a unit?

11 DR. BUEHLER: Yes, now we are. We didn't
12 previously.

13 MEMBER PECK: Through the Agency?

14 DR. BUEHLER: Yes but now we assign them
15 to the same team if we can if it's a small enough
16 number because many of the times they utilize common
17 DMFs so the DMF review, you know, can be utilized for
18 a couple of different applications.

19 And also the issues related to the review
20 of the application are many times common, too. And so
21 it helps to have a group of chemists being able to
22 discuss the issues with themselves and the team leader

1 in reviewing that.

2 And we found that the review is much more
3 efficient and actually done much faster that way.

4 MEMBER PECK: Yes.

5 CHAIR BOEHLERT: Dan?

6 MEMBER GOLD: Gary, you mentioned, I
7 thought, that some of the delays are caused by
8 inadequacies in the drug substance DMF.

9 DR. BUEHLER: Yes.

10 MEMBER GOLD: I have not seen any
11 publication by the Agency or by the Generic Division
12 as to what deficiencies they are finding and what
13 advice they might offer the industry in order to
14 improve the quality of the DMFs so that you can,
15 thereby, take advantage and review, you know, and
16 reduce the review cycle time.

17 Why not do that?

18 DR. BUEHLER: Well, that's a good
19 suggestion. You are right. There aren't any that I
20 know of. Frank? No. DMF guidance? We don't have --

21 PARTICIPANT: Well, historically we've
22 done this periodically.

1 MEMBER GOLD: I'm sorry. I cannot hear
2 you.

3 DR. BUEHLER: Frank said historically
4 we've done it with the industry.

5 PARTICIPANT: And probably 10, 12 years
6 ago, there was a series of DMF conferences within the
7 Agency where there were a number of instances
8 discussed. Part of that long series was here are the
9 most likely things that you will find wrong,
10 frequently with DMFs.

11 And it's not something that we repeat.
12 It's usually a special project when we go in and we
13 look at them.

14 MEMBER GOLD: May I suggest that you
15 consider putting out a type of document that other
16 sections have put out such as Q&As on --

17 DR. BUEHLER: Sure.

18 MEMBER GOLD: -- and this one directed to
19 DMFs to guide --

20 DR. BUEHLER: That's a good suggestion.

21 MEMBER GOLD: -- to guide applicants in
22 that area?

1 DR. BUEHLER: Sure. That's a very good
2 suggestion. And as I stated, we hope to have a
3 meeting through GPHA with some of the DMF holders
4 also, a webcast where we can connect people through
5 telephone if they can't attend a meeting personally,
6 and talk about these deficiencies, too. We've had
7 these meetings on other issues within the office.

8 MEMBER GOLD: And there's another issue
9 here, too, that since so many of the DMFs now are
10 coming from overseas, I think the estimate is of the
11 order of 80 percent of the drug substances are coming
12 from overseas, I think we really have to broaden the
13 approach we're taking in order to reach all the
14 applicants.

15 DR. BUEHLER: Yes, we have --

16 MEMBER GOLD: All the DMF applicants.

17 DR. BUEHLER: -- we have to very often
18 deal with their agents in this country with our
19 deficiencies and our communications.

20 MEMBER GOLD: No, but I'm thinking in
21 terms of international meetings in order to expedite
22 this because it is important to get generic drugs on

1 the market faster.

2 DR. BUEHLER: Yes. Okay.

3 CHAIR BOEHLERT: I have one last comment
4 before the break. Ken?

5 MEMBER MORRIS: Yes, just to follow up on
6 your point. I think one of the problems that gets
7 lost in the shuffle with DMFs is that the companies,
8 the drug companies themselves often don't have access
9 to much of the DMF so the audience for that sort of a
10 meeting is, of course, the DMF holders.

11 But depending on their stake in the
12 particular active that you're talking about for the
13 particular generic company, that may not be a
14 compelling enough reason for them to make a lot of
15 changes or to be a very forthcoming.

16 So I don't know the solution to that but
17 I've run up against that before.

18 DR. BUEHLER: Well, the drug industry is
19 clearly the customer -- or the DMF holder is the
20 customer of the drug industry. So, I mean, we sort of
21 do look to the drug industry, the generic drug
22 industry, to actually pressure the DMF industry to

1 submit better applications. That way their
2 applications won't be held up.

3 MEMBER MORRIS: No, I understand the
4 point. My point is in terms of delays that are a
5 result or a manifestation of that, may not be
6 something that lies within the control of the generic
7 company itself.

8 DR. BUEHLER: No, you are -- that's
9 absolutely correct. They don't even know what the
10 deficiencies are.

11 MEMBER MORRIS: Right.

12 CHAIR BOEHLERT: Okay. Thank you all for
13 very, very good discussions this afternoon. We're
14 going to take a break now and reconvene at 3:45.

15 (Whereupon, the foregoing
16 matter went off the record at
17 3:30 p.m. and went back on the
18 record at 3:47 p.m.)

19 CHAIR BOEHLERT: Okay. Our last speaker
20 of the day is Ken Morris. Certainly last but not
21 least. He's already at the podium and ready to go.

22 MEMBER MORRIS: Well, that's because

1 unlike Gary, who was only facing people who were
2 trying to go golfing, I'm facing people who I'm the
3 only thing between them and the bar. So -- what's
4 that? Yes, when I hear the clinking of ice, I'll know
5 I've overstayed my welcome.

6 Well, first of all, thanks for inviting me
7 Judy, and Helen, and Ajaz.

8 The purpose of this is to largely report
9 to the Committee on some of the activities that are
10 going on with the senior CDER and DVM, and ORA folks
11 to discuss and to flesh out the ideas of question-
12 based CMC review.

13 And in the course of doing this, I'll try
14 to differentiate my opinion from what we've actually
15 done. But in the first half of that talk at least,
16 what you'll largely see are the fruits of the work
17 that we've all done as a group to explore this and
18 brainstorm.

19 These are by no means final. And this is,
20 as I should point out, a work in progress. We intend
21 to continue this.

22 Lest you choke at another current versus

1 desired state, let me say that this is a little bit
2 different in that this is the assessment not only of
3 ourselves and the upper management but Directors,
4 Deputy Directors, Team Leaders, and Reviewers as well
5 as the odd academic.

6 Right now if you -- and you have these
7 slides so the fact that they're animated isn't going
8 to mean much. I'll go through them pretty quickly.

9 The companies, as we've heard, may or may
10 not have information. But it's not always in the
11 filing. And there's not a lot of incentive for it to
12 be.

13 The reviewers have to go through cycles of
14 information requests and questions and then wait for
15 the responses. So the companies may or may not have
16 the clear scientific rationales for the choices but,
17 again, they're not always sharing it.

18 And what this really results in is that
19 the reviewers have to piece together data and
20 observations to discover, if you will, the rationale
21 for a specification, a method, a formula, or a
22 process, et cetera.

1 And really we're saying that the reviewers
2 are in a large sense of the word, and I'm not laying
3 any blame here nor was the group, serving the function
4 that should actually be done in the company and may
5 well be being done in the company but just not shared.

6 In a desired state, what we'd like to see,
7 of course, is that companies would include needed data
8 with the filings and could share it prior to the
9 filings, the end of Phase II meetings being the sort
10 of the poster child for that concept.

11 They would include the data analysis to
12 produce meaningful summaries and scientific
13 rationales. So as opposed to the current state where
14 if there are data missing in the reviewer's opinion
15 and you ask for a data summary, in essence, and you
16 get three boxes of chromatograms, that doesn't really
17 serve anybody's purpose.

18 The idea would be to have meaningful
19 summaries of the data, that is data that have been
20 analyzed and interpreted in the light of what the
21 company believes is the proper interpretation and
22 shared with the reviewers and the Agency.

1 This should lead to the specific or the
2 scientific rationales, the product development history
3 sort of rationale we're talking about.

4 The reviewers then would assess the
5 rationales and the summarized data presentations as
6 satisfactory or not. And in that scenario, what you
7 see is the potential to gain all of the things that
8 we've been talking about all day and will continue to
9 talk about tomorrow.

10 We had talked -- at Purdue, we had talked
11 about sort of folding this into a risk-based
12 development concept. And now I'll have to couch all
13 this in terms of the Bayesian defensible risk and not.
14 But I'll try to do that as I go along, Nozer.

15 First of all, the idea, as I said, is a
16 simple concept. And if you use sound scientific
17 principles in the design of the dosage form in the
18 process, you've essentially met Phase I. Not Phase I
19 in the clinical sense.

20 You have to identify the critical
21 attributes for the raw materials, and we'll talk a
22 good bit more about this as we go, identify the

1 process critical control points for the processes,
2 employ the proper analyses and process analytical
3 technology concepts for process understanding and
4 control.

5 And tie it all together with the
6 appropriate informatics to feed the information
7 forward and backwards for quality by design and in
8 continuous improvement, which is the daughter of that.
9 And that all leads to innovation, which is supposed to
10 and should reduce risk.

