U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ADVISORY COMMITTEE FOR

PHARMACEUTICAL SCIENCE

AND CLINICAL PHARMACOLOGY

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WEDNESDAY

JULY 27, 2011

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The meeting convened in The Great Room of the White Oak Conference Center, Building 31, FDA White Oak Campus, Silver Spring, Maryland, at 8:00 a.m., Elizabeth Topp, Acting Chair, presiding.

PRESENT:
ELIZABETH M. TOPP, PhD, Acting Chair, Temporary Voting Member
MERRILL GOOZNER, Consumer Representative, Member
ARTHUR KIBBE, PhD, Temporary Voting Member
MELVIN KOCH, PhD, Temporary Voting Member
JOSEPH S. KOSLER, PhD, Temporary Voting Member
KENNETH R. MORRIS, PhD, Temporary Voting Member (Participating via teleconference)
MARILYN E. MORRIS, PhD, Temporary Voting Member
FERNANDO J. MUZZIO, PhD, Member
HARRIET B. NEMBHARD, PhD, Member
JAMES E. POLLI, PhD, Member
ANNE S. ROBINSON, PhD, Temporary Voting Member
FADIA T. SHAYA, PhD, MPH, Member
PATRICIA C. TWAY, PhD, Industry Representative, Non-Voting Member

GUEST SPEAKERS:
YATINDRA JOSHI, PhD, Teva USA, representing the Generic Pharmaceutical Association

EVDOKIA KORAKIANITI, PhD, European Medicines Agency
GERRY MIGLIACCIO, PhD, Pfizer, Inc., Representing the Pharmaceutical Research and Manufacturers of America
RACHAEL ROEHRIG, PhD, Director, Technical & Scientific Affairs, Consumer Healthcare

Products Association
KAREN RUSSO, PhD, Vice President, Small Molecules, United States Pharmacopeia (USP)
CATHERINE SHEEHAN, MS, Director, Excipients, USP

FDA PARTICIPANTS:

YVETTE WAPLES, PharmD, Designated Federal Officer

HELEN N. WINKLE, Director, Office of Pharmaceutical Science (OPS), CDER

KEITH WEBBER, PhD, Deputy Director, OPS, and Acting Director, Office of Generic Drugs (OGD), CDER

STEVEN KOZLOWSKI, MD, Director, Office of Biotechnology Products, OPS, CDER

MOHEB NASR, PhD, Director, Office of New Drug Quality Assessment (ONDQA), OPS, CDER

JON CLARK, MS, Associate Director for Program Policy, OPS, CDER

LARRY OUDERKIRK, Consumer Safety Officer, Office of Manufacturing & Product Quality, Office of Compliance, CDER

SARAH POPE MIKSINSKI, PhD, Branch Chief, Branch 2, Division of New Drug Quality Assessment I, ONDQA, OPS, CDER

REYNOLD TAN, PhD, Interdisciplinary Scientist, Division of Nonprescription Regulation Development, Office of Drug Evaluation IV, Office of New Drugs, CDER

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

Call to Order and Introduction of Committee 5

Conflict of Interest Statement 9

Introduction/Background 15

Topic 1: Implementation of Quality by Design (QbD): Current Perspectives on Opportunities and Challenges 20

Public Comment 194

Topic Wrap-Up 195

Discussion 200

Topic 2: USP Interaction: Monograph Modernization Program and Other Initiatives 270

Public Comment 385

Topic Wrap-Up and Additional Update on Interaction Activities 386

Summary Remarks 401

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

2 8:00 a.m.

3 CHAIR TOPP: Good morning. As I

4 said a few minutes ago, I'll read this

5 officially now. I'd like to remind everyone

6 present to please silence your cell phones,

7 BlackBerrys and other wonderful electronic

8 devices. I would also like to identify the

9 FDA press contact, Ms. Sandy Walsh, if she's

10 here. Ms. Walsh? She's not with us this

11 morning.

12 Well, my name is Elizabeth Topp.

13 I'm the Acting Chair of the Advisory Committee

14 for Pharmaceutical Science and Clinical

15 Pharmacology. I will now call the meeting of

16 the Advisory Committee for Pharmaceutical

17 Science and Clinical Pharmacology to order.

18 We will go around the room and

19 introduce ourselves, beginning on the FDA side

20 with Dr. Helen Winkle to my left, and go

21 around the table.

22 MS. WINKLE: Good morning,

1 everyone. I'm Helen Winkle. I'm the Director
2 of the Office of Pharmaceutical Science.
3 DR. WEBBER: Keith Webber. I'm
4 Deputy Director of the Office of
5 Pharmaceutical Science.
6 DR. NASR: Moheb Nasr, Director,
7 Office of New Drug Quality Assessment.
8 DR. KOZLOWSKI: Steve Kozlowski,
9 Director of the Office of Biotechnology
10 Products.
11 MEMBER NEMBHARD: Harriet
12 Nembhard, Professor of Industrial Engineering,
13 Penn State.
14 MEMBER MUZZIO: Fernando Muzzio,
15 Chemical Engineering, Rutgers University.
16 MEMBER ROBINSON: Anne Robinson,
17 Professor of Chemical Engineering, University
18 of Delaware.
19 MEMBER KOCH: Mel Koch, Center for
20 Process Analysis and Control, University of
21 Washington.
22 MEMBER GOOZNER: Merrill Goozner.

1 I am the consumer representative on the
2 Committee.
3 CHAIR TOPP: Liz Topp, Industrial
4 and Physical Pharmacy, Purdue University.
5 DR. WAPLES: Yvette Waples. I'm
6 the Designated Federal Officer for this
7 Committee.
8 MEMBER KIBBE: Art Kibbe, Chairman
9 of Pharmaceutical Sciences, Wilkes University.
10 DR. SHAYA: Fadia Shaya, Professor
11 of Pharmacoepidemiology, University of
12 Maryland School of Pharmacy.
13 MEMBER POLLI: James Polli,
14 University of Maryland.
15 MEMBER MARILYN MORRIS: Marilyn
16 Morris, Pharmaceutical Sciences, University of
17 Buffalo.
18 MEMBER TWAY: Pat Tway, Industrial
19 Representative.
20 CHAIR TOPP: And we also have a
21 phone-in member, phoning in from Hawaii, Dr.
22 Ken Morris. Ken, are you there?

1 MEMBER KEN MORRIS: I am here.
2 Ken Morris, Professor at the College of
3 Pharmacy at the University of Hawaii at Hilo.
4 CHAIR TOPP: Good morning everyone
5 and welcome. For topics such as those being
6 discussed at today's meeting, there are often
7 a variety of opinions, some of which are quite
8 strongly held. Our goal is that today's
9 meeting will be a fair and open forum for
10 discussion of these issues, and that
11 individuals can express their views without
12 interruption.
13 Thus, as a gentle reminder,
14 individuals will be allowed to speak into the
15 record only if recognized by the Chair. We
16 look forward to a productive meeting. In the
17 spirit of the Federal Advisory Committee Act
18 and the Government in the Sunshine Act, we ask
19 that the Advisory Committee members take care
20 that their conversations about the topic at
21 hand take place in the open forum of the
22 meeting.

1 We are aware that members of the
2 media are anxious to speak with the FDA about
3 these proceedings. However, FDA will refrain
4 from discussing the details of this meeting
5 with the media until its conclusion. Also,
6 the Committee is reminded to please refrain
7 from discussing the meeting topic during
8 breaks or lunch. Thank you.
9 Ms. Waples will now read the
10 conflict of interest statement.
11 MS. WAPLES: Good morning again.
12 The Food and Drug Administration is convening
13 today's meeting of the Advisory Committee for
14 Pharmaceutical Science and Clinical
15 Pharmacology under the authority of the
16 Federal Advisory Committee Act of 1972.
17 All members and temporary voting
18 members of the Committee are special
19 government employees or regular federal
20 employees from other agencies, and are subject
21 to federal conflict of interest laws and
22 regulations.

1 The following information on the
2 status of this Committee's compliance with
3 federal ethics and conflicts of interest laws
4 covered by, but not limited to those found at
5 18 U.S.C. Section 208 and Section 712 of the
6 Federal Food, Drug and Cosmetic Act, is being
7 provided to participants in today's meeting
8 and to the public.
9 FDA has determined that members
10 and temporary voting members of this Committee
11 are in compliance with federal ethics and
12 conflict of interest laws. Under 18 U.S.C.
13 Section 208, Congress has authorized FDA to
14 grant waivers to special government employees
15 and regular federal employees who have
16 potential financial conflicts, when it is
17 determined that the agency's need for
18 particular individuals' services outweighs his
19 or her potential financial conflict of
20 interest.
21 Under Section 712 of the FD&C Act,
22 Congress has authorized FDA to grant waivers

1 to special government employees and regular
2 federal employees if potential financial
3 conflicts were necessary to afford the
4 Committee essential expertise.
5 Related to the discussion of
6 today's meeting, members and temporary voting
7 members of this Committee have been screened
8 for potential financial conflicts of their
9 interests of their own, as well as those
10 imputed to them, including those of their
11 spouses or minor children, and for purposes of
12 18 U.S.C. Section 208, their employers.
13 These interests may include
14 investments, consultant expert witness
15 testimony, contracts, grants, CRADAs,
16 teaching, speaking, writing, patents,
17 royalties and primary employment.
18 At today's meeting, the Committee
19 will discuss current strategies for the FDA's
20 Office of Pharmaceutical Science
21 Implementation of Quality by Design,
22 principles within its review offices,

1 incorporate an update on the International
2 conference on harmonization of technical
3 requirements for registration of
4 pharmaceuticals for human use activities.
5 This topic is a particular matter of general
6 applicability, during which general issues
7 will be discussed.
8 The Committee will also receive
9 awareness presentation on FDA's current
10 partnering with the United States
11 Pharmacopeia, principally to discuss the
12 monograph modernization program. This topic
13 is a particular matter involving specific
14 parties.
15 Based on the agenda for today's
16 meeting and all financial interests reported
17 by the Committee members and temporary voting
18 members, no conflict of interest waivers have
19 been issued in connection with this meeting.
20 To ensure transparency, we
21 encourage all standing committee members and
22 temporary voting members to disclose any

1 public statements that they have made
2 concerning the issues before the Committee.
3 With respect to FDA's invited Industry
4 Representative, we would like to disclose that
5 Dr. Patricia Tway is participating in this
6 meeting as a non-voting Industry
7 Representative, acting on behalf of regulated
8 industry.
9 Dr. Tway's role at this meeting is
10 to represent industry in general and not any
11 particular company. Dr. Tway is an
12 independent pharmaceutical industry
13 consultant.
14 With regard to FDA's guest
15 speakers, the agency has determined that the
16 information to be provided by the speakers is
17 essential. The following interests are being
18 made public, to allow the audience to
19 objectively evaluate any presentation and/or
20 comments made by the speakers.
21 Dr. Yatindra Joshi is an employee
22 of Teva Pharmaceuticals. Drs. Karen Russo and

1 Catherine Sheehan are employees of the United
2 States Pharmacopeia. Dr. Gerry Migliaccio,
3 sorry if I mispronounced that, is an employee
4 of Pfizer and owns Pfizer stocks. Dr. Rachel
5 Roehrig is an employee of Consumer Health Care
6 Products Association.
7 As guest speakers, they will not
8 participate in Committee deliberations, nor
9 will they vote. We would like to remind
10 members and temporary voting members that if
11 the discussions involved any other products or
12 issues not already on the agenda for which an
13 FDA participant has a personal or imputed
14 financial interest, the participants need to
15 exclude themselves, for which such involvement
16 and their exclusion will be noted for the
17 record.
18 FDA encourages all other
19 participants to advise the Committee of any
20 financial relationships that they may have
21 with firms, that could be affected by the
22 Committee's recommendations. Thank you.

1 CHAIR TOPP: Thank you. We will
2 now proceed with the FDA opening remarks from
3 Ms. Helen Winkle. I would like to remind
4 public observers at this meeting that while
5 the meeting is open for public observation,
6 public attendees may not participate except at
7 the specific request of the panel.
8 Introduction/Background
9 MS. WINKLE: I hope you don't mind
10 if I stay at the table instead of making that
11 long walk to the podium. Anyway, I want to
12 start off today by welcoming everybody back.
13 I see we did lose a couple of people. I guess
14 it was the wild discussions we had yesterday.
15 I want to thank everyone. I
16 thought yesterday's topics and discussions
17 were very well-received. I felt like that the
18 FDA gained quite a bit yesterday from the
19 discussions, especially the discussion on NTI
20 and the Committee's contributions will be very
21 significant in helping us move forward in
22 determining where we're going with the

1 regulation of NTI drugs.

2 I especially appreciate the input

3 on the definition. I think this is really a

4 first step forward for us, as far as NTI

5 products. I also wanted to thank the outside

6 speakers, Dr. Midha and Mr. Johnston, who came

7 in and helped clarify some of the issues that

8 we had before us, and their input was very

9 helpful as well.

10 I also want to thank our own

11 speakers. There was a lot of work put into

12 the presentations that were given yesterday,

13 a lot of heart and soul put into them. So I

14 really appreciate everyone's time and effort.

15 Today, we're going to shift to issues that

16 have a broader effect on the OPS CMC review

17 processes in general.

18 This will include not only generic

19 drugs, but it will also talk about how we

20 regulate brain and biotech products. The

21 first topic that we're going to discuss today

22 is the implementation of quality by design.

1 As I mentioned yesterday, we've been in the
2 process of implementing quality by design for
3 about seven years now, and I think we've made
4 a great deal of progress.
5 As I mentioned yesterday, a recent
6 study that was conducted by McKinsey for FDA
7 on "Understanding Challenges to Quality by
8 Design," indicates that industry is stepping
9 up to the plate as far as implementing quality
10 by design.
11 The report also stated that QbD is
12 evolving, gaining momentum and passion within
13 the industry. I think with this change in how
14 the industry is implementing quality by
15 design, we at the FDA, although we've made a
16 lot of progress in being prepared to
17 facilitate this implementation, really need to
18 look at the challenges and the opportunities
19 that we now have, as we move forward with the
20 implementation.
21 So today, we're going to talk to,
22 update the Committee on where we are, and also

1 solicit some of your advice on how we could
2 further facilitate the implementation of QbD
3 across the center and across the industry. So
4 any comments that you might have. We do have
5 some questions, and any comments you have will
6 be well-received.
7 The second topic for today will be
8 on FDA's interactions with USP on monograph
9 modernization. Also, as I mentioned
10 yesterday, USP has a role in ensuring the
11 public health, through the issuance of new and
12 updated standards for use by industry, and
13 testing products for quality and safety. I
14 think that role goes hand in hand with what
15 we're doing here at FDA, in ensuring the
16 quality of --
17 (Audio interference.)
18 MS. WINKLE: Didn't want me to
19 talk any longer. So we're going today, we'll
20 bring several individuals in from the USP, to
21 discuss what their perspective is on their new
22 initiative on monographed modernization and we

1 will, from the FDA too, talk about some of the
2 activities that we have ongoing in partnering
3 with USP, to be better ensure the quality and
4 safety of drug products in general.
5 So I think it will be an
6 interesting conversation, and a lot of this is
7 new to us. And again, it's evolving. We just
8 in the last ten months or so began really
9 becoming active with the USP, in seeing what
10 we could do to improve upon the regulatory
11 processes.
12 We really look forward to another
13 day of, I think, excellent presentations by
14 the FDA staff, as well as those from the
15 outside, and we look forward to the
16 Committee's discussion. I think this
17 discussion, as always, will serve to enhance
18 our knowledge, as we move forward with the CMC
19 regulatory process, and how we're going to
20 make decisions in the future.
21 So with that, I thank each of you
22 for your time.

1 CHAIR TOPP: Thank you, Dr.
2 Winkle. We'll now move to Topic 1, which is
3 Implementation of Quality by Design: Current
4 Perspectives on Opportunities and Challenges.
5 Our first speaker on this topic this morning
6 is Dr. Moheb Nasr. Dr. Nasr is Director of
7 the Office of New Drug Quality Assessment with
8 CDER at the FDA, and his title this morning is
9 "Topic Introduction and ICH Update." Dr.
10 Nasr.
11 DR. NASR: Thank you. Good
12 morning, everyone. I think it's nice that we
13 have an opportunity to present and share with
14 you the progress we have made and some of the
15 challenges we continue to have, and since this
16 is an advisory committee, we will seek your
17 input and advice.
18 With that being said, my plan is to
19 introduce the subject, and there is a few
20 issues. That would be followed by two
21 industry colleagues, and the sequence of the
22 presentation is intended to illustrate how we

1 are approaching Quality by Design.
2 The implementation of Quality by
3 Design is not a regulatory process. It is an
4 industry implementation, and industry
5 colleagues will share with us where we are
6 with the implementation, and some of the
7 challenges and opportunities they identify to
8 facilitate our job internally here, because we
9 see our role as facilitators of the
10 implementation of both science and the
11 innovation in the pharmaceutical industry.
12 That will be followed by two
13 regulatory presentations from EMA and FDA, and
14 I think that also illustrates in some ways the
15 extensive collaboration and the interaction we
16 have among the international regulators, as we
17 continue to facilitate the implementation of
18 Quality by Design.
19 What I would like to cover in my
20 brief presentation this morning, if you
21 believe that, is ICH guidelines related to the
22 implementation of Quality by Design, the

1 implementation progress, as we have been
2 counting on the leadership of ICH, to
3 facilitate the implementation of Quality by
4 Design, and my perspective on some of the
5 remaining challenges and gaps.
6 There are three ICH guidelines that
7 are key to the implementation of Quality by
8 Design. The first and the most important one
9 is ICH Q8 (R2), addressing pharmaceutical
10 development. The guideline describes good
11 practices for pharmaceutical development, and
12 outline basic approaches to development, as
13 well as an enhanced approach on what we
14 describe as Quality by Design approach to
15 development and manufacturing.
16 In addition, this guideline
17 introduced for the first time some new
18 concepts, such as design space and
19 opportunities for flexible regulatory
20 approaches. Quality by Design has been
21 defined in ICH Q8 (R2) as a systematic
22 approach to development, begins with pre-

defined objectives, with emphasis on product and process understanding, and process control, based on good signs and the quality risk management.

What you will see on this slide is an illustrative example of how Quality by Design approach can be used throughout the product life cycle, starting with a determination of quality target product profile that will lead into determination of critical quality attributes, linking relationship or establishing relationship between material attributes, manufacturing parameter to these pre-determined critical quality attributes, opportunity to develop a design space, and design and implement the control strategy.

A key point here is the following. All earlier efforts are intended to develop a control strategy, because that strategy is what assures quality, safety and efficacy. Having this knowledge leads to opportunities,

1 and to provide opportunities to better manage
2 product life cycle, and proactive continual
3 involvement.
4 ICH Q9 quality risk management
5 describes systematic process for assessment,
6 control and communication and review of
7 quality risk. So risk-benefit analysis is
8 very much what we do here at the agency every
9 day.
10 This guideline focuses more on
11 quality aspects of risk, and includes
12 principles and examples and tools, and how
13 these approaches and tools are applicable over
14 the entire product life cycle, from
15 development through manufacturing and product
16 distribution.
17 What you see here in this example is
18 part of what's described in ICH Q9. I defined
19 some of the key steps and stages where quality
20 risk management approaches and tools can be
21 used, starting with risk assessment, risk
22 control and risk review, and risk

1 communication is in some ways utilized
2 throughout the process.
3 What I have added here is for
4 illustrative purposes only, how risk
5 assessment can be used in process development,
6 and risk control could be a component leading
7 to a risk-based control strategy development
8 and implementation, and risk review as it
9 provides Opportunities for continual
10 improvement.
11 The third key guideline is ICH Q10
12 for pharmaceutical quality system. It
13 describes system that facilitates
14 establishment and maintenance of a state of
15 control for process performance, facilitates
16 continual involvement and applies to drug
17 substance, drug product, throughout product
18 life cycle and supply chain.
19 Now I borrowed this from ICH Q10.
20 In some ways describe in another way a product
21 life cycle where GMP applies, and some of the
22 key elements of pharmaceutical quality system,

1 whether they are CA/PA, change management
2 system, management review and process
3 performance and product quality monitoring
4 systems.
5 It also outlines some of the key
6 enablers to facilitate the process, knowledge
7 management and the quality risk management.
8 Now I think it's important at this time, after
9 that brief introduction of the three key ICH
10 guidelines, is to provide some clarity, since
11 as Helen mentioned this morning, we have been
12 on that journey for about seven years, what we
13 clearly mean by Quality by Design.
14 So what Quality by Design is, and
15 what Quality by Design is not. So Quality by
16 Design, as described in ICH Q8, is a
17 systematic approach to development in
18 manufacturing. That's fairly clear.
19 It's equally important that this
20 knowledge and this information has to be
21 shared in regulatory submission, and also
22 important that once this information have been

1 shared and presented to regulators, that
2 regulatory decision must be based on
3 scientific and quality risk management
4 principles.
5 So three steps. Doing it right,
6 sharing the information and acting upon this
7 information, using both science and good
8 quality risk management approaches.
9 Now Quality by Design does not equal
10 design space or design of experiments. These
11 are important tools that facilitate the
12 development and the implementation of Quality
13 by Design. Design space is not required, but
14 establishing design space is useful to show
15 product and process understanding, and to
16 provide manufacturing and regulatory
17 flexibility.
18 And you will see more examples from
19 regulators and industry colleagues about how
20 these approaches are being put into practice
21 today. Public standards continue to have a
22 role, but some adaptation is needed. It's

1 interesting that this afternoon's session will
2 address some of these public standard relevant
3 issues.
4 Quality by Design doesn't have to be
5 expensive. I think if it's done right, it
6 could reduce manufacturing, as well as
7 regulatory costs. Quality by Design does not
8 change or reduce regulatory requirements.
9 However, it provides opportunities for
10 flexible regulatory approaches.
11 So the goal of Quality by Design is
12 not to change the regulation; the goal of
13 Quality by Design is to do the right thing and
14 the regulation can be used and utilized based
15 on good science and good quality risk
16 management approaches.
17 Quality by Design is important for
18 all products, including genetics and biotech.
19 Analytical testing is important and play a key
20 role in Quality by Design, both in the
21 development and the implementation stages.
22 This is one area that we are not elaborating

1 on in today's session, but I promise you it's
2 becoming very important, and we will need to
3 come back and seek to present you where we are
4 and seek your advice and input at a future
5 meeting.
6 End of product testing is a
7 component of control strategy. For example,
8 bioavailability and bioequivalence need to be
9 demonstrated by the solution testing or some
10 other means.
11 So what are the utilities of ICH Q8,
12 9 and 10? We believe that the implementation
13 of these three key guideline is available for
14 all drug products, regardless of the
15 pharmaceutical development approaches. It's
16 equally applicable for small and complex
17 dosage form, a small molecule, as well as
18 large or biotech molecules, traditional
19 development or enhancement of Quality by
20 Design approaches within and outside ICH
21 regions.
22 Both scientific development in Q8,

1 and combination of 9 and 10, should improve
2 drug quality and efficiency of pharmaceutical
3 manufacturing, and I think we all can agree
4 that quality is important for all drug
5 products throughout product life cycle and
6 supply chain.
7 The three guidelines that I outlined
8 earlier, 8, 9 and 10, are useful and can be
9 helpful throughout the product life cycle.
10 This is just an illustration to show that ICH
11 Q9, quality risk management, can be utilized
12 throughout.
13 There will be more emphasis using Q8
14 early on during development stages as
15 expected, and as you move into manufacturing
16 implementation, having a robust quality system
17 is a key to facilitate the implementation of
18 these enhanced approaches.
19 At ICH, an implementation working
20 group was established, to facilitate the
21 implementation of 8, 9 and 10. One of the
22 difficulties we had in the best of ICH, as

1 well as in other regions, is the fact that
2 once the guidelines are developed, the
3 interpretation and implementation of guideline
4 can be subject to regulatory interpretation
5 and differences.
6 We thought that the efforts we put
7 in 8, 9 and 10 is so important and will have
8 a great impact on shaping the pharmaceutical
9 development and manufacturing for years to
10 come. So we want to make sure this doesn't
11 happen.
12 So we establish implementation with
13 group to ensure harmonized implementation of
14 the guidelines, and we identified some key
15 areas that require further clarification,
16 since the guidelines have been developed at a
17 higher level with insufficient details and
18 description.
19 They are not descriptive guidelines,
20 and we thought that activities such as
21 publication of questions and answers, training
22 and collaboration for some non-ICH, not for

1 profit organization, can be a key to
2 facilitate harmonized implementation.
3 Here is what we have done so far at
4 ICH Quality Implementation Working Group. We
5 published 45 questions and answers addressing
6 how these guidelines can be applied in
7 different situations at different stages of
8 product life cycle. We developed an ICH
9 training, extensive training material that I
10 will describe briefly shortly.
11 Workshop results from this training
12 were compiled, analyzed, evaluated, to
13 identify where we are and some of the
14 challenges that we need to address. As well
15 as we identified several topics of potential
16 collaboration. Since we developed these new
17 guidelines, it was interesting to see how
18 these new ideas about using these enhanced
19 approaches impacts some of the existing
20 quality guidelines.
21 So we have done an analysis of that,
22 and we developed and we are in the process of

1 developing internal documents.
2 So what about the training? I think
3 training has been the measure achievement of
4 the Quality Implementation Working Group. We
5 developed a very extensive training program I
6 will outline shortly, and the program was
7 presented by the same faculty, using the same
8 material in the three ICH regions in Europe,
9 U.S. and Japan.
10 Information had to be shared as well
11 in two trainings, and we are in the process of
12 repeating this training using the lessons
13 learned from prior training activities, in
14 Canada next month, or September of 2011, as
15 well as in Seoul, South Korea in October this
16 year. Training material that has been
17 developed is available at ICH website by
18 everyone to use.
19 Now the training material was based
20 on a development of an extensive and
21 comprehensive case study. We have decided to
22 develop a case study that describes how active

1 pharmaceutical ingredient and dosage form can
2 be developed, not only using quote-unquote
3 "Quality by Design," but different
4 developmental and control strategy approaches.
5 Once it is done, we had the training
6 workshop with five preliminary presentation.
7 The first one described how these guidelines
8 had been used in the development of the case
9 study, and can be used in the implementation
10 of such case study. A presentation by
11 industry described developmental approaches
12 for active pharmaceutical ingredient and the
13 dosage form.
14 A regulator presented how such
15 information, if and when submitted, will be
16 evaluated during the same process. Industry
17 again described how Quality by Design case
18 study can be implemented in real manufacturing
19 environment, and our inspector colleagues
20 discussed how, and the five questions that
21 could be asked during GMP inspection.
22 In addition to that, we had four

1 discussion topics on design space, control
2 strategy, pharmaceutical quality system and
3 quality risk management, where we had
4 extensive discussion related to the case study
5 and in general.
6 Some of the key messages we tried to
7 convey in the workshops are the following.
8 First, as I repeated at least once this
9 morning, we believe that ICH 8, 9 and 10 are
10 linked together to provide a systematic model
11 of risk and science-based approach to
12 development and manufacturing.
13 Comprehensive implementation of the
14 three guidelines together is essential to
15 achieve our new quality vision. Guidelines
16 are applicable over the entire product cycle,
17 and it can be utilized by all stakeholders,
18 industry and regulators.
19 I think it was a key, especially
20 when I presented this at the training
21 workshops, that it is expected that our
22 regulatory colleagues on the assessment and

1 inspector side incorporate quality risk
2 management. So it's not that we're asking
3 industry to share information, and we have to
4 act accordingly.
5 Professional developmental
6 approaches, as outlined in ICH Q8 (R2), the
7 basic approaches are acceptable. However,
8 enhanced approaches provide higher assurance
9 of quality and opportunities. The use of
10 quality risk management is beneficial
11 regardless of developmental approaches and
12 manufacturing processes used. Pharmaceutical
13 quality system applies to the substance of
14 product throughout product life cycle and
15 supply chain.
16 Some of the key findings from the
17 training workshops are the new paradigm that
18 I described so far and you will hear more this
19 morning, has not been fully implemented.
20 There are some remaining concerns about the
21 cost and potential impact of time to market.
22 It will good to hear the perspective from all

1 industry colleagues on this point.
2 Lack of global harmonization,
3 especially outside the ICH regions, could have
4 a negative impact on the future
5 implementation, and in particular the impact
6 of different change management regulatory
7 processes over the life cycle of the product.
8 I mentioned the earlier analytical testing.
9 I think we will need to come to present to you
10 again, some time in the future, approaches and
11 issues related to change management.
12 There is a training need for
13 regulator and industry, and there is a need
14 for appropriate continuous dialogue between
15 industry and regulators, if we implemented
16 these approaches before, during and after
17 assessment.
18 So where are we now with the
19 Implementation Working Group? We are in the
20 process of developing implementation document
21 to address question raised at the training
22 workshops. We completed three Point to

1 Consider documents related to level of
2 documentation in enhanced Quality by Design
3 submission, practicality of quality attributes
4 and process parameters, and the control
5 strategy.
6 These were completed last month in
7 our meeting in Cincinnati. There are three
8 that we are currently working on and intend to
9 complete by the end of this year. One on
10 process validation, design space and the role
11 of modeling in Quality by Design.
12 These Point to Consider documents
13 are based on questions raised at the training
14 workshops. They are not intended to be new
15 guidelines, or to introduce new or increased
16 regulatory requirement. They are intended
17 mainly to provide clarity to industry and
18 regulator, and facilitate the preparation,
19 assessment, and inspection related to these
20 applications.
21 Development approaches should be
22 adopted based on complexity and specificity of

1 products and processes, and applicants are
2 encouraged to contact regulatory authorities
3 for further discussion.
4 I think I made the next point
5 earlier, but I think it's worth repeating now,
6 and that is using Quality by Design approach
7 does not change regional regulatory
8 requirement, but it can provide opportunities
9 for more flexible approaches to meet such
10 requirements. GMP will always be important.
11 So the three Point to Consider
12 documents that we finalized last month in
13 Cincinnati, the first one was criticality of
14 quality attributes, and two issues were
15 addressed. They are consideration for
16 establishing critical quality attributes and
17 the critical cost parameters, and the
18 relationship between these, such a
19 determination and control strategy.
20 The second was on control strategy,
21 addressing life cycle approach, suitability at
22 different scales, relationship between

1 specification, certificate of analysis,
2 especially as it applies to real-time release
3 testing, and regulatory processes for batch
4 release decisions.
5 Level of documentation for enhanced
6 Quality by Design in regulatory submission,
7 three topics were covered, briefly covered.
8 One on information in application related to
9 risk management methodologies, design of
10 experiments, manufacturing process
11 description, and two we are currently working
12 on to finalize by the end of the year, one on
13 modeling and one on design space.
14 So our approach was endorsed at the
15 meeting in Cincinnati last month. Now as we
16 get into what are the current challenges, I
17 think it's important to know that Quality by
18 Design did not and was not expected to address
19 or solve all quality challenges. It was a way
20 to focus the discussion and improve the
21 quality based on good science and quality risk
22 management.

1 So we are not done. We have some
2 challenges, and I think it's important to be
3 reminded of these challenges, to discuss them
4 and address them. One is the lack of clarity
5 of regulatory expectation. We tried to
6 address that in Quality Implementation Working
7 Group, but we don't have the complete answer
8 to all the questions raised.
9 Reluctance to share information in
10 regulatory submission, especially issues
11 related or information related to scientific
12 justification of control strategy. Control
13 strategy itself remains to be an important
14 topic.
15 As I mentioned earlier, it is the
16 key to assure quality, safety and efficacy,
17 and we will need to further discuss how to
18 provide clarity on the language between
19 control strategy, development, pharmaceutical
20 quality system and GMPs, and how a control
21 strategy can be developed and evolved during
22 and through the entire product life cycle and

1 supply chain.
2 Adoption of risk-based approach to
3 CMC review. We have been talking for years
4 about doing a better job here as regulators,
5 making our decision based on using risk-based
6 approach. I think we still struggle with
7 that, and we will need to focus more of what
8 we do and our activities to address that.
9 For example, I think we need to ask
10 ourselves what is needed for approval, versus
11 what's nice to know, because in order to have
12 better scientific understanding.
13 Change management. Robustness of
14 internal processes for all the changes, not
15 only those requiring regulatory implication.
16 I would consider this the most important point
17 I made this morning, and that is we have a
18 regulatory challenge, and we need your advice
19 and we need industry help and input.
20 The key is not to provide
21 information for us to approve the changes;
22 what is more important is industry to have

1 their own robust system to evaluate the
2 changes, regardless of whether regulatory
3 filing is needed or not.
4 If we don't solve this issue, we
5 will continue to have to challenge how much I
6 need to share, for what we need, and how
7 regulators could be perceived as impeding
8 continual improvement.
9 The role of reviewers and inspectors
10 need to be clarified. For example, we need to
11 provide clarity of what need to be submitted,
12 and what to evaluate during inspection, and
13 what, if any, pharmaceutical quality system
14 type information should be included in
15 submissions.
16 There are three questions that I'm
17 presenting to you this morning and seeking
18 your help, advice and input. The first one
19 are there additional efforts the FDA should
20 consider in order to facilitate the
21 implementation of Quality by Design.
22 The second, there is not sufficient

1 detail but hopefully that will be presented by
2 my colleagues from regulatory authorities and
3 industry, how should we address technical and
4 regulatory gap that will be identified this
5 morning by the speakers.
6 The third, and it's very important,
7 I'm glad that my colleague, Dr. Steven
8 Kozlowski, is here to facilitate that
9 discussion, can Quality by Design approaches
10 be valuable for biotechnology product
11 development? If so, are there any potential
12 scientific challenges that we should be aware
13 of. With that, I thank you for your attention
14 and I'll be happy to answer directly any
15 questions.
16 CHAIR TOPP: Thank you, Dr. Nasr.
17 Are there questions from the Committee? Dr.
18 Shaya, and then Dr. Marilyn Morris.
19 DR. SHAYA: Okay, thank you. So I
20 do have a question about the, perhaps the
21 evaluation of the efforts, and maybe that's
22 a question responding to your first questions

1 and the last three that you posed.
2 In order to be able to pose or to
3 think about additional steps that could be
4 recommended to optimize the efforts, it may be
5 helpful to know over the past seven years what
6 has helped and what has not, and I was
7 wondering if there was any process, formal or
8 informal, to evaluate, let's say, the return
9 on investment of the efforts?
10 DR. NASR: Right. I think this is a
11 very good question. I would suggest that you
12 hold on that question, because there will be
13 two presentations, several presentations this
14 morning.
15 I think you may get that partially
16 answered or completely answered. So I don't
17 want to steal the thunder, but if you are not
18 satisfied with the answers, I'll be happy to
19 share my perspective afterwards.
20 CHAIR TOPP: Thank you. Dr. Marilyn
21 Morris.
22 MEMBER MARILYN MORRIS: I was just -

- I had a question about the workshops. They appear to be very comprehensive, from what I've seen online. I was just wondering is biotechnology products covered to some extent in the workshops?

DR. NASR: They are.

MEMBER MARILYN MORRIS: Yes.

DR. NASR: But I also would suggest that as we further develop these workshops, and ICH Q11 will be finalized; that's the guideline that addresses development and manufacturing of active pharmaceutical ingredients for small molecules in biotech, there will be more of an opportunity to be, to provide a little bit more meat to address some specific biotech issues related to active pharmaceutical ingredients.

However, some of the general principles, whether we talk about quality, pharmaceutical quality system, quality risk management, design space, identification of critical quality attributes, design space, all

1 that stuff, I strongly believe, as well as the
2 agency across, that they are applicable not
3 only for small molecule, but for biotech as
4 well.
5 CHAIR TOPP: Thank you. Dr. Koch.
6 MEMBER KOCH: Excellent
7 presentation. If I reflect back, you deferred
8 comments on the advances in the analytical
9 area until later. But I think going back
10 some, just before the seven years of the QbD,
11 I think the basis for QbD was set with
12 discussions on this Committee by the process
13 analytical technology.
14 As you go through the critical
15 quality attributes, design space, developing
16 control strategy, I think as you pointed out
17 in the past, that process analytical
18 technology is really the way you gather the
19 data to implement each of those, and that
20 measurement continues to be the basis for much
21 of the success in QbD.
22 DR. NASR: This is an excellent

1 question. Let me clarify what I said. You
2 are correct. Process analytical technology is
3 a key enabler to fully implement Quality by
4 Design, and we are very serious about that.
5 As a matter of fact, Quality by Design and the
6 changes we have made in the CMC review process
7 facilitated that option, of these technologies
8 that we talked about for years.
9 You will hear this morning from the
10 regulators, as well as from industry,
11 specifics about how process analytical
12 technology have been used. To clarify what I
13 shared earlier, the more we implement process
14 analytical technology and some of these
15 analytical methodologies.
16 The more realize that we have some
17 technical and regulatory gaps related to
18 analytical testing that need to be addressed.
19 To be specific, as we discuss design space or
20 what you could consider as manufacturing
21 design space, input material attributes and
22 parameter related to quality, you then need to

consider how this applies to analytical method developments.

Ideas about analytical target product profile, similar to quality target product profile, need to be further developed and addressed. Also, different approaches about ability to be able to move from one analytical procedure to other, to another, based on how these procedures are intended for, and whether they fit the purpose for the intended measurement or not.

So I'm not suggesting that we are delaying the implementation of process analytical technology. What I'm saying is since we implemented process analytical technology, there are some additional technical and regulatory challenges that need to be addressed.

CHAIR TOPP: Thank you. Mr. Goozner.

MEMBER GOOZNER: Just a quick clarification question. On the workshops that

1 were held, I noticed the cities that are down
2 here in Asia. Were Chinese or Indian
3 manufacturers and regulators involved?
4 DR. NASR: Yes.
5 CHAIR TOPP: Thank you. Dr. Muzzio.
6 MEMBER MUZZIO: Yes, Moheb, a
7 question that I think I asked you this before,
8 but it's probably a good time to ask you
9 again. You know that, you know, I completely
10 support everything we're doing in QbD.
11 However, they're still in practice, right? A
12 significant number of legacy measurements, not
13 all of which make a lot of sense.
14 We have shown that in the last 10-15
15 years, and there is also still a reliance on
16 legacy methods, measures measurements, right,
17 things like deep sampling that's there, which
18 a number of people in industry tend to choose,
19 because either the culture is ingrained, or
20 because they think FDA expects those tools to
21 be used.
22 To some extent they're right for

1 some offices. We need to, at some point, have
2 some way to look again at these methods and
3 these measurements, and figure out what do we
4 want to keep and what do we want to get rid
5 of, or what kind of process can we put in
6 place, so that it's easier to stop doing
7 things just because we've done them forever.
8 Do you have any thoughts about how we're going
9 to accomplish that?
10 DR. NASR: Fernando, this is a very
11 good question, and you and I discussed that
12 offline for some time. I think I made it, as
13 I made it clear in my presentation this
14 morning, the implementation of Quality by
15 Design, these modern approaches, are not
16 intended for regulators; they are industry.
17 Because regardless of how we think
18 at the time how important we are as
19 regulators, we don't develop or manufacture
20 drugs. Industry does, and they are
21 responsible for quality. Our role is to
22 facilitate that.