11 Now we haven't talked very much about
12 informatics today but clearly this is something that
13 is an inescapable and inexorably linked to all of
14 these initiatives. That it doesn't do you any good to
15 collect data if it's not used much less shared between
16 the organizations within the company, within the FDA,
17 or between the FDA and the companies.

18 So what we'll do as we go along is expand
19 on the righthand side of this list to talk about the
20 associated regulatory question rationale or
21 rationales.

22 The concept of risk-based development is

1 really all about feeding forward, and I would add
2 backwards, but feeding forward at the outset. This is
3 after a set of quotes that Ali Afian had spewed at
4 Arden House very passionately.

5 So if you look at it with a little more
6 detail, what we're saying is you can explore the
7 characteristics of the raw materials and possible
8 variability in the raw materials and processing that
9 are expected, that is expected based on some either
10 previous knowledge or model, to impact on required
11 dosage form performance. And we'll come back to what
12 required means but, of course, that's another whole
13 discussion.

14 Deciding on a dosage form based on the
15 first step and the business case and selection of
16 possible processes would be the logical next step.
17 And what you'll see as a theme as we go through this
18 is pretty much what you would expect if you are in
19 companies you are doing now, and for the Committee, I
20 would say that this is one of the focal points of what
21 we're going to talk about. And I'll tender a
22 hypothesis in a moment that's -- well, maybe I won't.

1 Then deciding what data are necessary to
2 assess the probable success of No. 2, that is the
3 dosage form, this can be from first principles,
4 literature, design of experiments, et cetera.

5 Collect and analyze the data in the fourth
6 step and you can see where PAT would play a role here.

7 Then Gap analysis and refining models as
8 the development proceeds and finally the continuous
9 improvement, which starts the cycle over again.

10 I wanted to use as an example here, and we
11 sort of used this as an example in the team as we met,
12 Solid Oral Dosage Forms. But, of course, we're not
13 limiting any of the arguments or the hypothesis to
14 this dosage form.

15 But there are really only two issues with
16 Solid Oral Dosage Forms. One is does it work? That
17 is the performance. And the other is can you make it?
18 And that's the manufacturability.

19 If you look at the subsets of each of
20 these, for performance right now we have -- and when
21 I say dissolution, I'm not talking about the
22 dissolution testing. I'm speaking of it more as Ajaz

1 was this morning in that dissolution may be important
2 whether or not dissolution testing is measuring it is
3 a different question, dissolution in vivo, absorption,
4 and stability.

5 And then each of those have subsets which
6 are logically defined by the physical, chemical models
7 that are around or that need to be developed. Where
8 I have flags are places where we actually have models
9 in place. And if you look at this really, the big
10 unknown and the analogy here is on the old maps, when
11 you'd get to the end of the continents, they'd say and
12 here there be dragons, is the absorption, the clinical
13 aspects.

14 But really what we're talking about is the
15 manufacturability for most intents and purposes since
16 we can't really fill that gap at this stage. And for
17 manufacturability what I have here is physical
18 properties and processes and then those are broken
19 down into their component parts.

20 So this is an overall example of what the
21 requirements are for the dosage form. They're really
22 -- what we talked about the required part in the first

1 step here, the required dosage form performance,
2 that's really what we're talking about ultimately.
3 But, of course, we aren't there yet.

4 Well, how realistic is risk-based design,
5 if you will? Or the whole concept we're talking about
6 really. And I start this by stating this premise that
7 as all good pharmaceutical scientists and engineers
8 know, a formula without a process is really a pile of
9 powder if it's a solid oral dosage form.

10 So even during API characterization,
11 developing a formula implies an expected dosage form
12 and a process or range of choices. And the example is
13 here you don't care about the compressibility of a
14 lyophile, for instance.

15 But I'd submit that even at the very early
16 stages, if you're sitting at a pre-formulation desk
17 and somebody throws ten milligrams of material on your
18 desk, you know exactly at that point what the dosage
19 form is going to be.

20 Now you may not know exactly what option
21 within the dosage forms you are going to have, but
22 you're going to know if it's a tablet. If it's an

1 analgesic, you're not going to have an ocular
2 injection is my standard example.

3 So API characteristics are among the first
4 information you need to feed forward. So if we look
5 at that though for the people that are attending in
6 the gallery as well as the Committee, you have to be
7 saying well what's different about this than what we
8 do right now. We do all of this now.

9 A good formulator, a good scientist, a
10 good engineer will just tell you right away that this
11 is the thought process they go through. But the
12 difference is that we're not doing it model based.
13 We're not sharing and feeding the data forward and
14 backwards. And there's no informatics to capture this
15 in a meaningful way. In other words, it's the
16 process.

17 The process itself is what is new. And
18 the process itself is what's necessary to bring all of
19 these ideas to fruition.

20 Just as an example, just as dipping the
21 toe into the pond of biology here for the moment, even
22 at very early stages when you receive just a molecule,

1 you can -- even a molecular structure and a small
2 amount of material, you can assess solubility impact
3 on pre-formulation on absorption using relationships
4 such as the modified absorption parameter, which does
5 a fairly good job just based on molecular structure
6 and some estimates that you can make either
7 computationally or with simple experiments on whether
8 or not even a low soluble drug will be absorbed.

9 Well, you've already seen this slide and
10 I'm not -- this is actually from Rick Cooley from --
11 that Toby showed this morning so he didn't have to
12 cite it because it was his company but Rick Cooley
13 from Lilly actually presented this.

14 If we look at this in terms of the overall
15 variability of the process, a variable input will lead
16 to an invariable product if you hold everything in the
17 middle constant. This is just common sense.

18 So the idea is is to be able to adjust it.
19 The catch here is what are you going to adjust, that
20 is what are the critical attributes as well as what
21 are the critical process points, the critical control
22 points in the process? And that's what we're going to

1 talk about.

2 So the example that we started with in the
3 team was actually API selection. And the idea here
4 was to explore the question of how do you know what
5 questions to ask? So now you have people who are
6 going to be looking at your filings as they come in.
7 And presumably now data would have been shared early
8 on.

9 And the first question that we all agreed
10 on, we did this as a team, was what's the -- what the
11 first question you'd want to ask if you had your
12 choice is what dosage form are you going to be using?
13 So the first thing I want to know is what's my dosage
14 form?

15 Then the questions went on. What's the
16 second thing, et cetera? And the hypothesis that
17 we're proposing here, and that the Committee can
18 assess during our discussions is that the development
19 scientist and the regulator are or should be asking
20 many or all of the same questions. So the same
21 process that the scientist is going through in
22 designing the dosage form and designing the process

1 should be the questions that the regulators are
2 responding to because that's ultimately what will
3 determine whether or not the dosage form has been
4 designed by quality.

5 Well, if you -- I got permission from
6 Moheb to use the pyramid at Arden House so I extended
7 by non-exclusive license to it -- if you go through
8 this pyramid of questions, what you start with is what
9 is intended dosage form, which is what we just said.
10 What's the intended process? And then stepping up
11 through the various tiers of the pyramid to the point
12 where you've actually identified the critical
13 attributes.

14 And the other dimension here, much like
15 Ajaz's sixth dimension, is time, of course, because
16 that will change. And this will, in fact, be a cyclic
17 process.

18 So this is the hierarchy of questions that
19 you might expect to see if you were to make a filing
20 and certainly if you were designing your dosage form.
21 And it's really a fairly logical progression of
22 consideration of the physical chemical properties of

1 the API.

2 If you have an API, it will either be a
3 solid, liquid, semi-solid biological. And what the
4 question is is what are the critical attributes of
5 each of these?

6 Now if you select one, we'll select solids
7 here because that's what I know best, of course, not
8 that they have to limit it, then if your API is a
9 solid, you go down a logical process of deciding
10 whether or not it's crystalline or amorphous, whether
11 or not it's a polymorph, a hydrate, or something else,
12 and when you've selected the one that it is or
13 identified the one it is, there will be certain
14 criteria which will tell you what the characteristics
15 ought to be and then this might take you to not a
16 decision tree but an event tree as Nozer said, an
17 event tree in the Q6A.

18 Then this would at least give you the
19 range of possible critical attributes, which puts you
20 back on the path of this thinking.

21 Now I'm not saying that you have to follow
22 necessarily this sort of a chart. I'm saying this is

1 what most formulation people will follow -- or pre-
2 formulation people will follow intrinsically.

3 Then you say well, if the dosage form is
4 a solid, it's going to be a capsule, a tablet, or
5 other. There are no pills, by the way, Gary, left any
6 more.

7 So you go from tablets to selecting which
8 particular choice you have for manufacturing the
9 tablets, for the various critical attributes taken
10 into account. There's wet granulation, dry
11 granulation, dry compression.

12 Once you've selected that then the
13 attributes that are potentially critical should be
14 fairly well known. And this is a case where maybe
15 modeling gives you the prior knowledge in some cases.

16 This is then cycled on data to determine
17 what the risk really is. And in this case you might
18 think of it in light of what we heard this morning as
19 generating prior knowledge. And then hopefully you
20 identify the critical attributes.

21 If you move this on logically to the
22 process design, you start from where we just ended

1 with the raw material critical attribute selection,
2 take this up the ladder so that what is the model for
3 the process. And the what processes are viable,
4 you've already answered that in the raw materials
5 section based on the mechanical and chemical
6 properties of your material.

7 What's the model for the process critical
8 control points -- say that three times fast -- and
9 then the basis, the possible PCCPs based on the raw
10 materials and the choice of response factors. And
11 there you go continually until you do your design of
12 experiments and ID preliminarily what the PCCPs would
13 be, cycle back until you again optimize it.

14 So what I would say is that all of these
15 are logical top level questions. And the more
16 detailed questions are the ones that we were just
17 going through in the raw material or the API
18 selection.

19 Let's use an example. I actually picked
20 on Q6A quite independently of Ajaz. He knew that I
21 was going to do this because I sent him the slides.
22 But he didn't tell me he was going to be doing it.

1 I'm not picking on Q6A particularly but it
2 was just a good example to use because there are some
3 good things and some not so obvious things in the
4 event tree that Q6A represents. And I think what
5 we're really talking about doing is changing it into
6 a decision tree based on what we're talking about
7 here.

8 So Q6A in the first table, I can't
9 remember if this is 6 -- I think it's table -- I can't
10 remember what it is but at any rate, the first
11 question is can different polymorphs be formed? Okay,
12 this is fine. If you understand the solid state and
13 know polymorphs are formed, you're done. So there you
14 are at no and no further action.

15 If there are forms, they must be
16 understood. So it's not enough to just say yes, let's
17 characterize them. What you really have to ask is
18 what are the relative stabilities of the low energy
19 forms. And if you don't know the relative
20 stabilities, at least explore what it is that's --
21 what information you have that's possible to help you
22 explain that or at least elucidate it.

1 And those are the right questions for the
2 scientist and regulators. And as we go through the
3 next few tables, we'll try to carry out the same
4 analysis.

5 The second part of the table is do the
6 forms have different properties, solubility,
7 stability, melting point, et cetera? If it's no, then
8 no further testing or acceptance criteria for drug
9 substance required.

10 So that's okay. But when we're
11 considering the product, the logical first question
12 should be quite different because the answer here is
13 if they do have different properties, the question is
14 is drug product safety performance or efficacy
15 effected? Well, before you get to that question, you
16 really want to say based on what is known about the
17 material and the process, what, if any, change in form
18 would be expected?

19 So if I have something that is
20 particularly soluble and I'm wet granulating it and I
21 know that there are form possible, then I might expect
22 that I could either change a less stable form to a

1 more stable form during granulation or I might trap a
2 metastable form on drying. Those are the sorts of
3 questions you would ask long before you got to the
4 point of whether or not it actually occurred.

5 So if the answer is none based on the
6 scientific understanding, then a confirmatory test
7 during development should suffice because it is
8 possible but you're saying that there's no logic to
9 say that it should happen.

10 Otherwise, if there is a potential, the
11 next question should be is the observed change the one
12 that you expected? Now we've just gone through this.
13 You should know what change you expect to see based on
14 your process and the properties of the API. And the
15 question is does the change that occurs match what you
16 expect?

17 And then finally, this is the question
18 that will give hiccups to a few folks I suspect, is
19 what was the rationale for selecting the processing
20 step responsible for the change?

21 Then we're back to the tree again. So on
22 the third section, it says does the drug product

1 performance testing provide adequate control if
2 polymorph ratio changes during the formation of the
3 product?

4 And here it might be reasonable to ask
5 instead does the performance testing relate to the
6 performance of interest? And this is what we were
7 talking about before.

8 Now you may not have an answer for this
9 but that's clearly the question that you would want to
10 know. If the change in ratio makes no difference,
11 then it may not be an issue. If it does, obviously
12 you have to establish acceptance criteria. And if the
13 answer is based on scientific understanding, we're
14 back to here.

15 A next question would logically be based
16 on the understanding of the form's behavior, what
17 would the expected trend -- that should be expected
18 trend in transformation be? So if I have a ratio of
19 polymorphs and obviously one of them is more stable
20 than the other, you would expect against any other
21 information that the metastable form would transform
22 to the stable form.

1 If it doesn't then you've -- well, number
2 one, you have the paper. But number two, it brings
3 into question whether or not you understand what's
4 going on.

5 And now these questions are pretty
6 specific but these are the kinds of questions, these
7 are the level of specificity that you would really
8 like to know in advance of seeing the questions I'm
9 assuming.

10 Going to the second part of the third
11 table is does a change occur which could effect safety
12 or efficacy? And here I would say does the observed
13 change correspond to an understood and expected
14 transformation? If not, the system is not well
15 understood -- is not as well understood as you thought
16 it was.

17 And if that's the question, then
18 presumably you would have addressed these sorts of
19 issues early on but the value of this is that if
20 you've addressed each of these during development,
21 then by the time it gets to the regulator and they're
22 essentially echoing these questions, you'll have

1 answers for them and that would expedite the process.

2 Virtually all companies on the innovator
3 side are doing polymorph screens. We've recommended
4 focused polymorph screen for generics. Because of the
5 number of companies, I don't know the relative ratios
6 but as an example, this would be the case.

7 Well, let me use the last few minutes here
8 to talk about a couple -- a specific example. I may
9 skip the last section. Judy, just give me a high sign
10 if my time starts to run out. Six? Okay. Yes.

11 Okay, this is an example that is actually
12 from -- largely from Greg Amadon at Pfizer in
13 Kalamazoo from talks that he's given over the years.
14 But it illustrates one of the things that Dan had
15 raised and Garnet had raised with respect to
16 excipients. And that's the mechanical properties.

17 We treat table formulation more or less as
18 a black box. Not so much from the chemical sense
19 because the chemistry is often well known by the time
20 you get it. Certainly if it's generic you know it
21 pretty well but in terms of what you would use and how
22 and what the ratios you would use to give a tablet

1 that had acceptable strength characteristics, counting
2 uniformity as well as performance characteristics.

3 And if we look just at the mechanical
4 properties elements or aspects of the raw materials,
5 there are several tools and I'm just going to
6 introduce one here which are the Hiestand Indices.
7 And Everett Hiestand, when he was at Upjohn years ago,
8 developed indices for bonding, brittle fracture, and
9 strain measurements as a function of relatively easy
10 to get data from relatively small amounts of material.

11 And these data are tensile strength,
12 hardness, and things that you can get to fairly
13 easily. And I won't go into the details but let me
14 show you some of the results.

15 And if you look at the overall range of
16 materials that we are involved with in normal
17 manufacturing, I would say this extends even more so
18 to biologicals, is -- I should say even to
19 biologicals, not more so -- everything we deal with if
20 you look at in terms of the mechanical properties and
21 just focus on this column for a moment where we're
22 talking about the description, falls into the category

1 of moderately hard to soft. There's nothing that's
2 really hard. There's nothing that's really soft.

3 So everything falls into this category.
4 And here you see APAP at the top and starch at the
5 bottom. This is from a great chapter by Rowe and
6 Roberts in mechanical properties.

7 So we're really dealing with a fairly
8 limited range. And we're dealing with a fairly
9 limited number of excipients. But the APIs, of
10 course, can change.

11 Well, if you look at the importance of
12 evaluating these indices up front, this is an example
13 of Phenacetin. And here we have a case where in the
14 compaction -- in this compaction, in the tri-axle
15 compactor, we have a compound in Phenacetin with a
16 very low bonding index.

17 And the result of that is that even though
18 the Brittle Fracture Index is not too bad, that in the
19 dye it comes apart. Now this is -- I'll show you a
20 couple other summary slides but the point is that
21 there are threshold values, if you will, that I would
22 imagine would lend themselves fairly well to

1 statistical analysis apriori that have to do -- that
2 are shown here actually that have to do with their
3 relative properties that should dictate this apriori.

4 So if you look at that bonding index of
5 excipients versus drugs, you see as no surprise that
6 microcrystalline cellulose has very high bonding
7 index, right, which is also why it's a compaction aid.

8 If you look at drugs, they vary but drugs
9 tend to be, on average, lower. And if you look at
10 what it takes to make a good tablet, you'll have to
11 have some combination of those.

12 Brittle fracture index is the -- is, I
13 guess, in a sense one of the most dramatic of the
14 indices because when it fails, it fails spectacularly.
15 Here is an example with a very high brittle fracture
16 indices.

17 High brittle fracture is bad because it
18 means that on expansion, the compact can't maintain
19 itself. And what you see here is with a high brittle
20 fracture, as soon as the compact is ejected, it
21 laminates. It just comes apart. And if you were to
22 put an acoustic sensor on it, you could hear it. I

1 mean it's very noticeable.

2 And similarly, if you look at the brittle
3 fracture index now across a series of excipients, you
4 can quite easily determine which ones have the brittle
5 fracture indices that are less desirable or more
6 desirable.