1 But one point you are making now
2 that I think is very helpful, and that is it
3 may be useful to tell industry that some of
4 these traditional approaches, I'm not going to
5 cite specific examples, some of which you may
6 be more interested in than I do, that we need
7 to tell people that we are not expecting this,
8 and other approaches can be used. So I think
9 that would be good, and maybe we can discuss
10 that in the future.
11 CHAIR TOPP: Thank you. Let's close
12 questioning, then. Thank you, Dr. Nasr for
13 your presentation.
14 DR. NASR: Thank you very much.
15 CHAIR TOPP: Before we move to the
16 next speaker, we have one little item of
17 business. While Dr. Nasr was speaking, we had
18 a final member of our panel join us, Dr.
19 Joseph Kosler. I'd like to ask him to
20 introduce himself into the microphone for the
21 record.
22 DR. KOSLER: Hello. I'm Joseph

1 Kosler, National Agricultural Statistics
2 Services, USDA.
3 CHAIR TOPP: Thank you. Our next
4 speaker this morning is Dr. Gerry Migliaccio.
5 Dr. Migliaccio is with Pfizer, Incorporated,
6 and he's here today representing the
7 Pharmaceutical Research Manufacturers of
8 America.
9 His presentation this morning is
10 entitled "The Impact of Quality by Design,"
11 that's QbD, on manufacturing and product
12 quality, "Innovator, Industry Perspective."
13 Dr. Migliaccio?
14 DR. MIGLIACCIO: Thank you, good
15 morning, and I'm pleased to be here. Thank
16 you for inviting me to represent PhRMA, and
17 talk a little bit about the impact of QbD on
18 the industry over the last few years.
19 Now it's important to point out,
20 Helen said it's seven years old. Actually, in
21 practice out there in the commercial area,
22 it's about three or four old. It was born

1 seven years ago, but we've actually been
2 exercising it a little less than that.
3 So we're kind of still in our
4 adolescence, and no one company can produce
5 for you a sufficient body of data, to show the
6 comprehensive impact of QbD. But we do have
7 trends. So the data that I'll show you today
8 is to give you an inkling of the impact of
9 QbD.
10 It will take a few more years to
11 have the full business case for it, but I
12 think all of my innovator companies will agree
13 that a business case will eventually emerge,
14 showing the value of QbD. Most innovator
15 companies have been on a journey over the
16 last, oh, 10 to 15 years, toward operational
17 excellence.
18 Starting with understanding and
19 controlling variability through improved
20 process capability using Six Sigma approaches;
21 moving on to reducing waste, becoming more
22 efficient, using lean principles. Both of

1 those are possible without Quality by Design.
2 But with Quality by Design, they're extremely
3 effective, because with Quality by Design,
4 you're focusing on what's critical to quality.
5 Without Quality by Design, you're
6 applying Six Sigma and lean principles to
7 everything, whether it's critical to quality
8 or not. With Quality by Design, you've
9 narrowed down to what's important, and you're
10 creating much more value in the process, using
11 much less resource.
12 Of course, our ultimate is to get to
13 intelligence-based manufacturing, where we can
14 have predictive models and adaptive processes,
15 so that we can adapt our control strategy to
16 address variability of input, and still get
17 fixed output. That's the ultimate, and that's
18 not possible without Quality by Design. We
19 can't get to intelligence-based manufacturing
20 without Quality by Design.
21 So let's talk about the demonstrated
22 benefits over the last few years. Clearly,

1 enhanced process understanding, and that's for
2 both industry and FDA. With the sharing of
3 the information in the application, we're both
4 achieving enhanced process understanding.
5 Higher process capability, better
6 product quality are a result of that enhanced
7 process understanding. Certainly, increased
8 flexibility to implement continuous
9 improvement changes. That's not without
10 hurdles that I'll talk about, and I think
11 Moheb referred to some of those. But the
12 bottom line is there is value to Quality by
13 Design.
14 One of the first hurdles that any
15 company has to overcome is the fact that the
16 investment for QbD occurs in the R&D space,
17 the payback in commercial manufacturing. For
18 those of us who have actually adapted or
19 adopted QbD and are moving forward full bore,
20 we have had to collaborate across those
21 organizational lines. But it is probably one
22 of the biggest hurdles, is getting the R&D in

1 commercial manufacturing groups to understand
2 that one's paying and the other one's reaping
3 the rewards.
4 So Quality by Design, Moheb had a
5 different structure to this, but this is the
6 way we look at it, essentially three phases:
7 a process understanding phase, which is an
8 iterative process of design of a commercial
9 process; risk assessments using tools such as
10 FMEA.
11 PAT is used extensively to provide
12 additional process understanding, and then
13 experimental plans, design of experiments,
14 etcetera, multivariant analysis, too. And
15 it's an iterative process to get us to a final
16 commercial process, as defined by the design
17 space.
18 As Moheb discussed, the design space
19 is important, but it's the control strategy
20 that you develop from that design space which
21 is really the critical piece here. The
22 control strategy and then the associated

1 change control strategy are what drives the
2 process. That's what drives the benefit, the
3 commercial benefit of Quality by Design.
4 Then once we launch the product,
5 we're into a continuous improvement phase, and
6 as you know, you can see, Q8 at work under
7 process understanding and Q9 at work there,
8 Q10 kicks in, certainly in the continuous
9 improvement phase, where process capability
10 monitoring is critical. That obviously leads
11 to continuous improvement efforts, and those
12 loop back in to our development for future
13 candidates.
14 So it's a multi-step process. On
15 the next two slides, I have each element of
16 the Pfizer, and for sake of time, I am not
17 going to go through these. But it's starting
18 with, as Moheb said, you know, a product
19 profile. We have to know what we're designing
20 to be, okay.
21 Then understanding the properties of
22 the materials, understanding what the inputs

1 and the outputs are, experimental plans, risk
2 mitigation, and then defining what is
3 critical, what is critical, developing the
4 design base control strategy, and then on to
5 knowledge management and continuous
6 improvement.
7 So let me talk about Pfizer's first
8 pilot in Quality by Design, and the enhanced
9 process understanding that we developed. So
10 our assessment, we call it our PUP or Process
11 Understanding Plan, our assessment included
12 seven focus areas. Read seven focus areas as
13 seven process steps or seven unit operations,
14 with 52 attributes and 190 parameters.
15 Parameters are inputs; the attributes are
16 outputs, okay.
17 Now remember, that an output from an
18 earlier process step is an input to the
19 subsequent process step. Went through an
20 experimental strategy, design of experiments,
21 etcetera, and we developed what we call our
22 knowledge process understanding plan. From

1 that, a design space was established and on.
2 Now this is not intended to be read,
3 but this is an example of what comes out of
4 the QbD process, and that is multivariant
5 correlations of inputs to outputs. So what
6 impacts the critical quality attribute; well,
7 what inputs to quality attributes, and then
8 which of your parameters and attributes are
9 indeed critical, and how do they correlate?
10 How do multiple parameters interact to impact
11 a single or multiple quality attributes?
12 So this is how we go through the
13 process to establish this enhanced process
14 understanding. Now in the traditional
15 approach that I followed in the first 20-some
16 odd years of my career, you have a fixed
17 process, which you try not to change because
18 of the regulatory hurdles to change it.
19 The most you could expect is to get
20 up to about two, three sigma, when it came to
21 process capability. If you look at the QbD
22 approach, putting together all elements of

1 QbD, first of all the process understanding,
2 but as importantly, the flexible regulatory
3 approaches, you can truly achieve or approach
4 six sigma through incremental improvements in
5 process capability, that result in incremental
6 process change.
7 So let's see how that's worked in
8 actual practice. Process capability. On the
9 upper right is our traditional processes.
10 This was done in 2007, which was the year that
11 we introduced our first two QbD products. So
12 the upper right is our traditional development
13 process, and this is product-based process
14 capability.
15 So if you look at it, it's 150
16 studies. So that's 150 different steps,
17 process steps. Across those, there are 1,800
18 key quality attributes. We did process
19 capability on each of them, and the product-
20 based process capability is the weakest link,
21 okay.
22 So the weakest link in those 150

1 studies, and that we're measuring is that
2 weakest link, above what is considered capable
3 or below. So a process capability of one is
4 considered reasonably capable. As you can
5 see, about 80, 81 percent of the studies
6 conducted, the weakest link was capable.
7 As we move into our QbD-developed
8 products, so fewer studies obviously, we've
9 gone up to 92 percent that meet that
10 reasonably capable metric. This data, as it
11 builds, we expect to continue to increase.
12 Looking more specifically at our
13 first product that was introduced, now this is
14 the PpK of a specific quality attribute, the
15 assay of the dosage form. At lunch, the PPK
16 for that was 1.2, which is about 3-1/2 sigma.
17 Okay, that's pretty good, compared to where
18 the industry has been in the past, about 2-1/2
19 sigma.
20 Six months post-launch, because of
21 our ability to find the sweet spot in the
22 design space without regulatory filings,

1 because of our ability to move around the
2 design space, we were able to target that
3 spot, get our process capability for our assay
4 up to 1.8, which is about 5-1/2 sigma, okay.
5 So that is a direct benefit of
6 having the Quality by Design process, the
7 enhanced knowledge, a robust design space, and
8 a control strategy that allows us to move
9 around that design space and find the sweet
10 spot.
11 With respect to better quality from
12 higher process understanding, this is again
13 the first year of our pilot, our first pilot.
14 We selected three products, three Salerenol
15 dosage forms manufactured on the same
16 equipment lines at the same facility, just for
17 comparison.
18 You can see the first two products
19 have two strengths each. They were launched
20 in 1991 and 1992, so they've been out there
21 for 20 years. The percent of batches with
22 deviations in 2007 ranged from four to eight

1 percent and zero to 1-1/2 percent for those 20
2 year-old products.
3 Now a deviation means some form of
4 variability in the process that required an
5 investigation. Doesn't mean specification
6 failure. It just means something that
7 required -- some variability that required an
8 investigation. Our Quality by Design pilot,
9 which is C, which was launched in 2007, in its
10 first year had less than one percent, 0.7
11 percent batches with any variability that
12 required deviation.
13 That percentage has held steady in
14 the last couple of years. So you can see that
15 we've started off at the same level that 20
16 year-old products are at. So it gives you
17 quite the leg up in process and product
18 quality.
19 Now for the financial types, this is
20 some of the real benefit. For that first
21 Quality by Design product that we -- pilot
22 that we started with, the demand for the

1 product was four times what was forecast, and
2 due to a well-developed design space, the
3 site, manufacturing site, was able to increase
4 productivity by 66 percent, by optimizing
5 process parameters within the design space.
6 Again, finding that sweet spot, with no
7 regulatory filing required.
8 Now we had to further expand
9 capacity, so further improvements were made,
10 but we had to expand the design space in an
11 appropriate submission was filed to do that.
12 But we did not have to build additional
13 facilities. We were able to do this in the
14 existing facilities.
15 So increased flexibility is
16 important. Now the key issue here is there's
17 no standardized approach yet to achieve this
18 flexibility. We as a company, and some other
19 innovator companies, have chosen to be very
20 explicit in our application, as to what
21 flexibility we believe the science that we
22 have provided affords us. Once that

1 application is approved, that is what
2 flexibility we have.
3 It would be obviously better to have
4 a more standardized approach to this, but
5 until that standardized approach, and of
6 course that standardized approach would
7 benefit from international harmonization.
8 Until that is here, we will continue to be
9 very explicit in the level of flexibility that
10 we believe the science affords us.
11 So the value proposition, and I
12 think in a few more years, we'll be able to
13 put some good facts here. But you've seen
14 some trend data. You're starting off leaner
15 by design, and that obviously equals cost
16 savings. Product process robustness is
17 improved. You have reduced defects,
18 rejections, reduced deviations,
19 investigations.
20 You cannot imagine the impact of
21 reducing the number of investigations
22 required. We have extensive staff that exists

1 only to investigate, and that just puts more
2 cost into our products. If we can reduce the
3 number of deviations, reduce the number of
4 investigations, we can bring that cost down.
5 Obviously, process control is
6 greatly enhanced. Regulatory flexibility,
7 I've already talked about. But there's more.
8 So where do we go from here? Moheb referred
9 to real-time release. This clearly is our
10 next focus area.
11 Quality by Design, the enhanced
12 process understanding, the control strategies,
13 coupled with PAT and conventional online
14 analysis, allows us to shift analytical
15 control from the laboratory to the
16 manufacturing line.
17 There's a fallacy that real-time
18 release means we're eliminating finished
19 product testing. We're really not eliminating
20 testing. We're actually increasing testing.
21 But we're doing it online instead of at the
22 end, in a laboratory. So we're controlling it

closer to the source of variability, so that we can actually adapt the process when we see trends.

It allows for real-time release. What does that mean? It means that once the batch is complete, the batch record is complete, including the control data, the analytical data generated online, the quality assurance organization has everything they need. So whether it takes a few hours or a day, the batch can be released then. It doesn't have to wait for several days or weeks for laboratory testing to occur.

There's certainly then pilots, and approved RTR submissions, both in the U.S. and Europe. So the regulators are on board. We see no hurdles to moving forward. It's a matter of us, industry, satisfying ourselves that we have the level of process control to move to real-time release.

Here's just an example. Ralph can probably talk about this better than I can,

1 but you know, ID testing at dispensing. If
2 necessary, you could be doing blend uniformity
3 at the blending stages using near-IR or other
4 techniques. Weight, hardness, being done by
5 conventional online methods, assay, dose
6 uniformity by NIR or other methods,
7 disintegrating moisture online.
8 So that by the time the batch is
9 completed, tableted, coated, you have
10 everything you need to say that the batch
11 meets the quality attributes required.
12 Reduced lab costs are obviously -- reduced lab
13 costs in many reduce laboratory space
14 requirements. Reduced cycle time.
15 We've seen examples of this, where
16 the payback, the return on investment is as
17 short as 12 months, okay. Obviously, that's
18 variable, based on the volume of the product
19 that you're dealing with, the upfront
20 investment for PAT, and certainly for some of
21 these applications, the PAT sensors and
22 equipment are on, they're on the equipment,

1 and whatever product goes through it can
2 benefit from it.
3 Then of course the inventory value,
4 the value of the product. So all of those
5 will, you know, have an impact on the payback.
6 But real-time release, there is value to this,
7 and we're certainly moving as aggressively as
8 we can to go in that direction.
9 One of the hurdles obviously is the
10 fact that you have large N. You're sampling -
11 - instead of ten tablets, you're sampling 500,
12 and so new strategies are required, especially
13 for uniformity testing. This concept of zero
14 tolerance doesn't make sense.
15 There was a paper published in 2006
16 to address different options on how to treat
17 large N, and I know there are ongoing
18 conversations. But this is going to be a
19 case-by-case basis for the foreseeable future,
20 as we go in with real-time release with a PAT
21 application. Now we treat the sample size and
22 the specification will be a case-by-case

1 basis, until we have more guidance in this
2 area.
3 The discussion about existing
4 products, which came up in a question to
5 Moheb. Clearly, QbD can be applied. Now very
6 few companies will go back and redesign an
7 entire process that has been determined to be
8 reasonably capable. However, there are
9 process steps which benefit from a QbD
10 approach, and there are some products.
11 We redesigned a 30-some odd year-old
12 product using QbD principles, because it just
13 had too much variability. So process
14 redesign, partial design spaces for steps in
15 a process are value-added. Obviously, the
16 enhanced process understanding. As you go
17 into -- you know, as some of us move from
18 batch manufacturing to continuous
19 manufacturing, QbD will be a key enabler for
20 doing that.
21 Then the ultimate in our mind is
22 intelligence-based manufacturing or, as I call

it, adaptive processes. Being able to do, in the QbD process, to develop predictive models, to that when you are dealing with variable input, you can adjust your control strategy to always get a fixed output meeting the predetermined quality attributes.

I think many companies have isolated examples of adaptive processes, but this is the ultimate. The more effective we are in understanding what's critical to quality, developing robust design spaces, developing predictive models based on the learnings of our design space, we will eventually get to this adaptable process, which will allow us --

You know unfortunately, we are buying excipients that are used more broadly, in the food industry, in other industries, and we can't always get the suppliers to target down on exactly what we need. So we do get a fair amount of variability in those excipients.

The compendial specifications are

1 inadequate to use for the purposes of
2 targeting what batches or what manufacturers
3 of an excipient are appropriate. You have to
4 use other techniques, and getting to a
5 predictive model that says if my particle size
6 or surface area is between A and B, I use
7 these conditions. If it's B and C, I use
8 these conditions, and if it's between C and D,
9 I use these conditions.
10 That is real world now for some
11 isolated steps and processes, but that's what
12 we need to get to, so that we can use -- we
13 can take variable inputs and always get that
14 fixed output. So Quality by Design works. I
15 mean we as a company and PhRMA are converts.
16 We know it works. It enhances quality. It
17 increases the assurance of safety for
18 patients.
19 We think it's here to stay and, as I
20 said, with areas such as real-time release and
21 intelligence-based manufacturing, there are a
22 number of future opportunities. Thank you.

1 CHAIR TOPP: Thank you, Dr.
2 Migliaccio. We will now take questions from
3 the panel. The first question is from Dr. Ken
4 Morris. Dr. Morris.
5 MEMBER KEN MORRIS: Thanks. Gerry,
6 my question is within the control specs that
7 you put in place on your --which are --.
8 Obviously, the results are very impressive.
9 Is there any real-time adjust, that
10 is, feedback on what Mel was talking about,
11 with respect to the online sensors? Is there
12 any automatic real-time specs to adjust the,
13 or is this all being done manually or semi-
14 manually?
15 DR. MIGLIACCIO: It's a combination,
16 Ken. Obviously, we have fully -- let's talk
17 solid tablet process and encapsulation
18 machines. We have fully instrumented
19 equipment PAT online, that does allow us to
20 adjust real time. So there's a combination of
21 that.
22 But in a awful lot of cases, the

signal is seen by the operator. A trend is detected by an operator, and he has a protocol to follow, to adjust the process manually.

MEMBER KEN MORRIS: Yes, that's fine. So as the design space evolves, you know, are you capturing that as you go, in terms of the next batches, etcetera?

DR. MIGLIACCIO: Yes, yes. You know, I mean what we call it is the enrichment of the design space. But yes.

MEMBER KEN MORRIS: Thanks.

CHAIR TOPP: Thank you. Let me just read my queue here a minute, and if you're not on it, this is a good time to raise your hand again. So I have Tway, Robinson, Koch, Nembhard, Shaya, Muzzio, Kosler. Anybody that I missed? Jim, okay. Anybody else? Okay. Next, Dr. Tway.

MEMBER TWAY: Gerry, I have a question for you, related to one of Moheb's slides, because I think it's going to come up later in discussions, as far as what we can

1 recommend to address the challenges. One of
2 the challenges he focused on and he
3 highlighted was for those companies, those
4 companies that do detailed scientific work and
5 do QbD, they're reluctant to put all of that
6 science or much of that science in the
7 filings.
8 So I'm interested in your
9 perspective from the industry, as far as why
10 there is that reluctance, so that we could
11 figure out how best to address it?
12 DR. MIGLIACCIO: Okay. I'm going to
13 start at the point that we don't have a clear
14 understanding of what should be part of the
15 application, the review, the chemistry review,
16 and what should be part of the quality systems
17 review at the manufacturing site.
18 That is a key, and it's not resolved
19 within, you know, within FDA. It's not
20 resolved, certainly, within our organizations.
21 So until we understand, what is the science
22 necessary for the FDA to say that they can

1 approve the application, and then what should
2 be reviewed during a preapproval inspection,
3 to demonstrate that the quality system
4 effectively, so the control strategy is being
5 properly implemented, the change control
6 mechanisms are in place are there, all right.
7 That's the biggest issue I see right
8 now, and so I think the reluctance -- it's not
9 so much a reluctance. It's, you know, what is
10 sufficient science, and then what should be --
11 what is science and what is quality system?
12 I think that's the question we have to get to,
13 and then we have to address those two in their
14 appropriate venues.
15 CHAIR TOPP: Thank you. Dr.
16 Robinson.
17 MEMBER ROBINSON: Yes, I have two
18 kind of related questions. The first is the
19 process that you talked about or primarily
20 talked about is a small molecule process. So
21 the first question is you said you've
22 implemented this in more than one process.

1 Are all of them small molecule processes?
2 DR. MIGLIACCIO: We are -- so
3 Pfizer, up until the acquisition of Wyeth a
4 couple of years ago, was a small molecule
5 company. We had very little biotech. We are
6 now a biotech player as well, and we acquired
7 a group that was using QbD in the development
8 of their biotechnology products.
9 We have had to obviously have kind
10 of a summit, to make sure that our approaches
11 between small molecule and large molecule were
12 at least aligned conceptually. But it is
13 alive and well. I unfortunately am not the
14 expert on the biotech QbD process. It is
15 similar but has some distinct differences.
16 MEMBER ROBINSON: Right, right. I
17 mean one of the challenges in either case
18 really, as you've mentioned several times, is
19 the online or real-time measurements, and I
20 just wondered if you could elaborate a little
21 bit on really the challenges with, you know,
22 with having the ability to make the

1 measurements you need to make, and having the
2 control systems online you talked about.
3 DR. MIGLIACCIO: Well, I mean -- so
4 I'm going to go back in history, since I grew
5 up Pfizer's fermentation business. Remember
6 that fermentation, which is biotechnology in
7 its crudest form, that's where online analysis
8 started. I mean that's where the first
9 examples of continuous monitoring of key
10 parameters started, and it's alive and well in
11 the biotech world.
12 Now you know, we've got to remember
13 that, you know, PAT or online analysis is a
14 complement to QbD, but it's not an essential
15 element, okay, and its benefit is leading to
16 real-time release. Now we haven't even
17 cracked that egg for biotech yet, real-time
18 release for biotech. That's the blue sky.
19 We can deal with it because of our,
20 you know, historical knowledge base on small
21 molecules. But I don't think we're ready for
22 that in the biotech world. So online analysis

1 is -- again, it's a complement, but it's not
2 critical to achieve the benefits of Quality by
3 Design.
4 MEMBER ROBINSON: Okay, thank you.
5 CHAIR TOPP: Thank you. Dr. Koch.
6 MEMBER KOCH: Gerry, I've got a
7 comment and then a question. It's very
8 impressive that you're adapting some of this
9 to existing processes, with some of the
10 redesign, and then also to build on that the
11 realization of the changes in raw material,
12 and how to adapt the process to handle that
13 variety that takes place, and we'll probably
14 hear more about the need for that this
15 afternoon with some of the Pharmacopeia
16 discussions.
17 Question, and I know that it's not
18 easy from a proprietary point of view, but I'm
19 just curious. With the discussion that you
20 had on an example, you know, was there new
21 technology involved, say new unit operations,
22 of continuous versus batch or PAT tools that

1 were applied, that eventually, you know,
2 become discussed and implemented by other
3 companies?
4 DR. MIGLIACCIO: Well, I would say
5 that on the PAT tool side, we're using pretty
6 well-developed techniques right now in our --
7 in the QbD products that are commercialized.
8 So we are -- of course, we were on the
9 forefront of developing some of those many
10 years ago. But they're pretty well
11 established now.
12 So I wouldn't say there's any new
13 technology in the PAT space. We obviously are
14 taking, currently working on conversion of
15 some batch processes of established products,
16 to continuous processing.
17 So that's where QbD is obviously a
18 huge assist, in making that conversion,
19 understanding now what's critical to quality
20 in a continuous process, versus a batch
21 process, and there may be some newer
22 analytical PAT applications being used there.

1 I'm not intimately familiar with all
2 of them. But that's where we're seeing some
3 of the newer, the benefits of newer
4 technology.
5 CHAIR TOPP: Thank you. Dr.
6 Nembhard.
7 MEMBER NEMBHARD: Thank you very
8 much for this presentation. I'd just like to
9 ask a few questions, specific questions on
10 some of the slides. My background is in SQC
11 and I've done work in academia and scholarship
12 from that perspective. So my questions come
13 from that perspective.
14 Two questions. One on the
15 technology for Slide 4, and one on the
16 statistics for Slide 7, if you wanted to go
17 back to them. I don't know. But on Slide 4,
18 you have the process of Quality by Design, and
19 I'm understanding that a key part of this is
20 the change control strategy.
21 I was just wondering if you could
22 talk a little bit, for a moment, on perhaps

1 the technology that would be involved in
2 tracking and evaluating such change control
3 strategies in industry?
4 DR. MIGLIACCIO: Okay. So the
5 change control strategy. Within the quality
6 system, there is a change control process or
7 system, okay, and that's part of any company's
8 and any site's quality system.
9 For each product now, we are
10 proposing a change control strategy that will
11 allow us to move within the design space,
12 without -- with only our internal change
13 management activities, and I'll get to those,
14 our own internal change management activities,
15 no requirement for regulatory submission,
16 okay.
17 MEMBER NEMBHARD: Well, if I could
18 just sort of refocus a little bit there. I
19 was mainly interested from the standpoint of
20 I imagine that these must be massive amounts
21 of changes that you would have to keep track
22 of, and are there specific technologies or

evaluation systems, software systems, enterprise control systems that you would use to keep track of this? This is my question.

DR. MIGLIACCIO: So actually -- well yes, there is a change control electronic tracking system. Trackwise is the one we use. But it's the repository of all of our changes, all of the scientific data that justifies our changes, etcetera.

It's not -- we're not making that many changes. We are going through a process of optimization, usually Stepwise, and within that process, there will be a protocol to evaluate the impact of the change.

So that will generally go back to some of the experimental methods that were used in the original development of the design space, when we're making a change, making sure that we have not created any unintended consequences of the change.

So it's go through. It could be a design of experiments or some simple

1 univariant experiment, to demonstrate that the
2 change continues to produce a product that
3 meets the quality attributes. Then that is
4 all tracked effectively in our Trackwise
5 system.
6 MEMBER NEMBHARD: Dr. Topp, may I
7 ask a second follow-up question on --
8 CHAIR TOPP: Yes, you may.
9 MEMBER NEMBHARD: Thank you. On
10 Slide 7, where you've talked about this PUP,
11 you have here 52 attributes, 190 parameters.
12 Could you just speak broadly for a moment
13 about what type of experimental strategy
14 covers this many attributes and parameters?
15 There were some specific discussions
16 yesterday about a four period design, this
17 sort of thing. So what types of designs are
18 you using for this many variables?
19 DR. MIGLIACCIO: Okay. So I'm not
20 the -- I'm the manufacturer; I'm not the
21 developer, so I have to qualify myself there.
22 So first of all, the 190 parameters are

1 attributes of the excipients, of the API and
2 process parameters.
3 The attributes are, look at
4 attributes as specifications, in process or
5 finished, for the -- based upon the risk
6 assessment that is conducted, where through a
7 review of prior knowledge and use of tools
8 such as FMEA, Failure Mode Effect Analysis, we
9 will predict what the potential correlations
10 are between import variability and outputs
11 quality attributes.
12 Then a series of designer
13 experiments, which I do not have the intimate
14 details on this pilot, but a series of
15 designer experiments will be developed, and
16 it's iterative.
17 So after the first phase of designer
18 experiments, you may go back in with another
19 phase, to develop the correlations and
20 understand what is truly critical to the
21 finished quality, to the quality attributes,
22 what is critical, and what the correlations

are and potentially what the multivariant correlations are.

As far as the details of statistical design, I'm not an expert and I don't have the background on that.

CHAIR TOPP: Thank you. Next, Dr. Shaya.

DR. SHAYA: Thank you. If we can please go to Slide No. 12. Specifically in this slide, you show the percentage of variation in the batches as a potential proxy for quality, and show that lower variation is attributed to QbD.

The question is as you consider QbD for existing products, how much of QbD would you push to the existing products we see on this slide, for example, after eight percent variation? Do you go with that, or is there perhaps not a very tight correlation, and I'm always thinking causation versus association, between QbD and the actual --

Is there anything else that might be

1 attributed to that variation, rather than just
2 QbD?
3 DR. MIGLIACCIO: Well, the basic
4 differences between products A, B and C is the
5 level of knowledge that we in commercial
6 manufacturing started with, okay, and not only
7 the knowledge that we started with, but having
8 a control strategy that points us in the right
9 direction.
10 So if we see a trend, we know how to
11 address that trend, so we don't get into a
12 situation where we have excessive variability
13 that requires an investigation.
14 So that's the fundamental
15 difference. Remember that these three
16 products all happen to be very well-behaved.
17 So you can't measure quality by failed
18 specification. So we're going to the next
19 level and saying there was enough variability
20 that you had to do an investigation.
21 Four to eight percent, and that
22 eight percent is a bit of an anomaly for a

1 very low volume, but four to eight percent is
2 of products, so let's say around five or six
3 percent on average that you have to
4 investigate, is really not excessive.
5 We would certainly, if we have 50
6 percent deviation rate, that's what we would
7 go -- that's where we did go back in and use
8 Quality by Design, to redevelop and bring that
9 down to a more manageable number. I mean
10 you're always going to be -- because of the
11 strategy you set up, you have very tight
12 internal controls. If you go outside of those
13 internal controls, that's variability that
14 requires investigation, okay. That's nowhere
15 near specification failure.
16 But so these kind of numbers are not
17 alarming. But 50 percent variability is, and
18 that's where you go back in and use these kind
19 of tools.
20 CHAIR TOPP: Thank you. Dr. Muzzio.
21 MEMBER MUZZIO: Okay. Before I ask
22 my question, I just want to say that I believe

1 that the comprehensive framework that you're
2 presenting and the underlying strategy is
3 actually very impressive, and I find it -- I
4 mean I'm very, very encouraged by seeing the
5 full display.
6 I only really have one question, and
7 it only goes to one specific aspect of what
8 you're talking about. It's just something I'm
9 very curious about. For real-time release,
10 for modified release products, how are we
11 going to deal with dissolution?
12 You know, are you just doing the
13 stuff, or are you planning to work on PAT-2s
14 that actually are able to measure certain
15 attributes, structured attributes that get to
16 the release profile, etcetera? I mean I'm
17 very curious about that point, because I think
18 scientifically it's very interesting, and
19 strategically, it's I think very important.
20 DR. MIGLIACCIO: Yes. So we --
21 right now, we're targeting our immediate
22 release solid archos for, as you would expect,

1 go for the low-hanging fruit. You know, we've
2 done some work. In fact, part of the credo we
3 had with FDA was to look at chemical imaging,
4 and can chemical imaging look at a matrix and
5 tell you that it has been produced
6 appropriately to yield the release
7 characteristics that you've designed?
8 We're not there yet. We're not
9 there yet. So we don't have an answer to how
10 we will -- we need to come up with some online
11 measurement that will tell us that the
12 sustained release functionality has been
13 assured by something. We were looking at
14 chemical imaging, but it hasn't yet proven
15 out.
16 MEMBER MUZZIO: Follow-up? Yes.
17 Chemical imaging is promising. There are two
18 issues, right? I mean one is it's relatively
19 slow to me. The other is actually
20 representativeness, because you know, you have
21 to do it a whole bunch of times before you can
22 say you sample this base properly. But I

1 think it should be identified as a focal point
2 --
3 DR. MIGLIACCIO: It is a focal
4 point, and so there's the challenge. There's
5 that challenge, and also the challenge of
6 demonstrating uniformity is going to be even
7 more significant.
8 MEMBER MUZZIO: Yes.
9 DR. MIGLIACCIO: But you know, it's
10 something that we've been looking at, but it
11 is -- it's going to take some more work.
12 CHAIR TOPP: Thank you. Dr. Polli.
13 MEMBER POLLI: Yes. I really
14 enjoyed the presentation. Is this on? Okay.
15 Yes, I really enjoyed the presentation. You
16 said something about you used QbD to
17 reformulate a 30 year-old product because of
18 its variability, and to me that's really
19 interesting.
20 I'm going to look at Moheb. Moheb
21 was talking about future needs in QbD and
22 training. As I think you may have mentioned,

1 ICH has a good start. I know people are
2 actually pretty happy about the training over
3 the last couple of years.
4 But the thing I always hear are just
5 more case studies. I think people would be
6 very interested in this, and that would help
7 promote --
8 DR. MIGLIACCIO: This case study was
9 presented to a large portion of the --
10 Jarred's group at FDA when we finished it.
11 So they have seen this entire redevelopment.
12 MEMBER POLLI: Okay, that's great.
13 I guess just to -- you mentioned because of
14 variability and just thinking about
15 yesterday's conversation, which was very much
16 based on variability or just sort of unknown
17 variability, I think another area would be to
18 better bridging of this sort of work with the
19 clinical type of discussions that were
20 happening yesterday. So I think that would be
21 another area.
22 CHAIR TOPP: Thank you. Dr. Kibbe.

1 MEMBER KIBBE: Gerry, every time you
2 present to us, you impress me with (a), your
3 depth of understanding and your willingness to
4 share what the industry does with the general
5 public and the FDA, and I appreciate it. I've
6 appreciated it when I was chairman of the
7 Committee, and you came and I appreciate it
8 here.
9 Now I'm going to do a disclaimer.
10 I'm on the Steering Committee of the Handbook
11 of Pharmaceutical Excipients. I was editor of
12 the third edition. You said there are
13 problems with control on specific excipients,
14 and I admit we know that for years.
15 Is it within a certain category or
16 class that the issue is most difficult? Is it
17 the polymeric materials? Is it that kind of
18 thing? Is there any way to narrow down where
19 we can go after tightening standards?
20 DR. MIGLIACCIO: I don't know that
21 it can be narrowed down. It's really
22 formulation-dependent. So I'll give you,

1 let's go to the oldest excipient in the book,
2 mag stearate. Most formulations can
3 accommodate a very range of characteristics,
4 surface area, particle size of mag stearate.
5 But some formulations require a very
6 narrow surface area range, okay. I mean you
7 learn that mostly through PAT. We've learned
8 that. We've learned where it can be used
9 freely, multiple suppliers, we've learned
10 where we have to have an internal
11 specification.
12 Other excipients, more contemporary
13 excipients, the same thing. It's more
14 formulation-dependent. It's what it's being
15 mixed with, and the process it's going
16 through. Whether we can accommodate the
17 normal variability of that excipient, or
18 whether we have to have an internal limit to
19 make sure that we've controlled the
20 variability.
21 I don't know that we can -- if I get
22 some of the formulation scientists, they might

1 talk to them about that, and if they can
2 suggest any narrowing, I will let you know.
3 But to my mind, we've faced this with a number
4 of different, and of course, the variability
5 of the API is another complicating factor.
6 CHAIR TOPP: Thank you. We'll close
7 questioning for Dr. Migliaccio there. Gerry,
8 thank you very much for your presentation and
9 your responses to our questions. The next
10 speaker this morning is Dr. Yatindra Joshi.
11 Dr. Joshi is with Teva, and he is representing
12 the Generic Pharmaceutical Association. Dr.
13 Joshi.
14 DR. JOSHI: Thank you very much,
15 distinguished Committee and guests. Good
16 morning, and to my good old friend, Ken
17 Morris. A very early good morning to you,
18 Ken. I hope you're doing fine.
19 MEMBER KEN MORRIS: Not bad, thank
20 you.
21 DR. JOSHI: Okay, excellent, and
22 when I had this -- Lawrence asked me to make

1 this presentation. Lawrence, thank you very
2 much for the invitation, and I knew that I was
3 not going to be the first speaker or the
4 second, and my experience from GPhA is that by
5 the time you're a second speaker, you have
6 some chance of talking about QbD that's not
7 been discussed. If you are third, you've lost
8 it all.
9 So what I've done is I've structured
10 my presentation in a way that I'm going to be
11 actually presenting to you more questions that
12 I'm going to be answering, and a lot of these
13 things that I'm going to present are really
14 based on interactions that I've had over the
15 years with my colleagues in generic
16 industries, as well as pharma industries, and
17 coloring those with the biases of my own
18 perspective.
19 None of the views that I'm going to
20 be presenting are really that Teva, represents
21 Teva Pharmaceuticals in any way.
22 So can we do without QbD in

1 generics? I guess the other way you can ask
2 that question is do we want to get it right
3 the first time, every time? Then how do we
4 find the balance between speed and excellence,
5 and by applying, as you've seen in the earlier
6 presentation, by applying science efficiently
7 and utilizing our prior knowledge effectively.
8 So there was some discussion earlier
9 today, how old is QbD? Is it four years,
10 seven years? My own perspective is QbD for me
11 is about a 25 year-old. I'm talking about a
12 time when there were only clinical
13 statisticians in the industry.
14 There was no software package
15 available. We hired our first non-clinical
16 statistician in 1986 at a company that I
17 worked, and some of you that have more
18 experience than me, you will say QbD goes even
19 beyond that.
20 It's just in the last decade that
21 we've started to talk about QbD. So a few
22 points to consider. Affordability of health

1 care is important to all of us, very
2 important, and especially the budget debate
3 that's going on now. You know how important
4 that is.
5 Generic companies are making
6 medicine affordable, significantly affordable.
7 When your Wal-Mart says your prescription can
8 be filled for $4, you can imagine the selling
9 price for generic companies. Once the 180 day
10 exclusivity expires, and there are four or
11 five competitors, the price drop could be as
12 much as 90 percent or even more. It is really
13 making it affordable.
14 Seven out of every ten prescriptions
15 in the U.S. are filled by generic products,
16 and therefore uninterrupted supply of
17 medication is in the best interest of the
18 industry and all of our patients, because our
19 patients are depending on these medications.
20 So we need to make quality medicine available
21 and affordable.
22 A few additional Points to Consider.

1 Is QbD the only way to make quality products?
2 Some will say definitely not, and I think it's
3 just a matter of perspective what you think
4 really QbD is. But as they say, the point
5 they bring is has the generic industry not
6 provided quality products for many years?
7 72 percent market share. Can that
8 be maintained without quality products? Our
9 generics and branded companies are seeing
10 similar issues. The real way to look at what
11 our customers are feeling, are there supply
12 interruptions, and you can look for the
13 products that have, that are under short
14 supply, and that gives you some idea of how
15 complicated this is from.
16 Helen mentioned earlier, McKinsey
17 report. Michelle Holcomb is currently at
18 Teva. Ted Feuer, I spoke with him also. I
19 spoke to both of them. It's a very nice
20 article actually. If you haven't read it, I
21 think it's worthwhile reading. They describe
22 basically product and process development,

1 which they call PPD in most of the article, as
2 API formulation, analytical process
3 development, validation and preparation of
4 commercial manufacture and they also include
5 regulatory review and approval.
6 That all accounts for 15 to 30
7 percent of overall R&D expenditure, and I
8 think this research is mainly branded, company
9 oriented, for generics. In some cases, the
10 cost could be as much as 80-90 percent,
11 depending on how complicated is the biostudy
12 required and all that.
13 So it is -- and depending on how
14 complex is that API to synthesize and how
15 complex is their manufacturing process. In
16 that article, they say in effect, PPD is
17 costing companies up to 20 percent of
18 potential profits, 20 percent. For the
19 industry as a whole, PPD could represent an
20 incremental 20 to 30 billion dollars in cost.
21 It's an enormous amount, and PPD can increase
22 an individual compound's lifetime value by 30

1 to 50 percent. Those numbers are enormous.
2 The breakdown here is primarily
3 through cycle time reduction, through yield
4 and quality improvements, savings on the QbD
5 techniques, you know, many times you're
6 working with -- if you don't work with
7 statisticians you're optimizing it; you're
8 doing one parameter at a time.
9 It's no way to do that. Besides,
10 you are never able to measure interactions.
11 So it has the potential of savings four to
12 five billion dollars, a potential savings due
13 to reduced regulatory citations. Then
14 increased sales, as our former speaker talked
15 about, by providing quality products available
16 to our customers when they need it.
17 Because today, there are many
18 products that can be easily substituted with
19 another. So all of that accounts for about 20
20 to 30 billion dollars, as per these folks.
21 So they also make a very profound
22 statement in that article, is organizations

1 that embrace PPD can significantly reduce
2 costs, improve products, shorten time to
3 launch, reduce risk and improve patient
4 benefits. I think it's a profound statement.
5 So you wonder are they the only ones seeing
6 it, or do we all see it one way or the other.
7 Then in that article you see how
8 many companies have really converted into QbD
9 and what stage they are and yes, there is a
10 long way to go here still.
11 So questions we want to ask
12 ourselves is if QbD, I'm going to say rather
13 than PPD now, can indeed be beneficial to the
14 industry, as pointed out by our McKinsey
15 colleagues, why is the QbD implementation not
16 complete, as you saw in the previous slide,
17 and why is there so much concern or skepticism
18 that we're still talking about, you know,
19 where we are with respect to QbD?
20 So three points to consider. What
21 are our challenges in adoption of QbD, using
22 past success to predict the future. I see it

1 all the time. You know, this is how we've
2 done. We've made products this way, and
3 therefore predicting future. If I could
4 predict this way, I'd be the richest man, or
5 among the richest men, because I would be
6 playing stock all the time. I know from the
7 past I could predict the future. It doesn't
8 work like that.
9 Why are we doing? Oh, we're doing
10 just fine. No thanks, so you know, leave us
11 alone. It really boils down to resistance to
12 change, and those of you that have read this
13 book "Who Moved My Cheese," you know what I'm
14 talking about. If you haven't read, it's a
15 very nice, small book to read.
16 Difficulty to see long-term benefits
17 and a business case, and now we're talking
18 about, you know, not just a formulator,
19 analytical chemist, a process chemist or
20 scientist or a manufacturing person; we're
21 talking about a company, a philosophy, and
22 organizational decisions, and we made a strong

1 enough business case.
2 There are concerns like QbD will
3 slow us down, and we'll impact the ability to
4 achieve first to file. QbD will increase our
5 development costs significantly. The more we
6 tell the FDA, and I think the more questions
7 we will have and the more difficult it will be
8 to gain approval. Moheb, you touched on this
9 a little bit. It's need to know versus
10 important information to have, to make
11 decisions.
12 Will the review be consistent from
13 one application to another, from one reviewer
14 to another? So a lot of those challenges to
15 consider. So direction of the generic
16 industry.
17 Ken, are you there? Have we lost
18 you?
19 (No response.)
20 DR. JOSHI: We lost him. We made a
21 lot of progress in the generic industry
22 actually, and thanks to the leadership of

1 Lawrence and the discussions we've had.
2 So despite all these adoption
3 challenges, it is important to the generic
4 industry that not implementing QbD is not an
5 option, and really now I'm going to say QbD is
6 building the kind of science that you need to
7 build in your formulations, in your products,
8 in your processes, in your methodologies, in
9 your systems to address issues as they come
10 up.
11 It's really not an option. With 72
12 percent market share, it's not an option. So
13 can we do without QbD in generics? We do want
14 to get it right the first time, every time.
15 We do want to reduce costs, shorten time to
16 approval and launch, and provide uninterrupted
17 supply of high quality products that are
18 affordable to our patients.
19 OGD has made it clear that not
20 implementing QbD is not an option, and I don't
21 quite mean literally not implementing, not
22 having quality products, not building the

1 science in your products and processes. It's
2 not an option. Whether it comes after a
3 string of deficiency letters, or it becomes
4 clear at some point product that has not built
5 a quality is not approvable, it will come.
6 So what has OGD done well, really
7 done well? We've partnered with GPHN and
8 several companies have the industry to develop
9 QbD guidelines. Part of that relationship in
10 working together is actually building a buy-
11 in, to make sure that, you know, there's
12 collaborative effort to come together, and
13 practices that are implemented.
14 We've held several meetings with the
15 industry and reported work in progress, got
16 industry perspective, organized workshops on
17 key topics and reported results; provided
18 clear directions, developed guidelines, and
19 made design space and PAT optional. Have done
20 a lot of that, and there has been some
21 discussion about design space and PAT.
22 The moment you bring in statistics,

1 you talk about design space, and whether it's
2 one parameter, whether it's multiple
3 parameter, you talk about design space. To
4 me, PAT being optional, and I'm sorry, I've
5 been a little bit out of touch in the last
6 four years, but through my previous
7 organization I was a member of Purdue-MIT, a
8 group that worked on it, and the problem --
9 There are some good tools with PAT.
10 You can measure blending. So basically
11 essentially showing that no change is
12 occurring. You can measure moisture --
13 welcome back, Ken. You can measure moisture.
14 But I also saw that the standard curve for
15 most of these techniques that you want to
16 implement is very flat, and that means moving
17 from one measurement, with some variability,
18 can make a big difference in the result that
19 you get.
20 So to me, having design space and
21 PAT optional really is the way to go, until
22 the tools become available. As a formulation,

former formulation guy, you know, I've developed many products, to be able to see the product, how is it progressing as you are making the product is the best way. There's no other choice.