7 And as Garnet talked about earlier, corn
8 starch being one of our formerly primary diluents, had
9 its own issues with respect to brittle fracture index,
10 which is why a lot of it was granulated, wet
11 granulated.

12 So put this together and what Greg had
13 done here was to plot the brittle fracture index
14 versus the percent of drug mixed with an excipient for
15 several compounds listed here, Drug X, which is
16 Pfizer, I'm assuming that's not one of the bathtub
17 drugs.

18 And what it shows is that adding 30
19 percent of a non-brittle excipient makes a mixture
20 much less brittle and, in fact, quite compactible,
21 which could be predicted with grams of material. So
22 we're talking a long time before you get to a kilo lab

1 and certainly in the generic industry something you
2 could do Day 1 with the proper equipment.

3 And Greg went on to develop a semi-
4 empirical model that shows how H here is any of the
5 indices or properties so here we have hardness,
6 tensile strength, brittle fracture, and bonding index,
7 are all related via a logarithmic relationship so that
8 there at least is within products and within
9 excipients a predictability.

10 So if you think about this in terms of the
11 scope of excipients that are available to us, it's
12 already been -- data has already been collected on
13 most of these excipients so these are available in
14 literature.

15 So there is the possibility of using these
16 data as is to do prediction up front with either very
17 little measurement or at least feeding backwards.

18 As Ajaz had said, if you have in a big
19 company I don't know how many products a big pharma
20 makes. Over a hundred I suppose, right? And generics
21 can make up to 500 at a plant, the amount of data you
22 have is staggering. To be able to take these data and

1 bring them back, it's impossible to imagine that you
2 couldn't perform some data analyses that would give
3 you your prior information for your Bayesian
4 treatments, for instance.

5 No?

6 MEMBER SINGPURWALLA: There's a confusion
7 of concepts.

8 MEMBER MORRIS: Except for the confusion
9 of concepts --

10 (Laughter.)

11 MEMBER MORRIS: -- that's absolutely true.
12 Right. Yes, we'll get back to that.

13 Okay. So if we look at our beginning
14 slide again at this stage, then the questions that you
15 would expect to be associated with these steps so far
16 would be what were the principles applied and were
17 they appropriately applied?

18 So if you're using the bonding indices and
19 the brittle fracture indices, were they appropriately
20 applied? And I would say the answer is going to be
21 yes in most cases for the folks who have been using
22 them.

1 How are the critical attributes identified
2 in the formula design? I mean this is Product
3 Development History 101. It exists in many companies.
4 Whether or not it's shared is a different question.

5 The next level, as we talked about on the
6 second pyramid, is the identification of process
7 critical control points. And how am I doing time-wise
8 here? I'm over?

9 CHAIR BOEHLERT: Not so hot.

10 MEMBER MORRIS: Okay. I'll skip through
11 this section.

12 CHAIR BOEHLERT: Well, you know, we do
13 have some questions to address for Ajaz this
14 afternoon.

15 MEMBER MORRIS: I understand.

16 CHAIR BOEHLERT: I don't mind keeping you
17 late but I think, you know, the rest of your Committee
18 members might mind.

19 MEMBER MORRIS: Yes, I've got two slides
20 left.

21 CHAIR BOEHLERT: Okay, good.

22 MEMBER MORRIS: Because I'll skip the

1 example but I want to get in this point. And that is
2 if you look at the relationship between PCCPs and
3 scale up with monitoring, the basic approach is
4 captured as two simple process understanding premises.

5 First is that PCCPs are preserved
6 throughout the scale up process. That doesn't mean
7 that the magnitude doesn't change. It may. But the
8 variables being monitored reflect the state of the
9 process.

10 And second, as was alluded to this
11 morning, and I can't remember who, I apologize, is
12 that monitoring material properties makes scaling less
13 equipment dependent so that even as you change
14 equipment, if you're monitoring the same PCCP, the
15 value may change but the absolute -- or I shouldn't
16 say the absolute but the PCCP being monitored is the
17 accurate one.

18 And I'll just skip to the last slide which
19 says that based on that example that you just saw,
20 that in addition the next questions are how did you
21 identify the critical attributes?

22 The next question is how did you identify

1 the PCCPs? What were the basis for the analyses
2 selection? What are the supporting data for all of
3 the above? And finally, the product development
4 history should reflect everything that you've said.
5 And if it doesn't, it's a different issue.

6 And asking the right questions at the
7 right time, feeding forward and back between
8 disciplines, designing the product and process against
9 meaningful metrics must start in R&D. Development of
10 meaningful specs, of course, results only from the
11 identification of the scientific basis. Real-time
12 monitoring is a big advantage but not absolutely
13 necessary.

14 Process understanding for quality control
15 is known functionality; that is the models against
16 which data are used to control the mark. And I can't
17 emphasize the model basis enough.

18 What you get from this, I think we've
19 heard quite a bit. I'll just -- this last point here
20 is that in tech transfer, you get a more realistic
21 process to transfer, which is Gerry Migliaccio's leg
22 up statement from Arden House saying that we don't

1 need a final thing but we really could use a leg up so
2 we're not starting from zero.

3 And finally just to acknowledge Greg
4 Amidon from Pfizer in Kalamazoo, CAMP, again, with
5 G.K. as our leader in CAMP, of course, Abhay Gupta is
6 the graduate student who did the example you didn't
7 see. And finally the team, which was headed up by
8 John Clark but include Moheb and Rafad and a lot of
9 the people that are here as well so with that I'll
10 end.

11 Thank you.

12 (Applause.)

13 CHAIR BOEHLERT: Thank you, Ken. Any
14 questions for Ken before he departs?

15 (No response.)

16 CHAIR BOEHLERT: Sorry we missed the
17 example. I was interested but, you know, we are
18 running out of time.

19 MEMBER MORRIS: No problem.

20 CHAIR BOEHLERT: Okay. Ajaz did you have
21 a few comments?

22 MEMBER HUSSAIN: No, I think what we have

1 tried to do is to give you a sense of what is
2 happening outside FDA, especially in ICH, ASTM, what
3 is happening within FDA, especially from a more
4 management perspective but also from a science
5 perspective.

6 And we're hoping that I think if I could
7 just put the slides on the questions -- this is a
8 series of questions that we posed to make sure that we
9 are on the right track. And I'm hoping that your
10 discussion and general thoughts on some of these
11 questions might be useful.

12 You have a printed copy in your packet.
13 Usually we place this on the -- but maybe I can stand
14 here and maybe forward this for you. So it's up to
15 you how you wish to give us your feedback on these
16 questions posed. So --

17 CHAIR BOEHLERT: Well, I propose that we
18 go through these in order. First and third are
19 relatively short. The second one has many subparts.
20 So we'll start with the first one.

21 Do you agree that current activities
22 within ICH and ASTM are helping us, FDA, move toward

1 the desired state? They seek our recommendations on
2 how to ensure these activities are synergistic. So
3 I'm looking from comments from the Committee.

4 Everybody is saying yes. And particular
5 comments? G.K.?

6 MEMBER RAJU: I agree, very strongly
7 agree. I'm not that familiar with the ICH process but
8 I did go to the ASTM process. And it really is very
9 synergistic as Don had said. They're putting a lot
10 more detail to it and bringing in a lot of outside
11 industry expertise.

12 So I think they are synergistic. And the
13 synergies are happening with the individual people.
14 I don't know whether there is a possibility for a more
15 structural synergy among the people here but in terms
16 of what FDA does and what ASTM and ICH does, when I
17 spoke to Don earlier today and I asked him that
18 question, he didn't think so.

19 But there could be a time when it starts
20 becoming really duplicative. I've seen people talk
21 about pharmaceutical development in at least five
22 different organizations. Everybody's versions of what

1 they want and what is risk.

2 Everybody has risk tool box, these five
3 organizations. So at some point, it's good to have a
4 lot of people do it to get the debate. But at some
5 point it's probably not.

6 And we're not there yet but we probably
7 will be in the future.

8 MEMBER HUSSAIN: I think I'll just repeat
9 what Don had said in the sense, I think, the scope and
10 the depth and the details. These are two different
11 standards or guidances, whatever you want to call
12 them.

13 If you look at the E55 structure, what
14 we're hoping to do there is to create a framework.
15 E55's focused primarily on standards for PAT. And
16 development is clearly broader than that in a sense.

17 And we're hoping the details that would
18 come about through ASTM's standards would be standards
19 that can be cited. And we really don't have to issue
20 Agency guidelines on some of those things.

21 So Q8, Q9, Q10 will evolve with a very
22 different focus. And the ASTM would be more of a

1 technical standards rather than guidelines and so
2 forth. So I think there is a difference.

3 CHAIR BOEHLERT: Ken?

4 MEMBER MORRIS: That raises -- oh, I'm
5 sorry, were you not done, G.K.?

6 MEMBER RAJU: No, I'm all set.

7 MEMBER MORRIS: The one question and it
8 actually came up at the last ASTM meeting, will the
9 ICH be able to -- or not be able to but will they take
10 advantage of the ASTM standards in citing them during
11 their discussions?

12 MEMBER HUSSAIN: Well, that's a very good
13 question. And I had brief discussion with John
14 Berridge about this a the sense. The Yokohama meeting
15 in November is probably when I would like to sort of
16 bring this topic up to ICH and keep them in the loop
17 on this.

18 John and I discussed this before the
19 Washington meeting and felt that well, the ASTM had
20 not crystalized far enough to really share some of
21 this. But I think starting in Yokohama in Japan in
22 November, we'll make sure that the ICH is fully aware

1 of what's happening here and seek that synergy.

2 Informally, I have discussed this with all
3 of our regular counterparts in Europe and Japan. And
4 there are a number of European members on this ASTM
5 and Japanese members. And I'll broach the subject of
6 maybe the regulators joining some of the ASTM groups
7 also. That's a possibility.

8 MEMBER GOLD: Ajaz, you're -- I just want
9 to ask, you're not going too fast in contrast to the
10 regulators elsewhere, the Japanese or the Europeans,
11 are you?

12 MEMBER HUSSAIN: I hope we are.

13 (Laughter.)

14 MEMBER GOLD: Well, we have to move in
15 concert. And do you believe that you're going to be
16 able to move in concert?

17 MEMBER HUSSAIN: That's the real --

18 MEMBER GOLD: I asked the real question.

19 MEMBER HUSSAIN: -- question. Well, move
20 in concert in the sense we will lay the foundation and
21 hopefully they'll come and join us.

22 (Laughter.)

1 MEMBER HUSSAIN: No, I think the ICH
2 process, the Q8, Q9, and so forth, clearly are toe to
3 toe, we're moving together in a completely harmonized
4 fashion.

5 We have plans I think with respect to the
6 PAT process itself, we have an ongoing dialogue with
7 the European PAT Team. I think we are fairly aligned
8 in many ways the aspect which is of interest is our
9 European regulatory colleagues are hoping that a lot
10 of the PAT concepts will get incorporated in Q8.

11 And the definition of PATs exactly we
12 agreed in Washington will be the DA definition. And
13 Yokohama will get this concept in Q8 in a very broad
14 perspective. So that's one approach we've got.

15 Plus, I think, our PAT guidance is
16 becoming final soon with announcements. And we are
17 planning a series of workshops, inviting our
18 regulatory colleagues from Europe and Japan to
19 participate in the planning Committee. We're working
20 with ISPE in setting up some of these workshops in
21 Europe and Japan. And the process has just started.

22 MEMBER GOLD: Well, I want to say I'm very

1 impressed by what I've heard today and reading the
2 black book that you sent ahead of time. I just want
3 to make sure we're not so far ahead of the others that
4 we are not going to have unanimity.

5 CHAIR BOEHLERT: Okay. Joe?

6 MEMBER PHILLIPS: I think definitely I
7 support everything that's been said by the previous
8 commenters. But the activities in ICH and ASTM are
9 definitely moving us forward toward the desired state.

10 What do we need? We need continued
11 commitment of the key players, many of whom are
12 sitting in this room, from both sides of the ocean.
13 We have the regulators, we have academia, we have
14 industry on both sides.

15 And from what I'm hearing, I have a lot of
16 contact with industry and regulators in Europe and
17 Japan, there's a lot of interest in this activity.
18 And they just want to be kept abreast of what's
19 happening. And I think the FDA is to be commended for
20 their efforts to keep everybody well informed. Office
21 of Compliance has been working heavily in some of
22 these areas.

1 Any time some of my colleagues in ISPE
2 have had a question to raise, it's always easy to get
3 a direct answer from this team. So I just hope that
4 the same team stays committed and involved because it
5 takes prime movers and shakers, so to speak, to keep
6 this thing going.

7 But it's going very well at the moment.
8 But who would have thought two years ago we'd be at
9 this point?

10 MEMBER HUSSAIN: Okay. Should I move on?

11 CHAIR BOEHLERT: Yes, let's move on to the
12 next one.

13 Nozer?

14 MEMBER SINGPURWALLA: What is the desired
15 state?

16 PARTICIPANT: California.

17 (Laughter.)

18 MEMBER HUSSAIN: Well, I think I was
19 getting tired of showing my desired state slides,
20 maybe I ought to keep these. It's prior knowledge.

21 (Laughter.)

22 MEMBER HUSSAIN: So prior is all mixed up

1 right now so -- no, I think the desired state simply
2 is to -- in a -- sort of a conceptual way is to
3 increase the level of scientific knowledge that is
4 shared between the agencies so that we can make more
5 science- and risk-based decisions which removes --
6 brings or removes the hurdles for continuous
7 improvement and reduces the burden on all of us. And
8 improves the efficiency of the whole system.

9 I think clearly we believe that the
10 quality of the products available to the U.S. public
11 is adequate for intended us. We have an opportunity
12 to improve the efficiency but at the same time a few
13 years from now, the complexity of our systems is
14 increasing especially with biophysics, nanotechnology,
15 and others that are coming. And we are getting a
16 better handle on variability today through
17 pharmacogenomics and so forth.

18 So ten years from now, the current aspects
19 of quality may or may not be adequate. So I think
20 it's preparation for the future as well as improving
21 the efficiency of today's systems.

22 MEMBER SINGPURWALLA: Well, if that be the

1 case, then I'd like to comment on that particular
2 issue.

3 Based on what I've been hearing and what
4 I've been seeing, I find the progress of matters is
5 rather academic and conceptual. There are general
6 principles, principles of quality control, principles
7 of management, principles of data analysis. The focus
8 has been a discussion of the principles.

9 Somehow we have to get down to a
10 demonstration of how these things work. And I believe
11 I have said this before. What I think is really
12 needed are some concrete examples. And I'm proposing
13 that the FDA work in collaboration with industry, the
14 drug manufacturers, both the generic and what is it
15 called, the creative, the original --

16 PARTICIPANT: Innovators.

17 MEMBER SINGPURWALLA: -- the innovators --
18 actually I wouldn't like the word innovator if I was
19 a generic drug manufacturer but I think to work in
20 collaboration with them and come up with demonstrable
21 examples of how these new ideas come to work.

22 Otherwise it becomes like a lecture in a

1 business school where they talk about everything and
2 need to follow up with case studies.

3 MEMBER HUSSAIN: The point is well made
4 and I think well taken. That's a struggle because,
5 for example, with the PAT arena, we have about seven
6 submissions at different stages; one approved, one
7 major complete PAT submission from start to finish.
8 We actually have a comparability protocol in house
9 right now. So -- but it's proprietary. We cannot
10 share it.

11 And that's a struggle we often have is we
12 are unable to share what we get because we're not
13 allowed to share it. We are working with Pfizer, for
14 example, through a collaborative discussion
15 development agreement so you will see some
16 publications coming out on some technologies through
17 that collaboration.

18 We are in discussions with two other
19 companies on starting a collaborative discussion
20 development agreement so there will be publications
21 but I think G.K. Raju made that point also. I think
22 we have an acute need for a case study. Otherwise

1 this remains theoretical and I agree with Gary in the
2 sense we have been discussing concepts for the last
3 two, three years.

4 But at least we have agreed on the
5 concepts. It's time to move on to some tangible
6 examples that are necessary. And we can do some
7 through our research which we are doing at Purdue and
8 others. But I think you really need a real life
9 example. Somebody has to step up and say we want to
10 share this.

11 MEMBER SINGPURWALLA: And there is a
12 little bit more to that. Not only should there be an
13 example but in the end, industry should come up to
14 you, to the government, and say thank you, government,
15 because you made us do these things. We have
16 benefitted and these are things we would not have done
17 on our own or it didn't occur to us. And you have
18 paved the way and not only improved our profitability
19 but improved the general state of the art.

20 I think you need something much more
21 tangible so that industry can come back and compliment
22 you if that's possible.

1 MEMBER HUSSAIN: I'll look at Helen. Let
2 her answer that one.

3 (Laughter.)

4 CHAIR BOEHLERT: Ken?

5 MEMBER MORRIS: Yes, just -- we've talked
6 about this and in terms of the reduction to practice,
7 if you will, not in the patent sense, and we're doing
8 things now not exactly in lock step with FDA but in
9 terms of developing processes by -- in the quality by
10 design sense that certainly will serve as a partial
11 example, I think.

12 And even though it's not being done under
13 the -- it's not being funded by FDA but they're
14 participating in it so at least we'll get to the point
15 of formulation of process design, I think, which
16 should be a concrete example that will be publishable.
17 And that's ongoing now. So -- but I realize that's
18 only one and it's only partial but to the point.

19 MEMBER HUSSAIN: Okay. I think going on
20 to some other set of questions, two has subparts. To
21 facilitate momentum with the desired state, FDA is
22 providing incentives by ensuring that use of new

1 technologies and additional information about a
2 minimum acceptable submission standard will not be
3 regulatory requirements.