The question is, are the tools available that would allow us to do that? So how do we apply QbD and generics, and as I told you, I'm going to ask, I'm going to be presenting to you more questions than I'm going to be answering. So before we even do that, you know, so let's just see what are we facing? What challenges are we facing?

Race to first to file. It's an enormous race, and I've been in the generic -- you know, most of my career has been on the branded side. I've been with Teva for about three and a half years. From the time I've joined to today, if I look at life cycle management products, the first file occurs now within weeks, not years, not months, weeks after the product is launched, within weeks.

1 It's an incredible race for first to
2 file. Yes, it's for life cycle management
3 products, but the race is on for all of the
4 products. Frequently, limited amounts of API
5 and the need to go to pivotal fast. It's an
6 enormous challenge we need to face.
7 How much material is available for
8 you to really build an enormous amount of
9 science, and then to be able to get to the
10 pivotal batch? What are other companies
11 doing? What is competition doing, and how are
12 they getting through that race to first to
13 file. An important perspective to keep in
14 mind.
15 A balance between what parameters to
16 fix and what to keep variable. I'm going to
17 come back and talk to you from both a
18 development and a review perspective, those
19 sort of challenges. So keep that thought in
20 mind.
21 A balance between what to do before
22 and what do after submission. A balance

1 between risk and the opportunity that's
2 presented to you, and a balance between risk
3 and the cost and how you manage the budget.
4 So some very important perspectives to keep in
5 mind.
6 So now for me, if I were to think of
7 QbD, if you do the right science, it actually
8 -- when people say it takes longer, it won't
9 take longer. It's just the thinking process
10 that you have, and it may in some cases take
11 longer. But in the end, you get to where you
12 want to go faster.
13 Define your development goals. So
14 you need to know what do you want to make?
15 What's the QTPP? We heard earlier. How do
16 you want to make it? So previous speaker
17 talked about what are the variations that you
18 need to manage in the incoming materials and
19 the processes, to make sure that you make a
20 quality product.
21 What manufacturing site do you want
22 to make it in, and what equipment and

1 expertise will be needed? Now think about it.
2 If I am starting on a project, and if I were
3 to ask these questions to my boss, my boss
4 would tell you you're crazy. You haven't even
5 done anything.
6 But that's the way to think about
7 it, is where is it going, because we're
8 dealing in eventually when the product is
9 developed, it's going to a plant, and plant
10 needs to make it. They need to make sure they
11 have adequate capacity to make it. They need
12 to make sure they have adequate technology to
13 make it. So these are very important things
14 to keep in mind.
15 Then when you start, even before you
16 even start development, think about what is
17 that molecule telling you? Does that
18 molecule, is that molecule prone to oxidation,
19 hydrolysis or other problems, to say I know
20 now, based on this molecule, is there going to
21 be a bioavailable at issue? Is there going to
22 be soluble at issue? What is it that I need

1 to build in my thinking process, to address
2 those concerns, even before I begin?
3 Then are the referenced drug, listed
4 drug characterization. What is the brand that
5 we are making generic of, and what is that
6 brand can tell us, and what is important
7 aspects for the brand to know? API, it's just
8 when you get this initial samples, what does
9 that API mean? Generally, it doesn't flow.
10 You put it in a bottle, it's really
11 very fine material. It doesn't flow. But do
12 you want to know that how that API would be
13 when it's commercially supplied, and because
14 it helps you to build the right process to
15 begin with, there's an opportunity to do
16 direct compression. It's the simplest way of
17 making the product, very cost-effective.
18 So understanding of how that API
19 attributes could potentially change, and what
20 impact it would have on your product. Then
21 QTPP and CQA that you've heard before. So a
22 lot of information is available or can be

1 developed, to develop the right strategy to
2 attack development.
3 So build your strategy prior to any
4 development work, based on pre-defined
5 objectives and risk assessment. So understand
6 what you want to do, what are the risks,
7 address that problem. So if you don't have --
8 if you have a molecule that's prone to
9 hydrolysis, you need to know the impact of
10 moisture in the product, and then design
11 experiments to make sure that the moisture
12 range that you're going to qualify is going to
13 make it.
14 So identify those risks with the
15 API, with the formulation, with the process,
16 and use the knowledge that you have, the
17 expertise you have within the company,
18 expertise that's available, and then decide on
19 what experiments you need to carry, and what
20 scale those expenses would be. Are they
21 really small scale, and small scale would be
22 representative of what you're seeing.

1 So if I'm worried about moisture, it
2 doesn't matter small-scale, large-scale. As
3 long as I can define a moisture range, I know
4 how my product will behave.
5 This is where the complexity and
6 perspective, Moheb, that you talked about. I
7 think we really have to be careful as an
8 industry, and as reviewers. Here, you assess
9 the process-related risk with different things
10 that are listed. I'm going to focus on, for
11 instance, look at the second column in the
12 second row. We're talking about assay and
13 pharmacy dispensing.
14 We've estimated the risk is high,
15 and it's a matter of perspective. Now
16 somebody would say do our people know how to
17 weigh? Are they trained adequately? Do we
18 have the right scales, and do we have the
19 right checks and balances? If we do have
20 that, maybe pharmacy dispensing is not a high
21 risk at all.
22 And do we have the experience to say

1 are there mistakes made? Yes, sometimes
2 mistakes would be made. But not to make,
3 consider something as a trend, based on an
4 isolated case of erroneous mistake made. So
5 this is, really key is how much data do we
6 generate as an industry? How much data do we
7 ask as reviewers, and keeping that perspective
8 in mind to say whatever the assumptions are
9 made, are those assumptions leading to a
10 product, a process, methodology that's robust?
11 The goal is wherever you identify
12 risk to be high, how do you bring that risk
13 down, doing statistics and with your modeling,
14 to say that you know what those risks are, and
15 how do you control it? Idea is once you are
16 done, you say you've eliminated all those
17 risks, that we're really concerned with
18 something that you can control and manage it
19 within your facilities.
20 Don't forget. Identify and capture
21 critical information. A lot of times, the
22 problems occur in manufacturing because we

1 have not communicated information effectively.
2 Transfer knowledge effectively to
3 manufacturing plants, whether it's about
4 product, process, methods or other critical
5 information, and hand off at successful
6 completion of validation, so we can assure
7 timely launch, and that joint responsibility,
8 shared responsibility and having the right
9 process to get there, making sure all of the
10 knowledge is implemented.
11 Establish a clear process for
12 problem resolution, that if you have developed
13 a good product, hopefully the manufacturing
14 process, and Gerry, you would like that, would
15 be extremely boring. It would be simple and
16 boring.
17 But not everything is like that.
18 But if some problems come up, as you said, you
19 know what to do to overcome those, and some
20 are within the limits of the process that
21 you're qualified, that you're doing drying,
22 how much air volume you apply. You can make

1 those sort of changes to see how the bed is
2 flowing.
3 So create a mechanism for solving
4 these problem resolutions, and making sure
5 that you have a good process and the right
6 people managing it. Now actually, at the
7 least GPHN meeting, I want to go to this,
8 Grant Heinicke made a presentation, and
9 actually he made several points that after his
10 meeting, a lot of folks were talking about,
11 and some important points to consider.
12 How will industry assess that QbD
13 has worked? Faster approval, meaningful
14 regulatory flexibility and less regulatory
15 questions. If we have done it right, maybe --
16 and we have presented. Moheb, you talked
17 about is the information presented, is it
18 presented properly, and if it is, hopefully
19 all of those.
20 How will FDA assess activity has
21 worked? Reduction in product failures.
22 Reduction in product withdrawals. Reduction

1 in customer complaints. Some additional
2 thoughts, and I wanted to clarify actually.
3 It might not quite be Grant's thought, but he
4 was providing a general industry perspective,
5 and again similar kinds of things, as I
6 mentioned before in the disclaimer.
7 So from a review perspective, focus
8 on quality or curiosity. The endless "what
9 if." What if a polymorph changes? What if
10 the drug diffuses into the coat? What if
11 plasticizer evaporates? What if particle size
12 were at the upper limit? What if the
13 curiosity was at the lower limit? Viscosity,
14 sorry.
15 We've seen applications with
16 certain issues before, and therefore it could
17 always happen. Counterbalance all of that
18 with the industry success.
19 So just some final thoughts. It's
20 neither the strongest of the species, nor the
21 most intelligent, but those that are most
22 responsive to change that survive. In my

1 opinion, it's just the beginning. We have a
2 long way to go. But I think it's clear to the
3 generic industry that building good science,
4 good quality into the products is the way to
5 go, and I expect the QbD as we're talking
6 about today, that the change is coming and
7 change will come rapidly.
8 But as you saw from McKinsey slide,
9 we still have a long way to go. So thank you
10 very much.
11 CHAIR TOPP: Thank you. We'll now
12 take questions from the panel. First, Dr. Ken
13 Morris.
14 MEMBER KEN MORRIS: Oh, thanks Liz.
15 Thanks, Yatindra. Great talk. It seems to
16 me, and I wanted to get your feedback for our
17 sessions later, that there's a low-hanging
18 fruit with generics, in that in a branded
19 company, you make half a dozen products a
20 plant, but in a generic, they make 100
21 products that are very similar.
22 So you could do what, I can't

1 remember if it was Fernando or one of my other
2 engineering colleagues who said that you need
3 some sort of retrospective prediction in a
4 sense, which is to say were you able to
5 monitor the critical quality attributes that
6 really mattered during the process for a large
7 number of similar products, and you could use
8 that to get predictive capability and power,
9 before you start on a new product, as long as
10 it's a very similar type, let's say.
11 Given, of course, the caveat that
12 you raised with respect to the dynamic rates
13 of the sensors, et cetera. Does that sound
14 like any sort of -- does that have any
15 resonance with what your experience has been
16 since you've been in the generic industry?
17 DR. JOSHI: So it's true, Ken, that
18 the number of products we file are
19 significantly more than what I did in the
20 brand companies. So there was a lot that goes
21 through your R&D. I think the important thing
22 is that if you design it right, the kinds of

1 things that I'm talking about, what's the
2 advantage that the generic industry has?
3 A lot of information is already
4 available on the product. It's sort of
5 utilizing that information to focus, and I can
6 tell you that the kind of QbD that we were
7 doing in brand, you know, over the years of
8 development time, here, the development time
9 could be short as six months, nine months, or
10 it could be longer.
11 That you really need to focus on
12 critical aspects of that product and process,
13 to really develop a good control strategy.
14 Now even I have really not enough experience
15 to say that every time we are able to do all
16 of those things, and still win first to file,
17 I don't quite know.
18 Now all I know is if you have access
19 to API early enough, and you've really thought
20 through well, and you've really developed a
21 nice plan, you can do that. So this is where,
22 you know, in one slide where I talked about

1 the balance between what you do before, what
2 you do after.
3 But the important thing is once
4 you've made a pivotal batch, you locked
5 yourself. How do you make sure that you've
6 locked yourself in a product and a process
7 that works? I think it can be done.
8 MEMBER KEN MORRIS: Thank you.
9 DR. JOSHI: And Ken, just to add to
10 that, you might not be able to do everything
11 that you want on every product you are
12 developing, right? It's prioritizing your
13 resources in the way that you're managing.
14 MEMBER KEN MORRIS: Right, and I
15 guess, if I can, Liz, real briefly, because I
16 guess my point is that you can't do everything
17 on every product. But if you're doing 100
18 products that are similar, then if you are
19 collecting the right data at the right points
20 at the right time, it seems like that gives
21 you the ability to have a justification as you
22 file.

1 I know there's not as much data you
2 filed with a branding situation. So that it
3 gives more confidence, it seems like it would
4 give more confidence to the agency, as well as
5 to your own scientists, that your rationale
6 for your formulation development is based on
7 fact data and experience.
8 DR. JOSHI: Absolutely, Ken. You
9 know, you have an API that's very stable.
10 It's a nice, crystalline material with
11 controlled particle size. It flows well; it
12 compresses well. You have a direct
13 compression formulation. You don't need to do
14 a whole lot for a product like that.
15 If you have -- the complexity comes,
16 and you need to understand what complexity is
17 presented with the product that you're
18 developing, and then to define how much you do
19 on that. So you make a very good point, and
20 you can learn a lot from, you know, processes
21 that you have implemented, and the experience
22 that you've gained.

1 MEMBER KEN MORRIS: Thank you.
2 CHAIR TOPP: Thank you. Let me just
3 check with the panel about my queue. I have
4 Dr. Tway, Dr. Kosler, Dr. Robinson, Dr. Koch,
5 Dr. Marilyn Morris, and Dr. Muzzio. Am I
6 missing anyone? Okay, next. Dr. Tway.
7 MEMBER TWAY: Thank you very much.
8 I enjoyed it, and in looking at Slide 11,
9 which was your challenges in adopting QbD, it
10 seemed to me, and recognize I'm coming from
11 the brand side of the business, but you have
12 similar but again uniquely different
13 challenges than the brand side had, and that
14 your biggest challenge is, if I lump them all
15 together, kind of is to eventually be able to
16 build the business case to the companies, to
17 management, to say this is really good to do.
18 This is something we need to do, and
19 I certainly know on the brand side, people
20 move very slowly, going back four years or so,
21 as Gerry would say.
22 And then once there were a couple of

1 success stories out there, once they saw that
2 real-time testing could be accepted, that you
3 could move around in a design space.
4 Many other companies picked up
5 momentum, and from your perspective, is that
6 what the generic is kind of looking for,
7 needing now is, you know, being able to build
8 a strong enough business case and be able to
9 show some successes that other companies will
10 pick up on it as well.
11 DR. JOSHI: Yes, absolutely. I
12 think in the end, the results would speak
13 louder, and just to tell you, the difference
14 between first to file and, as some of my
15 former colleagues say, that if you're not
16 first to file, you might as well be last, is
17 enormous.
18 It could mean a several hundred
19 million dollar product, versus just a few
20 million dollar product, or maybe a product
21 that's not even profitable.
22 So it's going to be challenging. I

1 think the companies that are going to really
2 do a very good job managing that risk and
3 benefit, and addressing it early, because the
4 last thing you want to do is you have a
5 product that you can't launch, right. So
6 managing that risk.
7 But it's going to be not an easy
8 task, and in the end, I think it's doable, but
9 the results with then speak louder. I really
10 don't know, you know, how FDA, for instance,
11 levels the playing field to say the
12 application must have certain content.
13 Without that, they will not accept.
14 For the industry to say what is it,
15 how do you attain the risk, the kinds of
16 things that I've talked about. But I think
17 exactly.
18 CHAIR TOPP: Thank you. Dr. Kosler.
19 DR. KOSLER: Hello. I'm a
20 statistician, and I have a great interest in
21 process control, and the transformation of
22 culture that's required for that to take

place. I'm reminded of history, of Deming going to Japan with his ideas about quality, because they weren't accepted in Detroit, et cetera, and he went to Japan and had success there.

It really requires a transformation of culture from the top down. I wonder if you could comment on your feeling about transformation of culture within generics, toward a culture that would support process control, and what we have seen here as process understanding, process control and continuous improvement.

Those really evolve out of a culture of quality control. It's another evolutionary step. I wonder if you could comment on the preparedness for generics or the openness or whatever you want to focus on for generics. Also I wanted to say, I had questions for the previous speaker. Did we run out of time or --

CHAIR TOPP: We were just trying to

1 keep the agenda moving along, and notice on
2 the agenda, if you'll see, we have a Committee
3 discussion, a panel discussion really at the
4 end of this topic.
5 So you'll have time to bring those
6 up again, and so I hope Gerry will stick
7 around, in case there are questions for you
8 and the other speakers as well. So yes, so
9 you can bring them up again.
10 DR. KOSLER: Okay, great. So that's
11 really my question, is about cultural
12 transformation within generics towards process
13 control, and is there really a willingness,
14 openness, readiness, et cetera.
15 DR. JOSHI: Yes. So actually your
16 question is more like what I addressed very
17 early, to say when did we really start to talk
18 about QbD. I think to say that the generic
19 industry does not have process control, does
20 not have, you know, that sort of mind set,
21 might not be accurate.
22 To me, I think it's all about how do

1 you bring development, and what sort of
2 applications you're implementing in
3 manufacturing. If what Gerry described, if
4 that's what you put in, where an operator is
5 going to look at certain signals and making
6 decisions based on those signals, then you
7 need to acquire appropriate training. That
8 you need to create special expertise to manage
9 those set of things.
10 But you can also manage a product
11 and a process and plan without having to do
12 that. I mean, I remember my first product
13 being transferred to Italy. It was a fluid
14 bed granulation product, and Pedro Collostre,
15 300 pound guy, you can see me, a small guy.
16 He says "Why did you develop this process,
17 because we're losing eight percent on a
18 previous product that year?"
19 I told him at the time that our
20 yield will be much about what you're
21 anticipating, will be at least 98 percent, and
22 we made three batches with 99.1 percent, and

1 all the operators were saying the process was
2 absolutely boring. So it's what we build into
3 a product and a process, and how it
4 translates.
5 To me, really it's a mind set that
6 begins right from the beginning, and is it
7 prevailing on all products in the generic
8 industry? The answer is no. Do some
9 companies have it right? Yes. Do a lot of
10 companies have it right on certain products?
11 Yes.
12 But I think it's where the
13 transformation needs to occur on a larger
14 scale, as Ken was asking. If we apply on
15 every product, are we going to make a good
16 enough business case that our marketing and
17 business folks will say yes, we have
18 confidence in what you're doing. Have I
19 answered your question?
20 DR. KOSLER: Yes.
21 CHAIR TOPP: Okay. Thank you. Dr.
22 Robinson.

1 MEMBER ROBINSON: Thank you. So I
2 think I have a pretty good feel for the
3 cultural aspects, the impact of that on the
4 company, and or on companies in general, and
5 the issues sort of facing us in terms of
6 business decisions.
7 But I don't really have a good
8 sense, either from your talk or from the
9 previous speaker, sort of where the -- what
10 you see as the real technical gaps or
11 technical needs that you see, sort of facing
12 or blocking the implementation of this in
13 generic companies, companies making generics.
14 DR. JOSHI: I'm sorry. I'm going to
15 again qualify that, to say that there is --
16 it's not being implemented in generic
17 companies. I don't know how accurate that is,
18 right, and again, same question that I asked.
19 I think it's the race that you have
20 in the industry, and your need to get to a
21 pivotal batch really fast is a very
22 significant obstacle, in terms of what

resources you put in, to do all the things that you want, and then second is how well you've thought out what you need to do.

In the long run, you know, there are companies that are making products very successfully. You look at the number of recalls. They have very little recalls, and I would say that cannot be attained without really having a very good understanding of the product and process.

But I think in the end, it will really boil down to our business leaders, how we justify making the investment that we need to make in the API, in development costs and all that, in time and resources, to make sure we put more resources early enough to get better results at the end.

MEMBER ROBINSON: I guess maybe you misunderstand. I'm really asking are there technical obstacles facing implementation of QbD that we can better understand as a panel?

DR. JOSHI: I don't think so. You

1 know, I think as long as you keep the PAT out
2 from a technical perspective, it's all there.
3 None of that I talked about really is a
4 handicap that we cannot have. So there is
5 really no technical limitations.
6 Yes. Obviously, if we had good
7 tools, where you can actually monitor the
8 process as it's happening, it would certainly
9 help a lot.
10 CHAIR TOPP: Thank you. Dr. Koch.
11 MEMBER KOCH: I think the way the
12 presentation ended up, it seemed like the
13 generic industry, as you're representing it,
14 has an appreciation for QbD. However, it
15 seemed like the continuing phase in the
16 presentation was speed. Certainly impressive
17 the rate at which 72 percent of the market's
18 been achieved.
19 I have a feeling it's mostly through
20 cost and time will probably be the way to
21 measure whether there's quality in the
22 efficacy metrics that come up to balance that

1 percentage. I know that the speed to market
2 doesn't always guarantee the particular
3 quality that one is looking for.
4 Also that list that you had at the
5 end of the þWhat if's?þ, it's almost, you
6 know, effectively addressing the "what if"
7 column. It does require time. Just comments,
8 I guess.
9 DR. JOSHI: Okay, thank you.
10 CHAIR TOPP: Thank you. Dr. Marilyn
11 Morris.
12 MEMBER MARILYN MORRIS: So I think
13 most of my questions have been addressed, but
14 I did want to go onto one comment you made
15 with regards to limitations for implementing
16 QBD, and that is the unknowns with regards to
17 submissions to FDA. I don't know if you want
18 to comment a bit more with regards to this.
19 DR. JOSHI: I think there's a lot of
20 discussion that occurs is what information, as
21 Moheb was saying, we put together in our
22 application. That's really the big transition

1 that needs to occur, that understanding that
2 more information doesn't always they would
3 have negative implications.
4 This is a big debate that goes on,
5 and I think that's -- one solution we need to
6 find is exactly that.
7 CHAIR TOPP: Thank you. Last
8 question, Dr. Muzzio.
9 MEMBER MUZZIO: Hi. As I was
10 listening to your presentation, I was reminded
11 of many discussions I had with the branded
12 companies in years past, when you were talking
13 about, you know, where to start.
14 In there, the answer was a concern
15 that if you start with a product you are
16 developing, you increase the regulatory risk,
17 and it was hard to convince the organization
18 that they should do that, right.
19 So in some sense, applying similar
20 logic to you, I wonder why so much emphasis
21 on, you know, applying to the products that
22 you're developing now, where you could impact,

you know, your ability to being first. Why not do something similar to what many of the branded side did, which is they actually selected a product that they already had in the market, to bring QbD into their organization.

The other reason why that was interesting, not only because -- is because if you look at the experience in statistical product and process development and control, which is, you know, a more explanatory name for these, in other industries that have been doing it for 20, 30, 40 years, what you will learn is that it was hard to start, because of the cultural change, because of the new tools, because of the investment.

But once you got going, and once the organization got good at it and the right tools were there, your system got faster. So once they developed the expertise with the existing products, then beginning to use the tools for the things you're developing as

1 perceived as less risky.
2 Number two, I think I want to build
3 on what Ken said. Because of the platforming,
4 you know, a company like Teva, you make what,
5 300, 400 products. So you could actually
6 group into families the share, excipient
7 share, you know, drug release, etcetera.
8 So you have, you know, Class 1,
9 Class 2, Class 3, Class 4, and you begin to
10 significantly cut down the size of the
11 problem, when you develop the 103rd product in
12 Class 3. Because now you more or less know 90
13 percent of what you need to do, and there's
14 only a little bit more, yes.
15 I would say in the generic
16 environment, I wonder how you would react to
17 this, addressing existing products and just
18 defining it as lowering the cost and
19 increasing the effectiveness of manufacturing.
20 It's even more important than on the branded
21 side, because your profit margins are lower,
22 so you know, every penny counts for more. So

1 that's, you know, my dissertation, I guess.
2 DR. JOSHI: Just a comment, as I see
3 it, right? Not a question, or is there a
4 question.
5 MEMBER MUZZIO: And there were
6 questions for reaction basically, whether you
7 see this as a viable option or --
8 DR. JOSHI: I think you're right on
9 really. We make a lot of products, and you
10 know, brand will submit three, four a year.
11 We'll submit quite a few more. So we do make
12 a lot of products.
13 So we should have really lots of
14 experience, both in manufacturing R&D to deal
15 with, and you know, bracketing these products
16 in groups and types and processes and all
17 that, and gain information.
18 It's a question that is how much of
19 this data mining has been done? How much of
20 that information is available at your
21 fingertips when you're starting on something
22 else? But there is enormous value in what you

1 say. There's a lot to be liked.
2 CHAIR TOPP: Thank you. Thank you,
3 Dr. Joshi. We will now take a ten minute --
4 sorry, I'll give you 15. We'll now take a 15
5 minute break. Panel members, please remember
6 that there will be no discussion of the
7 meeting topics during the break amongst
8 yourselves or with members of the audience.
9 We will resume at 10:45. So if you
10 want to synchronize your watches, my watch now
11 says 10:30. So you have 15 minutes from now.
12 So see you back here at 10:45.
13 (Whereupon, the above-entitled
14 matter went off the record at 10:27 a.m. and
15 resumed at 10:43 a.m.)
16 CHAIR TOPP: Okay, everyone. It's
17 time to resume. We will now continue with
18 presentations from the FDA and guest speakers.
19 I would like to remind the public observers at
20 this meeting that while the meeting is open
21 for public observation, public attendees may
22 not participate, except at the specific

1 request of the panel.

2 Our next speaker this morning is Dr.

3 Evdokia Korakianiti of the European Medicines

4 Agency. The presentation this morning will be

5 "Regulatory Assessment of Applications

6 Containing QbD Elements, a European Union

7 Perspective." Dr. Korakianiti.

8 DR. KORAKIANITI: Hello, and thank

9 you very much for this invitation to present

10 the European perspective on the assessment of

11 publications that contain Quality by Design

12 elements. This is the overview of my

13 presentation. First, I will give a very

14 general description about the agency and its

15 core activities, so to set the picture.

16 Then I will move on on the European

17 perspective on the importance of Quality by

18 Design for the patient, what is the current

19 status, where we are; what we have done so far

20 to facilitate implementation of Quality by

21 Design; what are the challenges that we are

22 facing; and most important, what needs to be

1 done further.
2 So the mission of the European
3 Medicines Agency is to foster scientific
4 excellence in the evaluation and supervision
5 of medicines for the benefit of public and
6 animal health. The European Medicines Agency
7 is a decentralized agency of the European
8 Union, and is located in London.
9 It's mainly dealing, mainly with
10 innovative products, and one of its key
11 activities is the centralized review
12 procedure. Once, if there's a positive
13 outcome of the centralized review procedure,
14 then a market authorization is granted that is
15 valid throughout the whole European Union.
16 The European Medicines Agency is
17 working very closely with the national
18 competent authorities of the member states,
19 and there are 27 member states, that have
20 nominated more than 5,000 European experts for
21 the purposes of the centralized review
22 procedure.

1 Also, the agency is part of a
2 network of a European network for medicinal
3 products. Other parts of the network is the
4 European Commission, the European Parliament,
5 other EU agencies, and we are also interacting
6 very closely with EDQM, which is the European
7 Directorate for Quality of Medicines, which is
8 responsible for the European Pharmacopeia.
9 So where do our experts come from?
10 The experts are nominated by the national
11 competent authorities, and they may serve as
12 members of our scientific committees or
13 working parties. The EMA Secretariat, that is
14 the staff of the agency, is responsible for
15 the procedural and administrative aspects of
16 the centralized review procedure, and also
17 providing scientific support in the scientific
18 evaluation of the safety monitoring of
19 medicines, as well as contributing in the
20 development or revision of guidelines.
21 The agency has six scientific
22 committees. Their composition is independent

1 experts that are nominated by the member
2 states, and of relevance to this meeting is
3 the Committee for Medicinal Products for Human
4 Use. The work of this committee is to provide
5 all, is to prepare all the opinions of the
6 agency relating to medicines for human use,
7 and its work is supported by several working
8 parties that provide technical expertise in
9 their own scientific area.
10 For example, we have the Quality
11 Working Party, the Biological Working Party,
12 which are relevant to qualified design
13 applications, and on top of these permanent
14 working parties, it is possible to establish
15 on an ad hoc basis other working parties, for
16 example, the Biosimilar Working Parties, or
17 working groups that would provide expertise in
18 specialized areas.
19 For example, that is the European
20 PAT team, and I will focus a bit, I will
21 describe the activities of this team later on
22 this presentation.

1 So the agency issues opinions about
2 medicinal products based on balancing the
3 benefits, that is the desired effects of a
4 medicine, versus the risks, the designed
5 desired effects. To weight the benefits
6 against the risks is a very complex process,
7 and of course there are always -- it's not
8 straightforward. There are always some
9 uncertainties, and the reason is that we have
10 only an estimate of the benefit and the risk-
11 based on data that are available at that given
12 point of time.
13 Quality by Design is a way, is a
14 scientific, a systematic approach to
15 pharmaceutical development in manufacturing,
16 that focuses on building an intense product
17 and process understanding like that, using
18 some science and quality risk management. In
19 this way, we understand better the risks, and
20 we are able to manage them in a better way,
21 and therefore reduce uncertainties that come,
22 that arise from the product and the process.

In this way, it is possible to have a better assurance of the quality of the product, which is of course of benefit to the patient. This is setting the picture about how Quality by Design can contribute to increase the assurance about the benefit-risk ratio of a medicinal product.

What will be different in Quality by Design? What do we see as different? A systematic use of the following tools: risk assessment, statistical tools, process analytical tools for monitoring the progress of the process at any time, or controls for adjusting the process at any time. For the benefit of time, I will skip this slide, because this has been addressed by previous speakers.

So this is the picture where we are standing at this point of time. In the centralized procedure, we have received so far ten authorizations for chemical products. Four of them include real-time release

1 testing, and we have also approved six post-
2 authorization variations. So that would allow
3 the implementation of Quality by Design
4 principles in all authorized products.
5 We've also received some scientific
6 advice requests about how to implement Quality
7 by Design in products. With regard to
8 biologicals, the numbers are lower at the
9 moment. We have received 20 market
10 authorizations, and there are some at pre-
11 submission level. We have not received by
12 Quality by Design applications for generics so
13 far.
14 Just some observations. The numbers
15 of applications with Quality by Design or PAT
16 elements are steadily increasing, and the
17 content, not only the numbers but what is
18 important is the content of these
19 applications. Now it's more comprehensive.
20 It started slowly with some elements
21 of Quality by Design throughout the dossier,
22 and now they've become more and more

1 comprehensive. It seems that the companies
2 that have received approval for Quality by
3 Design approach are then quickly implementing
4 the same principles across several of the
5 products.
6 Now applicants start exploring more
7 complex approaches, like real-time release or
8 continuous process verification as an
9 alternative to the traditional process
10 validation approach. We've also had some
11 first contacts on continuous processing, and
12 what is the regulatory tool box? What do we
13 have as regulators to facilitate
14 implementation of Quality by Design?
15 This has extensively been presented
16 by Dr. Nasr, so just for the sake of time, I
17 will mention that we have the ICH guidelines,
18 the questions and answers documents that are
19 prepared by the ICH Implementation Working
20 Group, as well as the recently-published
21 Points to Consider.
22 What we've done in Europe in order

to facilitate implementation. This is a continuous process that consists of the following steps. First of all, we need to identify what have been called knowledge gaps, and we do that through interactions with the industry, or through the evaluation. We identify topics through the evaluation of publications.

Then try to bring knowledge to address these gaps by either with workshops or expert meetings, and then what is very important is because, taking into account the complexity of our network, is to share this knowledge with our European experts. This is done through the development of guidance and extensive training. Of course, this is non-stop, this is a continuous cycle.

I would like to focus a bit that your attention to the activities of the European PAT team, and the role of the working parties in developing and revising guidance at the moment.

1 So the PAT team was established in
2 Europe, in order to prepare a harmonized
3 approach on the assessment and inspection of
4 Quality by Design submissions. Its main role
5 is to be a forum for discussion. It consists
6 of assessors and inspectors, and it's a forum
7 for discussion with companies at the pre-
8 submission level, to provide advice about the
9 Quality by Design strategy.
10 The team can also provide
11 scientific input upon a request during the
12 evaluation of actual applications. It has
13 heavily been involved in organizing training
14 for assessors, and also in the organization of
15 workshops with industry. Also, the team is
16 involved in reviewing mock submissions or has
17 participated in mock inspections, in an
18 attempt to gain more understanding about
19 elements of Quality by Design.
20 In addition to the activities of the
21 PAT team, taking into account that we have a
22 very wide network of experts that we need to

1 reach, we have been looking at the guidelines,
2 the existing guidelines and how they need to
3 be revised, in order to facilitate Quality by
4 Design.
5 So at the moment, we are revising
6 the NIR guidance, in order to take into
7 account its applicability, the use of NIR for
8 PAT applications. We are revising the real-
9 time release testing guideline and the process
10 validation guideline, in order to take into
11 account the alternative approach of continuous
12 process verification.
13 All these guidelines are revised by
14 the Quality Working Party, which I remind you
15 is one of the working parties that is
16 supporting the work of our main Committee for
17 the Human Medicinal products, and can be found
18 on the MEA website.
19 But there are still challenges.
20 What are the challenges that lie ahead of us?
21 First of all, there are still a lot of common
22 misconceptions that we need to address.

1 Another, the way that the information is
2 presented in the dossiers needs to be
3 improved, and there is a lot of work that
4 needs to be done with regard to clarifying the
5 regulatory requirements, in order to
6 facilitate the implementation of Quality by
7 Design.
8 Another very important point is how
9 do we facilitate continuous improvement post-
10 approval? How do we create a flexible
11 regulatory framework? And of course, both for
12 within Europe and together across the ICH
13 regions, how do we ensure a harmonized
14 implementation, taking into account the
15 global, the fact that industries manufacturing
16 globally?
17 So some of the common misconceptions
18 are procedural. For instance, quite often we
19 hear that Quality by Design might mean that
20 there is more regulatory scrutiny, that at
21 least would result in raising more questions
22 and therefore delays in approvals, which is

1 actually not correct, because in the
2 centralized review, there is a standard time
3 table of 210 days.
4 In some of -- another common
5 misconception is that Quality by Design
6 necessarily means, equals to pre-approval
7 inspection. That's not the case. We've only
8 had four pre-approval inspections out of all
9 the applications we have received so far.
10 There are, of course, some other
11 misconceptions not relating to procedure but
12 more to regulatory aspects. One very common
13 misunderstanding is that design for
14 experiments equals a design space, or that if
15 there is a design space, there is no longer a
16 need for specifications, for release
17 specifications.
18 Or even further, that if a parameter
19 is controlled, then it stops being critical,
20 it stops having a risk, posing a risk to the
21 finished product quality. These are just
22 examples of misunderstandings that we see and

1 that we need to address.
2 Another challenge, very important
3 for us, is how the information is presented in
4 the dossiers, and this is a feature that we
5 need to give, to provide more guidance to
6 applicants. Quite often, we're faced with
7 tables like this, that show a summary of how
8 different -- of the risks that different unit
9 operation might have to the critical quality
10 attributes.
11 But this is just -- this table can
12 be the only thing that is included in the
13 dossier, and the question is how do you
14 establish this risk, based on which criteria?
15 We would prefer to see a table like that, that
16 would give some more explanations of how the
17 company is reaching certain conclusions, and
18 this is an excerpt from the ICH Implementation
19 Working Group case study.
20 So in summary, it feels that quite
21 often companies do not explain well in the
22 dossiers what they've done through the

development. Quite often, what we see is only conclusions about the studies, and it's not presented how these conclusions have been reached, and of course this raises questions.

Another problem is that quite often, companies apply for a design space and the boundaries of the design space, or the parameters that consist of this design space, are not very clearly defined. But of course, this has regulatory implications.

Or for instance, the design space is developed at lab of pilot scale, and then the ranges that are applied for the production scale design space do not correspond. Information about statistical validity of models or design of experiments cannot -- is not often found in those case, and the question is do we need -- how much do we need, how much statistics do we need, how much into depth do we need to go?

The answer is well in some cases, it is very, very important if that model is the

1 sole indicator of the finished product
2 quality. In some other cases, it might not be
3 quite important, if it is used for in early
4 screening studies. So we need to step back
5 and look how important, what is the role of
6 that model or that study for the finished
7 product quality?
8 But quite often we are missing that
9 information. Of course, this would raise
10 another question. So as a summary, we see
11 that the Quality by Design dossiers, we need
12 to issue some further guidance, and the
13 Implementation Working Group is working on
14 that, on how to better structure the Quality
15 by Design dossiers, to make the information
16 more transparent and clear.
17 The applicants just need to tell the
18 story and tell it right, so that the assessor
19 can understand what they've done, and can make
20 an informed decision on whether that is
21 adequate or not.
22 What are the challenges that we are

1 facing? Apart from the presentation of the
2 information from the dossier, as we gather
3 experience, we see that there are certain gaps
4 that we need to clarify requirements, and for
5 instance, one big area is that of the design
6 space.
7 We know from experience that the
8 design space is developed at lab or pilot
9 scale. How do we ensure that it is still
10 valid, the ranges are still valid at
11 production scale throughout, within the whole
12 area of the design space? What should be the
13 regulatory requirements concerning the
14 verification of the design space?
15 Would it be enough to have some
16 experiments at the center point? Would we
17 request additional controls if a company is
18 moving to areas that are not well-verified?
19 What does the -- these should not be addressed
20 anymore on a case-by-case basis. It needs to
21 be better clarified.
22 Modeling is another area that is

raising questions. When is a model appropriate for real-time release testing or continuous process verification? If a model is developed based on limited data coming from development, is it robust enough? Is there a need for pilot testing using a model and end product testing for -- and which are the acceptance criteria that should be used, for instance, for product resolution models?