4 Gary raised that again. I think that's an
5 important point. But will be opportunities for
6 companies to demonstrate a higher level of process
7 understanding and risk mitigation. And, therefore, a
8 basis for regulatory flexibility. That is example to
9 reduce the need for prior approval of supplements and
10 so forth.

11 For implementation of these concepts a
12 clear demarcation of "minimum" and optional
13 information is necessary. And I think this was a
14 significant point of discussion at our ICH Q8. And as
15 ICH Q8 goes to Step 2 in November, you will see how we
16 have tried to sort of address that.

17 But I thought I'll pose this question to
18 you in the sense this is a significant challenge to
19 sort of achieve this goal. And especially because the
20 European and the U.S. systems were quite different.
21 And the expectations in Europe were different than
22 what we have, the minimal expectation.

1 So any thoughts that you can share or any
2 insight that you can share on this would be very
3 helpful. But let me just complete the question, Part
4 B of that also.

5 Quality by design and manufacturing
6 science are considered foundation for rationale risk-
7 based decisions. Please recommend how these
8 principles should be linked to risk to suggest failure
9 mode effect analysis. So we're looking for general
10 principles that, I think, you would wish us to keep in
11 mind as we progress in this area.

12 MEMBER SINGPURWALLA: I think I can
13 respond to Question B. Question B, of course, the
14 failure modes and effects analysis is basically a
15 technology mostly based on engineering or whatever
16 subject matter discipline is at hand to essential work
17 your way up towards probabilities of certain
18 undesirable events.

19 And so those probabilities feed in to the
20 decision, you know, to the decision tree. So the
21 failure modes and effects analysis would be an event
22 tree, which traces the course of events which lead to

1 failure.

2 And superimposed on that would be the
3 probabilities of the various sub-events which lead to
4 failure. And that probability will be fed into the
5 decision-making paradigm. So those two are easily,
6 you know, are easily put together as a package. And
7 that's the right way to go.

8 So the question is a good one. And there
9 is an answer to it.

10 CHAIR BOEHLERT: Gerry?

11 MR. MIGLIACCIO: Let's talk about A, Ajaz.
12 I guess I have this -- it almost implies and A or a B,
13 one or the other.

14 And when I think about the optional
15 information, the optional information will come in
16 degrees, not you either have it or you don't, you
17 know, we can't look at the NDA as a line in the sand.
18 So you may get some of that optional information in
19 the NDA and six months later, you may get much more.

20 And so the regulatory flexibility granted
21 with the NDA is at a certain level. And the
22 regulatory flexibility granted six months down the

1 road when we supplement with that greater process
2 understanding becomes greater.

3 So I'm a little concerned about the clear
4 demarcation statement that it's yes, there is some
5 information that will be optional. But the degree
6 also has to be understood. And I like Gary's if this,
7 then that, you know? If we could put that map
8 together.

9 If you get this, then that's the
10 regulatory flexibility that comes along with it. And
11 then if you get more of that, that's what comes along
12 with that.

13 MEMBER GOLD: Gerry, I'm not clear -- I
14 don't see it your way. I interpret that question as
15 saying what more than we give presently would be
16 advisable for improving our knowledge or improving the
17 knowledge of the process that we provide to the FDA?
18 And that I see this as not asking for necessarily more
19 than we're giving now in order to get approval.

20 MR. MIGLIACCIO: No, in fact, we're not
21 talking about, you stated more. We're saying
22 different. The knowledge that we're providing is

1 different. It's more science based, more risk based.

2 MEMBER GOLD: No, I understand. But I
3 don't see that as asking for anything more in terms of
4 more science or more knowledge than we're currently
5 supplying in order to obtain an approval. There is
6 nothing in that that I see that requires us to
7 elaborate beyond the information we're providing
8 currently.

9 However, if we do provide more
10 information, then this presumably allows us to make
11 changes with lower requirements, that is lower time
12 limit requirements. So we may be able to go from a
13 PAS to a CB30 or whatever. But I do not see that
14 statement as saying we must provide more.

15 MR. MIGLIACCIO: No, and I didn't imply
16 that we must. What I'm saying is that what we provide
17 will be in degrees.

18 MEMBER GOLD: Yes, I certainly think
19 that's possible.

20 MR. MIGLIACCIO: There's an impression
21 sometimes in these discussions that it's all coming in
22 the NDA. And it's not all coming in the NDA. It will

1 be learned. It's a continuous learning process. It
2 will be learned in the first six months of commercial
3 manufacturing.

4 And, therefore, the flexibility has to be
5 there to go back in with more process understanding
6 and, of course, get greater regulatory flexibility.

7 MEMBER GOLD: But, Gerry, I've also seen
8 instances where companies have more information
9 available to them at the time of the filing that they
10 don't believe they need to provide because the FDA has
11 not called for it. And so they just hold it in their,
12 you know, they hold in their own file.

13 MR. MIGLIACCIO: Because the perception
14 now is if we supply it, it will extend the review
15 period.

16 MEMBER GOLD: Correct. Or may extend the
17 review period.

18 MR. MIGLIACCIO: That's correct.

19 MEMBER MORRIS: Is this trying to get,
20 though, at the question we were talking about earlier
21 which is, you know, instead now we have, you know,
22 three batches and then you file? Or is this saying

1 that there's no set number?

2 MEMBER HUSSAIN: No, I think -- well, let
3 me give you an example that I think might be relevant
4 here. I think Gary had some of that information in
5 his slide in the sense, in particular on the generic
6 side we have a tendency to be quite conservative in
7 terms of actually requesting an executive batch
8 record.

9 And in some cases or sometimes, that
10 executive batch record is your sort in process control
11 and so forth. So any change requires a supplement.

12 But that is because we often have limited
13 information in how to establish specifications, one
14 biobatch and so forth.

15 So that is the current way of thinking.
16 That's fine.

17 What I might suggest is the optional type
18 of information might be you have pharmaceutical
19 development information and other information that
20 provides much more flexibility that would not -- that
21 would allow us to move away from that executive batch
22 record as the sort of a basis of sort of establishing

1 something to something more of process understanding
2 basis.

3 So that's how we're sort of approaching
4 it.

5 MEMBER HUSSAIN: Gary and Moheb, any
6 thoughts on this?

7 (No response.)

8 MEMBER RAJU: Judy?

9 CHAIR BOEHLERT: Yes, G.K.?

10 MEMBER RAJU: On the two questions, Ajaz,
11 I go B first and A second.

12 On B, I believe that the priority should
13 be since manufacturing science and quality by design
14 are both levels of performance and states of knowledge
15 and can be changed by processes, that on B the
16 priority should be on defining those levels and the
17 processes that enhance it.

18 And the tools -- so the tools only have
19 context in that -- only have meaning in that context.
20 I do not want to say please recommend how these
21 principles should be linked to risk tools yet. We
22 have to focus on the characterization and the

1 processes for it.

2 The tools can be a tool set just like we
3 have a lot of tool sets. The links shouldn't be made
4 too early because we haven't done the first step
5 first. So let's keep the tools in a portfolio of
6 tools and understand them, bring them in from outside
7 the industry into ours.

8 Let's focus on our industry and defining
9 what we do transparently based on principles of
10 science. And then connect the tools. So that would
11 be my thought on that.

12 And there's a scientific process to the
13 tools, too.

14 MEMBER HUSSAIN: If I may --

15 MEMBER RAJU: Sure.

16 MEMBER HUSSAIN: -- suppose we remain with
17 an empirical approach to this so we don't have a
18 mechanistic understanding and so forth, so we are
19 seeking causality or we're seeking correlation through
20 an empirical model approach, say design of experiment,
21 okay?

22 Now the number of potential factors that

1 may be critical can be a large number depending on the
2 process. And an approach could be is this is -- I'm
3 basing this on the presentation by Amgen at Arden
4 House, is you start with a failure mode effect
5 analysis based on all your expert opinion information
6 that's there based on historical know how to sort of
7 tease out what may be the critical variables. And
8 then design your experiments around that.

9 So that is sort of another way of looking
10 at it. So that's -- there are many different options
11 there because I think if somebody wants to do a design
12 of experiments, they really have to manage the
13 resources and their commitment very carefully.
14 Otherwise that can get out of hand.

15 So that's one way of approaching that.
16 But the other way of approaching that is through
17 screening experiments early on and then sort of
18 designing -- defining your design space and then doing
19 a failure mode effect analysis. So you need to have
20 flexibility of going either way.

21 MEMBER RAJU: So this is Bob Sweeney's
22 work at Amgen?

1 MEMBER HUSSAIN: Right.

2 MEMBER RAJU: He did a nice job of saying
3 this is the process. Here are the variables. And then
4 he put fault modes into context.

5 MEMBER HUSSAIN: Correct.

6 MEMBER RAJU: Because he did that, it was
7 a very good story.

8 MEMBER HUSSAIN: Yes.

9 MEMBER RAJU: But it's not clear that
10 that's been done. And if it's not been done, then it
11 has to be done first before we bring the FME -- the
12 tool only has context within a goal and a process to
13 get to that goal. So I think it works fine that way.