These are all raise the need for further clarification of these points. A model also is not valid forever. How will the validity of the model be verified throughout the product life cycle? Again, stepping back, are all models equally important? Do we need to have the same regulatory scrutiny for all sorts of models that might be included in a regulatory submission? Possibly the level of regulatory scrutiny should be relevant to the risk of that model, to the finished product quality.

Another point that we see as a big

1 challenge is how industry is describing
2 manufacturing process. So the main issue here
3 is that quite often, in an attempt to
4 facilitate changes post-approval, certain
5 process parameters that seem to have low risk
6 on the finished product quality are not
7 included in the manufacturing process
8 description.
9 Therefore, this sometimes raises
10 questions, because we see limited description
11 of the manufacturing process. Therefore, we
12 need to start -- on the other hand, it is
13 understandable that we need not to overburden
14 industry.
15 So the question is how do we strike
16 the balance between the information that needs
17 to be in the dossier, to make an informed
18 assessment, and at the same time how do we
19 facilitate post-approval changes?
20 Relevantly, what is the interface
21 between the quality systems of Quality by
22 Design? For instance, what change could be

1 handled under the quality system of the
2 company, and what change should be a
3 variation, should be a supplement? This needs
4 to be better clarified, and quite a lot of the
5 problems come because there is not a good
6 clarification on this point.
7 Of course, it was mentioned by Dr.
8 Migliaccio in his presentation that the
9 Quality by Design has silenced some
10 established regulatory standards. For
11 instance, the acceptance criteria for content
12 uniformity is one of the, one of when large
13 sample sizes are being used, and this is one
14 topic that there is ongoing work at the moment
15 from EDQM.
16 As mentioned before, a very
17 important aspect is how do we facilitate post-
18 approval changes? How do we create the
19 regulatory framework that will facilitate
20 continuous improvement of the process? We
21 need to depart from the one-size-fits-all
22 approach. We need to step back, and the

1 question is how do we do that?
2 Should the better understanding of
3 the process risk mean less regulatory
4 commitments? Should a better understanding,
5 not only of the risk, but also if there are
6 controls in place that could demonstrate that
7 that risk can be better managed, mean that we
8 should -- that this could, a sudden change
9 could be implemented easier?
10 Do we need to step back and see how
11 we can create a risk-based framework, that
12 enables continuous improvement post-approval?
13 In an attempt to do that, within the -- the
14 agency has published a draft Q&A that is a
15 guidance on post-approval change management
16 protocols.
17 What are these protocols? These are
18 protocols that could be included in the
19 initial market authorization that is in NDA,
20 or submitted as standard on protocols. At the
21 moment, when a change is going to be
22 implemented, what we are looking into is

1 looking at the strategy that has been
2 followed, in order to assess the effect of the
3 change to finished product quality, and the
4 actual results of the studies. This is
5 evaluated currently as a whole, in one go.
6 The protocols would allow to define
7 the strategy, describe how the effect of the
8 change on finished product quality is going to
9 be evaluated, and then once this is agreed,
10 have a very quick step, a minor variation to
11 implement the actual change. So this could be
12 a way to address, to facilitate post-approval
13 flexibility.
14 For example, if in a Quality by
15 Design application it was described what would
16 be the strategies that would be used to
17 implement certain changes post-approval
18 through protocols, then these changes could be
19 implemented in a faster way, using minor
20 variations post-approval. This could be one
21 of the ways that could be used.
22 As mentioned before, Europe is a

very extensive network, where experts have been mobilized, come from different member states and different competent authorities. Of course, this makes a lot of variability. So one of the challenges we are facing is how do we ensure adequate expertise at a time of limited resources, both at national and at European level?

Not only that, how do we ensure that there's a harmonized implementation, that there is the same understanding about how we implement the Quality by Design principles during the evaluation of dossiers? For this reason, there's a need for extensive training, developing guidance, and also peer review during the actual evaluation of those years.

Another point that we really need to work is how do we ensure, how do we improve the way that information is shared between assessors and inspectors? We need to define better the borderline between assessment and inspection. We cannot expect that the

1 inspector could go in the manufacturing side
2 and can review models or all data, unless
3 there's a specific reason for that.
4 The inspectors focus on system-
5 related issues. For instance, how is the
6 design space implemented in a batch record?
7 How deviations from the design space are
8 handled through the company's quality system,
9 and things like that. But quite often, we
10 need to better define what is the borderline,
11 what should be in a dossier and what should be
12 left for the actual implementation in the
13 site?
14 We have had some joint inspections
15 where reviewers were participating in an
16 inspection, which we found to be very, very
17 useful. But again, we have to balance that
18 off with the burden that we are putting to
19 industry.
20 So harmonization is a complicated
21 issue and it's not only within Europe, but how
22 do we ensure that we are harmonizing, that

1 there's harmonizing implementation in the ICH
2 region? Of course, the work of the ICH
3 Implementation Group is very important in
4 ensuring this, and on top of that, EMA and FDA
5 published earlier this year an announcement
6 about a pilot for parallel assessment of
7 Quality by Design applications.
8 What is the reason for that? The
9 reason is to allow assessors having concrete
10 examples, real applications, to discuss about
11 how -- about Quality by Design concepts and
12 maybe try to address some of the gaps I
13 presented earlier on in my presentation.
14 The outcome, what will be the
15 outcome of that? We have committed and we
16 will try to have an agreed list of questions
17 with the industry, and a list of outstanding
18 issues. So for those parts of the application
19 that are subject to the pilot, for the Quality
20 by Design aspects of these dossiers.
21 We believe that through this pilot,
22 we'll be able to better define what are -- and

1 clarify some of the regulatory requirements,
2 and maybe this will be helpful to further
3 develop some guidance.
4 So what needs to be done further?
5 First of all, we need to publish more
6 guidance, through draft guidance, to address
7 the challenges that I presented earlier on.
8 Of course also, there are some future trends.
9 For instance, continuous manufacturing is one
10 of the trends that we are being faced now.
11 How would Quality by Design be
12 implemented for analytical methods? How do we
13 handle models, or devise the risk release
14 control models, when they are being used for
15 release testing? How do we ensure that the
16 design space is clinically relevant, and is
17 there a difference -- should we step back and
18 think how do we set clinically meaningful
19 specifications, instead of the current
20 approach?
21 These are some of the future trends
22 that we might need to address. And of course,

1 what is very important in Europe is that we
2 need to continue to set the knowledge that we
3 build with our network of assessors and
4 inspectors, through training and guidance, and
5 of course, to continue working towards a
6 harmonized implementation code.
7 As a summary, issues keep arising as
8 we gather experience. More and more issues
9 come up, and assessors are requested often to
10 evaluate new types of data, and this needs, of
11 course, appropriate expertise. For this
12 reason, we are trying to work on guidance
13 documents, to revise existing ones when
14 there's a need for that, and of course there's
15 a need to continue the dialogue with industry.
16 I would like to say also that Europe
17 is actively participating in the ICH
18 Implementation Working Group activities.
19 So as a closing remark, for the
20 European Union Quality by Design means a
21 better process and product understanding.
22 What does this mean? This means the highest

1 range of product quality, and of course better
2 management of the risks. Of course, this is
3 of benefit to the patient, which is of
4 interest to all of us. So thank you very much
5 for your attention.
6 CHAIR TOPP: Thank you, Dr.
7 Korakianiti. What I would like to do now is
8 just take one or two questions from the panel.
9 We have a discussion section of our morning
10 coming up fairly soon.
11 So if you have questions that I
12 don't manage to include now, please hold them
13 and we'll ask Dr. Korakianiti to come back
14 later and address these questions then. So
15 one or two questions now from the panel. Dr.
16 Polli and then Dr. Marilyn Morris.
17 MEMBER POLLI: Thank you. I have a
18 question about your Slide 26. So I
19 understand, this is a pilot with EMA and FDA.
20 To what extent has this -- has this started or
21 has it progressed at all?
22 DR. KORAKIANITI: Actually, we have

accepted the first candidate product that will be submitted in U.S. late September, I believe, and Europe in late October, because there are different time lines. So yes, there's also some other interest from industry.

MEMBER POLLI: Is there a plan to maybe list or publish the list of questions and outstanding issues?

DR. KORAKIANITI: It's not possible to -- there's a plan to publish a lessons learned at the end of this assessment. Specific questions on these issues cannot be published because these include company confidential information or trade secret information. So they cannot be sent to the public. But the idea is to share the lessons learned.

CHAIR TOPP: Thank you. Dr. Marilyn Morris.

MEMBER MARILYN MORRIS: Thank you. Very nice presentation. I had a question on

1 Slide 27, and under what needs to be done.
2 You talk about a clinically relevant design
3 space. Can you elaborate a little bit on
4 that?
5 DR. KORAKIANITI: Yes. This is an
6 issue that keeps coming up. For example, if
7 dissolution testing is used as a surrogate for
8 in vivo, that would indicate -- as an
9 indicator of the in vivo performance of the
10 product. Then if this original testing is
11 used also in order to define what the design
12 space is, would we use a dissolution test that
13 it is indicating of --
14 I need to go back. But would we
15 need a dissolution test that is really very
16 sensitive, sometimes over discriminatory, and
17 would just show the capability of the process,
18 or do we want a dissolution test that is
19 biorelevant? This would define how wide the
20 design space can be.
21 The answer to my mind is that we
22 would be needing proper controls real time for

1 the process, and look at the dissolution test
2 in biologically relevant way.
3 So has this answered a bit your
4 question? So the question is how do we ensure
5 that the design space not only reflects
6 capability of the process, but at the same
7 time changes are -- changes outside the
8 design, within the design space ensure that
9 the in vivo performance of the product remains
10 the same. Right?
11 CHAIR TOPP: Thank you very much.
12 Thank you, Dr. Korakianiti. No, I didn't say
13 that correctly. I've been practicing all
14 morning. Korakianiti. Thank you. I got it
15 right most of the time, and failed right at
16 the last moment. That's because I've been
17 practicing saying the name for our next
18 speaker.
19 Our next speaker this morning is Dr.
20 Sarah Pope-Miksinski. Dr. Miksinski is a
21 branch chief of Branch 2 of the Division of
22 New Drug Quality Assessment 1 with the FDA,

1 with CDER and the FDA. Her presentation this
2 morning will be "Regulatory Assessment of
3 Applications Containing QbD elements: an FDA
4 perspective. Dr. Miksinski.
5 DR. MIKSINSKI: Thank you. Good
6 morning, and you got my name exactly right.
7 So my talk, my presentation this morning will
8 encompass four major topics.
9 I'll begin with an overall
10 background of QbD submission updates in terms
11 of new drugs, followed by a review of QbD-
12 based submissions. This will be a brief
13 discussion of the tools and utilities that we
14 have in place, as we review QbD elements in
15 our regulatory submissions, including
16 guidances and MaPPs training efforts, team
17 review and participation in inspections.
18 I'll then shift slightly and move on
19 to our generic and biotechnology products, and
20 give you some brief background and history on
21 implementation and current status in
22 implementation, in regards to those products

1 as well.

2 So reference is made initially to of

3 course the 21st Century Initiative announced

4 in 2004, which had five specific objectives.

5 I'll quickly read through them, although I

6 know that 99 percent of this room already

7 knows this.

8 Encouragement of the early adoption

9 of the new technological advances, the

10 facilitation of the application of modern

11 quality management techniques, the

12 encouragement of implementation of risk-based

13 approaches, and the assurance that regulatory

14 review, compliance and inspection policies are

15 based on state-of-the-art pharmaceutical

16 science, thereby resulting in an enhancement

17 of the consistency and coordination of FDA's

18 drug regulatory programs.

19 As an extension of that initiative,

20 ONDQA announced a pilot program in July of

21 2005, with two specific objectives, of

22 providing participating firms an opportunity

1 to submit and share their own QbD elements in
2 CMC sections of regulatory submissions, and
3 also to enable the agency to implement new
4 Quality by Design concepts.
5 The size of that pilot is that it is
6 complete. There were nine original and three
7 supplemental NDAs that were accepted. Of
8 those, 11 were approved and one was withdrawn
9 for non-CMC reasons.
10 Now overall, the CMC pilot did
11 provide valuable experience for both industry
12 and the agency in implementation of Quality by
13 Design, including the assessment of elements
14 of QbD in submission, as well as risk-based
15 regulatory decisions and how they were
16 enabled. These learnings have been
17 incorporated in ICH Q8 (R2).
18 So in terms of current status, the
19 number of QbD-containing applications of new
20 drugs has been increasing over the past six
21 years. Quality by Design approaches such as
22 defining critical quality attributes and

1 developing and proposing design spaces, have
2 been fairly well fleshed out by both
3 applicants and agency reviewers.
4 More experience is still needed for
5 some of the more advanced concepts, such as
6 real-time release testing. But overall, QbD
7 concepts are often utilized across many
8 applications. These applications do often
9 include much more development information.
10 A picture here. This is actually a
11 graph representing the number of QbD
12 submissions from 2005 to current or May 20th
13 of this year actually. What you can see are
14 just a comparison of colors here. The purple
15 would be the NDAs containing QbD components,
16 and the blue will be supplemental NDAs
17 containing QbD components. You, of course,
18 can see a pretty dramatic increase to the
19 current time.
20 A different way of presenting this
21 data and these numbers is to stratify it by
22 clinical division and clinical indication. So

1 what this slide actually has is a number of
2 things. In addition, we have the QbD PDUFA-
3 driven meetings, which are in purple. The
4 supplements are now in a light blue, and the
5 applications -- sorry, the new drug
6 applications or new molecular entities are
7 also submitted in this slide.
8 You'll see some distinct increases
9 in the drug oncology and metabolic
10 endocrinology sections of the agency there.
11 This is again new drugs.
12 So as we look forward in ONDQA,
13 where we want to be is the development and
14 implementation of policy and procedures for
15 reviewing these QbD applications, such as
16 documenting approaches for how to review QbD
17 elements and applications; development of
18 MaPPs and guidances; training our reviewers,
19 to make sure that they are capable and can
20 accommodate the review of Quality by Design
21 applications; the development of a cadre of
22 experts for some advanced concepts that we

1 often see in Quality by Design applications;
2 and finally the institution and maintenance of
3 systems for knowledge retention and capturing
4 precedents.
5 So overall, ONDQA envisions both a
6 continuing increase in the utilization of QbD
7 elements in regulatory submissions, as well as
8 a broader utilization of QbD elements for all
9 applications. This leads us to the
10 fundamental question I think we're considering
11 this morning, of how can we facilitate this?
12 So a brief time line of some
13 quality-related guidance and initiatives that
14 have been developed at the agency is
15 presented, and a number of these are very
16 familiar and have already been discussed. I
17 do just want to point out, moving from left to
18 right on this slide, in the 2005 to 2006 area,
19 you'll see the ONDQA CMC pilot program, which
20 I just discussed.
21 You'll also see, right after 2006,
22 the Office of Generic Drugs question-based

1 review announcement. Then moving on, you'll
2 see the Office of Biotechnology Products pilot
3 program between 2008 and 2009. My colleague
4 from EMA just presented the EMA/FDA QbD pilot
5 program, which is one of the most recent
6 advancements in this slide.
7 Additional tools that reviewers have
8 in terms of assessing Quality by Design
9 components in these applications would be the
10 guidances and MaPPs on this particular slide,
11 including draft guidances on both
12 comparability protocols and meter dose
13 inhalers, as well as a final guidance on
14 residual drugs and transdermals.
15 We've discussed already considerably
16 the implementation of Working Group Points to
17 Consider documents, as well as some MaPPs that
18 are recently published and in progress, such
19 as applying ICH Q8 through Q10, and the review
20 of analytical procedures using NIR.
21 In addition to those resources,
22 there are a number of internal and external

1 trainings and opportunities that are available
2 for reviewers, to prepare and in order to
3 facilitate the review of these Quality by
4 Design components, including technical course
5 work, internal discussions, invited speakers,
6 mentoring team reviews, and external academic
7 collaboration, hands-on training and
8 conference participation.
9 Most QbD-containing submissions in
10 the new drug field will be team-based reviews,
11 and the ONDQA review team will consist of a
12 number of people. Primarily, you'll have
13 assigned reviewers, both CMC and
14 biopharmaceutics.
15 There will also an ONDQA project
16 manager, supervisors as needed, oftentimes
17 including a branch chief and/or division
18 director, and additional technical experts
19 also as needed. Oftentimes, a statistician or
20 microbiologist will be called into the team.
21 The expanded review and inspection
22 team also includes the partner representatives

1 from the Office of Compliance and the Office
2 of Regulatory Affairs.
3 So the distinct QbD review process,
4 and this would apply to applications that
5 employ any kind of Quality by Design approach,
6 there will be initially a kickoff meeting very
7 early in the review cycle, and at that kickoff
8 meeting the entire review will be invited,
9 including additional ONDQA experts as needed
10 and representatives from compliance and the
11 Office of Regulatory Affairs.
12 At that meeting, there is a
13 discussion of the potential product and
14 process risks, as well as review precedents.
15 We discuss review deliverables, timing and
16 deadlines. Additionally, we often discuss the
17 product quality and manufacturing memo. Now
18 we call it the PQM memo. It was recently and
19 previously called the Considerations For
20 Inspection memo or the CFI.
21 This is a document that I'll go into
22 shortly, that is communicated very early in

1 the review cycle to our colleagues in the
2 Office of Compliance and Regulatory Affairs.
3 Another component of the team review process
4 is periodic team meetings that include all
5 members of the team as needed, and a team
6 developed information request which is issued
7 shortly after mid-cycle.
8 Once the response to that
9 information request is received, it's
10 reviewed. The inspections are conducted and
11 oftentimes the inspections are conducted in
12 parallel to the entire review process. The
13 review is finalized, and this all does happen
14 within good review management practice of the
15 dates for ten month and six month reviews,
16 respectively.
17 For the product quality and
18 manufacturing memo, here are some additional
19 details regarding that. It is an ONDQA-
20 prepared memo. It aids in communicating
21 application-related information to Compliance
22 and Regulatory Affairs. It is prepared

1 relatively early in the review cycle to assist
2 with inspectional planning, and the contents
3 can include, but are not limited to, process
4 description, product description, description
5 of critical steps, critical controls and a
6 summary of product and process-related risks.
7 Currently, these are prepared for
8 complex products and processes, regulatory
9 approaches that are somewhat complex, and
10 applications that may have questionable
11 manufacturing capabilities or suspect data
12 integrity issues.
13 Now this is actually a picture of
14 the merging of good review management
15 practices here at the agency, with some of the
16 distinct elements of our Quality by Design
17 team-based review process, and I'll just walk
18 you through this slide.
19 Moving from left to right, you see
20 the numbers 1 through 6 of the certain steps
21 in the CMC review, performing pre-submission
22 activities, submission processing, planning

1 for review. Step No. 4, most importantly
2 conducting the review, and then leading to the
3 official action.
4 On the top in red, you'll notice the
5 days, which represent the days from
6 submission, day zero being the date of initial
7 submission of an application to the agency,
8 and moving on in the review clock as you move
9 on to the right in the slide.
10 When you add in the specific
11 deliverables from the QbD perspective, you see
12 where the QbD kickoff meeting occurs very
13 early in the review. You can see the periodic
14 CMC review team meetings that incorporate the
15 entire team during the review, as well as the
16 preparation of the PQM memo also very early in
17 the review.
18 Additionally, you'll also see that
19 the reviewer participation and inspection is
20 conducted in a window that usually falls
21 within -- between very early in the review and
22 usually around mid-cycle.

1 So reviewers actually have always
2 had the opportunity to participate in
3 inspections. However, traditionally very few
4 pre-approval inspections have had reviewer
5 participation.
6 So in ONDQA, the frequency of
7 reviewers participating in inspections has
8 recently increased, mostly due to some of the
9 more complex regulatory approaches, as well as
10 an increased emphasis on shared knowledge and
11 expertise.
12 The numbers behind this observation
13 are in this table, ranging from 2007 through
14 2010, and you can see a dramatic increase in
15 fiscal year 2010 relative to earlier years.
16 There are a number of advantages to both the
17 reviewer and of the inspectional team, of
18 having the reviewer on the inspection.
19 The value to the reviewer, there are
20 numerous. A few of these would be increased
21 understanding of the process and product, the
22 ability to help resolve certain review issues

that are related to the application, and the understanding of scaled up process control and the implementation of online monitoring systems and related models.

Value to the team, also numerous. A few are listed on this slide. The reviewer can provide specific expertise and a knowledge of the application. An indepth discussion and exchange of ideas is facilitated by having the entire team on the inspection, thereby hopefully resulting in a more productive inspection.

The reviewer also has an understanding of product quality assurance and can offer that to the inspectional team, thereby hopefully also resulting in an overall increased understanding and appreciation of other division's roles and responsibilities for the entire team.

So the traditional model of reviewer, compliance and investigator communication has been linear. For example,

1 if the reviewer had a comment or observation,
2 that reviewer would go through the compliance
3 officer. The compliance officer would then
4 communicate that same observation to the
5 investigator, and vice-versa. It happens both
6 ways.
7 Now the integrated approach that we
8 use for our Quality by Design-containing
9 applications is actually one in which all
10 three entities work in concert together, and
11 very, very collaboratively. So that we have
12 a communication flow that really is unending
13 and continuous.
14 Now at this point, I'd like to shift
15 slightly and talk about Quality by Design for
16 biotechnology products. There are some
17 similarities to the previous learnings I've
18 presented to you from the small molecule side.
19 However, implementation can differ. The
20 definition of critical quality attributes may
21 be complicated by product complexity, and
22 linking a large number of these quality

1 attributes to complex processes can be very
2 challenging.
3 OBP did have a pilot program which
4 was announced on July 2nd of 2008, with three
5 specific objectives of defining clinically
6 relevant attributes for protein products,
7 linking those to the manufacturing process,
8 consideration of Quality by Design approaches
9 to unit operations in both supplement and
10 original applications, and the exploration of
11 the use of protocols in QbD submissions.
12 Now to go further into the Office of
13 Biotechnology Products' biotechnology products
14 biotech pilot, that's a mouthful, the pilot
15 was closed to new participants on 9/30/2010.
16 At that point, there were six original
17 applications and four manufacturing
18 supplements.
19 Since then, multiple meetings have
20 been held with many of these participants to
21 discuss their proposed QbD strategies. The
22 biotech pilot also included the approval of

1 one QbD manufacturing supplement, that
2 included an expanded change protocol covering
3 multiple products and sites. The evaluation
4 and approval of this supplement did involve
5 effective interactions between review and
6 compliance functions at CDER.
7 Additionally, as a status update,
8 OBP continues to see risk assessments and DOE
9 in some applications outside of the pilot
10 program. So from an overall implementation
11 standpoint, there is a link to small molecule
12 learnings, based on the ONDQA pilot and
13 previous application experience.
14 We've seen already a lot of
15 discussion of the Implementation Working
16 Group, as well as Q8 through Q11, staff
17 participation and conferences, forums and
18 training, and some mock case studies that are
19 available.
20 Now moving on to the Quality by
21 Design for generic products, and this would be
22 OGD, Office of Generic Products, there have

1 been multiple meetings with the generic
2 industry beginning in 2009 and lasting until
3 now, including three QbD workshops and four
4 QbD round table discussions.
5 There have been multiple
6 presentations at annual professional meetings,
7 as well as over 15 peer-reviewed publications
8 on QbD concepts for generics. At this point,
9 industry feedback has focused on the use of
10 prior knowledge and risk analysis. There are
11 some QbD examples that are available, that are
12 intended to illustrate the types of
13 development studies AMDA applicants may use as
14 they consider how to implement Quality by
15 Design.
16 There is a concrete illustration of
17 QbD principles from ICH Q8 (R2), actually two
18 examples, both IR and modified release,
19 immediate release, illustrate QbD principles.
20 However, it's important to note the
21 development of real product may differ from
22 these examples, and that the number of

1 experiments may depend on the experience of
2 the applicant.
3 From an implementation standpoint,
4 all ANDAs currently are being submitted in
5 question-based review format, and we are
6 already receiving applications containing
7 Quality by Design elements. OGD has developed
8 the previously-mentioned immediate release and
9 modified release Quality by Design examples.
10 These will be finalized shortly.
11 As well as the office will begin a
12 comprehensive internal training on QbD in the
13 fall of this year. Further discussion with
14 industry is anticipated through 2012, with a
15 full implementation target date of January
16 2013.
17 So implementation of Quality by
18 Design is progressing well. There is a steady
19 increase in both interest and applications.
20 Team-based approaches have been successfully
21 utilized, and the approaches are now being
22 extended beyond QbD applications.

1 Acknowledging a continued integration and
2 communication is still needed.
3 So in conclusion, the Office of
4 Pharmaceutical Science does envision a broader
5 utilization of Quality by Design elements for
6 all applications. Thank you.
7 CHAIR TOPP: Thank you, Dr.
8 Miksinski. Again, we'll take one or two
9 questions as we move toward discussion later
10 in the morning. So any questions from the
11 panel? Mr. Goozner.
12 MEMBER GOOZNER: Was there any
13 effort to assess, from maybe the Inspections
14 Division, about what the penetration of QbD is
15 in existing products?
16 DR. MIKSINSKI: I have to offer a
17 qualifier, that I'm from the new drug and I'm
18 from the review side of things. I know that
19 what we do for Quality by Design applications
20 involves a tremendous amount of communication
21 between compliance, ORA and the review side of
22 things. I don't think I can offer a specific

1 answer to your question, though,
2 unfortunately.
3 CHAIR TOPP: Thank you. Dr. Ken
4 Morris.
5 MEMBER KEN MORRIS: Thanks. Just a
6 real quick question. From what you've
7 presented, which is pretty impressive by the
8 way, what would you say would be the biggest
9 gap in terms of reviewer expertise you've
10 seen, in terms of --
11 DR. MIKSINSKI: Okay. Thank you for
12 the question. I think that's an excellent
13 question. I think the biggest gap -- I would
14 actually say that there are two answers. My
15 experience, again at the operational level, I
16 think that it is very difficult to assess a
17 Quality by Design-based application in
18 anything but a team paradigm.
19 I think that it is important to have
20 a number of people involved in the team. I
21 think it is important to make sure that these
22 people are involved early, and I think it's

1 important to facilitate that discussion
2 internally, as part of the assessment of the
3 application.
4 Now historically, new drug
5 applications, and I can speak for the new drug
6 applications here, were assigned mostly to
7 single reviewers, and the Quality by Design
8 applications are very rarely assigned to a
9 single reviewer.
10 So it's a cultural shift, and we're
11 working on establishing a process whereby we
12 facilitate that interaction, and also in
13 conformance with the deadlines we have here at
14 the agency, such as the good review management
15 practices deadlines, and obviously PDUFA
16 deadlines.
17 In terms of reviewer understanding,
18 I think it's going to be various. What is
19 happening now is as QbD is percolating through
20 our office, is that we have different people
21 who have different expertise. Every new
22 application that comes in that involves a

1 Quality by Design element, has a new challenge
2 for us, every single one of them, and I think
3 we learn from every single one of them.
4 So there's going to be a wide spread
5 of what certain people understand and what
6 other people understand, and I think that
7 applies to everybody. So what we have to do
8 when we see these applications is we need to
9 really consider very carefully who we assign
10 to these applications, making sure that we're
11 assigning the best team of people to assess
12 that application, with the expertise that we
13 need.
14 MEMBER KEN MORRIS: Thank you.
15 CHAIR TOPP: Thank you. Thank you,
16 Dr. Miksinski, for that informative
17 presentation. Thanks very much.
18 CHAIR TOPP: We have no speakers
19 registered for the open public hearing, which
20 is the next item on the agenda. So we will
21 therefore move to the topic "Wrap-Up" by Dr.
22 Moheb Nasr. So Dr. Nasr.

1 DR. NASR: Well first I would like
2 to start by thanking the four invited
3 speakers. I think they have done a great job,
4 and I thank the Committee members for their
5 intensive questioning and the good discussion
6 we had.
7 A few years ago, I used to come to
8 this meeting prepared with some closing
9 remarks, and I soon realized it's not the most
10 effective way to do that. What I learned is
11 to listen more, and to take some notes and to
12 share few thoughts that can facilitate
13 decision.
14 Here is my few remarks that I would
15 like to share with you before we engage into
16 the discussions. I think as we learned,
17 considerable progress has been made. Some
18 challenges are remaining. I will try to, in
19 my way of presenting these challenges, as I
20 heard them from the speakers and as I lived
21 them every day myself, recite them to
22 facilitate the discussion.

1 I think we need to start thinking
2 about new development strategies for to fully
3 implement Quality by Design, rather than an
4 add-on approach to existing strategies that
5 have been part of the development culture for
6 years. We need to do that from industry
7 perspective, but also we need to do that in
8 the regulatory processes as well.
9 I think the approach that we develop
10 every product from scratch is not a good
11 development model. We need to start thinking
12 more about platform technology, and using
13 these platform approaches to develop
14 manufacture pharmaceutical in the 21st
15 century, and to have an appropriate expertise
16 within the review staff to deal with these
17 approaches as well.
18 I think we need to convince
19 ourselves, more so than we have done before,
20 that extensive and more testing does not
21 improve quality, and does not change quality.
22 I think we need to move, into more predictive

1 modeling of quality.
2 The analogy that I can think of here
3 is building an airplane. You don't think of
4 people now, or even years ago, did that task
5 by building the skeleton, took it up in the
6 air, test it, brought it back down, added the
7 doors, took it up in the air again, did some
8 more testing.
9 That's what, to some extent what we
10 have done in pharmaceuticals. I think we need
11 to start trusting the science, and to develop
12 predictive modeling to release the product
13 based on that, realizing that there is no zero
14 risk. But we address the most key risk that's
15 related to quality, safety and efficacy.
16 Another key gap is linking the
17 process understanding, design space and all
18 this good stuff to in vivo performance. We
19 need to start thinking about our specification
20 to be performance-based specifications, rather
21 than a list of conventional testing approaches
22 that may or may not be relevant for all

1 products.
2 In order for us to do that, we need
3 to better link. Some of the quality science
4 that we have now, I think we have it very well
5 to some of the in vivo measurements, that at
6 times is provided to the agency. For some
7 reasons, we don't connect the two pieces
8 together.
9 So in order to have, in my mind, a
10 real design space, bioavailability is a key
11 quality attribute. So how can we do that? We
12 can do that by doing dissolution testing, note
13 if the product failed dissolution testing and
14 test it some more. If it fails, we test it
15 even more. I don't think this is right
16 approach.
17 If bioavailability is a key quality
18 attribute and I argue it is, we need to start
19 relying more on IVIVC models to link that, and
20 to see what are the key parameters upstream,
21 to assure the bioavailability of the drug when
22 the patient ingests this drug. So this is

1 something that we need to do.
2 Integration between biopharm and CMC
3 is one of the major tasks that we have in
4 ONDQA and within the Office of Pharmaceutical
5 Science. I think some addition of technical
6 gaps that we need to start thinking of is
7 process control, and because of that, we
8 started the process of having more engineering
9 components into our CMC review.
10 But the statistical process control
11 and relying on these concepts is a key to move
12 Quality by Design to its next successes, and
13 also as we start moving more into continuous
14 processing and continuous manufacturing, we
15 cannot do that without having definite way to
16 assure the process control, because we cannot
17 use some of the traditional testing approaches
18 and environment, even at a very small scale of
19 continuous processing.
20 Because of that, we at the agency
21 have some research projects to have better
22 understanding of how to do that.

1 So this is in summary some of the
2 key issues I heard this morning. I think we
3 have made considerable progress, and the
4 progress we have made was made by the
5 industry, and I hope we facilitated the
6 progress and we are looking for further
7 discussion and decision and input from you,
8 Advisory Committee colleagues, in order to
9 move us to the next -- our next successes.
10 Thank you very much.
11 CHAIR TOPP: Thank you, Dr. Nasr.
12 We are now moving to the discussion section
13 for this topic, and I would like to remind the
14 Committee members, of course, we're all going
15 to get in the queue. Just give me one second.
16 I would like to remind you that many
17 of our speakers from this morning are still
18 here, but they can't speak to you unless you
19 ask them to speak to you.
20 So if you would like to hear from
21 them again, please know that they're here, and
22 if you didn't get questions answered from them

1 and you would like to hear from them, please
2 know that you may do so. We'll call them to
3 the front or give them a microphone or
4 something like that. We'll figure out a way
5 to get them to communicate with us. So please
6 remember that they're still here.
7 Okay. So my queue now looks like --
8 do that again over here? Dr. Kibbe, Dr.
9 Shaya, Dr. Kosler.
10 DR. NASR: Do I need to be here or
11 would you like me seated or --
12 CHAIR TOPP: You may be seated if
13 you'd like. So we'll bring you back or you
14 have a mic, and that would be fantastic. Dr.
15 Muzzio. Anybody else to start, and Dr. Koch.
16 Okay. Dr. Kibbe.
17 MEMBER KIBBE: First, I think that
18 the general direction in what we're doing to
19 put more science and more control into the
20 process and encourage it is wonderful. A
21 little more than 20 years ago, I was involved
22 in some things, and one of the suggestions we

1 made at that time, to try to improve the
2 process, was to have the reviewers and the
3 inspectors work together.
4 When we were talking today about
5 that, it just seems to me that it is the ideal
6 way of understanding what's going on in the
7 industry, is to have the people who go in and
8 inspect, and the people who review, talk to
9 each other on a regular basis about
10 submissions.
11 I hope that the team review process
12 is also working on non-QbD. If it becomes a
13 culture, then I suggest that it would in
14 itself be a stimulus, because the reviewers
15 generally write questions after they see a
16 review.
17 Questions like what part of your
18 process development have you used the
19 principles of QbD to do, means that the
20 submitters are going to be under the gun to at
21 least have an answer of why they did or
22 didn't, that would stimulate it.

1 You know, ask them if you have any
2 real-time release parameters for any review
3 process. Ask them those questions, because if
4 we really believe that that's an essential
5 part of improving the overall process of both
6 old drugs and new drugs, then we ought to ask
7 those questions during the process.
8 I don't think we could demand that
9 they do it, but we can always ask, right? I
10 agree with you that what we need to look at,
11 in terms of our quality control testing, is
12 are they truly performance-predictive tests?
13 Do they help us understand what the product
14 will do, and help us then know that the next
15 batch that passes that test will also perform?
16 We assume a lot. We look at
17 dissolution and we use it as a quality control
18 test, and we say the first batch had that
19 dissolution and it had good bioavailability.
20 So all the other batches with that
21 dissolution. Well, do we know that for sure?
22 Do we actually have IVIVC on all of that

1 stuff?

2 I don't know, but it would be nice.

3 I would love to see new drug applications come

4 in with a multi-phase bioavailability study,

5 so we knew the variability of that product

6 before we approved it. So that we have a feel

7 for what that meant for the overall

8 productivity of that product for the work

9 place.

10 The patients, as we all know, phased

11 clinical trials start out very highly

12 controlled under very controlled situations,

13 drugs that are used exactly the way they're

14 supposed to be used by clinicians who are

15 trained to do that, and eventually they get to

16 the point where they're being given to

17 clinicians who are good at controlling

18 patients and good at stimulating patient

19 compliance, and then we dump them on the

20 general public.

21 If we had some better understandings

22 of what was going on with the product before

that happened, we would not be nearly as surprised about the problems with non-compliance and some other things.

In general, this is a wonderful process. I really think that it's like the snowball rolling down a hill, right. We're starting to see people get into it, when you have people like Gerry who are willing to come and tell us all about the successes.

In fact, us being told all about this isn't nearly as important as the public hearing at an open meeting about this, and it being kept in front of the industry as the gold standard for where they should be going. If we keep doing that, and I don't mean to be -- you know, I'd be happy to come listen again. We don't have to be dragged in here to do that, but it might be that dragging us all in here to hear it is one of the best ways to keep building it.

So I commend you for that. I actually think, I was at the beginning of some

1 of this years ago, and we have moved not as
2 fast as some would like. But we would have at
3 least moved in the right direction, and
4 generations that follow us will benefit by the
5 quality of products that will come out of this
6 kind of thing. Thank you for the mic.
7 CHAIR TOPP: Thank you, Dr. Kibbe.
8 That's an excellent introduction, I think, to
9 what we're going to discuss here today, and I
10 would like to apologize to the Committee and
11 panel members, because I have been remiss in
12 failing to keep us focused on the questions
13 that were put before us by the FDA.
14 So I would like to return to that
15 now at this point, and I've put them on the
16 screen for you, and let me just read them to
17 you now. So the first question is are there
18 additional efforts that the FDA should
19 consider, to facilitate the implementation of
20 QbD?
21 Question 2, how should we address
22 the technical and regulatory gaps that have

1 been identified by the speakers? Question 3,
2 can QbD approaches be valuable for
3 biotechnology product development, and if so,
4 are there any potential scientific challenges
5 that we should be aware of?
6 Now one way that we could approach
7 this is to split these out into one at a time.
8 Does the FDA have a preference for how we do
9 that?
10 DR. NASR: One at a time would be
11 good.
12 CHAIR TOPP: One at a time would be
13 better. Okay. So in that spirit, let's begin
14 with Question 1. So and I will take names all
15 over again, and we'll try again. So Dr.
16 Shaya, you were on the list next anyway.
17 DR. SHAYA: I want to modify the
18 original question that I had, because it would
19 answer partly the answers to the question
20 really. So we have heard about the benefit of
21 implementing QbD. Obviously, any investment
22 put into that way offsets, is way offset by

1 the benefits that are provided to patients and
2 the quality of the product.
3 We have also heard, however, and
4 this is the answer to this, a consideration
5 about the -- from the perspective of those who
6 are implementing QbD, the huge opportunity
7 costs of not filing first. So is there any
8 consideration in the implementation of the QbD
9 that could be sensitive to that need, and that
10 in that sense would help implement QbD?
11 DR. NASR: I can address that in
12 part, and I may defer to my colleague, Keith
13 Webber, for the difficult one. So as far as
14 finding first, I'm responsible for the new
15 drug side, if you wish, and we have made, the
16 agency has made a commitment, and we have met
17 that commitment.
18 That is, if you file using Quality
19 by Design approach, we will continue to meet
20 PDUFA and GRMB time lines, and we have never
21 retreated from such commitment. So there is
22 no concern, there should not be a concern on

1 the new drug side, that if you file a QbD
2 application, there will be any delay
3 whatsoever.
4 I think we as managers are
5 responsible to utilize internal resources as
6 available, to make sure we meet such
7 commitment, and we have done that. As far as
8 finding first, language is not an issue for
9 new drug. It's a generic drug issue. I hate
10 to put you on the spot, Keith, but I will let
11 you answer it. I like it sometimes.
12 DR. WEBBER: Not a problem. You
13 like to put me on the spot sometimes. Yes,
14 there are two aspects, I think, of the filing
15 first issue. One is related to QbD, and one
16 is preparing the information and the
17 documentation that is required for, or in
18 doing the product development within the time
19 frames.
20 There is pressed on industry for
21 being first to file. I think that aspect, the
22 sort of prior knowledge, I think, is one area

1 where I think we'll have to rely a great deal
2 for those products that industry. The generic
3 industry will, I think, rely a great deal more
4 on the prior knowledge they have from other
5 products and other QbD developments, in order
6 to maintain that first to file abilities, or
7 to also do QbD in a post-approval world.
8 The other aspect of it is the
9 potential for losing your, you know,
10 forfeiting your position, if you gain
11 tentative approval in the appropriate time
12 line. I don't think that will be a problem.
13 I think that the reviews of QbD applications
14 will not run up against that 30 month rule.
15 So that I don't anticipate being a problem.
16 DR. KOZLOWSKI: To comment from the
17 biotech side, we also don't intend to delay
18 time lines in reviewing a biotech application
19 with QbD. In fact, one of the things to think
20 about in the QbD application is is there some
21 part of it, that if it would delay things, it
22 could be approved without that.

1 So in other words, if there's a
2 particular flexibility where there is some
3 concern scientifically, that that shouldn't
4 hold the application. We would figure out a
5 way to separate that out.
6 DR. NASR: If I may add, because
7 it's a key question that was discussed this
8 morning. In order to show quality, and we
9 believe that quality product using traditional
10 approaches are sufficient. I hope we also
11 believe that using better science and better
12 quality risk management to provide higher
13 assurance for quality, and that's what we are
14 discussing here.
15 I think there are great
16 opportunities for the generic industry to
17 consider. I think we heard specifically two
18 comments from you this morning, from members.
19 One from Ken Morris, if Ken is still there,
20 and one from Dr. Muzzio. That is using the
21 platform technology can be greatly beneficial
22 to generic industry, and I would argue that

1 the financial reward on this small investment
2 in Quality by Design is considerably more
3 where manufacturing costs constitute a large
4 portion of the price of the product in the
5 generic versus in vitro product.
6 So I would like to encourage the
7 generic industry to start utilizing these
8 approaches, and there's several different ways
9 to do that. But I think we need to start
10 thinking about different development strategy.
11 CHAIR TOPP: I have a question for
12 clarification for this topic. One of you
13 suggested, and I can't remember which one in
14 that panel over there. But one of you
15 suggested that once the generic industry in
16 particular develops experience with this QbD
17 kind of filing, then it will be easier for
18 them.
19 But is there any effort on the part
20 of the agency to make that first sort of
21 generic QbD filing, to lower the bar for that,
22 to encourage that, or is that something that

1 you just say well no, that's up to the
2 industry to figure out how to clear the bar
3 the first time?
4 DR. WEBBER: I think that the
5 perspective we have on review of applications
6 is not to lower any bars at all with regard to
7 what's required for a good quality product.
8 That said, I think that we would -- we're not
9 looking so much at an application in this
10 regard, whether it's QbD or not QbD, and in
11 many regards I think that this is true for the
12 new drug world as well.
13 It's very rarely you get an
14 application which is entirely QbD. There are
15 aspects of it that are QbD and aspects that
16 aren't. So we are really looking toward
17 better quality assurance through this process,
18 better understanding of the product, the
19 design of the product.
20 If it's modified release dosage
21 form, what is critical to getting it to
22 release at the appropriate points in the body

at appropriate times, and designing that into the product? That's one aspect. Then establishing manufacturing processes that are going to assure that the product is going to achieve that performance.

So I would say that it's -- we're not so interested in getting QbD applications as we are in getting applications that have good product design and process design.

CHAIR TOPP: Thank you. Dr. Tway.

MEMBER TWAY: Thank you. Well first, I love your vision of the future that you were focusing on at the end there. I'm not sure industry is quite ready to go there yet. I agree with everything that you basically are suggesting, and part of it is driven by the fact when I look at one of the slides we saw this morning, 22 percent of branded industry is totally on board with QbD.

I think 22 percent is rolling it out. So you've got more than 50 percent that's still in the process of moving forward.

1 So when I listen and look at everything we've
2 seen, I think there are a couple of areas that
3 I think the agency and industry is doing a
4 great job, that we need to continue to focus
5 on.
6 One clearly is where information
7 belongs. Does it belong in the filing, or
8 does it belong at a site for the inspectors to
9 review? I love the idea of the team
10 approaches. I think we have to use them even
11 more. I think we have to make sure that the
12 whole team is involved from the beginning.
13 Not that they're invited to the meeting and
14 may not choose to show up, and I don't know if
15 that occurs.
16 I think industry, we're trying to
17 use new models. We're trying to put more
18 statistics into our filings. These are areas
19 that the industry is working on, that there
20 may not be consistent agreement between the
21 statisticians at the agency and the
22 statisticians in industry as far as what's

1 needed.

2 So I think those dialogues need to

3 occur early, and not seven months into the

4 review cycle or something like, because those

5 are the things that will make a company shy

6 away and say I'm not doing that again, because

7 we just weren't on the same page.

8 So if it really is a team effort,

9 and if there are ways to make sure all the

10 appropriate people are involved in those areas

11 which may be problematic, we force the issues

12 earlier, rather than alter, and also that we

13 have mechanisms so we can get feedback, that

14 there are concerns about Point A or Point B

15 early on, and have, you know, conversations,

16 dialogues, get together and resolve the issue

17 quickly.

18 I think that will move a long ways

19 toward making sure people don't pull away from

20 it, but they also put the appropriate

21 information in, but then we can have a

22 discussion as need be.

1 CHAIR TOPP: Thank you. Dr. Kosler.
2 DR. KOZLOWSKI: If I could respond a
3 little. So I think the team approach is very
4 valuable, and for biological products,
5 reviewers have gone on inspection
6 historically, even before these new
7 initiatives. That's a very helpful thing.
8 Also, planning in advance for that inspection,
9 sharing the information, has been very useful.
10 I think the pilot, which we're in
11 the midst of, and ONDQA has completed, offers
12 a lot of opportunity for extra meetings. I
13 think one challenge for us is the resources of
14 lots of extra meetings, outside of the venue
15 of a special pilot, and I think that's
16 something we are very interested in doing,
17 again allowing the appropriate, you know,
18 ability to support that.
19 CHAIR TOPP: Thank you. Any
20 additional response. I didn't mean to cut you
21 off earlier. I apologize.
22 DR. NASR: I think Dr. Tway is

1 really hitting the nail on the head. I think
2 one of the many challenges we have is related
3 to expectations in regulatory filing, and what
4 need to be done there, versus what needs to be
5 on inspection. It was raised also by Gerry
6 Migliaccio this morning and others.
7 I try to start the discussion or I
8 think I start the discussion by saying what we
9 really need to know, versus nice to know for
10 scientific reasons. In my views, and I
11 presented that in public forum last month, and
12 that is we focus on what is the goal of the
13 regulatory process.
14 The goal of regulatory process is to
15 assure the quality, safety and the efficacy.
16 So we start from that terms and then we go
17 down. So what allow us or what evidence do we
18 have to assure quality, safety and the
19 efficacy. In my views, it is a control
20 strategy. How can you develop a control
21 strategy using the Quality by Design and all
22 this good stuff?

1 So if we focus on the control
2 strategy, as defined in ICH Q10, and
3 everything related to the control strategy and
4 justification need to be submitted in the
5 application. What we approve, in essence, is
6 a control strategy, and additional information
7 in the application is there as supportive
8 information.
9 I think that will help us clarify
10 the expectation. It will also clarify the
11 role between reviewer and inspectors, as the
12 assessors, reviewers, approve control
13 strategy, implementation takes place not at
14 White Oak, but it takes place at the
15 manufacturing facility, and then inspectors
16 make sure that's implemented, and the quality
17 systems are in place to assure such
18 implementation.
19 So it may be simple, but I think at
20 times we tend to make things also more complex
21 than it needs to be.
22 CHAIR TOPP: Thank you. Dr. Kosler.

1 DR. KOSLER: Hello. I would like to
2 ask two questions of the gentleman from
3 Pfizer, Gerry Migliaccio, and I think both are
4 pertinent to your question, number one, if
5 he's willing to take the questions. Thank
6 you, sir.
7 I have two questions for you. The
8 first one is about the transformation of
9 culture, and the second one is about process
10 capability. So for the first one though, in
11 your talk this morning, I was interested in
12 hearing you comment on what you thought was
13 the primary obstacle to, I think, forwarding,,
14 moving forward with QbD in your home work
15 environment.
16 I would like to ask you to clarify a
17 remark that you made. I think the joys of
18 transformation are enforced at Pfizer, where
19 you're coming from, because I heard this
20 comment, with I hope you receive with humor.
21 But you commented that one part of the
22 business does all the pain, and another is

1 reaping the rewards.
2 I think that's objective, you know,
3 to discuss which part of the business is doing
4 which. So I'd like to give you the
5 opportunity to specify in objective terms what
6 you see as the obstacle, the primary obstacle
7 to moving forward with QbD from your
8 background of experience, of actually
9 implementing QbD.
10 DR. MIGLIACCIO: Okay. So within
11 Pfizer, the tools that are, you know, employed
12 in QbD, and I think this was bought up
13 earlier, they started to be used first in
14 commercial manufacturing to solve problems,
15 okay. So we had variability that we couldn't
16 explain. We had to explain it. We had to get
17 rid of it, okay. So those tools, the value of
18 those tools became evident, including PAT, but
19 other tools, six sigma tools, root cause
20 analysis, et cetera.
21 So the tools became, the value of
22 the tools became evident, and of course we're

1 working closely with the Development Group on
2 new candidates. They saw the impact of the
3 tools, because we feed that information, the
4 learnings we get back to them, okay. So now
5 they became extremely attracted to using these
6 tools in development. So effectively, Quality
7 by Design, as it was emerging at the time.
8 Now the challenge you have is
9 similar to the generic industry, first to
10 file. The Development Group's job is to
11 develop an application which will be approved
12 right the first time, okay. So how do you
13 approve it first time? You do it the way
14 you've always done it, okay.
15 DR. KOSLER: Right.
16 DR. MIGLIACCIO: So there were
17 debates. We said "use these tools; they said
18 "but it may not get approved." It wasn't
19 until, in fact, we started to have these open
20 discussions with FDA, and FDA said no, bring
21 it to us, that the culture started to shift.
22 We had a few, you know, it was a grassroots

thing in our Development Group, and they finally could demonstrate to their management that it was worth the investment, even though the payback, as I said, is in commercial manufacturing.

The efficiency, the lower cost is there. So we saved the company money. Probably that cycles back into research hopefully. But they don't see that. They see that the investment is going in to new tools, new approaches, but they don't see the payback at the end. Does that --

DR. KOSLER: Thank you. Yes, that helps a great deal. My other question is a departure from this. It's a completely separate question, but yesterday, we voted on tightening limits for a particular characteristic, and a particular product attribute. I didn't bring this up yesterday, because I didn't think it was pertinent to the vote.

But it was on my mind, that we are I

interested in process capability, and having strong capability for the manufacturing process. The calculation for capability does depend on the product specifications themselves. So when you tighten the specifications, you are changing the capability of the manufacturing process for every manufacturer, you know, just de facto.

What I'm curious to hear about is in this environment, which I think is not new; I think it's been several years of an environment of tightening limits on things. In this environment of tightening limits on attributes that you must meet for release, I'm wondering how do you view the relationship between regulatory specifications, the tightening thereof, and industry readiness for developing new test methods on legacy products, to be able to get your capability to where you want it to be?

I saw that you had strong capability; you were getting out to six sigma

on some things, and you're working on it. But you know, when you change capability, you're back down to a capability, or when you change specs, you're back down to a capability of one. How do you respond to that, I think, is my question? Readiness of industry to respond that.

DR. MIGLIACCIO: Well I mean, there's no doubt that as we lose exclusivity, and products go generic, and specifications frequently do change, we are faced with the challenge of meeting a new set of specifications for a 20 some odd year-old product.

I think most innovator companies who choose to compete in the generic space are prepared, and you know, this is a life cycle approach. We --

DR. KOSLER: Excuse me, are prepared or are not prepared?

DR. MIGLIACCIO: Are prepared.

DR. KOSLER: Are prepared.

1 DR. MIGLIACCIO: We have a life
2 cycle approach, so you know, as our -- there's
3 a number of LOEs coming up for many companies
4 in the industry this year, next year.
5 There's been a continuous
6 development activity, both process and
7 analytically, to bring these processes and the
8 analytical methods, keep them current, and
9 actually put us on a better footing to compete
10 post loss of exclusivity.
11 I don't think any company stands
12 still, any innovator company stands still with
13 the product that they developed, you know, 20
14 years ago. If you're doing that, you're
15 basically saying as soon as you lose
16 exclusivity, you're out of the business.
17 DR. KOSLER: Do you run into a
18 bound, though, with what can be done with test
19 methods --
20 DR. MIGLIACCIO: We haven't. I
21 can't say that we -- we've had some
22 challenges. Yes, we've had some challenges.

1 But I don't think we've run into something
2 that hasn't been solvable, all right. But you
3 know, obviously there are challenges.
4 Any time you're throwing a new spec
5 at a product that's been around for a long
6 time, okay, and certainly the area of
7 impurities is a key focus area and API, and
8 you know, employing --
9 I mean the technology is always
10 there to search deeper. The question is how
11 deep do you search?
12 DR. KOSLER: All right.
13 CHAIR TOPP: Thank you. Thank you
14 both. I'm going to move us along, because we
15 have two more questions to get to and a number
16 of other contributors' questions on this
17 question before we get there. Dr. Muzzio.
18 MEMBER MUZZIO: Okay. So I want to
19 try to maybe get back to the questions
20 precisely, and I see a close relationship
21 between 1 and 2, so I'm going to say goes to
22 both, to some extent. So in listening to

1 everybody, and you know, remembering things
2 I've heard in forums and conversations with
3 companies and in the McKinsey report, et
4 cetera, there seems to be about four things
5 right now, I think, in my opinion, that are
6 gaps or roadblocks or whatever.
7 So there's lingering skepticism, you
8 know. Does the FDA really mean it, that we
9 have to do this? I did hear that in places.
10 There is a repeated statement of lack of
11 clarity in regulatory expectations, and there
12 is, another question of how could they even
13 have reviewed this? But what do you really
14 want? How QbD do I have to be kind of thing.
15 Number three, you know, we heard
16 this wonderful presentation by Pfizer. I
17 think there are a few other companies that are
18 also fully invested, that have developed
19 strategic plans and expertise. But then
20 there's a large segment of branded formula is
21 in there, and then there is most of the
22 generic industry and a lot of the smaller

1 pharma and a lot of other places, right, and
2 measures in the U.S. and Europe and Japan.
3 In Japan, I don't think it really
4 has progressed that much. I was there a
5 couple of months ago with one of the biggest
6 companies, and we were doing introductory
7 stuff there, right? So what do we know about
8 that?
9 I think that number one, in many of
10 these places, there is still the culture's not
11 there. There is not enough resources that
12 have been brought in-house to do it. They
13 might not have the right training, yes? So
14 what can you do to overcome all of these?
15 So about the skepticism and the lack
16 of clarity, maybe it's time to issue, you
17 know, a report, you know, QbD after seven
18 years, how far have we come, how much do we
19 mean it, yes? Once you write it up and you
20 post it, if everybody can get it, then it gets
21 around much more than the talks you give in
22 forums, because most of the people I talk to

1 don't go to the forums, yes.
2 So I would recommend that a strong
3 written statement will go a long way towards
4 skepticism and lack of clarity. About the
5 other fact, which I think is much harder to
6 deal with, and this may also help with
7 reviewers and inspectors, by the way, which is
8 the large number of people who don't have
9 either the right background or access to the
10 right tools.
11 Moheb had mentioned this a while
12 ago. I think as a community, we have to find
13 some way to share the tools. So I think one
14 thing we should think about is creating a
15 resource center, some place where the
16 companies who don't have everything yet could
17 go and get pieces of what they need, yes, at
18 lower cost or you know.
19 I mean Pfizer and others can afford
20 to have people on staff. But there are many
21 others that cannot, because they don't need
22 them full-time because they just can't. So if

we create some kind of resource center, where you know, it's relatively easy to test technologies and incorporate them and access them, you will actually speed up the process, I think.

Then the last thing I want to say, and it goes to one and two, but I keep coming to the same point. We need to make an effort to identify, as a community, what are the most important scientific gaps. If you do that, then you get the academics to pay attention, you get the companies to pay attention.

We academics can use that statement of the critical scientific gaps to write proposals, not just to you but to NIH, to NSF to whoever, and hopefully get them funded, right, so that we can make progress.

Among scientific gaps, one that comes up again and again yesterday and today is our lack to predict performance, and ideally non-destructively. So at the same time, I can predict the solution and then I

1 can use on a patient and I can measure, you
2 know. But really, then I can begin to bridge
3 the gap between the in vitro and in vivo,
4 because I might have a chance to know both for
5 the same tablet, you know, within the limits
6 of predictability. So that's my contribution.
7 CHAIR TOPP: Thank you. FDA
8 response, Dr. Winkle.
9 MS. WINKLE: You make some excellent
10 suggestions there. I think communication is
11 extremely important, and the more ways we can
12 find to communicate, the better off we are.
13 Moheb and I have an article that's coming out
14 next month on some of the challenges and
15 opportunities that we've had, as far as QbD,
16 implementing QbD goes.
17 But I think that we need much more.
18 I think we need to put out, as you said, I
19 think a report is an excellent idea, talking
20 not only about where FDA has gotten to but
21 where industry has gotten to and what we've
22 seen and what lessons we've learned. So I

1 really appreciate that, and I think we just
2 need to look at every different forum we can
3 find to communicate, and we have been trying
4 to make that effort.
5 I think even spending some time in
6 the individual companies, talking about, you
7 know, what we've seen as successes would be
8 really good too, for those companies that are
9 somewhat hesitant to move forward in this
10 area. So I appreciate that suggestion.
11 I think your idea of a resource
12 center is really good. But mainly we need to
13 dig in a little bit deeper and look for an
14 area where not only are we able to research
15 and find out different aspects of
16 manufacturing science, as far as QbD is
17 concerned, but also where we might either one,
18 come and take advantage of the resources
19 there, or come together and talk about some of
20 the things that we have learned and been able
21 -- so that we can use those and go back to our
22 respective places and put those into use.

1 The scientific gaps are going to
2 continue for a while, and I agree the lack to
3 predict performance is a very big gap. We
4 continue to look at those gaps and appreciate
5 anything the Committee can offer, as to ways
6 that we might better be able to close those
7 gaps.
8 DR. NASR: Can I make one additional
9 comment quickly, because I think it's very
10 important.
11 CHAIR TOPP: Sure.
12 DR. NASR: I agree with everything
13 Helen said, not only because she's my boss,
14 but I think she summarized it very well. I
15 think as we move on, and I'm very pleased with
16 the discussion we have here, in part because
17 the majority of people are clinicians. I
18 think academia can play a key role in
19 facilitating moving forward, because I think
20 we have made good progress based on what we
21 know.
22 We also, I think, find area where we

1 need indepth knowledge, that may or may not be
2 existing across. So a suggestion for the
3 Committee to consider, and maybe we'll have
4 comments on or we can have additional
5 discussion in the future, is having more
6 focused round table discussions, facilitated
7 by academic institutes, and to bring in not
8 only academics interested to submit grant
9 proposals if you wish, but to serve as a not-
10 for-profit technical center to identify key
11 implementation issues.
12 It may not really lead to several
13 peer-reviewed publications and promotions and
14 so forth. But it really address what we need
15 to do. So my suggestion in summary is I would
16 like my academic colleagues, on this panel and
17 others, to get others involved and invite some
18 thought leaders from industry and regulatory
19 agencies, to stop by and find some of these
20 key technical gaps, whether they are modeling,
21 protective modeling, whether it's in
22 protective or performance basis specification

1 and more leveraging of in vivo information and
2 things of that sort, to move on to the next
3 step.
4 I will also advise when you do that
5 please, do not make it only U.S.-centric.
6 Invite our colleagues across, and most
7 importantly our European colleagues, not
8 because they are close friends of mine and we
9 work together very well, but I think it's very
10 important to make it more of a global
11 initiative. Maybe that's what will take us to
12 the next step.
13 CHAIR TOPP: Thank you. Dr. Marilyn
14 Morris, you're next.
15 MEMBER MARILYN MORRIS: Dr. Nasr
16 really led into what I wanted to comment on.
17 You know, I was very excited to see this
18 EMA/FDA pilot project for a parallel
19 assessment of QbD applications, and I think
20 that this, you know, having the ability to
21 provide or to interactively provide more
22 similar reviews for applications will be very

1 beneficial.

2 I think that this will really

3 stimulate, actually, the area and the

4 applications, and provide, you know, I guess

5 some feedback on what we see as a limitation,

6 what the speakers have identified as sort of

7 the unknowns in the application process, what

8 information is needed in these applications.

9 But having, you know, this sort of

10 interaction and maybe increasing it, and again

11 communicating it to all of the colleagues in

12 PhRMA and the generics, I think, will be very

13 beneficial. So I was very excited to see

14 that. Thanks.

15 CHAIR TOPP: Thank you. FDA

16 comment?

17 DR. KOZLOWSKI: I was going to add

18 to the comments on scientific challenges. So

19 this idea of linking to clinical performance

20 is really critical and hard to do. One of the

21 things I think that's a challenge is you need

22 the clinical side of your companies and your

1 academic world to work together, and I think
2 they are not as sold on QbD as some of them
3 are.
4 So the idea of involving them,
5 because without doing that, it's very, very
6 hard to link to performance. For biotech,
7 there's an example that a few companies have
8 done, where in a normal PK study, the time
9 samples were analyzed by mass spec. So not
10 only did you get the pharmacokinetics of the
11 overall mix of the drug, but you could
12 actually show that different glycoforms did or
13 did not have different PKs.
14 I think that was actually very
15 efficient. Not a single extra patient was
16 exposed. Nobody was exposed to a variant.
17 There was different, and there may be other
18 novel strategies. So that piece of this sort
19 of had a link to the clinical side, with novel
20 biomarkers and tools, so that you can really
21 define those specs.
22 Because if you go back to the

1 comment on specifications, you know, narrowing
2 specifications reduces process capability.
3 You don't want to narrow them for a wrong
4 reason, right? If they need to be narrowed or
5 updated, then you pay that price in process
6 capability. But ideally, you should never pay
7 that price for something that's not clinically
8 meaningful.
9 CHAIR TOPP: I'm going to interject
10 here for just a minute. In the interest of
11 time, I'm keeping my eye on my watch a little
12 bit, and I want to question my FDA members
13 sitting at the table and elsewhere. Are we
14 addressing the questions that you've posed to
15 us? Would you like us to refocus our
16 discussion on another question or questions?
17 We probably should wrap up in the
18 next ten minutes or so, if we are really going
19 to finish today. So is there something else
20 that we can do to help you better?
21 DR. NASR: I am very pleased with
22 the input I have received already.

1 CHAIR TOPP: We have not really had
2 significant discussion of Question 3 at all,
3 and we really have only peripherally addressed
4 Question 2. Do you want to hear more about
5 Question 3, or do you want to table Question
6 3? Tell me what you'd like.
7 MS. WINKLE: I think it's important
8 that we talk a few minutes about Question 3.
9 I think this is an area where we feel like
10 we're having some challenges in moving
11 forward, and I think any input that the
12 Committee had would be really valued.
13 CHAIR TOPP: Okay. Let's do that,
14 then. So those of you who are in the queue
15 for Questions 1 and 2, I just cut you off. So
16 sorry about that, and I'm going to ask you to
17 re-queue up to talk about Question 3 now.
18 So I have Dr. Robinson, Dr. Kosler.
19 Anybody else? I'll put myself at the end, and
20 anybody else can add on. Now that doesn't
21 mean I get the last word, but we'll just start
22 there. So Dr. Robinson.

1 MEMBER ROBINSON: Thanks. Yes, this
2 is an area that I'm quite interested in, and
3 I think one of the issues that Steven touched
4 on was this issue of linking process
5 performance to in vivo specs or
6 bioavailability. I think one of the key
7 challenges is there's just so little data.
8 I think one thing that you mentioned
9 is that I agree it would be wonderful if more
10 academics were involved in this, and of
11 course, the issue is always there's no funding
12 to support really things that a lot of federal
13 agencies feel should be supported from
14 industry.
15 But one suggestion that might help
16 on this is at least that is related, is that
17 perhaps, again putting together, the idea of
18 putting together a working group and issuing
19 a report, that at least articulates. I mean
20 what I hear, you know, from people in industry
21 is that yes, these things are challenges, but
22 it's more on a longer time scale than they can

deal with.

So you know, putting together a working group with industry and academics, and identifying a set of scientific challenges, to just be able to say here are the issues and here are the key things that are going to be issues in terms of regulation, in terms of everything, I think, would be nice to have out there, that academics can cite, that industry people can cite. It just would be a good way to move the process forward, I think.

CHAIR TOPP: Thank you. Dr. Kosler.

DR. KOSLER: Hello. The topic on my mind is scientific probability-based sampling of materials, and I think that that's an important issue to address at many stages of, you know, production and manufacturing, et cetera, for pharmaceuticals.

I'm on a Committee with ASTM International. Currently, I'm leading a task group to review for revision Deming's industrial standard for probability sampling

of materials. Something that I would suggest or reach out to you to say is that maybe in this process, we could --

Maybe in this process, the FDA might consider what its expectations are for probability sampling, with new measurement technologies, you know, PAT, and also new automated production systems, new manufacturing systems where physical sampling methods are being newly developed, et cetera.

There are many issues that are coming up around that, and as a matter of outreach, I can say also that you do have two FDA officials who come to the Statistics Committee meeting, where this review of Deming's standard for industrial statistics is being reviewed and revised. So maybe there's some connection there that can be made.

I'd like to hear what the needs are for QbD, and also for things, you know, Code of Federal Regulations, USP, et cetera, regarding probability sampling with PAT, and

1 also the new engineering for automated
2 systems. Thank you.
3 CHAIR TOPP: Any response you guys
4 want to make?
5 DR. NASR: Just quickly. I think
6 this is a great need, and I think as we move
7 more into the implementation of real-time
8 release testing and some of these automatic
9 release and some of these concepts, I think we
10 don't, we are very much --
11 I hate to admit, but it is -- in
12 reality it's ad hoc-ish, based on individual
13 knowledge, rather than based on well-
14 established scientific and statistical
15 criteria.
16 DR. KOSLER: If I can, I'll just
17 add, there's also a lady here from Europe, I
18 believe, EMA. There are some interesting
19 currents of thought. There were some
20 interesting currents of thought in Europe over
21 the last ten years about probability-based
22 sampling in production and manufacturing of

1 pharmaceuticals.
2 Those are very interesting, and also
3 through ASTM, I'd be interested in hearing
4 what's going on in that part of the world, in
5 terms of interest in probability sampling in
6 pharmaceuticals.
7 CHAIR TOPP: Thank you. I'm going
8 to return us to Question 3, because it's my
9 personal favorite. I work in biotech
10 molecules. My group is interested in
11 stability and formulation of protein drug
12 products. So this is quite near and dear to
13 my heart, the question that you've asked here.
14 I essentially wrote a treatise that
15 I will refrain from reading to you here this
16 morning, because I know we all have lunch on
17 our minds. But you know, the question really
18 is are there potential scientific challenges
19 that we should be aware of with regard to
20 biotech molecules.
21 I think it gets to, you know, the
22 definition or the identification of critical

1 quality attributes, and behind that, to what
2 are the parameters, what are the process
3 parameters that are important for this? What
4 really matters here?
5 Behind that is what, as Dr. Robinson
6 suggested a few minutes ago, what is this
7 molecule? What are these molecules? They
8 are, as people have mentioned today, they are
9 polydispersed.
10 So large molecules are not different
11 from small molecules just because they're
12 larger. They larger and more heterogeneous
13 than small molecules. So defining what is the
14 API and what is an impurity in the API becomes
15 a little more difficult, because we're no
16 longer talking about a single chemical entity.
17 We're talking about a population of chemical
18 entities.
19 So for example, and some of the
20 changes, chemical or physical in the molecules
21 matter, in terms of in vivo performance and
22 some of them probably do not. So for example,

1 deamidation in the Fc portion of an IgG at 297
2 may not matter at all. Changes in glycoforms
3 may not matter or may radically alter the
4 biodisposition, the half life of the molecule.
5 All of those things may or may not be affected
6 by some of these changes.
7 At a scientific level, we understand
8 that very poorly, I think, at this point. So
9 if you take a small molecule approach and say
10 any chemical change in this distribution of
11 molecules is now an impurity and we now have
12 a new, we have an impurity in the product,
13 then we could go on forever and identify lots
14 and lots of changes that may or may not make
15 a difference.
16 So at a scientific level, I think
17 the challenge is to try and understand what
18 kinds of chemical and physical modifications
19 make a difference, and which kinds of chemical
20 and physical modifications are essentially
21 irrelevant to product performance. For small
22 molecules, all chemical changes are bad. For

1 large molecules, that may not be so.
2 So understanding what those changes
3 are will enable us to approach, I think from
4 a regulatory perspective, enable us to
5 approach these molecules more rationally, and
6 to home in on what are the changes that are
7 likely to be most, to pose the most risk to
8 the patients. Please.
9 DR. KOZLOWSKI: So I actually think
10 you can break up that challenge into two
11 pieces and I think both of them are very
12 important. One of them is we talked about
13 before. The scientific challenge is does this
14 five percent glycoform variant matter, either
15 positively or negative in the mixture, and how
16 do we learn that?
17 Then the other challenge is even
18 with current methods, we only have so many
19 specs, traditional methods, right. So we're
20 usually not looking at everything. Even the
21 deep characterization of molecules, as
22 characterization gets better, we learn more

1 and more about what we weren't looking at
2 before.
3 So I think there is always some need
4 to prioritize or rank. So aside from
5 scientific evidence, there is also how to use
6 risk management to organize that. So at least
7 if you focus, you focus on the 30 or 50 or
8 whatever it is attributes that are more
9 likely, even though some of those are
10 uncertain, and you may later have evidence
11 they don't matter.
12 I think that is, as Moheb has said
13 and repeatedly said, the concepts are the
14 same. I think one of the real differences in
15 implementation is how to deal with ranking
16 risks, when you have so many potential
17 candidates, you know, and some of them could
18 have -- if you consider combinatorics, there
19 are lots of slides of that. You could have
20 millions of potential combinations of
21 attributes. So that approach to risk needs to
22 be really worked at too, and I know we talked

about examples. There's a case study, ANAB. There are various examples of that, how different companies have tried to rank that.

So I think that challenge is good risk strategies for ranking attributes, aside from the science of really defining them, and I guess those link. So any advances or suggestions in those areas about thinking about those complex lists would be very useful.

CHAIR TOPP: I think I agree wholeheartedly. I think there's a whole universe of very interesting things, and I'm totally in my nerd science mode. Totally interesting things to explore there, to try and understand, for example, what glycoform changes matter and which ones don't; which parts, which chemical degradation things, some particular class of molecules like mAbs, may matter and which are completely indifferent.

So I think that, as you said, will link hand in glove with this sort of modeling

statistically-based assessment of risk. Right now we don't know enough to know where the risks really are, or to even be able to assess it adequately. So now I have to shut myself up, which is always really hard to do. Dr. Koch is next.

MEMBER KOCH: Excuse me. What I wanted to do is emphasize the process understanding characterization, and it goes all the way from media through nutrients and on into the obvious process conditions and effects. I think eventually, with the improvement and characterization and getting into things like genetic algorithms, etcetera, we'll begin to prioritize and have a better approach to achieving the QbD eventually.

Then one of the first points, in terms of what can the agency do, and it builds a little bit back into Question 1, is the reviewer/inspector combination in some of the discussions. I think a next step would be to actually not look for formal QbD submissions,

1 but to have discussions that are question-
2 based review type, that ask the right
3 questions to lead people into considerations
4 for QbD approaches.
5 CHAIR TOPP: Thank you. Dr. Muzzio,
6 you're next.
7 MEMBER MUZZIO: Yes. Just one more
8 thought about things we could do that might be
9 helpful and useful. You know, nowhere in this
10 discussion have we talked about the technology
11 providers. I mean, there is that player too,
12 right, the people who develop modeling
13 methods, the people who develop analytical
14 methodologies, etcetera.
15 Usually, if you leave the vendors,
16 you know, to their own devices, they're going
17 to come up with whatever they have, and
18 they're going to try to convince you that it
19 is what you need, right? That's the sales
20 job.
21 But on the other hand, if you tell
22 them clearly this is what we need, then they

1 actually work convergently towards creating
2 those tools in a commercializable fashion,
3 which is what the companies then need so that
4 they can plug them in. So once again, I think
5 clear statements of what are the critical
6 needs, not just the scientific gaps.
7 I mean we need a gizmo to measure
8 this, because this is where it's important.
9 We'd like to trigger a little activity in that
10 community, to create tools that will actually
11 work for what they're intended. So once
12 again, I think that, you know, it's very
13 important that as a community we identify
14 where the critical needs are, be it
15 scientific, technological or whatever.
16 About bio. I've seen presentations
17 by Siemens, for example, where they've done
18 QbD and PAT for bioreactors apparently very
19 well. I wonder whether one contribution would
20 be that we need to demystify it a little bit,
21 because on the one hand there are all these
22 complexities that Dr. Topp talked about.

1 But on the other hand, I think that
2 there's a sort of fear that in that area, that
3 restrains us from doing things that maybe work
4 already but, you know, bio is difficult. So
5 yes, I don't know.
6 CHAIR TOPP: Would the FDA like to
7 respond?
8 DR. KOZLOWSKI: Yes. No, I think we
9 are very interested in encouraging industry to
10 do that, and talking about the complexity of
11 attributes of some of these things is not
12 meant to be discouraging, but to say we need
13 a way to deal with it.
14 We may never have absolute
15 scientific knowledge about all these
16 attributes. But we need a risk-based way of
17 making good judgments, because we do that
18 anyway now. Whether, even for non-QbD
19 reviews. We don't look at every potential
20 attribute, and our process isn't designed to
21 deliver every potential attribute.
22 So adding risk only makes it better.

1 Understanding the risk only makes it better,
2 and using it appropriately.
3 CHAIR TOPP: Dr. Robinson, you have
4 the last word, because we're running of out
5 time.
6 MEMBER ROBINSON: Okay, I'll be
7 quick. I just want to -- one is just a
8 comment. But let me first address one of Dr.
9 Muzzio's comments, which is yeah, we're far
10 from really being able to control.
11 What I started to want to say is
12 that, not to mention you know, besides being
13 able to follow all these things and connect
14 process performance with in vivo specs for
15 biotech products, which I think would be
16 wonderful, the other side of it, which is even
17 more, you know, would be even more exciting is
18 the control aspect of it, which I think is
19 right now very far from possible.
20 Right now, just getting batch to
21 batch variability, which from a small molecule
22 side is not an issue or is a very small issue,

to be able from a biological perspective to get sole viability of the scene from batch to batch, when the initial conditions are the same, is a real challenge.

That's something that we, because we don't understand the process, the process being what the cells do as well as we should. It's a continuing challenge that I think is scientifically very interesting and very compelling, but is something that we need progress on, in order to deal with the regulatory issues.

DR. KOZLOWSKI: I do think the tools are growing day by day, and people are looking at all kinds of the state of cells, you know, metabolism, markers. So it's a long path, but I think it's a path that really can have a lot of progress.

MEMBER ROBINSON: No, agreed, agreed.

CHAIR TOPP: Thank you. So in the interest of time, not in the lack of interest

1 or the lack of further discussion, I'm going
2 to close us off here. It is incumbent on me,
3 Ms. Winkle's to my right, left, right,
4 whatever that side is at this point in the
5 day, tells me that it is incumbent on me to
6 summarize our discussion.
7 So I will attempt to do so briefly,
8 and I beg the FDA's indulgence. If you guys
9 said no, there's no way you're going to do
10 this list, I would say that would be fine. So
11 would you like me to try, or are you going to
12 let me off the hook? Dr. Winkle says no, no.
13 So I will do my best, and I will
14 count on my fellow members of the panel to
15 interject at the end if I miss something
16 critical. So we've had a wide-ranging
17 discussion here this morning about these three
18 questions that you see before you.
19 Essentially we addressed questions 1
20 and 2 at the same time. So the first two
21 questions are are there additional efforts the
22 FDA should consider to facilitate

1 implementation of QbD, and how should we
2 address the technical and regulatory gaps that
3 have been identified by the speakers?
4 Let me just try to hit the high
5 point. So Dr. Kibbe kicked us off with a nice
6 recap of what's happened with QbD over the
7 last couple of decades or so, and he's really
8 quite congratulatory of the agency and the
9 strides that have been made.
10 Dr. Shaya then helped us focus on
11 question 1, with a question to the FDA, how do
12 we help implement, how do you help implement
13 QbD when there's this issue of filing first,
14 you know, that particularly impacts the
15 generic industry?
16 The FDA responded really by saying
17 that you have a commitment to meet the time
18 lines. So that commitment is unchanged, and
19 you also reminded us that no Liz, we're not
20 lowering the quality bar. The quality bar
21 remains the same.
22 Dr. Tway then weighed in and said,

1 commented on some important information about
2 where the information should reside, whether
3 with the agency or at what part of the filing
4 should information about process control, for
5 example, should that reside in the filing
6 documents or with the industry.
7 She also complimented the team
8 approaches that are developing and said that
9 those were great. Again, I'm going to try and
10 do high points. There was a conversation with
11 Dr. Kosler about transformation of culture and
12 process capability. So there was quite a bit
13 of detail and back and forth there, which I am
14 not going to attempt to summarize.
15 But the importance of transformation
16 of culture and also of the relationship of
17 process capabilities to product
18 specifications, and that's part of that
19 conversation.
20 Dr. Muzzio then made some
21 suggestions with regard to addressing
22 skepticism and lack of clarity in regulatory

1 expectations.

2 He suggested that an FDA report at

3 this time might be particularly helpful in

4 addressing that skepticism and lack of

5 clarity. He also suggested, for some of the

6 reasons that I won't list here, the formation

7 of a resource center, in which tools that

8 might facilitate QbD would be shared.

9 Dr. Winkle mentioned that some of

10 that has happened through NIPDE already, but

11 that perhaps additional efforts would be

12 useful. Dr. Marilyn Morris then complimented

13 the EMA/FDA pilot project and was highly

14 supportive of that project, and commented that

15 that, she felt that that joint effort between

16 the EU and the FDA really would stimulate QbD

17 applications, because they kind of go, that

18 they went hand and glove with the EU and the

19 FDA, she felt would be very helpful.

20 We then turned our attention to

21 Question 3. You're all nodding, so I'm not

22 seeing anyone throwing daggers or swords at me

1 so far. So I'm feeling really affirmed.
2 That's all really good.
3 We turned our attention to Question
4 3, and Question 3 really states can QbD
5 approaches be valuable for biotech products,
6 and if so, are there scientific challenges
7 with regard to those products that the FDA
8 should be aware of?
9 Dr. Robinson commented that process
10 performance and in particular the link between
11 process performance and what happens with
12 biotech products in vivo is not very well
13 understood, and she recommends the formation
14 of a working group and sort of seconds the
15 formation of a working group in this area.
16 Dr. Kosler addressed the issue of
17 scientific probability-based sampling of
18 materials, and how that scientific
19 probability-based sampling might lead to new
20 sampling methods and really better ways of
21 controlling these processes.
22 I then had some comments about my

1 deep love for biotech materials and how
2 biotech molecules differ quite a bit from
3 small molecules, and how there are significant
4 challenges even in just defining what the
5 molecules are, and that that kind of sets the
6 stage for some of what's going on here.
7 Dr. Koch mentioned the importance of
8 process understanding characterization in
9 biotech is hugely important, and that that is
10 something that we don't understand quite very
11 well at this point, and recommended some
12 question-based approaches.
13 Dr. Muzzio suggested that with
14 biotech and perhaps your suggestion was
15 broader than that, Dr. Muzzio, with regard to
16 other areas that the potential approach for
17 facilitating QbD would be to approach not only
18 pharma industry but also technology providers.
19 That is, people who provide modeling programs
20 or analytical processes, analytical
21 instrumentation, that they could be enlisted
22 to help demystify biologics in particular, but

1 help facilitate the development of QbD
2 approaches.
3 Dr. Robinson got the last word on
4 this topic, and returned to the idea that we
5 really understand very poorly how biotech
6 processes work, because the cells still remain
7 a little bit of a mystery to us.
8 You didn't use exactly that word,
9 but that understanding the factors that
10 control cell viability and productivity is
11 something that we really don't understand
12 well. So that's a key component to
13 understanding biotech products.
14 So with that, any corrections or
15 comments from the Committee about things that
16 I've missed?
17 MEMBER KIBBE: If I might.
18 CHAIR TOPP: Yes, Dr. Kosler, and
19 Ken Morris has a comment, did you say? Okay.
20 Dr. Kosler, a comment, and then Dr. Morris.
21 MEMBER KIBBE: Okay. I'd just like
22 to comment that many of my questions have been

1 motivated by the notion that a manufacturer
2 might look at the list of risk, costs,
3 challenges, what is the limits of what's known
4 to science and some of these other things.
5 It's a more sophisticated production process
6 under QbD, and simply decide to discontinue
7 production of a particular drug. That is an
8 option that a manufacturer has.
9 So I just wanted to put that out
10 there and say that is one of the things
11 motivating my questions about capability. If
12 we don't have the capability to make it, maybe
13 it's better to not take on the risk. So that
14 is something to hold in the balance. Thank
15 you.
16 CHAIR TOPP: Dr. Ken Morris.
17 DR. KEN MORRIS: Just real quickly.
18 I think there -- I actually had a bunch of
19 comments, but I think they're all pretty much
20 covered. The one thing, though, that Moheb
21 raised that I think is really critical is the
22 IVIVC issue.