14 In terms of A, I have a somewhat similar
15 answer but at this point because the demarcation, you
16 said that what you get in a submission is variable.
17 And you said you have some information, more
18 information, sometimes you have less information, and
19 sometimes you have different.

20 The criterion of what is more and what is
21 important has not been laid in place yet. So it's
22 somewhat dependent on the company and their

1 interpretation and their strategy.

2 It seems like two things would help on A.
3 First, you said it was minimum and optional.

4 Probably independent of the answer to A,
5 to make sure that everybody believes -- that everybody
6 in the FDA believes that and will implement that is
7 extremely important because everybody -- I can hear a
8 number of cases where people say I know Helen and
9 Ajaz, they would believe that. But how do I know
10 about the guy who is going to do my review? Or the
11 person who is at the field, for example, which may not
12 be relevant in this case.

13 So just making sure that what you believe
14 in is somewhat uniform although we all, as human
15 beings, we'll never be uniform.

16 Second, how about making it one of two
17 possibilities? Making it the company's choice because
18 it's still somewhat not fully characterized, to
19 present to you here is minimum. And have here is the
20 optional, what shall we do with it? Either submit
21 them both and say you make a decision based on this
22 and we can get a better deal based on this?

1 Or here is the optional. Can we discuss
2 with you whether we should submit it or not?

3 So they make their first call on minimum
4 versus optional. They decide to submit it. You start
5 with the minimum and your specifications get changed
6 based on that. But they don't pay the price for the
7 optional because you say they wouldn't.

8 You get the minimum and the paying the
9 price is more in the context of a reward. And it
10 could be done informally first before it's formal.
11 How about that? It seems like -- just think aloud
12 now.

13 DR. NASR: If you allow me to make a
14 simple comment here. I think this is very good
15 discussion. But in my mind the issue before us is
16 much simpler. And let me elaborate a little bit.

17 I think the existing system that we have
18 is working. Why is it working? Because we have
19 quality pharmaceuticals in the market. So the
20 existing system is working.

21 So in the future, I think companies,
22 sponsors, will have to follow one of two approaches.

1 The existing regulatory process and the regulatory
2 framework with the guidances in ICH and the
3 submissions and the meeting or lack of or whatever.

4 And we will continue on and when you make
5 a change, you have to come to us, we'll supplement.
6 And we'll evaluate the supplement and we'll make
7 recommendation. And you go ahead and you manufacture
8 or not manufacture.

9 The future paradigm we are describing and
10 sharing with you today and Ajaz, I think would agree
11 with that over the years now is you share with us in
12 advance, and advance means either at the NDA stage or
13 shortly after or long after, your understanding of the
14 manufacturing process, your ability to deal with the
15 change, and then back to such a change on the critical
16 quality attributes.

17 And based on that understanding, you're
18 sharing in the form of pharmaceutical development
19 report or comparability protocol or whatever, we will
20 give you the freedom to manage your own change.

21 So in my mind, it's very simple. You can
22 stay put and do what we are doing now and continue to

1 have quality pharmaceuticals in the market. Or if you
2 want to follow the quality by design and the new
3 approach, which we believe is beneficial to you, to
4 us, and to the public, and that provide you with the
5 regulatory relief that you have been asking for for
6 years and years to manage your own manufacturing
7 process.

8 So in my mind, it's fairly simple.

9 MR. MIGLIACCIO: Judy?

10 Moheb, do you accept that we will have
11 some hybrid situations?

12 DR. NASR: We do. When I said
13 comparability protocol, that's a hybrid.

14 MR. MIGLIACCIO: Yes.

15 DR. NASR: When you talked about
16 supplements shortly after, that's a hybrid.

17 MR. MIGLIACCIO: Right. So we'll have --

18 DR. NASR: It's not a clear cut --

19 MR. MIGLIACCIO: Right.

20 DR. NASR: -- either or.

21 MR. MIGLIACCIO: Okay.

22 DR. NASR: And I think the third point

1 that I failed to make, Gerry, and I'm glad you made
2 this comment, is I think our role collectively is how
3 to move from the existing system to the future
4 paradigm.

5 So we're going to have two different
6 regulatory approaches. I hope we don't call this two
7 different quality system. One if more inferior than
8 the other. We will have two different regulatory
9 processes, the existing one and the one that fits
10 better with the future paradigm.

11 And we should make products available to
12 the public based on both processes. What we should
13 work on collectively, because I think from what I'm
14 hearing today and I heard before, we are in agreement,
15 is how to move from the existing system to the future
16 paradigm without penalizing industry or the public.

17 CHAIR BOEHLERT: Ken?

18 MEMBER MORRIS: Something that's bothering
19 me a little is that, you know, what we've been talking
20 about all along is that industry should essentially be
21 telling FDA what it thinks it needs to do in order to
22 justify its decisions in dosage form and process

1 development manufacturing. Not dictating but saying
2 here's what we think we should do -- which is sort of
3 what we're saying in Part A.

4 And I don't have an answer to this. But
5 what bothers me a little bit is that if that's what
6 we're really saying, then in principle what you would
7 expect is that the company would put together what it
8 considers necessary for itself in terms of a
9 development report and share that.

10 Now the question of what's minimum then
11 really is almost a moot point because minimum would
12 have been passed long before you got to that point.
13 Because if you're going to do minimum, then you're
14 using Moheb's other -- you're using your other
15 eventuality where you're just following the old
16 system.

17 So it seems like you've long passed --
18 that ship's sailed, I think.

19 MEMBER HUSSAIN: No, Ken, I think the
20 point you're making is a good one. And I think the
21 only -- I think the primary reason for asking this
22 question is because this is the question that seems to

1 come up again and again in our expert working group
2 discussions.

3 And primarily I think I agree with Moheb
4 in that at least in the U.S., with our peer review
5 process, with our quality system, it's not an issue
6 within the U.S. to manage this. I think we can easily
7 manage this with the new way.

8 It's simply a question to sort of prepare
9 ourselves for the future discussions in say Japan in
10 November. Is, I think, Judy, if you would permit me,
11 if John Berridge wants to come -- maybe I'll invite
12 him to comment also on that -- my thoughts were that
13 in a sense the uncertainty level seems to remain
14 within the regulatory affairs, within the industry
15 itself. The hesitation to share any information is
16 there. So you still have that.

17 And what I'm hoping is we can find an
18 opportunity to minimize that concern also at the same
19 time I think get to the right decisions, ask the right
20 questions, and get the right answers fairly quickly
21 instead of going through an elaborate process.

22 There is a level of concern, hesitation

1 out there, which is quite significant let me tell you,
2 I'll share this. It's trying to minimize that.

3 DR. NASR: Before John comes in, I want to
4 add one thing in response to G.K., who raised a very
5 good point. Because what you heard from you that
6 people out there are saying Ajaz, Helen, David, Janet,
7 and so forth believe in this. How about the
8 reviewers?

9 I think, I hope I made it clear today that
10 the Office of New Drug Chemistry has made a commitment
11 to change the way we do our work and reorganize in a
12 way to facilitate the implementation of the new
13 paradigm.

14 And this is not just me talking. I think
15 we have senior leadership here of the Office in
16 attendance and the Office is committed to do that. It
17 is not just Helen and Ajaz.

18 MEMBER RAJU: And if you look at this
19 presentation you made and the one you made at Arden
20 House, the amount of changes you are making in the new
21 drug chemistry seems to be really rapidly different
22 from a year ago. I've never seen that kind of

1 momentum in any place before. It's clear.

2 CHAIR BOEHLERT: John?

3 DR. BERRIDGE: Yes. So I don't want -- I
4 don't think there is any point in my repeating the
5 points that have been made. But I think there's one
6 other thing to consider about the communication and
7 the way we get the new paradigm across.

8 One of the things we discussed in the
9 expert working group is to build on the model that was
10 designed, and Joe will probably be very familiar with
11 this, that was adopted by the Q7A Team, which was
12 actually to construct an education process that could
13 be rolled out around the world, that would use a
14 common set of training materials that would be
15 available to regulators and industry alike that would
16 clearly articulate exactly what it was we wanted to
17 achieve and the implications thereof.

18 I think that would actually strengthen the
19 understanding and remove the degree of uncertainty and
20 I'm almost bound to say fear that exists. And I think
21 an element of the fear is driven by the unknown.

22 So the development of a training program,

1 you mentioned particularly regulatory affairs
2 colleagues who haven't been quite as intimately
3 involved in this process as maybe their scientific
4 counterparts, if we can get that adopted and pushed
5 out, I think that would be also a very valuable
6 process for removing some of the concerns that have
7 been expressed this afternoon.

8 MEMBER HUSSAIN: I think that's an
9 important point. And there are a number of aspects,
10 if I may see the Committee's thoughts and
11 recommendations on this.

12 Helen and I have sort of discussed this at
13 length in the sense we have met with a number of
14 companies, one on one basis. They have shared some of
15 their ideas of how this report might be and how the
16 case studies might develop and what the criteria
17 should be and so forth.