1 To the extent that there are some
2 pretty viable approaches out there, I think
3 that any effort we put in that direction is
4 going to be good, and this stretches right the
5 way through from the first question and
6 particularly the third question, you know,
7 given the IPO example, et cetera.
8 So I would say any effort in IVIVC
9 is really money well spent and time well
10 spent.
11 CHAIR TOPP: Okay, thank you. In
12 the interest of time and in the interest of
13 allowing time for our afternoon session, I
14 will conclude this morning's session on Topic
15 No. 1. So Dr. Winkle is telling me that I
16 need to allow Dr. Kibbe to have a comment. So
17 I have been preempted. Dr. Kibbe.
18 MEMBER KIBBE: Thank you, Helen. I
19 just wanted to get back to two points I
20 thought I made in the summary, and one is that
21 team approach, of reviewing everything, is
22 absolutely the best way to go. You're

1 working it here, but you should consider
2 working it for IBD, whatever kind of
3 submission you get.
4 Second, I think the agency has the
5 authority to ask anybody who's making any
6 submission at all some very simple questions,
7 which is have you done any QbD in any of your
8 process? Where is it? Have you done this,
9 have you done that? The minute that they get
10 those notes, they scurry back to do something,
11 okay.
12 That is going to be more stimulus
13 than practically anything we do, is for you
14 just to ask them if they do that. Also, I
15 consider biotechnology products to be natural
16 source products. If we had an old
17 pharmacognocist here, he would help you with
18 that a lot, and there is an old, old product
19 which I'd love to bring up, just because I
20 like to beat it up, and that's conjugated
21 estrogens, which the agency has never
22 determined what the components are that work

1 or don't work.

2 CHAIR TOPP: Thank you, and I

3 apologize for missing your two initial

4 important comments. They were early in our

5 discussion, and I have, you know, amnesia or

6 something. So any other remarks that we need

7 to capture?

8 If not, we'll now close this

9 morning's session on Topic No. 1. We are

10 adjourned for 45 minutes for lunch. So we're

11 going to cut our lunch 15 minutes short,

12 because we got to have discussion instead.

13 So we will reconvene here at 1:30.

14 So back here at 1:30. I remind members of the

15 Committee that there will be no discussion of

16 these important and wonderful topics during

17 lunch. So we're done. Thank you. See you

18 back here at 1:30.

19 (Whereupon, the above-entitled

20 matter went off the record at 12:48 p.m. and

21 resumed at 1:33 p.m.)

22

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:33 p.m.

CHAIR TOPP: Okay. Welcome back everyone. It's time for the afternoon session. We will now proceed with presentations from the FDA and guest speakers for Topic 2, "USP Interaction, Monograph Modernization Program and Other Initiatives."

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We begin this afternoon with a topi introduction from Larry Ouderkirk. Dr. Ouderkirk is Consumer Safety Officer in the Office of Manufacturing and Product Quality, Office of Compliance at CDER and the FDA. The title of his presentation this afternoon is "Topic Introduction: FDA Monograph Modernization Task Group" or MMTG.

MR. OUDERKIRK: Okay. Thank you

very much, and I'm happy to be here to introduce this Topic 2, all about the FDA and USP Monograph Modernization Initiative, and I'm going to introduce the topic and then talk a little bit about FDA specifically and what we're doing with our Monograph Modernization Task Group. I'm the co-chair, along with Paul Seo of the Task Group.

I will start by giving you an overview of the topic, go over the presentations that you will hear this afternoon, just kind of summarize briefly, and then I'll give a bit of history of monograph modernization.

It's not an entirely new topic, but it has a new emphasis. It has taken on added importance recently. So that's why we wanted to bring it to your attention and discuss it a bit.

I'll go over some aspects of our Task Group, how we're working with USP and interfacing with them to effect monograph

1 modernization, and I'll talk a bit about what
2 we have accomplished so far, and future
3 objectives we hope to accomplish.
4 These are this afternoon's topics.
5 As I said, I'll start off and then a colleague
6 of ours in FDA, Reynold Tan from the Office of
7 Non-Prescription Drugs, will talk about --
8 specifically talk about OTC drugs. We have,
9 as you know, an FDA/OTC monograph system,
10 which is not to be confused with compendium
11 monographs.
12 So he'll go over that in his talk,
13 and then we'll have speakers, two speakers
14 from USP. Karen Russo will talk about efforts
15 to modernize monographs for small molecules,
16 and Catherine Sheehan will talk about
17 modernization of monographs for excipients or
18 inactive pharmaceutical ingredients.
19 Then we'll have Rachel Roehrig give
20 an industry perspective, to represent the OTC
21 drug industry, and how they are also working
22 with USP to effect these changes to the

1 monograph, these improvements. Finally, my
2 colleague, Jon Clark, from OPS will wrap up
3 the session, and kind of give an overall
4 summary and talk a little bit about some of
5 the research initiatives that are going on in
6 the agency and collaboration with USP on those
7 initiatives.
8 So I'd like to start by giving you
9 some introduction to the topic of compendial
10 monograph modernization. As you know, USP
11 contains monographs, many thousands of
12 monographs for active drug substances and drug
13 products, while the National Formulary or NF
14 has monographs for inactive pharmaceutical
15 ingredients, also known as excipients.
16 They're recognized in the Food, Drug
17 and Cosmetic Act as official standards of
18 strength, quality and purity. So the FD&C Act
19 is what kind of marries FDA and USP in terms
20 of our concern about having appropriate
21 standards in the USP and the NF.
22 USP and NF standards have been

1 continually revised over the years. As you
2 know, USP has a long history, dating back to
3 the early 1800's. So obviously they have
4 revised their monographs more or less
5 continually. But with the evolution of a
6 global drug supply, this emphasis has
7 increased greatly on the need to revise
8 monographs and have modern standards in them.
9 It has become an increasingly
10 important tool to FDA to have these modern
11 methods in our enforcement planning. For many
12 years, FDA, particularly CDER, has assisted
13 USP in revising monographs, in that we
14 communicate with USP when monograph revisions
15 are proposed.
16 So we do have an office that's
17 dedicated to that, that Paul Seo heads up, the
18 Compendial Operations staff in CDER. That's
19 a full-time job, believe me, and we've put a
20 lot of effort into that.
21 This slide summarizes why we're
22 interested, why there's a need for monograph

1 modernization, and why we're -- essentially
2 why we're having this meeting today. Here's
3 the basis of our concerns, things that can
4 happen when compendial monographs are not up
5 to date.
6 We'll note that inadequate test
7 methods, especially for critical tests like
8 identification, can often render the articles
9 and the monograph more vulnerable to incidents
10 of contamination or adulteration, and
11 sometimes these adulteration incidents are
12 actually economically motivated.
13 So they're actually planned, what I
14 would call criminal acts, that purposely
15 adulterate USP NF articles for economic gain.
16 I'll go over some examples of that later in my
17 talk.
18 Also, we're concerned about
19 inadequate, missing tests for impurities.
20 It's important to have proper and adequate
21 tests for impurities, because the USP is
22 recognized as the legal minimal standard, at

1 least, for quality and purity.
2 The USP monographs for OTC drugs, or
3 what I mean is active pharmaceutical
4 ingredients that are used to make OTC drugs,
5 can be especially important, because unlike
6 prescription drugs, which are addressed by FDA
7 in a review of an NDA or ANDA, most OTC drugs
8 do not undergo a pre-approval review before
9 they're marketed.
10 So they rely upon the compendial
11 monograph for the active pharmaceutical
12 ingredient. Dr. Tan will talk more about that
13 in his talk. Often overlooked are the NF
14 monographs for the excipient or inactive
15 pharmaceutical ingredients.
16 Those also can be very important, in
17 that purity issues, economics, substitution,
18 adulteration issues are important for
19 excipients as well, because they are often,
20 often comprise a high proportion of the drug
21 product.
22 I'd like to take a moment now to go

1 over some examples, past examples of FDA-USP
2 cooperation and working together to modernize
3 critical monographs.
4 The first example is the USP
5 glycerin monograph, and this slide just
6 captures a partial history of this, and I
7 think that Catherine Sheehan, in her talk,
8 will go over this in greater detail. But I'm
9 just going to highlight some of the later
10 history of this.
11 In May of 2007, FDA issued a
12 guidance on testing of glycerin for diethylene
13 glycol. As you might probably know,
14 diethylene glycol is a common, has been used
15 as the substitute for glycerin or has been an
16 adulterant in glycerine. DEG is cheaper than
17 glycerin and the problem is that it's a highly
18 toxic substance.
19 So it has a long history of being
20 substituted for glycerine, and while incidents
21 in the United States are not common, incidents
22 internationally still happen on a semi-regular

1 basis. There was a serious incident, I think,
2 in 2007 that prompted this guidance to be
3 issued.
4 What we did was the guidance was
5 issued in the Office of Compliance. We
6 requested USP to take the test and limits for
7 the diethylene glycol adulterate and put it
8 actually into the identification test in the
9 monograph.
10 That's critical because under the
11 good manufacturing practice regulations, drug
12 manufacturers, drug product manufacturers are
13 required to perform at least an identification
14 test on all of the components of a finished
15 drug product.
16 So moving that test for diethylene
17 glycol into the identification section of the
18 monograph was something that FDA wanted very
19 much as an enforcement tool, an added
20 enforcement tool. We worked closely with USP
21 on that, and you can see that in May of 2009,
22 that monograph was modified to include a test

1 and limit for diethylene glycol and also for
2 ethylene glycol, which is another toxic
3 substance similar to DEG. So that was
4 completed in May of '09.
5 Following that, there's many similar
6 monographs for substances that are similar to
7 glycerin. So you can see five of them listed
8 here, and those five monographs were also
9 modified or improved to have a diethylene
10 glycol/ethylene glycol test and limit included
11 in their ID test as well.
12 A second example of a very critical
13 monograph improvement project was caused by
14 the heparin adulteration incident. It was
15 first detected back in March of 2008. Heparin
16 that had been imported from China into the
17 United States, the heparin drug substance, was
18 found to be adulterated with over-sulfated
19 chrondroitin sulfate, or OSCS for short.
20 OSCS is kind of a chemical cousin of
21 heparin, but certainly is not heparin. When
22 this adulterated drug substance was used to

1 make drug products, at least 81 deaths were
2 recorded in the United States from that. So
3 this was a public health emergency, and it had
4 to be addressed, you know, expeditiously.
5 So USP, FDA, along with industry and
6 consultants from academia, formed a consortium
7 to develop new test methods that could be put
8 into the monograph for heparin sodium. So you
9 see proton NMR method and capillary
10 electrophoresis method were actually included
11 into the identity test for heparin sodium drug
12 substance, and this was completed in June of
13 2008.
14 USP actually used its power to post
15 things to its website in a revision bulletin,
16 in order to effect this change in the most
17 expeditious manner. Those were the Stage 1
18 revisions. They were followed a little over
19 a year later by some Stage 2 revisions that
20 further strengthened and refined the test in
21 the monograph. I believe there's some Stage
22 3 revisions that are also in the works.

1 Now I'd like to go to what I call
2 Phase 2 or the modern phase of monograph
3 modernization. This dates back to spring of
4 last year, when USP held its five year
5 convention.
6 USP holds a convention every five
7 years, and the convention is somewhat like a -
8 - I liken it sort of to a political party's
9 convention, in that there's a platform; there
10 are goals that are set for the next five years
11 that USP wants to complete.
12 There are resolutions that are
13 proposed. They're voted on or adopted; they
14 are modified and changed, but eventually
15 adopted, and that kind of thing. So among the
16 resolutions that were presented at the 2010
17 USP convention, FDA does comment on the
18 resolutions, and we sent our comments to USP.
19 In those, we agreed with USP's
20 resolution to focus its core compendial
21 activities, to ensure that USP and NF contain
22 relevant, timely and accurate public

1 standards. A second resolution that we
2 supported was to strengthen the USP-FDA
3 relationship, in order to better provide and
4 maintain up to date national standards for
5 legally marketed drugs.
6 Then specifically was mentioned the
7 importance of modernizing the USP and NF
8 monographs. Some of the reasons for that
9 modernization or some of them I've touched on
10 earlier, to help prevent these
11 adulteration/contamination incidents, to
12 promote the use of modern spectographic
13 methods in the identity test, which I
14 explained was very critical.
15 Also to specifically focus on over-
16 the-counter drugs, in order to strengthen the
17 monograph tests for those, the ones that some
18 -- especially the ones that do not have FDA
19 pre-approval for marketing, and to provide
20 appropriate and consistent limits for
21 impurities.
22 So a month following the convention,

1 USP posted to its website some lists of
2 monographs in need of modernization. You can
3 go to the USP website and they're still there.
4 They're updated monthly.
5 There's a Top 200, although I think
6 there's more than 200 actually listed. But we
7 call it a Top 200 small molecule monographs in
8 need of modernization, and a Top 96 excipients
9 monographs were posted.
10 Some of the criteria used to select
11 these, that USP used to select there, were
12 that they were high volume articles, used in
13 high volumes in the pharmaceutical industry,
14 and many of them have older, what we would
15 obsolete analytical tests that need to be
16 replaced with more modern tests and limits.
17 USP tracks the progress of these revisions on
18 its website, and they're updated monthly.
19 In October of last year, our CDER
20 director, Janet Woodcock, sent a letter to
21 USP, acknowledging the importance of this
22 monograph modernization program, and requested

1 USP to focus additional energies and to effect
2 this modernization with urgency. So it is a
3 very high priority project in the FDA and in
4 CDER.
5 Also in the letter, Dr. Woodcock
6 announced formation of a new FDA task group,
7 and that is the Monograph Modernization Task
8 Group, which I'll talk a little bit more about
9 later. This task group will assist USP in
10 prioritizing monographs that need
11 modernization, and of course FDA's perspective
12 is usually that of a public health
13 perspective.
14 So we bring that public health
15 perspective to the USP monographs, and help
16 USP focus on those that we think will most
17 benefit the public by being modernized. Such
18 things as, you know, economically,
19 vulnerability to economically motivated
20 adulteration in the OTC drugs that I mentioned
21 before were especially emphasized.
22 Shortly after that, the monograph

1 modernization task group is chartered. It
2 comes under the larger Pharmaceutical Quality
3 Standards Working Group, as I mentioned, Paul
4 Seo and I co-chaired the MMTG.
5 We have nine other members drawn
6 from not only CDER, but also the Center for
7 Veterinary Medicine and Office of Regulatory
8 Affairs, which comprises the -- what we refer
9 to as the field, and has field laboratories
10 and field laboratory facilities and many great
11 scientists out in the field.
12 The proposal in the -- for the task
13 group was to identify -- the purpose, rather,
14 was to identify and develop risk-based
15 prioritization schemes, so that we could
16 focus, help USP focus on modernizing
17 antiquated missing, antiquated monographs that
18 might be missing specific tests or have non-
19 specific tests.
20 We communicate with USP.
21 Periodically, we will communicate to USP which
22 monograph revisions are of highest importance

1 to the agency, based on that potential public
2 health benefit. We did send our first letter
3 to the USP in November of 2010, in which were
4 listed our "Top 10." I think there are more
5 than ten listed, because some of them have
6 more one dosage form. But we call it our Top
7 10 USP NF monographs in need of modernization.
8 So they're the highest priority.
9 We put special emphasis, as I said
10 before, on OTC drugs and widely-used
11 excipients. There were some known impurity
12 issues for some of the OTC drugs that you will
13 see listed on our list, and USP has posted all
14 of this on its website. It has a hot topics
15 page and a monograph modernization page, and
16 I urge you to go there if you want to see more
17 about this, get more information.
18 Here's the list that was initially
19 sent back last fall to USP. You can see that
20 it has several OTC drug substances and drug
21 products, as well as some high volume
22 excipients. Following our letter, FDA and USP

1 have met to discuss the issues, and see how
2 the modernization is progressing.
3 So our task group meets periodically
4 with representatives from USP. Karen Russo
5 and Catherine Sheehan have met with us a few
6 times, and we've talked about, you know, how
7 progress is going. We've had other meetings
8 and it's been talked about in public meetings
9 too.
10 USP, I want to emphasize that USP
11 not only is working on the priority
12 monographs, but from a list of 200 or more
13 monographs, there's actually a larger list.
14 USP is also continuing to work on other
15 monographs, modernizing them. These are the
16 ones that we've identified, but there are
17 others that information comes into to USP, and
18 they also work on those simultaneously. They
19 don't just work on these Top 10.
20 But they do track the revisions, and
21 those are posted, as I said, monthly.
22 Currently, our task group plans to continue to

1 provide periodic lists of monographs that we
2 regard as the highest priority to modernize.
3 We are developing a risk-based scheme, as I
4 said before, to prioritize the monographs on
5 the Top 200 and Top 96 list, but that doesn't
6 limit us to that. We're not limited to any
7 certain monographs. We can range over all
8 monographs, if we find that they need to be
9 modernized.
10 So our prioritization will include,
11 can consider multiple factors, such as to
12 focus on the back to pharmaceutical ingredient
13 or the drug product. Sales volumes can be
14 taken into account, the potential for EMA or
15 economically motivated adulteration is an
16 important consideration in the FDA.
17 The drug's regulatory status, that
18 is, whether it's a non pre-reviewed OTC or is
19 it an NDA product could enter into our
20 decision to prioritize the drug's therapeutic
21 class, and many other factors.
22 I would also say that, as I said

1 before, we're not limiting ourselves in any
2 way. There could be other non-chemical tests.
3 There could be microbiological tests in some
4 of the monographs to be updated. We do have
5 microbiologists on our task group.
6 We may have to suggest to update
7 some of the tests that are in the general
8 chapters. So we're not limiting ourselves to
9 just this category of the Top 200 that are
10 published on the USP's website, but that is a
11 good starting point in many ways.
12 Then we're going to refine our
13 prioritization model as needed, as our project
14 goes forward. Probably we'll develop this
15 prioritization somewhat separately for drugs
16 versus excipients, but they will share some
17 common characteristics. For example, sales
18 volume data and potential for economically
19 motivated adulteration would be considerations
20 that we would give, whether the monograph is
21 for a drug or for an excipient.
22 We do plan to send another set of

1 priority monographs to USP in the near future.
2 I do want to take a moment here at the end, as
3 I close my talk, to acknowledge members of
4 monograph modernization task group.
5 There are, as you can see, they're
6 drawn from several places throughout the FDA,
7 not just CDER, and there's a lot of expertise
8 that resides on this task group. I'm very,
9 very humbled to be able to work with them on
10 this project, and also to work with the
11 representatives from USP and from industry on
12 this.
13 I'd like to also thank my colleague
14 Paul Seo, my co-chair, for helping me to
15 prepare these slides. Thank you very much.
16 CHAIR TOPP: Thank you. I'd like to
17 now take one or two questions from the
18 Committee, and I remind the panel that this is
19 an awareness issue. Topic 2 this afternoon is
20 an awareness issue. So any questions that you
21 have for the speaker.
22 Mr. Ouderkirk, don't leave us alone.

1 Oh, you're just going right there. That's
2 good. So yes, absolutely. So if there are
3 one or two questions from the Committee, that
4 would be great. But I remind you that these
5 are awareness topics, and so these should be
6 questions for clarification only. I do have
7 a question from Dr. Ken Morris. Ken.
8 MEMBER KEN MORRIS: Thanks, Liz.
9 Yes. Good talk. You know, USP has always
10 done a great job on purity, but particularly
11 with excipients, so much of the functionality
12 actually comes from the physical, the
13 materials properties. Is that a focus or
14 maybe that will be treated in the other talk.
15 Is that going to be a focus for modernization
16 of the excipient monograph?
17 MR. OUDERKIRK: No, I don't think
18 that's going to be a focus of our concern.
19 That won't be a main focus. We're focused --
20 you notice that talc was one of the excipients
21 that was on our list, and that really goes to
22 the presence of asbestos in talc. So that's

1 a -- you know, that's more of a serious health
2 concern than the functionality.
3 I know that some -- that often for
4 excipients, you know, certain very small
5 quantities of what we might consider
6 impurities are considered to be -- add to
7 functionality. But I don't think we're
8 focused on that. I think we're focused on the
9 more serious public health issues that might
10 arise with excipients.
11 CHAIR TOPP: Thank you. Any
12 additional questions from the panel? Oh, Dr.
13 Polli.
14 DR. POLLI: Larry, I enjoyed that.
15 So I'm kind of under the impression that
16 historically, USP tries to use methodologies
17 that are easily within reach of everyone. I'm
18 just asking about the NMR. So that's the
19 first time I have ever seen reference to NMR
20 on a monograph, and of course this was under
21 sort of special conditions.
22 But then I say to myself "NMR is all

1 over the place." So just with the background
2 that I think I have, that test method should
3 be easily available to virtually everyone. Is
4 the group considering technologies that have
5 not necessarily been used a lot before, in
6 terms of characterization, et cetera?
7 MR. OUDERKIRK: Yes, it may become
8 necessary to do that, as you point out. Some
9 of the more advanced methods are becoming more
10 widely available. But I think, you know, on
11 a case by case basis, we'll have to evaluate
12 the public health benefit versus the
13 traditional concept of keeping the USP methods
14 widely accessible.
15 So you know, in the case of heparin,
16 it did go the other way. It went toward the
17 public health benefit and the necessity of
18 having the proton NMR, which I know not every
19 laboratory has the exact model that was
20 mentioned in the monograph.
21 CHAIR TOPP: Thank you. Our next
22 speaker this afternoon is Dr. Reynold Tan.

1 Dr. Tan is an interdisciplinary scientist in
2 the Division of Non-Prescription Regulation
3 Development in the Office of Drug Evaluation
4 IV, in the Office of New Drugs with CDER. Dr.
5 Tan's presentation this afternoon is entitled
6 "Over-the-Counter Monographs: Improving
7 Quality Assessment Standards." Dr. Tan.
8 DR. TAN: Thank you very much.
9 Right. So I'm here to discuss the OTC
10 monograph process, and the intention in
11 discussing this process is to show, in its
12 current state, this monograph process doesn't
13 ensure adequate quality assessment. Then
14 finally I'll talk about why improving quality
15 assessment can be helped by modernizing USP
16 monographs.
17 So to start out, just to be clear on
18 what over-the-counter drugs are, they're
19 products like these. So there's a general
20 understanding of what OTC drugs or non-
21 prescription drugs are. You go into a
22 Walgreens, CVS, you get these over the

1 counter. You don't need a prescription from
2 a doctor or health care provider.
3 There's actually a regulatory
4 definition. So in 1951, the Durham-Humphrey
5 amendment to the Food, Drug and Cosmetic Act
6 said that some drugs had to be marketed
7 specifically prescription, okay. So drugs are
8 actually by default over-the-counter drugs.
9 If you're not specifically required to be
10 prescription, you're non-prescription or over
11 the counter, okay.
12 The other thing you should know, for
13 all the OTC drugs that are legally marketed,
14 they're marketed according to one of two
15 processes by FDA. So the products that
16 they're using are either marketed under an
17 approved OTC NDA, or allowed to market under
18 an OTC drug monograph.
19 Okay. So the OTC NDA process is
20 almost identical to the prescription NDA
21 process. If you're a manufacturer of one of
22 these products, you have to show us data to

1 prove the safety and effectiveness of your
2 product before we even consider allowing you
3 to market that product.
4 That's not the case with OTC drug
5 monograph products. So in that case, we're
6 actually FDA. We write the safety and
7 effectiveness standards for these products.
8 As a manufacturer, you can market that
9 product, as long as you follow our written
10 standards for safety and effectiveness.
11 So going back to my picture, now
12 I've divided them into products that are
13 marketed according to approved NDAs, and
14 products that are allowed to market under OTC
15 drug monographs.
16 Just by looking at the labels,
17 there's nothing apparent in these labels that
18 suggest that there should be two processes, or
19 that there are two processes for regulating
20 these drugs. So I'm not going to explain why
21 we have these two processes by showing this
22 time line.

1 So the general idea here is just to
2 show that it wasn't until 1938 that we
3 required safety pre-approval, and it wasn't
4 until 1962 that we required efficacy pre-
5 approval. So you had many years where you had
6 OTC drugs marketed without established safety
7 and effectiveness standards.
8 There's hundreds of thousands of
9 these products. So I mean it's not feasible
10 to do product by product NDA reviews for all
11 these products.
12 So what we decided to do was, rather
13 than doing these hundreds of thousands of
14 product reviews, we could knock the products
15 off in bunches under OTC drug categories, by
16 just doing reviews of the active ingredients
17 in OTC drugs.
18 That process is that OTC drug review
19 in 1972. It's another name for the process
20 through which we developed OTC drug
21 monographs. So what we said when we started
22 the OTC drug review was this: If you are a

1 product marketed before this process started
2 in the 70's, you would be covered by an OTC
3 drug monograph.
4 If you came into the market after
5 the 70's, you would have to come in under an
6 approved NDA. So now go back by my picture
7 and explain to you now that your products on
8 the left are under NDAs because, if you
9 notice, the active ingredient and their
10 therapeutic indication for the products on the
11 left, those came into the OTC market after the
12 70's. So they have to come in under NDAs.
13 The products on the right, the
14 active ingredient and their therapeutic
15 indication was in the market prior to the
16 70's, so they're covered by monographs.
17 Just to hammer the point home, with
18 the Aleve versus the Tylenol, okay, they're
19 both for pain relief/fever reduction. Aleve
20 has naproxin though, whereas Tylenol as
21 acetaminophen, all right. So acetaminophen
22 for pain relief was marketed before the 70's.

1 It's covered by a monograph, the internal
2 analgesic monograph.
3 Aleve, naproxin came in after. They
4 had to come in through an NDA. So now we just
5 see focus on the monograph process itself.
6 How did we create them?
7 Well, first we start out with the
8 data request. So there's a general request
9 that goes out in the Federal Register and a
10 notice for the public to submit data, and then
11 we can make specific requests to industry,
12 health care professionals and consumers, their
13 trade groups and associations.
14 Then back in the 70's what we did
15 was we formed expert review panels to review
16 the data that we gathered. There were 17 of
17 these review panels, like the Antacid Panel,
18 Antimicrobial Panel and so forth. They
19 reviewed the data and they held public
20 meetings every couple of months.
21 These panels classified the active
22 ingredients that are found in the products and

1 their drug category as either Category 1, 2
2 and 3. Category 1 active ingredients were
3 active ingredients that had data showing that
4 they were generally recognized as safe and
5 effective, a term referred to as GRAS/GRAE.
6 Category 2 active ingredients
7 actually had data showing they were not safe
8 or effective, and Category 3 active
9 ingredients were actually active ingredients
10 that didn't have enough data to make a
11 classification.
12 Okay. So following an expert review
13 of the data, what we have is a three-step
14 process for creating a final OTC monograph,
15 and each of those steps requires a publication
16 in the Federal Register. The panel's
17 recommendations, the expert panel I was just
18 talking about, those go into the first
19 publication, the Advanced Notice of Proposed
20 Rulemaking or the ANPR.
21 That publication opens up a public
22 comment period, typically for 90 days. So the

1 public weighs in on the proposed monograph in
2 the ANPR, and hopefully if they want to make
3 changes, they support it with data. We look
4 at this data in the comments, and if we think
5 the requested changes are merited, we revised
6 the proposed monograph that published in the
7 ANPR, and publish the revised proposed
8 monograph in the proposed rule as a tentative
9 final monograph. So that's Step 2.
10 That publication opens up a second
11 public comment period. Again, we weigh the
12 comments and the data before publishing a
13 final monograph. Once that final monograph is
14 published, there's typically one year for
15 consumers to comply with the requirements in
16 that final monograph. If manufacturers don't
17 comply with that final monograph, then their
18 product can be deemed misbranded or
19 adulterated, and we can take action against
20 the product.
21 Here's what's in an OTC monograph.
22 It's basically a listing of the generally

1 recognized and safe and effective conditions,
2 including active ingredients, labeling
3 requirements, sometimes final formulation
4 testing and more recently we usually include
5 an example for labeling.
6 This is just an example of a product
7 that complies with the monograph. What you
8 have on the left are sections from the OTC
9 antacid monograph, and on the right, you have
10 a label from Tums, which is antacid monograph
11 product that's legally marketed.
12 You can see Tums contains calcium
13 carbonate, which is an allowed active
14 ingredient under the monographs. It uses
15 labeling language that complies with the
16 labeling language that's required under the
17 monograph.
18 Here are the key differences between
19 the NDA process and the monograph process.
20 The NDA process is a pre-market approval
21 process. We review each drug product
22 separately and it's all confidential. In

1 contrast, the OTC monograph process has no
2 pre-market approval. We review active
3 ingredients per OTC drug category, and it's a
4 public process.
5 It's because of these differences,
6 particularly because there's pre-market
7 approval required on the NDA side and not on
8 the monograph side, that we have this
9 discrepancy, this inferiority of quality
10 assessment on the monograph side. So that's
11 what's shown in this slide. So for the NDA
12 process again, we evaluate each product for
13 characteristics of the product that can affect
14 quality.
15 That includes drug substance
16 synthesis, formulation and local methods,
17 manufacturing and process controls and
18 stability. On the monograph side, we evaluate
19 active ingredients, but we don't evaluate each
20 active ingredient for each product. We
21 evaluate active ingredients going by
22 representative products that contain that

1 active ingredient.

2 The way we ensure quality assessment

3 is just to say that that active ingredient has

4 to have a corresponding USP monograph, and it

5 has to comply with that monograph. Here is

6 the actual regulation that says an OTC drug

7 active ingredient has to have a USP monograph.

8 What the regulations says is that

9 inclusion in an OTC drug monograph requires an

10 official USP monograph for the active

11 ingredient, or a proposed standard for

12 inclusion in an article to be recognized in an

13 official USP drug monograph for the active

14 ingredient.

15 So in other words, if you're a

16 manufacturer of an OTC monograph product, you

17 need to be sure that your active ingredient

18 either has a USP monograph, or you need to be

19 working with USP to create such a monograph.

20 Consumers likely have the same

21 quality expectations for products, regardless

22 of what process we regulated under. Here, you

1 have a picture of Aleve versus Tylenol
2 product. They both have the same active
3 ingredients and the same indication. They're
4 labeled with a similar labeling style.
5 But as I described, the Aleve
6 product has a higher standard of quality
7 assessment than the Tylenol product. That can
8 lead to potential quality problems. Dr.
9 Ouderkirk already talked about the heparin and
10 diethylene glycol examples, and there's
11 potential for these various unintentional
12 quality failures as well.
13 What's judged to be the biggest
14 potential quality problem is the problem with
15 impurities. What you're seeing here is a
16 table on the left. You have OTC drug
17 monograph active ingredients. These are the
18 11 top-selling active ingredients that are
19 sold under or under the monograph.
20 On the right you have, represented
21 by the number, existing USP monographs related
22 to that active ingredient, and the letter is

1 Division Director Scott Furness' rating of
2 whether the impurity protocols in that USP
3 monograph is either adequate, inadequate or
4 non-existent.
5 So for example, for acetaminophen,
6 there are eight USP-related monographs. Two
7 of them were judged to be inadequate, and six
8 of them had actually no existing USP impurity
9 protocol in it. As you can see for all these
10 top-selling active ingredients, the USP
11 impurity testing protocols were either judged
12 inadequate or non-existent.
13 So it finishes with a time line
14 showing how we've been addressing this
15 concern. The Consumer Health Care Products
16 Association discussed the concern in a seminar
17 in 2008. The FDA Working Group developed a
18 prioritization scheme for tackling the
19 monographs and monographed products, based on
20 sales volume and available toxicology data for
21 active ingredients.
22 The Working Group conducted a brief

1 survey of marketed OTC drugs and found that
2 some OTC drug products under the monograph
3 would not meet the quality standards for NDA
4 products. The Office of Pharmaceutical
5 Science approached USP in 2010. USP
6 approaches CHPA in 2010, and the Joint
7 Committee formed in the summer of 2010.
8 Sticking with the time line, we've
9 already talked about FDA's Monograph
10 Modernization Task Group, and we also talked
11 about the letter to USP, which prioritized USP
12 monographs. Prioritized 15 USP monographs, 13
13 drugs, substances, products and two
14 excipients. For those 13 drug substance
15 product monographs, USP monographs, all were
16 for drugs containing acetaminophen and
17 diphenhydramine.
18 That's why in the USP letter to FDA
19 in 2010, the recommendation was for an expert
20 panel on acetaminophen, an expert panel on
21 diphenhydramine, and going back to the
22 impurities concern, an expert panel to discuss

1 USP's 1086 general chapter on impurities. In
2 a USP Symposium in 2011 on OTC drugs, we also
3 addressed the concern.
4 So working with the Joint Committee,
5 USP has identified a list of 200 small
6 molecules, molecule monographs and 96
7 excipient monographs, which you'll hear about
8 in the next presentation.
9 Just to summarize some of the items
10 for modernization, there's a plan to update
11 storage conditions; update assay methods;
12 replace non-specific ID procedures like IR
13 spectroscopy and thin layer chromatography;
14 add missing procedures, particularly
15 impurities testing.
16 They found that 142 of the
17 prioritized list of monographs needed the
18 addition of impurities testing. So that's a
19 high percentage. Working with the Joint
20 Committee, the MMTG plans to oversee all
21 modernization prioritization; make sure the
22 modernization and prioritization is science

1 and risk-based; work with USP to achieve
2 improvements in accordance with the USP
3 resolutions for the 2010-2015 cycle; focus on
4 those monographs that present the greatest
5 risk to public health; and to provide
6 recommendations to the USP regularly.
7 So last slide, just to rehash the
8 key next steps. For the short term, the MMTG,
9 in collaboration with USP and CHPA, will
10 continue to identify and develop science and
11 risk-based prioritization schemes for
12 monographs, and then to add or modernize the
13 assay methods or just the methodology in those
14 monographs.
15 Long term, the plan is to address
16 impurities comprehensively. So one idea I
17 understand that's been discussed is moving the
18 USP 1086 general chapter on Purities to
19 chapters below 1,000, making a general
20 informational section, a required section and
21 to include a lot of the content of the ICH Q3A
22 guidance, which is guidance for industry on

1 impurities in new drug substances, which
2 includes a lot more specificity on impurities
3 testing.
4 With that, I'll just leave you with
5 a link to OTC drug monograph information, and
6 thank you for listening.
7 CHAIR TOPP: Thank you, Dr. Tan.
8 Questions from the panel. Dr. Kibbe?
9 MEMBER KIBBE: When you said that
10 they didn't have a test, did you mean that
11 there was no test at all, or that the test
12 that was in the monograph wasn't sufficient?
13 DR. TAN: Are you talking about that
14 impurities testing protocol?
15 MEMBER KIBBE: Yes.
16 DR. TAN: I didn't do the -- that's
17 just an informal rating by Scott Furness, our
18 division director. The C rating or non-
19 existent was not existent at all, and the B
20 was inadequate. A note from him, when he said
21 B inadequate, inadequate by a mile, not you
22 know, close to adequate.

1 CHAIR TOPP: Last question, Dr.
2 Polli.
3 MEMBER POLLI: Yes. The same
4 question about same slide, 16. Since I'm not
5 familiar with OTC, is Slide 16 about
6 inadequate or does not exist impurity testing?
7 Is that a reference to the API or the product?
8 DR. TAN: That's correct. So for
9 example, for acetaminophen, the reason you
10 have eight monographs, that's the API.
11 There's different formulations and
12 combinations. So that's why you have the
13 multiple monographs. That's my understanding
14 of it.
15 MEMBER POLLI: So for example,
16 aspirin may not have an inadequate API
17 impurity?
18 DR. TAN: That's correct, yes,
19 right.
20 MEMBER POLLI: I guess one comment I
21 would have is, you know, since you may not
22 know what impurities could be added by a

1 criminal. I think there's cheap way to do
2 purity testing, to see if the major component
3 of something is indeed what you think it is.
4 It seems like that would be a good idea.
5 DR. TAN: Yes, I think that's a
6 valid point.
7 CHAIR TOPP: Okay, thank you. Thank
8 you, Dr. Tan. Our next speaker this afternoon
9 is Dr. Karen Russo. Dr. Russo is Vice
10 President for Small Molecules in the USP, and
11 her presentation this afternoon is "USP
12 Perspective: USP Monograph Modernization
13 Initiative for Small Molecules." Dr. Russo.
14 DR. RUSSO: Good afternoon, and I
15 want to thank the Committee for this
16 invitation to speak on this very important
17 topic. My name is Karen Russo. I do
18 represent the USP. I lead the team
19 responsible for all the small molecule
20 monographs in the USP. This, right now, is
21 about 3,600 official monographs. So it's the
22 bulk of the monographs that we have in the

1 compendium.

2 Larry mentioned in his talk about

3 the convention in April 2010. This is the

4 resolution that was adopted at that time. So

5 it talks about strengthening our relationship

6 with the FDA and stakeholders, and to provide

7 and maintain the up to date national standards

8 for legally marketed drugs and excipients.

9 So this is where this really took

10 shape, and represents USP's commitment to this

11 initiative. Now the primary driver for this

12 has been discussed, and it's really

13 maintaining the up to date standards to

14 support the commitment to public health.

15 The needs for modernizations are

16 quite obvious, but some of the monographs have

17 been developed over several years, decades in

18 some cases. The content that's current now

19 does not reflect the current expectations for

20 procedures and acceptance criteria, current

21 methodology, etcetera.

22 So we have had -- we do have some

1 gaps in our procedures obviously, and we've
2 also gotten compliance not just from
3 manufacturers, but of course we've noticed the
4 challenges over the years from our expert
5 committee members, our staff, the FDA. So
6 this is coming from many sources.
7 There's a general lack of
8 specificity in all of these monographs. Even
9 where there is testing, it's outdated. So
10 it's relatively non-specific. So that could
11 led to other problems, such as economically
12 motivated adulteration.
13 Now when we say "modernization,"
14 it's really a subset of our ongoing revision
15 work. We started using the term modernization
16 specifically in 2009, and tracking these
17 efforts separately. So when we refer to this,
18 it's really our usual process. But we have
19 been tracking this separately for a couple of
20 years.
21 The benefits of modernization would
22 be to strengthen the public standards, moving

1 from the non-specific to specific procedures.
2 It also addresses some practical concerns that
3 come up from our colleagues in the industry.
4 There's a lot of unnecessary testing on
5 monographs, so modernization also could remove
6 some of the unnecessary tasks, and therefore
7 they don't have to spend their time and
8 resources to do these tests.
9 There's also some safety or
10 environmental issues to be addressed, such as
11 some of the procedures still currently call
12 for use of chlorinated solvents or mercury
13 salts, that sort of thing, and there is
14 certainly an interest in reviewing the
15 monographs of those reagents.
16 Some of the equipment is harder to
17 find. The packed column GC procedure is
18 increasingly the manufacturers are having
19 trouble just finding the packed columns to do
20 the procedures, if they're following the
21 procedures exactly as written. Then we want
22 to also increase the consistency across the

1 monographs.
2 One of the things that we're doing,
3 we refer to what we call a monograph family,
4 is a drug substance and the related dosage
5 forms. It also helps to get the consistency
6 across the monographs.
7 So if we're missing or if we added
8 an impurity test to one of the monographs, we
9 want to add it to all of them, so we don't
10 have a tablet monograph for one drug that has
11 an impurities test, but the oral solution
12 doesn't. So we want to look at everything
13 across the board, and increase the consistency
14 that we have.
15 Our greatest challenge in this
16 effort is really getting the update in
17 procedures and the acceptance criteria, to add
18 to the monographs, and we really want to
19 encourage manufacturers to support this effort
20 and submit proposals to USP NF. So the rate
21 at which we can accomplish the modernization
22 is directly linked to availability of these

1 procedures.
2 We also feel that FDA's involvement
3 in support of this very important activity is
4 likely to encourage the manufacturers to
5 participate in these efforts, more than if we
6 were just trying to do this on our own. So we
7 do appreciate that support.
8 We are trying to do whatever we can
9 on USP's side to effect these changes. Here's
10 just a few of the things that we've done in
11 the recent years to increase the visibility of
12 this initiative. There was, of course, the
13 convention resolution from April 2010. The
14 web page, we're working with the FDA Monograph
15 Modernization Task Group.
16 We also launched a special, what we
17 call a hot topics web page in February of this
18 year. That's where they -- that really came
19 about with the FDA high priority monographs,
20 and a way to really target those and get those
21 out there to the industry. We had a webinar
22 of modernization in February, and we had about

1 over 100 participants from 70 companies, just
2 to get the word out about modernization and
3 encourage their participation.
4 We also had an update on our
5 activities as the USP Prescription/Non-
6 Prescription Stakeholder Forum in May.
7 There's some other efforts as well, but these
8 are just a sampling of what we've been doing.
9 Now modernization of the monographs
10 is achieved by replacing outdated procedures,
11 like the packed column GC procedures, TLC, web
12 chemistry test, etcetera, adding critical
13 tests. I think the most critical of these are
14 the impurities or degradence testing, and
15 deleting some of the older tests, the non-
16 value added tests, such as melting points.
17 We follow our usual or our routine
18 standard-setting processes. We do publish
19 these proposals in the Pharmacopeia Forum or
20 the PF for the 90-day comment period. Where
21 needed, we can use the accelerated revision
22 process, as we did for heparin and the

1 diethylene glycol monographs.
2 A typical time line for these to go
3 through the entire process and become official
4 is about two years, but that does depend on
5 many factors. We do have to allow for the
6 comment period. We have expert committees
7 that we work with; they evaluate comments. We
8 have a balloting process. Once these get
9 approved, they are published in a book or
10 supplement, and then become official six
11 months after that.
12 So everything together can take
13 about two years before it becomes official,
14 and therefore legally enforceable public
15 standards.
16 We talked a lot in the recent
17 discussions here about what we call our Top
18 200 list. So I just wanted to spend a moment
19 to tell you how that all came about. We
20 started, we recognized the need to modernize
21 monographs. Actually back in 2005, our
22 scientific liaisons and expert committee

1 members reviewed monographs and noted where
2 there was modernization needed.
3 We proceeded to work on these. It's
4 just regular revisions. We weren't really
5 calling them modernization or noting them as
6 any special initiative at that point. As we
7 were getting ready for the 2010 cycle to
8 begin, we were getting much more organized
9 about this, and of course by that time, had
10 gone through the heparin and the diethylene
11 glycol, and we were seeing the need to get
12 much more organized with this initiative.
13 We compiled what we had for small
14 molecules into this master list and
15 prioritized it. This prioritization was based
16 on USP information. So I'll just clarify; it
17 was not based on potential for economically
18 motivated adulteration or some other factors,
19 and there are many, many ways to prioritize
20 the information.
21 But we did use some information in
22 our therapeutic category, and the extent of

1 the USP reference standard used. That was
2 some information about how widely these
3 monographs might be used out there in the
4 public. So for small molecules, we identified
5 over 700 monographs in need of modernization,
6 and this we don't think is an exhaustive list
7 by any means. There's still other monographs
8 that could be added to this.
9 We took a portion of this list, what
10 was originally the Top 200 and posted it on
11 the website in May of last year. Now some
12 monographs have more than one test that were
13 identified as being in need of modernization.
14 So original posting, it was 200 monographs,
15 but over 300 line items. So that's where we
16 look at the spreadsheet and see so many items,
17 because it was more than one per monograph.
18 This is a spreadsheet that we do
19 update on a monthly basis. Part of that is,
20 of course, our commitment for transparency and
21 our standard-setting processes. So we updated
22 to show when proposals have been committed or

1 received, or maybe something has advanced to
2 the PF stage. Just a way to keep that out
3 there.
4 But the list was originally posted
5 as they call, like an open call for
6 procedures. Manufacturers had told us for a
7 couple of years that, you know, they recognize
8 the need for the modernization effort, but it
9 would be very helpful to them if we could post
10 or give them a list of what needs to be done,
11 so they don't have to go through and find all
12 the procedures on their own.
13 So that was another reason why we
14 did this. So it was visibility, transparency,
15 and a way to show the industry here's what we
16 needed, specific tests for specific
17 monographs.
18 The major categories that were
19 identified were no, a missing impurity test,
20 meaning that it just does not exist at all;
21 the non-specific ID and assay procedures; and
22 other updated procedures like the web

1 chemistry, packed column and the safety-
2 related concerns.
3 Now as focusing on the Top 200 list,
4 we look at the major ones here, the missing
5 impurities, assay by titration, which is
6 considered relative and not specific, and then
7 the other procedures. That really doesn't
8 count for the majority of the items on there.
9 Some of the other items, we still
10 have some procedures in there that have open
11 column chromatography, for example. It's not
12 for the majority of the tests on there, but
13 that's where we do have some of these more one
14 of and two of situations on that list.
15 Now also more importantly here is
16 the majority of the work on this list has not
17 even started yet, because we don't have
18 procedures. So that's why we're really hoping
19 to work with industry and other stakeholders,
20 to get some of the procedures in here, in
21 addition to what USP is already doing to this
22 point.

1 So we're also looking at options for
2 improving efficiency and the impact of this
3 work. That has a lot to do with
4 prioritization, and we really welcome any of
5 the recommendations from the task group from
6 FDA, to help direct our efforts and refine our
7 prioritization.
8 There are many ways to look at this
9 information and many approaches, all of which
10 are valid. But we're looking for the greatest
11 impact for the public health. Working on
12 monograph families rather than individual
13 monographs seems like the most practical way
14 to do it.
15 But we can also look at drug
16 substance versus dosage forms. We can address
17 biotechnique; for example, try to address all
18 the procedures for packed column on our Top
19 200 list. Or we can look at all the safety
20 issues. Or it might turn out to be, in some
21 cases, a combination of some of these options.
22 As Larry mentioned earlier, we are

1 working on acetaminophen and diphenhydramine.
2 We've also got some other monograph
3 modernizations in progress as well, and these
4 are submitted from manufacturers. So it's a
5 combination of maybe some monograph-specific
6 ones, and then some of these for the larger
7 families as well.
8 So again, we really do welcome any
9 recommendations for how we can direct our
10 efforts for the maximum impact. I just wanted
11 to point a little bit on our hopefully I
12 consider success here.
13 Over the past two years, as we've
14 been focusing on the modernization effort and
15 really tracking this, of all the monograph
16 proposals, revision monograph proposals
17 submitted to PF for small molecules, almost a
18 fourth of them have been for modernization.
19 So we're making some progress, but
20 it's like chipping away at a very large
21 mountain at this point. So we really need to
22 find a way to get some bigger impact for

1 these. We have a lot of work in progress. We
2 have work on the 71 monographs with active
3 modernization work, and USP is devoting a lot
4 of its resources to this effort.
5 It's roughly half in half right now,
6 what we're devoting from USP side, going into
7 our own laboratories, developing and
8 validating these procedures, and the proposals
9 that we're getting from the manufacturers.
10 This is where we really hope to get
11 more support from manufacturers, because we're
12 -- like every company, we're limited in what
13 we can do. But we are putting the full
14 resources of our labs and our technical
15 resources into this effort.
16 Here's just a few examples of some
17 recent proposals that have been published in
18 the Pharmacopeia Forum. As you can see, the
19 glycolpyrrolate monograph, for example. We
20 replaced the titration assay with HPLC,
21 replaced ordinary impurities by TLC with an
22 HPLC procedure; deleted melting range. We

1 added a test for an isomer that did not exist.
2 Spironolctone, we replaced
3 chloroform with alcohol. These are some of
4 those things that -- they're very specific,
5 but these all amount to just improving each of
6 the procedures and the monographs overall. In
7 November, we did get the letter from the FDA
8 Monograph Modernization Task Group, asking us
9 to focus on acetaminophen and diphenhydramine
10 monographs.
11 These are very high volume OTC,
12 primarily OTC. There are some of the
13 acetaminophen combinations that are
14 prescription, and the primary issue was
15 missing impurities or degradence test. But
16 there are some other, as we look at the
17 monograph families, we're looking at some of
18 the other monograph tests to be updated as
19 well.
20 Acetaminophen is actually, for USP
21 terms, it's found in about 37 monographs,
22 because there are, in addition to single

1 ingredient dosage forms, there are many of
2 these that are in combinations with one or two
3 other dosage forms. So that's where it really
4 starts to multiply.
5 So we're looking at this as an
6 entire monograph family, and FDA specifically
7 requested the addition of a test for para-
8 aminophenol to each of these dosage form
9 monographs, for nephrotoxic impurity. And
10 then general degradence for a purity of
11 degradence test for all the dosage forms.
12 We formed an Acetaminophen Panel in
13 May of this year, and had our first meeting
14 last month. This panel does include
15 representatives from the FDA, industry and USP
16 expert committees, and the scope of this panel
17 is including all of the monograph, the entire
18 monograph family for acetaminophen.
19 The para-aminophenol was recommended
20 by the FDA through this panel, at .15 percent
21 for oral liquid dosage forms and .01 percent
22 for the solid oral dosage forms. We're also

1 going to involve the USP Expert Committee for
2 Toxicology, headed by Dr. Bob Osterberg.
3 We're going to request that he actually
4 participate in the panel as well. But this
5 was the major issue listed in the FDA letter
6 that we got in November.
7 The acetaminophen drug substance
8 monograph needs extensive revision. We're
9 essentially starting over with this monograph.
10 It does have currently a test for para-
11 aminophenol, with a limit of 50 parts per
12 million.
13 We plan to keep that limit, but we
14 are updating the procedure for determination
15 of para-aminophenol, and we're doing some lab
16 work in our own labs, to make sure that
17 procedure works on what we're intending to
18 propose on the monograph, and we're also doing
19 some work on the assay.
20 We anticipate publication of this
21 proposal in early 2012, and we may be able to
22 post it pre-PF on our website. So that's our

1 time line for right now, as we get through the
2 lab work. The acetaminophen dosage forms are
3 more challenging, because of the complexity of
4 the single and multi-active ingredients. We
5 have solid oral dosage forms and liquid
6 formulations.
7 We need to add a procedure for each
8 one of those, that will determine para-
9 aminophenol and other degradants in those
10 dosage forms. We have some starting points,
11 based on what we have already in our
12 monographs, and the proposed limits that came
13 from FDA to the expert panel.
14 We're proposing that we're going to
15 start lab work in the next month or so on this
16 to move forward. We're trying to do some more
17 novel ideas for, implement some more novel
18 approaches for how to implement these major
19 changes. For the acetaminophen family,
20 because it's so large, we're thinking that
21 rather than doing 37 revisions, we would like
22 to draft a chapter, and the chapter could be

1 impurities or degradence in acetaminophen
2 products, for example.
3 So we would update the monographs to
4 direct everyone to this chapter. So we would
5 just have one chapter, and that would impart
6 some consistency, because all the monographs
7 would direct everyone to the same chapter. So
8 that's the sort of approach that we're
9 planning to do, and hopefully that will work
10 and we can leverage that for other revision
11 needs as well.
12 Diphenhydramine is a little bit of a
13 smaller family, and the request from FDA was
14 that these just need general impurity
15 procedures, or where an impurity procedure did
16 exist in a dosage form monograph, it needed to
17 be updated. There's a diphenhydramine
18 hydrochloride drug substance monograph. That
19 proposal was published in PF-37-3 in May and
20 the comment period ends in just a few days.
21 In that test, we added an impurities test
22 based on the impurities test and the EP

1 monograph. So that's, that was the basis for
2 that revision, along with some other minor
3 changes.
4 There's also a diphenhydramine
5 citrate drug substance monograph, and we're
6 going to do some work in our own laboratory,
7 to make sure, see if we can use the
8 hydrochloride impurities procedure for the
9 citrate. So that could be something fairly
10 easily accomplished.
11 So we have to complete that lab work
12 first, and then we'll move forward to
13 publication of that PF for the 90-day comment
14 period at some point. The diphenhydramine
15 dosage for monographs. They have, I think
16 there's four that are just diphenhydramine
17 only, and there's a couple that are
18 combination.
19 Again, we need to plan to add or
20 update the existing impurities test, and
21 anticipate that we'll do some lab work at USP
22 for that, with a subsequent publication and

1 PF. Again here, we'd like to see if we could
2 find one procedure that would work for all the
3 diphenhydramine monographs.
4 So that in a company that say, for
5 example, has more than one diphenhydramine
6 product, they're not switching from one
7 procedure to the next based on product. We'd
8 like to have some consistency within
9 monographs, and that also translates to more
10 efficiency in the lab as they performed the
11 testing.
12 So some of our current activities.
13 Of course, we're working on the FDA
14 monographs. We have the ongoing
15 collaborations with the task group, and the
16 very generous support that we've got from CHPA
17 and their efforts and their commitment on this
18 as well.
19 We're also working with
20 manufacturers and sponsors of the various
21 other monograph modernization proposals. Our
22 expert committees and expert panels are

1 involved and aware of this. We have built
2 modernization into the work plans of the
3 expert committees for this five-year cycle,
4 and again we have about 70 monographs or so
5 that are also in progress.
6 Our USP efforts. As I said, we're
7 reviewing options for the optimization of
8 prioritization efficiency. We're looking for
9 procedures from other compendia, the
10 literature, anything we can develop on our
11 own. We have and will continue to use our USP
12 labs to support this effort, and we can form
13 expert panels, as necessary, to address some
14 specific topics.
15 Our expert panels are formed as
16 advisory to our expert committees. So we can
17 reach into the FDA and manufacturers from
18 other areas to address some of these topics.
19 So it's very useful to support our work. For
20 collaboration efforts, we are hoping to
21 explore some possible lab support from an
22 agreement that we have with the FDA on

1 modernization, and we can get some help on
2 that as well, and continual collaboration with
3 the task group and CHPA and other interested
4 parties as well.
5 Communication and outreach is very
6 important to get the word out here. We're
7 using what we call a design phase approach,
8 where we're starting at the beginning of the
9 process, as we're developing the ideas and to
10 let people know that these revisions are
11 coming, so they can participate early on.
12 We do this through web meetings,
13 public forums such as this, workshops, and
14 other ways that we can get the word out.
15 That's how we also use our -- what is
16 available to us on our web page. It's like
17 our monthly updates, our topics page, and
18 there's the links there for that, and our
19 expert committee panels.
20 We do have an OTC workshop coming up
21 in September, September 8th and 9th, and we're
22 very pleased and proud to say this is co-

1 sponsored by FDA. Modernization activities
2 will certainly be discussed on Day 1. Day 2
3 is devoted to future directions. There are a
4 lot of -- we do have OTC product monographs in
5 USP, but there are many, many products, OTC
6 products, for which there is no corresponding
7 USP monograph.
8 So we'd like to engage industry and
9 the FDA in ways to move forward for how we can
10 do this, and to set standards, very current
11 and modern standards, for these products.
12 There's also participation with the CHPA
13 Product Quality and Operations workshop
14 upcoming in October, and that should continue
15 what we call our three-legged stool approach.
16 That is, we're engaging industry, the FDA and
17 USP in these efforts. These are specific for
18 OTCs as well, not this modernization.
19 So in conclusion, I just wanted to
20 note that this really is a very major
21 initiative for USP, and we're devoting as many
22 resources as we can to this effort. We

1 believe collaboration with FDA and industry
2 and other key stakeholders is critical to
3 making this successful.
4 We feel that with FDA's involvement
5 with this initiative, industry is much more
6 likely to come to the table than if we were to
7 approach them just strictly on our own. There
8 is a longer-term goal in sight here. In this
9 cycle, I feel like we have a lot of heavy
10 lifting, so to speak, to get a lot of these
11 monographs where they should be and fill a lot
12 of these gaps.
13 What we're looking for ultimately,
14 perhaps in the next cycle, is to put every
15 monograph on a review cycle, so every year,
16 every five-year cycle, every monograph gets a
17 thorough and critical review. So if we need
18 to change something, modernize it, get it on
19 a schedule, much like people do for their
20 documents, SOPs, etcetera, where you review
21 them on a regular basis, so we don't have some
22 things that languish and become outdated.

1 So that's the long term goal for
2 what we're heading toward. We just have a
3 long road ahead of us at this point to get
4 there. So with that, I'll leave you with some
5 contact information, and thank you for your
6 attention.
7 CHAIR TOPP: Thank you, Dr. Russo.
8 We have time for one or two questions for
9 clarification from the panel. Any questions?
10 Dr. Polli.
11 MEMBER POLLI: Thank you. I'm
12 looking at your Slide No. 9, where you
13 differentiate between lack of impurity
14 testing, non-specific ID and non-specific
15 assay. Can you elaborate on -- I guess when
16 I was thinking of Larry's presentation about
17 the diethylene glycol and heparin, it seems
18 like non-specific assay, non-specific ID would
19 be maybe very important. Can you elaborate on
20 to what extent you think that's an issue, or
21 is it really more lack of impurity testing per
22 se?

1 DR. RUSSO: It's really a
2 combination of both. I think we have more of
3 an issue, I believe, with no impurity test in
4 a monograph, than the non-specific ID. I'll
5 give you an example of a non-specific ID
6 procedure. Many of the dosage form
7 monographs, it could be a tablet, an oral
8 solution injection for example, the ID test is
9 only a retention time agreement between the
10 peak and a standard solution, and the
11 corresponding peak in a sample solution, and
12 that's it.
13 We need something much more specific
14 than that. We need something where the dosage
15 form, the active is extracted from the dosage
16 form and compared by IR, perhaps even NMR, if
17 we wanted to go that far too, any reference
18 standard, and a definitive ID, as opposed to
19 something like retention time agreement.
20 So that's why it's much more
21 critical. So in the monograph, the ID test is
22 very important, and we can't test out of the

1 ID test. So we have to really shore up the ID
2 test as part of that. The impurity test comes
3 along with some tests are there, but they are
4 inadequate. That may be by TLC. We have a
5 test called ordinary impurities, where it's
6 just a general test, which just says by TLC
7 with a limit of two percent.
8 So it's there, but that's not very
9 definitive. So I think the first two are
10 probably a little bit more critical. The non-
11 specific assay procedures are more like a
12 spectrophotometric procedure on a dosage form,
13 or even a drug substance. So that's where
14 we're getting debatable in some circles, but
15 even titrations are considered relatively non-
16 specific compared to a chromatographic
17 procedure.
18 CHAIR TOPP: Thank you. Other
19 questions from the panel? Yes, Dr. Morris.
20 MEMBER MARILYN MORRIS: You
21 mentioned that you have some OTCs, but you'd
22 like to have them all included in the USP; is

1 that correct?

2 DR. RUSSO: Well, our mission is to

3 have a public standard for basically

4 everything that's on the market. Now that's

5 the mission, but the practicality of that is

6 very challenging. We do have a drug substance

7 -- USP monographs for OTC drug substances, and

8 in many, probably a few hundred monographs for

9 the dosage form, such as the acetaminophen

10 tablets, that sort of thing.

11 But there's a lot. The slide that

12 Dr. Tan showed earlier of the toothpaste,

13 things like that, we don't have monographs for

14 those. We don't have monographs for medicated

15 shampoos, mouthwashes, toothpastes, any of

16 that.

17 So what we would like to do is

18 figure out a way to create USP monographs to

19 compliment the FDA OTC monograph system, to

20 have public standards for testing in there.

21 That's what we'd like to do. That's what Day

22 2 of our workshop is devoted to, how we could

1 do that going forward.
2 CHAIR TOPP: Thank you very much.
3 Thank you, Dr. Russo, for that presentation.
4 Our next speaker this afternoon is Ms.
5 Catherine Sheehan. Ms. Sheehan is Director of
6 Excipients at the USP, and her presentation
7 this afternoon is entitled "USP Perspectives:
8 USP Monograph Modernization Initiative-
9 Excipients." Ms. Sheehan.
10 MS. SHEEHAN: Thank you for inviting
11 me to this meeting this afternoon, and I am
12 going to pick up where essentially Karen left
13 off, Dr. Russo, in the sense of Slide 8 pretty
14 much gives the similar approach to how we
15 prioritized the excipient monographs, in
16 creating a master list, and from that master
17 list, that Top 96 excipient list was created.
18 So on this slide here, you can see
19 the major categories that we identified for
20 excipient monograph modernization, was
21 basically the lack of an identification test
22 or, if there was one, it was non-specific. No

1 assay was present, or if there was one, it was
2 non-specific in the sense that a titration
3 versus an HPLC method.
4 A lot of times, we had very outdated
5 procedures as you know. Excipient monographs,
6 as Larry alluded to, they have been around for
7 decades and are, you know, under revision
8 quite frequently. But sometimes their
9 procedures are outdated, and these are some
10 examples. Also finally, the absence of
11 impurity tests. So the majority of our work,
12 in terms of that master list, is still to be
13 done.
14 Again, just to give a sense of USP's
15 focus here, is constantly updating the USP NF.
16 This is a list of revisions and the current
17 modernization term that we're using since
18 2009. But this is a list of 67 excipient
19 monograph revisions and modernizations since
20 2005.
21 Those that are in italics I will go
22 into a little bit more detail, and I will also

1 cover, in a little bit more detail, on the
2 high priority glycerin monograph revisions.
3 So one subset of that previous list
4 was revisions that we did to a group of seven
5 USP NF fixed oil monographs, and those
6 monographs were revised with collaboration
7 with industry. What we did was we focused
8 here on revising those monographs, in order to
9 prevent economically motivated adulteration.
10 Key points within the revisions of
11 these fixed oil monographs was the primary
12 goal was to protect against, as I said,
13 economically motivated adulteration, and in
14 doing so, what we did was we assured the
15 identity, strength, quality and purity of
16 those fixed oil monographs.
17 Fixed oil monographs are expensive,
18 and they are prone to substitution with
19 cheaper oils. So an example of this would be
20 that a mixture of almond oil or persic oil,
21 one to one ratio, this would actually pass,
22 would have passed the almond oil NF-23

1 monograph.

2 So in our efforts to modernize and

3 bring in more specific, and get rid of those

4 outdated methods, what we did was we included,

5 there was no identification test. We included

6 a fatty acid composition test that is a more

7 modern technique that's used today.

8 We included impurities that

9 controlled the residues due to either the

10 origin or refining steps or residual catalysts

11 that would be involved in its manufacture. A

12 very critical test, peroxide value, which will

13 be a primary indication of the state of the

14 material if it's oxidized, and affecting the

15 stability of that oil.

16 Again, acid value. I'm not going to

17 go into the details here, but labeling,

18 another place that is critical in determining

19 presence of additives, and also the

20 suitability, if there's any restrictions, in

21 terms of its use, say for example, in

22 injectable dosage forms. The sterile

1 composition, which is a very specific, modern
2 identification test that has been added to
3 these seven monographs.
4 Finally, a fatty acid composition
5 test, another modern technique that's being
6 added. So all in all, these were value-added
7 tests. I'll give you an example of the NF-23
8 almond oil. You can see here there was no ID
9 test. There was no assay. There was no
10 labeling, and what we had here was a laundry
11 list of efforts to prevent economically
12 motivated adulteration by specific tests here.
13 So what we did was in the revision,
14 and the NF-25 second supplement, we introduced
15 a specific identification test, the fatty acid
16 composition. That was also able to duplicate
17 as the assay, because you got a sense of the
18 purity of the material, and any potential
19 impurities could be determined by those two
20 tests.
21 A labeling test was included, and
22 then what we did was we got rid of all the

1 outdated, unnecessary, non-specific tests. In
2 addition, we added the peroxide test and
3 sterile composition. So to move on into those
4 high priority monographs that Larry alluded
5 to, this is a snapshot in time here, prior to
6 the 2007 letter that we received from FDA.
7 In the late 1990's, the Haiti
8 incident was in the news at that time. USP
9 revised the glycerin monograph, and how they
10 did it here was they introduced into the
11 identification test and ID Test B, and that
12 was kind of what Dr. Russo was referring to,
13 in that they added retention time.
14 So that was included in the ID test
15 at that point. They also included in the
16 impurities section a test for the limit of
17 diethylene glycol, and related compounds test.
18 So at that point, in the USP glycerin
19 monograph, we actually did add a limit of
20 diethylene glycol.
21 But of special note here is that we
22 added it in the impurities section of the

1 monograph.
2 So this is the history here of the
3 adulteration of glycerin with diethylene
4 glycol, and I highlight here the Haiti
5 incident. That was what I had mentioned in my
6 previous slide, was our efforts to introduce
7 a limit test for diethylene glycol. But at
8 that point, we added it to the impurities
9 section of the monograph, not to the
10 identification section.
11 So in 2007, we received a request
12 from FDA to modernize the glycerin
13 identification section, to include an
14 identification and quantitation test for
15 diethylene glycol. So essentially a limit
16 test within the identification section of the
17 monograph.
18 That was followed on in January of
19 2009, we received a second letter from FDA,
20 requesting modernization of sorbitol solution
21 and propylene glycol, which was consistent
22 with what we had achieved with the USP

1 glycerin monograph. This is -- here is the
2 critical rationale for their inclusion in the
3 identification section.
4 The GMPs allow the use of
5 identification testing alone, by dosage form
6 manufacturers for raw material qualifications.
7 So manufacturers could therefore not deviate
8 from the diethylene glycol limit, so as this
9 would be an aspect of identity.
10 This was a challenge, because it
11 related to a requirement that a contaminant,
12 adulterant could be considered part of the
13 article's identification. At the same time,
14 and that alludes to the ethylene glycol part,
15 at the same time industry had submitted a GC
16 method, a gas chromatography method, to detect
17 ethylene glycol in a request for revision to
18 USP sugar alcohol monographs.
19 They indicated the reason being that
20 ethylene glycol was a process-related impurity
21 for the manufacturer of at least seven of the
22 sugar alcohol monographs that we had in USP.

1 This request arose, as I said, because the
2 residual solvents, 467 chapter, did not have
3 a specific test related for ethylene glycol
4 determination.
5 So at that point, FDA agreed to
6 include the ethylene glycol in the
7 identification test for those high priority
8 monographs that they had requested in their
9 letters. This essentially just gives you a
10 list of all those revisions that resulted from
11 the 2007 and 2000 letters that we received
12 from FDA. These are all now currently
13 officialed in the USP NF.
14 So the background to the revision of
15 these monographs, and the letter from FDA,
16 stemmed from an FDA guidance that was issued
17 in 2007, wherein it specifically indicates
18 that you had to perform a specific identity
19 test that includes a limit test for diethylene
20 glycol per the cGMPs, and the limit would be
21 not more than 0.10 percent.
22 It also indicated that reliance on a

1 certificate of analysis is not sufficient to
2 ensure quality of the glycerin. It also
3 recommends intimate knowledge of the supply
4 chain. So those three aspects were clearly
5 indicated in the guidance.
6 So as a result of the collaboration
7 with FDA and stakeholders, the USP lab
8 developed a capillary gas FID method, and it
9 was validated for both ethylene glycol and
10 diethylene glycol with a limit of not more
11 than 0.10 percent.
12 So now we're at today's, the
13 November 16th letter that we received from
14 FDA, the modernization so to speak. They
15 included USP and NF excipient monographs in
16 the pharmacopeial discussion group. So that's
17 those two excipient monographs that Larry
18 spoke about.
19 They are the USP talc, USP povidone,
20 NF crospovidone and NF copovidone. The
21 important part to take from this slide is that
22 they are part of the pharmacopeial discussion

1 group. Now the pharmacopeial discussion group
2 has a workload of approximately 60 excipient
3 monographs.
4 Those monographs are the most highly
5 used excipients in the pharmaceutical
6 industry. So obtaining procedures and
7 acceptance criteria for these are one of the
8 challenges in the revision of these,
9 modernization of these monographs.
10 But with FDA involvement in
11 prioritizing and requesting submissions,
12 industry is much more likely to come to the
13 table. So manufacturers are encouraged to
14 submit proposals to USP.
15 In addition, because these are part
16 of the PDG work program, we need to coordinate
17 with the members of the PDG Group on these
18 specific monographs. PDG comprises of the
19 three pharmacopeias, EP, JP and USP. I've
20 given their website if you want to find out
21 more information on them.
22 So the November 16th letter

1 requested us, in terms of the povidones, that
2 the povidones essentially were non -- they
3 were not consistent with respect to the
4 impurities specifications, and that they
5 recommended that they should be harmonized
6 within USP, and also with the EP monographs.
7 The tests that were inconsistently
8 harmonized were the limit of hydrazine, the
9 limit of aldehydes, peroxides and heavy
10 metals. The letter also indicated that the
11 nitrogen assay test is non-specific, and they
12 would prefer a more specific method, due to
13 concerns about economically motivated
14 adulterants, and the one in question was
15 melamine.
16 On the USP talc, the letter
17 indicated that the labeling statement should
18 be revised to match the statement from the FCC
19 food chemical codex monograph's description,
20 thereby assuring that talc is not sourced from
21 mines that are known to contain asbestos.
22 They also recommended that USP should consider

1 revising the current test for absence of
2 asbestos, to ensure adequate specificity.
3 So the progress to date on the
4 request, on the November 16th letter, in terms
5 of povidone. The povidone has reached the PDG
6 Stage 6 adoption. It's essentially the last
7 step in their process, and that Stage 6
8 document monograph includes the tests for
9 limit of hydrazine, limit of aldehydes and
10 peroxides. So we have satisfied the request
11 from FDA in that respect.
12 It was posted on the harmonization
13 website on February 25th, and will be official
14 December 1st, 2011. For crospovidone, again
15 that one has reached the final step in the PDG
16 process, and it includes now the addition of
17 the tests for peroxides and limit of monomers.
18 Again, that satisfies FDA's letter,
19 the request that it made in the November 16th
20 letter, and it will be official December 1st,
21 2011, as well.
22 This is just a snapshot for

1 information purposes on the USP website for
2 more information on the PDG process, and how
3 we post our harmonization Stage 6 monographs.
4 Finally, the copovidone in those povidone
5 monographs. This is at the inquiry stage
6 within the PDG process.
7 What we've done is: we have posted
8 that -- sorry, we have published this revision
9 in 37-4, and we've included the addition of
10 the heavy metals test for lead, and also the
11 test for limit of monomers. We've also issued
12 a Notice of Intent to Revise, that will be
13 posted on the UPS website, to announce this PF
14 proposal. It's scheduled for publication in
15 USP-35, Second Supplement.
16 Now our progress, in terms of the
17 talc, the USP talc monograph, is that we've
18 established a joint Talc Expert Panel. That
19 was initiated on May 30, 2011. It consists of
20 the Excipient Monograph Expert Committee, in
21 conjunction with the Physical Analysis Expert
22 Committee.

1 We do have an FDA liaison to the
2 Talc Expert Panel. We had a kickoff meeting
3 on June 21st, and our second meeting is
4 scheduled for August 15th. The scope of that
5 is again to address the November 16th letter
6 from FDA, in that we update the talc labeling
7 statement to indicate that talc is not derived
8 from deposits that are known to contain
9 associated asbestos.
10 This will be consistent with
11 statements in the FCC talc, in the talc FCC
12 monograph's description section. So based on
13 positive stakeholder comments, the expert
14 committee posted the revision via an
15 accelerated revision proposal, prior to the
16 expert panel formation.
17 In addition, they're also addressing
18 the current methods for absence of asbestos
19 tests be not specific, and the Talc Expert
20 Panel will evaluate the existing asbestos
21 methods in USP, and offer potential
22 alternative analytical methods and procedures.

1 So this essentially captures the revision
2 bulletin that was posted May 1st, 2011, and
3 that had an official date of August 1st.
4 In this slide, it describes some
5 additional information that we received from
6 talc manufacturers, where they revealed
7 significant challenges to the implementation
8 of that proposed FCC statement in the labeling
9 section of the USP talc monograph.
10 The reasons they gave were that
11 there was an absence of a clear definition for
12 the term "talc deposits," and the differences
13 in the regulatory expectations between the
14 statements in the labeling section of USP NF,
15 which is mandatory, versus the statement in
16 the description section of the food chemical
17 codex monograph, which is non-mandatory.
18 So as a result, USP did receive a
19 request for postponement of the talc revision
20 bulletin, and based on discussions with FDA,
21 it was agreed that the final language and
22 placement of the proposed statement would be

1 handled best by the Talc Expert Panel. So our
2 Excipient Expert Committee voted and postponed
3 the talc revision bulletin, and that was
4 posted June 30th, 2011.
5 So our current activities on the
6 remaining requests from the FDA November 16th
7 letter, those outstanding are in terms of the
8 povidones. Ongoing work on replacement of the
9 non-specific nitrogen assay test, because
10 currently that test is the 467 nitrogen
11 determination by keveldol method.
12 FDA indicates that they would prefer
13 a more specific assay, due to the concerns
14 with the economically motivated adulteration
15 involving melamine, and indicating that the
16 current method is a non-specific assay method.
17 We are currently working with experts from
18 industry and stakeholders, to look at other
19 possible methodologies, to detect the
20 potential economically-motivated adulteration
21 and adulterants.
22 Ongoing activities with regards to

1 the Talc Expert Panel. As I said, they're
2 working on a revised version of the originally
3 proposed FCC description statement, to address
4 the labeling section of the USP talc
5 monograph. They will also evaluate the
6 existing asbestos methods in USP and offer
7 potential alternative analytical methods and
8 procedure, and our next meeting is August
9 15th, 2011.
10 So our current activities are
11 specific to the povidones and talc monographs,
12 with what I described in the previous slides,
13 and also collaboration with the Task Group,
14 industry and stakeholders. We're also working
15 with manufacturers and sponsors of the
16 individual modernization proposals.
17 The expert committee and the expert
18 panel involvement and awareness, in the sense
19 that we formed the Talc Expert Panel, the
20 modernization is included in our work plan for
21 the Excipient Monographs Expert Committee. We
22 have about six monographs with modernization

1 proposals in progress.
2 We update the -- as Dr. Russo said,
3 we update the web page monthly, and we
4 indicate the activity on those Top 96
5 excipients. We also maintain a modernization
6 hot topics page, and we update progress on the
7 Excipient Committee work plans, which are
8 posted via the USP website.
9 Our key strategies and approaches to
10 the modernization, monograph modernization
11 initiative is that we rely a lot on
12 communication and outreach, and what we do is
13 we -- this involves a design phase approach,
14 bringing together manufacturers, regulators
15 and stakeholders.
16 We hold web meetings, public forums,
17 conferences and meetings, workshops and
18 stimuli articles, and we avail to those a lot
19 as part of the glycerin and the polyol
20 revisions, and they worked very well. We also
21 use the USP's hot topics page, and pre-
22 publication. That was another thing that we

1 used as part of the glycerin, because they
2 were so -- they were high priority.
3 What we did was we did a pre-
4 publication of high impact revisions on the
5 web site, in advance of the PF publication.
6 That way, it would give industry the added
7 opportunity to comment on these methods before
8 they actually got into PF. So they actually
9 got two chances, opportunities to engage in
10 discussion. We also established the expert
11 panels and conduct relevant workshops.
12 So in conclusion, excipient
13 monograph modernization is a major initiative
14 in the 2010-2015 revision cycle of USP, and we
15 are devoting resources to this effort.
16 Collaboration with FDA, industry and other
17 stakeholders is key to advancing this work,
18 and the long-term goal is to implement a
19 regular monograph review process, to monitor
20 the needs for further modernization.
21 And again, just to emphasize, the
22 challenges that we have in these

1 modernizations of the excipient monographs are
2 -- is obtaining the procedures and acceptance
3 criteria. But it's anticipated with FDA
4 involvement in prioritizing and requesting
5 submissions, industry is much more likely to
6 come to the table. Again, manufacturers are
7 encouraged to submit proposals to USP. And my
8 contact information.
9 CHAIR TOPP: Thank you, Ms. Sheehan.
10 Questions from the panel? Dr. Koch?
11 MEMBER KOCH: I'm just curious. In
12 our department, no one has excipients. How
13 many of the excipients, if you were to list
14 from one to some number, are natural products?
15 MS. SHEEHAN: Naturally occurring?
16 MEMBER KOCH: I would assume the
17 majority, maybe.
18 MS. SHEEHAN: I'm giving a
19 guesstimate here, because given the current
20 submissions to USP NF, mostly synthetic
21 polymers, I would say now, today, those would
22 be probably 40-50 percent.

1 MEMBER KOCH: Okay.
2 MS. SHEEHAN: As opposed to say, 20
3 years ago. I would say they would have been
4 maybe 70-80 percent. But today, with the type
5 of submissions, new monographs to come into
6 USP NF, they're mostly the synthetic polymer
7 type.
8 MEMBER KOCH: Where I was going is
9 that with the globalization of purchasing,
10 etcetera, some things that were maybe easy to
11 identify, based on one source that one was
12 familiar with, changes with drought
13 conditions, etcetera, and then microbial
14 content, particle size, etcetera.
15 I'm just wondering, I can see
16 responding to requests that, you know,
17 somebody would like to see something done for
18 adulteration or other things. Are there
19 active programs to try and make a consistent
20 global approach to assay, etcetera?
21 MS. SHEEHAN: Well, the examples I
22 gave on the fixed oils, where those types of

1 materials, they're naturally-occurring
2 substances, they are expensive, and they are
3 adulterated by cheaper oils. What we tried to
4 do was -- is look at value-added tests that
5 could help prevent adulteration. So what we
6 did was, we eliminated non-specific tests and
7 introduced tests that would more adequately
8 define the purity.
9 So in the instances of the fixed oil
10 that I gave, we added the fatty acid
11 composition. So no matter where you sourced
12 that material in the world, if you sourced it
13 from China or from the U.S., a fatty acid
14 composition test that is giving you the
15 identity, quality, purity, basically the
16 authenticity of the material, the composition,
17 you are -- you're adding a test that will
18 better assure prevention of adulteration.
19 MEMBER KOCH: That reminds me. In
20 Europe, in some of the EFSA-related things,
21 European Food Safety Authority, they've done
22 a fair amount of toxicogenomics, where they

can tell the regions of the adulteration, and I don't know. It's getting sophisticated with some of the DNA-related tests. But at some point, quickly determining where it came from is important also.

CHAIR TOPP: Thank you. Dr. Polli.

MEMBER POLLI: Yes. I'm looking at your Slide No. 2, this issue of no identification or non-specific identification assay, non-specific assay. It just kind of reminds me of, you know, I think a lot of university environments probably all have access to NMR mass spectrometry and combustion analysis -- are very wide, like any pharmaceutical, medicinal chemistry lab would.

So I kind of view these tools as very widespread, and maybe I don't know the USP enough. But I don't see them very often. To me, it seems it would be very easy to have IED and assays, since these are pure compounds that have pretty good specificity, very easily.