18 I think meeting each company one at a time
19 clearly is what we are going for, but we're not
20 getting something in the public domain which would be
21 an example, the case studies, and so forth.

22 The proposal might be to the Committee

1 just to consider maybe we form a working group under
2 this Committee to actually get to some of this
3 tangible outcomes quickly because I think we need a
4 framework to work on this.

5 So if the Committee would agree, I would
6 propose that I think we might, following this meeting,
7 start the dialogue and put a working group under this
8 Committee to work on some of these aspects.

9 CHAIR BOEHLERT: Any comments on that
10 proposal?

11 MEMBER SINGPURWALLA: It's a good idea as
12 long as I don't have to be on it.

13 (Laughter.)

14 CHAIR BOEHLERT: Okay. Are we either
15 ready --

16 MEMBER HUSSAIN: Okay. I think there are
17 a number of activities going on in ONDC and OGD and we
18 actually just talked about that. We have Office of
19 Biotechnology Products also gearing up for a number of
20 things. And if you saw the pharmaceutical technology
21 report, you saw what Keith Beverly is doing.

22 But at this meeting, we didn't have time

1 to bring him on board also. But what do you think,
2 what advice, or what recommendations do you have for
3 Moheb and Gary that might help move them further?

4 I think they're doing a tremendous job
5 already. I think there is still aspects of
6 communication, coordination, and so forth that will
7 occur. But anything you can add would be a real help.

8 DR. FACKLER: Judy? For a number of
9 companies, somebody mentioned just a minute ago the
10 unknown. A delay in an approval has a series economic
11 impact on a company. And submitting more information
12 than we have been doing historically to an
13 organization that confesses to being hopelessly
14 understaffed seems like a prescription for delaying
15 one's approval.

16 MEMBER HUSSAIN: Hopefully it is not more
17 information. It is less data, more knowledge, and
18 then more concise. Hopefully we can transition to
19 that.

20 DR. FACKLER: Well, and that's what I
21 think needs to be clarified to companies in general is
22 that not just a reassurance that things will go

1 smoother or faster but some -- certainly a concrete
2 example would be a good thing but it's too ill defined
3 right now, I think, for companies to risk changing
4 something that they can measure right now.

5 You know you make a submission and you
6 have a fairly good understanding for when you might
7 get the first review back or the first approval. And
8 it's the unknown that really is causing I think a lot
9 of hesitation in companies.

10 MEMBER HUSSAIN: If I may, sort of
11 building on that, I think the whole thing begs for
12 some concrete examples, criteria, and so forth.
13 That's what the next step logical is. And I think to
14 get there a working group might be the best option to
15 do that.

16 And maybe I'll follow up with Judy and try
17 to assemble a group under this Committee that will
18 report to this Committee.

19 CHAIR BOEHLERT: And Pat?

20 MEMBER DeLUCA: Yes, I got the impression
21 that in the submissions that there was information
22 that was lacking. And the reviewers had to, at times,

1 try to tease out information or try to even decipher
2 what the rationale was for doing something.

3 And I'm just wondering if that in moving
4 from the existing system to the new paradigm that the
5 filings should include from the companies the
6 rationale, the summary, and then plans for improvement
7 on the process that's going to take place?

8 So it's just not, you know, the process
9 improvement should not be optional. It should be
10 something that is expected even after approval.

11 (Laughter.)

12 MR. MIGLIACCIO: Judy?

13 CHAIR BOEHLERT: Gerry?

14 MR. MIGLIACCIO: In the ideal case that
15 there are no undesirable sources of variability in the
16 process, why would you change it in the ideal case?

17 MEMBER DeLUCA: Well, you wouldn't change
18 it. I mean the only thing is is that you should have
19 some idea is there a way to improve the process. But
20 saying that that's going to work but at least you have
21 some strategy that you can look into and investigate.
22 And either prove or disprove it. If it is possible to

1 improve the process, then there is some effort to
2 improve it.

3 MR. MIGLIACCIO: An examination for
4 example?

5 MEMBER DeLUCA: That's right. I mean it's
6 not compulsory that you improve it. It's just that
7 did you have a plan or some strategy for improving it?

8 MEMBER HUSSAIN: I think we probably will
9 touch upon this tomorrow also. I think the key aspect
10 is in terms of a decision to approve, I think in some
11 ways you have to look at that as a decision of an
12 acceptable risk assessment that allows the product to
13 come out. Sometimes you have to have special
14 decision-making criteria for a very essential drug and
15 so forth.

16 But generally a decision to approve means
17 you have met the safety and efficacy standard. And in
18 many ways continuous improvement the way I see it is
19 is an improvement to improve efficiency, improvement
20 to bring new technologies, simply from a business
21 case.

22 But at the same time, there is a category

1 of changes which are necessary. The process is not
2 capable of meeting those standards that we approve.
3 Tremendous failure and so forth.

4 So when the process is not capable, there
5 has to be a way to sort of improve that. And we do it
6 through enforcement action today, concern degree and
7 so forth. So there is a category change which the FDA
8 will come back to ask you for the change.

9 So -- but the other type of changes are,
10 I think, are continuous improvement, to a large extent
11 efficiency improvements. With that, I think -- oh
12 sorry. Go ahead.

13 MEMBER RAJU: There are two presentations.
14 The Office of New Drugs' presentation was extremely
15 impressive. One of the best I've seen. The whole
16 science into the mission and the science principles
17 were very powerful, knowledge gaining, bringing in
18 pharmaceutical development.

19 I will echo, however, that probably
20 process capability shouldn't be in there. It should
21 instead be process stability because it's too early.
22 Process capability comes later. It should be stable

1 first.

2 But if you include process stability, it
3 would fit in beautifully.

4 In terms of the overall piece, if you say
5 special cause analysis before you go to statistics,
6 that's a beautiful place to bring in the FMEA
7 actually. That's the right tool for that.

8 So this is actually quite strong. I'd be
9 curious to hear your good scientific principles
10 sometime in an offline.

11 In terms of the Office of Generic Drugs,
12 this is the first time that I've learned about the
13 size of the submissions and how long it takes. It
14 doesn't seem acceptable from a social point of view.
15 I was really worried as a citizen.

16 I think there should be a synergy of
17 leveraging the old innovator drug's knowledge back
18 here. But then there's a whole other dimension of
19 resources and prioritization that's beyond probably
20 the scope of this Committee or at least me that is
21 extremely important that there has to be something
22 done about.

1 MEMBER HUSSAIN: G.K., just a comment on,
2 I think it's a matter of semantics and vocabulary. I
3 think process capability often we use it in the new
4 drug side from a slightly different perspective in a
5 sense. How we often -- I'm very familiar with how we
6 set dissolution specifications. I use that as an
7 example.

8 If you have say ten batches that you have
9 used in the clinical setting, so you have ten clinical
10 batches over the clinical drug year. What we often
11 will do is, I think, the decision to set a
12 specification and an acceptance criteria, mostly
13 acceptance criteria would be to maybe fail a couple of
14 batches. That's what we often refer to. But it's not
15 truly a calculated process capability.

16 CHAIR BOEHLERT: Garnet, did you have a
17 comment?

18 MEMBER PECK: Just what I'm thinking about
19 is an overview without coming with specific
20 recommendations or answers to Question 2 and 3.

21 I feel that you have given in the
22 beginning of Question 2 a great preamble. You have a

1 number of suggestions here about what might be done
2 within a particular organization to demonstrate that
3 they understand the process, that they probably
4 understand the product, the system required to put
5 together the product, which then would allow the
6 Agency to have this flexibility in terms of the
7 regulatory affairs.

8 I couldn't come up with something better
9 than minimal or optimal. I think there's got to be
10 another way of expressing that. I don't think that's
11 the right way to do it. But there's got to be some
12 demarcation.

13 But if we can have some feeling for PAT
14 guidance, ICH newer thoughts, and we start to apply
15 these, it seems to me that we would have a total
16 confidence in all avenues that we were proceeding in
17 be it new drug or be it generic.

18 And I think the generic situation is a
19 tough one because of the number of filings. That is
20 -- this number, I hadn't seen this year's number and
21 it's getting pretty large.

22 But you are attempting to present, if you

1 will, the possibilities of regulatory flexibility with
2 better understanding of the process and the product.

3 CHAIR BOEHLERT: Anyone else?

4 (No response.)

5 CHAIR BOEHLERT: Ajaz, are you satisfied
6 with what you've heard?

7 MEMBER HUSSAIN: No, I think this was a
8 very valuable discussion.

9 CHAIR BOEHLERT: Okay.

10 MEMBER HUSSAIN: And I think I was just
11 kicking myself for not bringing a piece of paper and
12 pen to take some notes but the transcript will have
13 that.

14 But again, thank you very much for the
15 discussions.

16 CHAIR BOEHLERT: Okay. Well, I'd like to
17 thank everybody as well. And if that's it, then we
18 will adjourn for this evening and reconvene tomorrow
19 morning at 8:30.

20 (Whereupon, the above-entitled meeting was
21 concluded at 5:10 p.m.)

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