1 MS. SHEEHAN: Well, you're actually
2 hitting on the core reason for the
3 modernization effort, and as Dr. Russo pointed
4 out, our prioritization was that our
5 committees and staffs looked at these
6 monographs, because in the context of
7 excipient monographs, they have been around
8 for decades. They are going back to times
9 when a GC, you know, was probably, you know,
10 the rocket science of the day.
11 So for some of these excipient
12 monographs, having an older test was a
13 standard, having -- you know, and you didn't
14 have an ID test for the simple fact that you
15 didn't have at your disposal at that time,
16 when the monograph was introduced, an
17 adequate, specific analytical method that
18 could ensure a sound ID test.
19 So part of our whole modernization
20 effort is to identify the deficiencies where
21 we can, and with the, you know, with help from
22 both FDA and industry, get these methods, as

1 you say, the current analytical capabilities
2 that are out there, to adequately identify the
3 material and make sure that we can avoid
4 another glycerin type of situation.
5 So that is the fundamental kind of
6 reasoning behind our USP initiative for
7 modernization, and then in collaboration with
8 FDA's Modernization Task Group, essentially
9 we're both focusing on the same end.
10 MEMBER KOCH: I mean, I guess the
11 only thing I would add is like carbon-
12 hydrogen-nitrogen, I mean this is a $20 test.
13 MS. SHEEHAN: Yes. It is one of the
14 tests that --
15 MEMBER KOCH: You can't publish in
16 the Journal of Medicinal Chemistry without it.
17 So it seems like a very doable thing.
18 MS. SHEEHAN: Yes. It's one of the
19 tests actually that we're looking at, to
20 replace the non-specific nitrogen in the
21 povidones. This is one of the tests that we
22 are actually discussing as part of that

1 dialogue with industry and stakeholders. So
2 that is on the table.
3 But by itself, it will not ensure,
4 you know, absence of impurities, because it
5 will give you a certain aspect of the
6 composition, but it won't give you everything.
7 So what we're struggling with now is, we want
8 to develop orthogonal tests, maybe within the
9 ID, that will also, in conjunction with the
10 composition, give you the impurities. So that
11 is one of the ongoing discussions on the
12 revision, the remaining revision that we have
13 for the assay test for povidones.
14 CHAIR TOPP: Thank you. Dr. Kibbe,
15 a quick question.
16 MEMBER KIBBE: Just a couple of
17 things, and I'll admit that I'm associated
18 with another reference text that has all of
19 the excipient monographs in it, with
20 information from the three main compendia and
21 a bunch of other stuff. There is another text
22 out there that has all of the IR and ramman

1 specter for all the excipients in it.
2 I don't know how useful that is, but
3 I hate to see them reinvent the stuff, if it's
4 already out in some form and they can just use
5 it.
6 CHAIR TOPP: I need to remind the
7 panel that our questions are for
8 clarifications. It's very easy for us to get
9 into discussion. We've kind of done that a
10 little bit here.
11 So Ms. Sheehan, thank you very much
12 for your presentation --
13 MS. SHEEHAN: Thank you.
14 CHAIR TOFF: -- and we'll conclude
15 now. Our next speaker is Dr. Rachel Roehrig.
16 Dr. Roehrig is Director of Technical and
17 Scientific Affairs for the Consumer Health
18 Care Products Association.
19 Dr. Roehrig will speak this
20 afternoon on "USP Monograph Modernization:
21 The OTC Industry Initiatives." Dr. Roehrig.
22 DR. ROEHRIG: Thank you for that

1 introduction. Good afternoon. Again, my
2 name's Rachel Roehrig, and I'm the Director of
3 Technical and Scientific Affairs at the
4 Consumer Health Care Products Association.
5 First, I want to say thank you to FDA for
6 allowing me to speak on behalf of my
7 membership today. It's a really important
8 topic, USP monograph modernization.
9 CHPA is a national trade association
10 representing the leading manufacturers of
11 over-the-counter medicines. These companies
12 account for over 90 percent of the U.S. OTC
13 market, and they represent both the leading
14 name brand and private label manufacturers and
15 OTC medicines.
16 I look forward to sharing with you
17 today our commitments regarding the
18 modernization of USP monographs, as well as a
19 summary of our efforts and progress to date.
20 But first, I want to say that, unequivocally,
21 our consumers deserve and expect the highest
22 quality medicines, and CHPA companies are

1 devoted to fulfilling those expectations.
2 Therefore, to ensure safe and
3 effective medicines, CHPA member companies are
4 taking aggressive and proactive actions to
5 meet and exceed these standards, and CHPA is
6 committed to working with both FDA and USP, to
7 achieve the leading edge technical standards
8 that in turn will help us to continue to
9 ensure safe and effective medicines.
10 CHPA and the manufacturers of over-
11 the-counter medicines have taken a leadership
12 role in addressing the gaps that may exist in
13 the USP ingredient monographs. I would like
14 to emphasize first that these gaps that we
15 speak of today do not imply less-than-high-
16 quality medicines.
17 CHPA manufacturers consistently take
18 into account domestic and global guidelines
19 and standards, and where that standard or that
20 universal standard doesn't exist, they develop
21 their own internal company methodologies, and
22 they help -- that will help determine and

1 assign their own specifications.
2 But these gaps do indicate potential
3 areas for harmonization and for modernization,
4 and it's all societies and it's all industries
5 that strive for continual improvements, and
6 that is really the primary contributor to
7 advancement, to innovation and to growth.
8 The OTC industry, alongside FDA and
9 USP, views USP monograph modernization as
10 another opportunity to expand upon the
11 already-existing robust and scientific
12 procedures and standards. CHPA has brought
13 together technical, analytical, quality and
14 toxicology experts, to drive science and risk-
15 based discussions.
16 Our companies' subject matter
17 experts are the ones working in the labs every
18 day on these procedures. They're the ones
19 working directly with the ingredients and with
20 the medicines that we're talking about today.
21 Typically, it is the individual
22 companies themselves that submit data and

1 proposals to USP. But CHPA members agree that
2 when it comes to modernization priorities, the
3 most efficient way to move forward is as an
4 aligned industry, working side by side with
5 both FDA and with USP and their experts.
6 So today, I'm going to review a time
7 line illustrating the USP monograph
8 modernization milestones to date. I will
9 introduce CHPA's commitment letter and present
10 the industry's kind activities and progress.
11 In addition, I will highlight the activities
12 planned for the near future, and then I'll
13 conclude with some key points.
14 So here's our time line of events.
15 In May of 2010, USP posted a comprehensive
16 list of USP monographs in need of
17 modernization. This document allowed us to
18 identify the gaps and to proceed with
19 prioritizing areas on which to move forward
20 and to focus.
21 CHPA approached FDA with the idea --
22 and USP with the idea -- of gathering

1 everybody at the table to discuss USP
2 monograph modernization, and in August of
3 2010, this FDA-USP-CHPA planning committee was
4 formed. What we did was consider paths -- and
5 we continue to consider paths -- moving
6 forward, taking into account the publication
7 that USP has with the monographs in need of
8 modernization.
9 It was evident from this first
10 meeting that having all three organizations,
11 this three-legged stool that Dr. Russo talked
12 about, having them all at the table would
13 prove more efficient than all three
14 organizations moving forward separately.
15 So soon after that, the FDA
16 established criteria prioritizing the USP
17 monographs, and it was in November that they
18 provided this rationale in their letter to
19 USP. During this time, FDA also participated
20 in CHPA's 42nd Annual Manufacturing
21 Conference, and this is where they presented
22 the ingredient monographs on which to

1 concentrate.

2 While continuing discussions with

3 USP and FDA on the most suitable paths

4 forward, CHPA member companies began

5 immediately to detail what our role would be,

6 the OTC industry. In January, we sent a

7 letter to USP and to FDA, outlining our

8 commitments.

9 So in the spirit of transparency,

10 last February USP hosted a public webinar, to

11 educate and to inform the audience on USP

12 monograph modernization. Also, we informed

13 them on our collaboration, and we wanted to

14 gather feedback on the overall process.

15 In March of 2010, CHPA established

16 working groups to fulfill the commitments that

17 we delineated in our letter. As of today, I

18 can proudly state that we have submitted

19 monograph revisions for diphenhydramine drug

20 substances, and have proposed specific

21 degradant limits for all compendial OTC

22 acetaminophen formulations. Both

1 diphenhydramine and acetaminophen were
2 ingredients determined by the FDA as
3 priorities.
4 So I really believe that pooling our
5 expertise and working jointly, FDA, USP and
6 the industry can fully achieve our existing
7 goals and all of our future goals. As I've
8 already stated, each organization plays such
9 an important role in successfully modernizing
10 USP monographs. In our commitment letter, we
11 proposed tasks for each institute to consider.
12 CHPA believes that FDA's role is to
13 identify and prioritize OTC drug products in
14 need of modernization, based on consumer
15 exposure data or market volumes for that
16 ingredient or drug product in question, and
17 also based on the safety profile of specified
18 degradants.
19 FDA should also share in the process
20 of offering a degradant limit for each
21 ingredient or drug product in the
22 prioritization list, with due consideration

1 and transparent communication of appropriate
2 scientific data. We also recommend that FDA's
3 involvement extend throughout the
4 modernization process, to provide continued
5 insights.
6 We propose that USP translate FDA's
7 letter, the priority list in FDA's letter,
8 into a prioritized list of monographs that
9 require either updating individually or as
10 monograph families. USP should then use
11 existing or novel approaches to form teams or
12 expert panels, comprised of subject matter
13 experts from all three stakeholder
14 organizations, to develop modernization
15 strategies and to implement those strategies.
16 USP should also assure that these
17 monograph modernization improvements go
18 through full public review, as this process
19 will provide the most efficient and widely-
20 accepted final product.
21 So let me state again that our
22 consumers, they demand and expect the highest

1 quality medicines. So to ensure the safe and
2 effective medicines that are on the market,
3 CHPA and member companies are taking
4 proactive, aggressive actions to meeting and
5 exceeding standards. The overall goal is to
6 meet consumer expectations, while ensuring
7 they receive high quality over-the-counter
8 medicines.
9 CHPA will continue to identify and
10 provide industry experts to participate on
11 each USP team or expert panel, and they will
12 provide expertise and laboratory support to
13 each of those teams.
14 Again, these are the individuals
15 that work in the labs every day. These are
16 the individuals that analyze the safety
17 studies and write the company procedures. So
18 we feel that they are the subject matter
19 experts on these medicines.
20 Currently, we have established
21 working groups of member companies, dedicated
22 to addressing the need for modernization of

1 the USP monographs. There will be a specific
2 focus on degradants related to over-the-
3 counter drug products. The working group has
4 committed to proposing and submitting
5 revisions to USP for either existing
6 monographs or even developing a new general
7 chapter, specific to one or more monograph
8 families, again with a focus on the specific
9 degradants.
10 The first monograph revisions are
11 based on the prioritization list that was in
12 FDA's letter to USP. The agency has
13 classified certain acetaminophen and
14 diphenhydramine monographs as a priority, due
15 to their degradant profiles. CHPA member
16 company experts will provide these limits
17 where needed.
18 So here you can see the CHPA member
19 companies that have provided the experts --
20 the quality experts, the analytical experts
21 and the toxicologists -- to CHPA's
22 Acetaminophen Degradant Working Group. These

1 companies represent the vast majority of
2 acetaminophen drug product manufacturers, and
3 the group also has participation from a
4 leading drug substance manufacturer of
5 acetaminophen, and that's Covidien.
6 All of these members have worked
7 every week, hours upon hours, on monograph
8 modernization. Many of these companies also
9 have experts participating in USP's
10 Acetaminophen Expert Panel. So in addition to
11 this group that you see here, all CHPA member
12 companies manufacturing acetaminophen products
13 participate in the review and the vetting of
14 our published proposals and our submissions to
15 USP. Together, this group represents over 90
16 percent of the U.S. OTC acetaminophen-
17 containing medicine market.
18 So product or API degradants may be
19 a part of routine synthesis. They may be a
20 part of your manufacturing process, and they
21 may be a part of metabolism. When degradants
22 exist under the scientifically-determined

1 thresholds, they are present at safe levels.
2 Although CHPA has asked FDA to consider
3 proposing limits for prioritized degradants,
4 our member companies have taken a leading role
5 in reevaluating a specific acetaminophen
6 product degradant.
7 Our commitment included a first
8 phase proposal of modernized monographs that
9 specify 4-aminophenol limits, and this is a
10 product degradant that's formed through the
11 hydrolysis of acetaminophen.
12 Recently, this CHPA Working Group
13 met and aligned on conservative limits for 4-
14 aminophenol, and the value proposed will be
15 included in our future USP submission, and is
16 based on data that has been collected from
17 CHPA member companies that are part of this
18 working group. The data depicts ranges of
19 degradant concentrations throughout the
20 product shelf life.
21 You know, when it comes to USP
22 submissions, it is significant that our

1 manufacturers have shared, through CHPA, their
2 stability data. They have shared their safety
3 study results. They have collaboratively
4 analyzed compiled information, and have
5 discussed internal manufacturing process
6 capabilities.
7 Members are encouraged by the fact
8 that FDA and USP are also at the table, and
9 that we're all working to arrive at an outcome
10 that is scientifically-based, that is
11 practical and that is safe. In our July
12 letter to FDA and USP, we proposed a limit for
13 4-aminophenol in all acetaminophen OTC
14 compendial dosage forms, and this includes
15 solids, oral solutions and oral suspensions.
16 In choosing this limit, many
17 criteria were heavily considered. We
18 considered risk assessments and the safety
19 profile of 4-aminophenol. We took into
20 consideration global, international and
21 domestic guidelines; company data, which is
22 representative of achievable process

1 capabilities; and the current USP and British
2 pharmacopeia acetaminophen product monographs.
3 CHPA member companies were eager to
4 share these limits with FDA and USP prior to
5 our proposed full submission that's to come
6 later, and this was to really increase the
7 transparency of our progress and our process.
8 Currently, the group is working diligently to
9 develop that more detailed submission. This
10 process could potentially serve for a
11 subsequent -- as a model for subsequent
12 modernization activity.
13 CHPA has also established a working
14 group focused on the degradants of
15 diphenhydramine. This was the second of the
16 two ingredients that appeared on FDA's
17 priority list to modernize. Here, you can see
18 the member companies that have provided
19 toxicologists, quality and analytical experts
20 to the CHPA Diphenhydramine Degradant Working
21 Group.
22 These companies here that you see

1 represent the leading manufacturers of over-
2 the-counter diphenhydramine-containing
3 products. Our Working Group has evaluated and
4 provided feedback on USP's proposed revisions
5 for both diphenhydramine hydrochloride and
6 diphenhydramine citrate drug substances.
7 Once again, through member
8 collaboration, the OTC industry aligned on
9 general procedures, identification techniques
10 and additional analytical methodologies. We
11 plan to continue to focus our efforts on
12 reevaluating diphenhydramine degradants as an
13 industry.
14 We want to develop flexible,
15 harmonized analytical approaches, and share
16 the outcome of our scientific discussions with
17 both USP and the agency.
18 Similar to the Acetaminophen
19 Degradant Working Group, this Working Group
20 will consider shared information, such as
21 manufacturing process capabilities and
22 degradant safety studies, to propose

1 appropriate universal degradant limits.
2 So in addition to today's FDA
3 Advisory Committee, the agency, USP and the
4 OTC industry are devoting time and effort in
5 preparing for additional opportunities to
6 inform the public of our process. We want to
7 create these opportunities so that we can
8 gather feedback and share also in the
9 complexities of the process.
10 USP has teamed up with CHPA and FDA
11 to plan a September workshop, focused solely
12 on compendial operations and standards for OTC
13 medicines. In October, CHPA will host its
14 43rd Annual Manufacturing Conference. The OTC
15 industry's 2011 Product Quality and Operations
16 workshop has dedicated an entire track to USP
17 monograph modernization, seeking discussions
18 for creative solutions. Both of our workshops
19 are open to the public.
20 So in conclusion, the Consumer
21 Health Care Products Association and its
22 members recognize the need for monograph

1 modernization. We believe it is imperative
2 that the U.S. Food and Drug Administration,
3 the United States Pharmacopeia and the
4 pharmaceutical industry partner in the effort
5 to advance the quality of USP monographs, and
6 to provide safe and effective medicines.
7 We believe that modernization should
8 be a part of an overall process of compendial
9 harmonization. Therefore, the changes
10 advocated by any of the stakeholders should
11 not be in conflict with any other global
12 compendial formats. I would like to emphasize
13 that it's the science and the risk assessments
14 that will be the most important factors on
15 which to rely when modernizing USP monographs.
16 Although progress has been made,
17 more discussions are necessary to move forward
18 in the appropriate and the most efficient
19 manner. So thank you again for your time and
20 your consideration, and we at CHPA look
21 forward to continuing our collaborative
22 efforts, and providing transparency when

1 fulfilling our commitments. Thank you.
2 CHAIR TOPP: Thank you, Dr. Roehrig.
3 Questions from the panel.
4 (No response.)
5 CHAIR TOPP: Okay. If no questions,
6 thank you again. In view of the hour and the
7 absence of any registered speakers in the open
8 public hearing, I am going to forego the break
9 that's listed on your agenda next, and we will
10 also forego the open public hearing.
11 So our next presentation is from Mr.
12 Jon Clark. Mr. Jon Clark is Associate
13 Director for Program Policy at OPS at the FDA,
14 and his presentation this afternoon is on
15 "FDA-USP Scientific Collaboration." Mr.
16 Clark.
17 MR. CLARK: Thank you for this
18 opportunity to speak to you about the science
19 collaboration. I'll also serve to wrap-up a
20 little bit of what we've heard this afternoon,
21 and I wanted to point out that what I hope you
22 take home in these last couple of hours is

1 this -- we have brought together a large,
2 diverse group of people with similar interests
3 in the monographs and the standards supported
4 by USP, and that these monographs are, in some
5 cases, archaic.
6 Some of the tests are archaic, and
7 everyone agrees that there is a problem and it
8 must be solved. We brought that group
9 together, and realized that we had a large
10 management problem, and we formed this
11 Monograph Modernization Task Group, which --
12 the original intent was to just simply
13 modernize some monographs.
14 But in fact, it had become so useful
15 that we wound up coordinating most of our
16 overall USP modernization program into that
17 group. Now at what point when you own an old
18 car and you start putting new parts on it, do
19 you go from modernizing it to overhauling it?
20 I don't know.
21 But we have a big job in front of
22 us. We look at the resources that we have

1 available to apply to that job, and it can
2 look to be a little bit -- well, a little bit
3 laughable actually, because there is no way in
4 all of the careers of all the people involved
5 right now, to actually fix this problem before
6 we each retire.
7 So what do you do? Well, we brought
8 that group together, and I think that they
9 have chosen a good path for picking
10 priorities, see where you can have the most
11 effect with those resources, and then make
12 moves accordingly.
13 Now you've seen a lot of work that's
14 gone on. Some of it predates the group. But
15 it certainly set a model for the group. We
16 looked at the melamine problem that needs to
17 be solved, with the modernization of how we
18 detect protein in food additives and things
19 like that.
20 In particular in the news was the
21 high protein wheat gluten was the big problem,
22 but it certainly spreads to other products, as

1 you saw in the povidone assay. We had the
2 glycerin contaminations that's been going on
3 since the beginning of the FDA, and in the
4 world it goes on even today.
5 Yet we did get resistance when we
6 tried to modernize that test procedure, and
7 putting it into the ID section, so that it has
8 to be tested all the time. People may say,
9 why do you have to do that?
10 I say, why you have to do it is
11 because we continue to kill people from not
12 doing it. So what we have here is you bring
13 these people together. We cooperate. We have
14 similar goals, and we manage to fix these
15 problems.
16 You saw the list on the board. I
17 have my own list written down, most of it from
18 memory, some of it from help. But I won't go
19 through it, because we are relatively late in
20 the afternoon in a long program.
21 I wanted you to know that in spite
22 of my dedication to improving the testing

1 programs, the dedication of the people that
2 you've seen in front of you today from all of
3 FDA, across various management groups, silos
4 that normally don't communicate much are
5 working together in this effort, between USP
6 and the FDA, two sister organizations that can
7 get along and sometimes can't get along. But
8 in this, we're getting along very well, and
9 with the industry representatives from CHPA,
10 as you saw before.
11 Of course, in these cooperative
12 efforts, you'll see people that even though we
13 have common goals, we have slightly different
14 opinions. So look forward to differing
15 opinions being resolved in the future. Not
16 all of that will be entirely pretty, but it
17 will be managed, and it will be civil.
18 Keep in mind that although we're all
19 dedicated to these testing modernization
20 programs, that testing alone will not solve
21 these problems. You went through an entire
22 QbD program this morning, which illustrates

1 what we intend to do in that area. So as you
2 can see, we are totally dedicated to
3 modernizing our approach to improving and
4 assuring the products that we regulate and the
5 consumers will consume, of course.
6 That said, I want to involve you a
7 little bit in being informed about another
8 program we have going on, and that is a true
9 science collaboration. It has not been
10 covered yet today, and it may not be covered
11 in detail for some time to come, because it is
12 a rolling program. It is nowhere near
13 finished, and I wanted to tell you about it.
14 If this thing works the way it looks
15 like it should work, bingo, good. We have
16 these two projects going on right now. One is
17 a CRADA between the USP and our Office of
18 Regulatory Affairs, ORA, and another program
19 is at the -- well, it's the first bullet
20 point, but it's intended to be the second
21 bullet point -- is the pharmacy compounding
22 monographs that the USP is putting forward.

1 They have some 28 pharmacy
2 compounding monographs, and most of them are
3 not supported by robust laboratory work that's
4 easily available to us. So what we have done
5 is put together a program to pick apart those
6 monographs, and to try to see if they are
7 regulatorily suitable for enforcement
8 activity.
9 But first the Cooperative Research
10 Development Agreement, the CRADA between ORA
11 and FDA. They are going to be looking mainly
12 at reference standard candidate assessments.
13 Though they have the capability in that CRADA
14 to work on monograph updates, and as well as
15 that any laboratory work that had to do with
16 economic adulteration.
17 The primary goal of the CRADA
18 reference standard effort is to be looking at
19 controlled substances, and to use the FDA as
20 a test reference -- as a laboratory resource
21 for testing reference standards. We intend to
22 test at least 40 candidates a year, and I will

1 tell you now that the first candidates are
2 underway right now.
3 The monograph updates are part of an
4 add-on program to that laboratory testing
5 function, and then when we come across a
6 monograph update that needs laboratory
7 support, we can in fact use this CRADA for
8 some of it, to help to coordinate the USP
9 laboratories, as well as to coordinate within
10 the FDA Monograph Modernization Task Group.
11 This is still in a bit of a planning
12 stage, and in fact we had initially thought we
13 would use this CRADA as a platform to do the
14 pharmacy compounding monographs. But the
15 Pharmacy Compounding Monograph program was
16 actually running a little bit ahead. So we
17 held off and did it in an independent way.
18 The economic adulteration program
19 will focus on new technology, focus mainly on
20 portable devices and being able to do screen
21 testing on materials in the field, without
22 having to wait for full-blown laboratory

1 testing.
2 We're coordinating all of our
3 enforcement people to be able to see the
4 feasibility of these hand-held devices. We
5 want them targeting their efforts on APIs and
6 dietary supplements.
7 I want to move on now to the
8 pharmacy compounding monographs. By now, you
9 should be able to tell that this is going to
10 go relatively quick.
11 The compounded products, we want to
12 have products tested for regulatory
13 suitability, according to -- when they're
14 compounded according to the monograph,
15 analyzed according to the monograph, and then
16 assess whether or not the monograph is
17 suitable for enforcement.
18 Right now, we have the USP is
19 preparing most of these compounds for our FDA
20 laboratories, where they'll be analyzed, and
21 it will have a team of people in the FDA CDER
22 and the FDA ORA, to conduct an assessment.

1 Timing is a little bit sensitive for this. We
2 had to make sure the logistics work out, so
3 that we could have the compounded product
4 available to the laboratory, in time to test
5 it before it expires.
6 The scale of the project. You can
7 see there are ten monographs shown up here on
8 this slide. The status is that nine of those
9 ten -- now that's 10 out of 28 -- so nine of
10 those ten are compounded and delivered to FDA
11 laboratories, and I'd like to thank the USP
12 for that. They volunteered to help us out and
13 compound these materials for us.
14 One of them we had to go and
15 compound at NIH for a logistical reason. So
16 I want to thank NIH when that one is underway
17 as well. Our intent is to eventually make all
18 the results public in great detail, but we
19 have not made our plans out that far, as to
20 how that will be done yet.
21 The next steps. Well, next steps
22 are about larger than the laboratory testing.

1 We want to keep the collaboration between the
2 FDA and the USP as broad-based as we can, and
3 to keep up with the standards updates, keep up
4 with the laboratory collaboration to continue
5 our work and finish up any of the,
6 particularly the compounding monographs that
7 need to be finished, as well as any other work
8 that might have to be done, to help do some of
9 the work you've seen in front of us.
10 There are common interests between
11 the USP and the FDA. It results in a very
12 productive cooperation when we go ahead and
13 focus on those end goals, as to what we want
14 to get done. The collaboration is ongoing and
15 it will be fruitful on into the future, as far
16 as I can see. I want to thank you for
17 listening. Thank you very much.
18 CHAIR TOPP: Thank you, Mr. Clark.
19 We have several questions in the queue from
20 the panel. First, Dr. Kosler.
21 DR. KOSLER: Oh hello. Thank you
22 for your talks this afternoon. I remember,

1 you know, if I needed to look up a compendial
2 limit or find out where USP stood on
3 something, I would go get this very large red
4 volume, I think, and find the USP.
5 I'm wondering with all of these
6 changes being planned, say I have a specific
7 item in mind, how do I know that it's up to
8 date? Where should I look to find the current
9 version, and how do I know the life cycle for
10 the current version that I'm looking at? Is
11 it going to be changed within the next year,
12 or is this something that's not prioritized
13 for revision? How can I tell for the one USP
14 item that I'm working with today, for example?
15 MR. CLARK: May I respond with a
16 question? How would you do that today?
17 DR. KOSLER: Pardon me?
18 MR. CLARK: How would you do it
19 right now, because we don't intend to change
20 that. If you're working in a paper volume,
21 you would be part of a program subscribing to
22 those paper volumes, receiving supplements and

1 receiving updated volumes occasionally. So
2 there is that program. It's been ongoing for
3 as long as I've been aware of this industry,
4 in fact.
5 So there is also an Internet version
6 of that same document which is available, and
7 that's the version I prefer to use, because I
8 don't run into these problems. Unless I
9 intentionally dig into the archive, I know
10 that I have the current version. So we don't
11 intend to change any of that.
12 DR. KOSLER: (off mic) If something
13 is coming, say on the Internet I see that it's
14 coming, how do I know how long that --
15 COURT REPORTER: Use the microphone.
16 DR. KOSLER: Oh, I'm sorry. The one
17 other piece was -- say I find something on the
18 Internet. I see that it's current. How long
19 can I expect that to be the current version or
20 the living version of that document? Would I
21 have a notice on there that says "This is
22 prioritized for revision" or no?

1 MR. CLARK: I'm not aware of a
2 notice that occurs on the monograph, that says
3 that it is up for revision on the website,
4 that would give you a tag for that. That
5 doesn't mean one doesn't exist. I simply as
6 an individual am not aware of it, and was not
7 prepared to present on that particular feature
8 of the USP website.
9 However, the USP does have -- their
10 PF is on the web. You can look through that
11 PF. If you're interested in that level of
12 assurance of being current, you would be a
13 subscriber to the Pharmacopeia Forum, and you
14 would be involved in that. You would see that
15 update on the Pharmacopeia Forum.
16 If you are familiar with that giant
17 red book, you would notice that it always
18 tells you to refer first to the supplements.
19 Before you go looking up something in the
20 index of the big red book, you should be
21 looking in the index of the supplements first.
22 That will tell you that the thing

has been changed, you know, have a different official version in the supplement, and if something was, had changed that was minor, well then you could go to the full text in the large book. So that's the mechanics of how that works.

CHAIR TOPP: Thank you. I have one additional question from Dr. Ken Morris. Dr. Morris.

MEMBER KEN MORRIS: Hi, Jon.

MR. CLARK: Yes, hi, Ken.

MEMBER KEN MORRIS: I have two quick questions. One is with respect to the hand-held analyses, is there -- it didn't occur to me, but you know, just thinking about the limitations and sensitivity we suffer when we're looking for impurities with the PAT initiative, I was just wondering if we're just -- if we just have a higher threshold that we're looking for, or is that not an issue?

MR. CLARK: You're so smart, Ken. You're right in the middle of what our biggest

1 issues are. We need to assure that when our
2 person who's doing a scan test for a material
3 -- a screen test rather, not necessarily a
4 scan test, but a screening test. If they
5 should find a result that indicates there's a
6 problem, what is the next step to do before
7 you hold up the shipment or whatever it is
8 you've got to do with that?
9 That is in fact one of the things
10 that we're working on right now to fix. So
11 you've hit right on a sweet spot.
12 MEMBER KEN MORRIS: Right, and then
13 my second question is actually on compounding.
14 One of the things that, you know, the pharmacy
15 students always struggle with when they're
16 looking at compounding, whether it's monograph
17 or not, but it seems like this would be an
18 opportunity is beyond-use dating.
19 I just wondered if that's going to
20 be part of the review, as you start looking at
21 the compounding monographs?
22 MR. CLARK: We hadn't targeted the

1 beyond-use dating specifically. However,
2 should it present itself as a problem, we
3 would certainly bring it up and try to repair
4 that. Our main focus is to whether or not
5 the, following the monograph in the
6 compounding procedure, and following the
7 analytical procedure, whether or not it's
8 usable for regulatory purposes.
9 MEMBER KEN MORRIS: Right, right.
10 It just seems like that would be -- it would
11 be a pretty useful thing to do, and plus it
12 may actually have an interaction, depending
13 on, you know, how rigorous the procedure
14 really is, in terms of the stability. But
15 thanks.
16 CHAIR TOPP: Okay, thank you. That
17 concludes the presentations on Topic 2, USP
18 Interaction Monograph Modernization Program
19 and Other Initiatives. Thank you to all the
20 speakers who presented on this awareness topic
21 this afternoon.
22 Finally, the last item on our agenda

1 for this afternoon, that is the last item
2 before the item that says "Adjournment" in
3 big, bold letters, is some concluding remarks
4 from Dr. Helen Winkle. So, Dr. Winkle.
5 MS. WINKLE: I certainly won't stand
6 in the way of those big letters, Adjournment.
7 I have just a few things to say.
8 First of all, I want to thank all of
9 the presenters for the last two days. I think
10 each of them did a wonderful job. That's both
11 the presenters inside FDA, as well as the
12 numerous people who came from outside
13 organizations to join us and help us get a
14 clearer picture of what some of the issues
15 were.
16 I secondly want to thank the
17 Committee. I think you all have done a
18 wonderful job this time. I was very pleased
19 with a lot of the input, a lot of the
20 recommendations that were made, as well as
21 some of the suggestions that have been made,
22 to further some of our thinking as far as

1 communication, better ways to handle certain
2 situations. I really appreciate that. That's
3 what the Committee is here for.
4 I think that the information that
5 you've been providing us really helps underpin
6 the sound science that we want to have in our
7 regulatory decision-making processes. So I
8 appreciate that.
9 Again, I think we have to go back
10 now to the drawing board, look at many of the
11 things we talked about today, incorporate some
12 of the recommendations that we've heard over
13 the last two days, and some of these will come
14 back to you.
15 Some of them, I said, maybe we'll be
16 going out to numerous other groups, trying to
17 find out what stakeholders, get stakeholders
18 more involved, like in the definition for NTI
19 drugs.
20 But many of these things will come
21 back to the Committee, to follow-up or to get
22 additional recommendations as we move forward.

1 So again, I want to thank all of you for
2 sharing your expertise over the last two days,
3 and have a nice trip home. Adjournment.
4 CHAIR TOPP: Yes, thank you. That
5 does bring us to adjournment. Thank you,
6 everyone. This meeting of the Advisory
7 Committee is now adjourned. Safe travels.
8 (Whereupon, the above-entitled
9 matter went off the record at 3:56 p.m.)
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A

abilities 210:6
ability 49:7 62:21 63:1 78:22 105:3 123:21 137:1 184:22 217:18 236:20
able 45:2 49:7 63:2 65:3,13 66:12 72:1 90:14 102:10 109:2 110:9 121:4 122:15 123:10 125:15 126:7,8 145:20 165:22 224:19 233:14,20 234:6 242:5 251:3 255:10,13 256:1 288:9 327:21 344:16 392:20 393:3,9
above-entitled 140:13 267:19 404:8
absence 341:10 352:1 354:18 355:11 366:4 385:7
absolute 254:14
absolutely 124:8 126:11 131:2 265:22 289:2
academia 82:11 234:18 278:6
academic 179:6 235:7,16 238:1
academics 231:11 231:13 235:8 241:10 242:3,9
accelerated 316:21 354:15
accept 127:13
acceptable 36:7
acceptance 158:8 160:11 311:20 314:17 350:7 360:2
accepted 126:2 128:3 169:1 174:7 375:20
access 122:18 230:9 231:3 363:13
accessible 291:14
accommodate 95:3 95:16 176:20
accomplish 51:9 270:3 314:21
accomplished 270:2 330:10
account 149:12 150:21 151:7,11 152:14 286:14 368:12 369:18 372:6
accounts 101:6 102:19
accurate 129:21 132:17 279:22
acetaminophen 296:21,21 304:5 305:16,20 309:9 323:1 325:9,13,20 326:12,18 327:7 328:2,19 329:1 339:9 373:22 374:1 377:13,22 378:2,5,10,12,16 379:5,11 380:13 381:2 382:18
achievable 380:22
achieve 35:15 61:3 65:17 80:2 105:4 214:5 307:1 369:7 374:6
achieved 134:18 316:10 346:22
achievement 33:3
achieving 56:4 251:16
acid 343:6,16 344:4 344:15 362:10,13
acknowledge 288:3
acknowledging 191:1 281:21
acquire 130:7
acquired 78:6
acquisition 78:3
act 8:17,18 9:16 10:6,21 36:4 271:17,18 293:5
acting 1:22 2:2 3:5 5:13 13:7 27:6
action 183:3 299:19
actions 369:4 376:4
active 19:9 33:22 34:12 46:12,16 271:12 274:3,11 295:16 296:9,14 297:21 298:2,3,6 298:8,9 300:2,13 301:2,19,20,21 302:1,3,7,10,13 302:17 303:2,17 303:18,22 304:10 304:21 324:2 337:15 361:19
actively 167:17
activities 4:19 12:4 19:2 31:20 33:13 42:8 83:13,14 141:15 142:11 144:21 149:19 150:20 167:18 182:22 279:21 316:5 331:12 334:1 356:5,22 357:10 371:10,11
activity 118:20 226:6 253:9 315:3 358:4 381:12 391:8
acts 273:14
actual 61:8 87:21 150:12 162:4,11 163:16 164:12 302:6
ad 144:15 244:12
adapt 55:15 68:2 80:12
adaptable 72:14
adaptation 27:22
adapted 56:18
adapting 80:8
adaptive 55:14 72:1,8
add 123:9 183:10 211:6 237:17 240:20 244:17 290:6 306:14 307:12 314:9,17 328:7 330:19 345:19 365:11
added 25:3 197:6 269:16 276:19 309:22 314:7 316:16 319:8 325:1 329:21 344:2,6 345:2,13 345:22 346:8 359:6 362:10
adding 254:22 316:12 362:17
addition 22:16 34:22 150:20 176:2 178:21 199:5 306:18 321:21 325:22 326:7 345:2 350:15 352:16 353:9 354:17 371:11 378:10 383:2
additional 4:18 43:19 45:3 49:16 57:12 65:12 99:22 119:1 157:17 178:7 179:18 180:9 181:18 206:18 217:20 219:6 234:8 235:4 257:21 260:11 282:1 290:12 355:5 382:10 383:5 399:8 403:22
Additionally 180:16 183:18 188:7
additives 343:19 387:18
address 28:2 32:14 37:21 40:18 41:4 41:6 42:8 44:3 46:15 55:16 70:16 76:1,11 77:13 88:11 106:9 113:1 114:7 149:10 151:22 154:1 162:12 165:12 166:6,22 168:14 197:14 206:21 208:11 235:14 242:16 255:8 258:2 307:15 322:16,17 332:13 332:18 354:5 357:3
addressed 39:15 48:18 49:6,18 129:16 135:13 146:16 157:19 240:3 257:19 261:16 274:6 278:4 306:3 313:10
addresses 46:11 313:2
addressing 22:9 32:5 39:21 127:3 135:6 138:17 239:14 259:21 260:4 304:14 354:17 369:12 376:22
add-on 196:4 392:4
adequate 112:11 112:12 156:21 163:6 273:20 292:13 304:3 308:22 352:2 364:17
adequately 115:17 251:4 362:7 365:2
adjourned 267:10

404:7
adjournment 402:2 402:6 404:3,5
adjust 72:4 74:9,12 74:20 75:3
adjusting 146:14
Administration 1:1 9:12 384:2
administrative 143:15
admit 94:14 244:11 366:17
adolescence 54:4
adopted 38:22 56:19 279:13,15 311:4
adopting 125:9
adoption 42:2 103:21 106:2 173:8 352:6
adulterant 275:16 347:12
adulterants 351:14 356:21
adulterate 273:15 276:7
adulterated 277:18 277:22 299:19 362:3
adulteration 273:10,11 274:18 277:14 282:20 286:15 287:19 312:12 318:18 342:9,13 344:12 346:3 356:14,20 361:18 362:5,18 363:1 391:16 392:18
adulteration/con... 280:11
advance 217:8 359:5 384:5
advanced 175:5 176:22 291:9 298:19 320:1
advancement 370:7
advancements 178:6
advances 47:8 173:9 250:7
advancing 359:17
advantage 122:2 233:18
advantages 184:16
advice 18:1 20:17 29:4 42:18 43:18 147:6 150:8
advise 14:19 236:4
advisory 1:5 5:13 5:16 8:17,19 9:13 9:16 20:16 200:8 332:16 383:3 404:6
advocated 384:10
Affairs 2:19 180:2 180:11 181:2,22 283:8 367:17 368:3 390:18
affect 301:13
affirmed 261:1
afford 11:3 230:19
Affordability 98:22
affordable 99:6,6 99:13,21 106:18
affords 65:22 66:10
afternoon 80:15 265:13 268:4,14 268:19 269:12 288:19 291:22 292:5 310:8,11,14 340:4,7,11 367:20 368:1 385:14,20 388:20 395:22 401:21 402:1
afternoon's 28:1 270:4
agencies 9:20 143:5 235:19 241:13
agency 2:17 13:15 24:8 47:2 124:4 141:4,14 142:3,6 142:7,16 143:1,14 143:21 144:6 145:1 161:14 174:3,12 175:3 176:10 177:14 182:15 183:7 193:14 198:6 199:20 208:16 212:20 215:3,21 251:18 258:8 259:3 266:4,21 271:6 284:1 377:12 382:17 383:3
agency's 10:17
agenda 12:15 14:12 129:1,2 194:20 385:9 401:22
aggressive 369:4 376:4
aggressively 70:7
ago 5:4 54:1 78:4 81:10 195:7 197:4 201:21 206:1 226:14 229:5 230:12 246:6 361:3
agree 30:3 54:12 203:10 214:15 234:2,12 241:9 250:11 371:1
agreed 162:9 165:16 256:19,20 279:19 348:5 355:21
agreement 215:20 332:22 337:9,19 391:10
agrees 386:7
Agricultural 53:1
ahead 151:20 336:3 392:16 395:12
aids 181:20
air 117:22 197:6,7
airplane 197:3
alarming 89:17
alcohol 325:3 347:18,22
aldehydes 351:9 352:9
Aleve 296:18,19 297:3 303:1,5
algorithms 251:14
aligned 78:12 371:4 379:13 382:8
alive 78:13 79:10
allow 13:18 72:14 74:19 83:11 109:7 147:2 162:6 165:9 218:17 265:16 317:5 347:4
allowed 8:14 293:17 294:14 300:13 371:17
allowing 217:17 265:13 294:2 368:6
allows 63:8 67:14 68:4
alluded 341:6 345:4
alludes 347:14
almond 342:20,22 344:8
alongside 370:8
already-existing 370:11
alter 216:12 247:3
alternative 148:9 151:11 354:22 357:7
AMDA 189:13
amendment 293:5
America 2:18 53:8
aminophenol 326:8 327:11 328:9 379:14
amnesia 267:5
amount 72:20 101:21 110:8 191:20 325:5 362:22
amounts 83:20 110:4
ANAB 250:1
analgesic 297:2
analogy 197:2
analyses 399:14
analysis 6:20 24:7 32:21 40:1 57:14 67:14 79:7,13,22 86:8 189:10 221:20 349:1 353:21 363:14
analytical 28:19 37:8 47:8,13,17 48:2,11,14,15,18 49:1,3,8,14,15 67:14 68:8 81:22 101:2 104:19 146:12 166:12 178:20 226:8 252:13 262:20,20 281:15 354:22 357:7 364:17 365:1 370:13 377:20 381:19 382:10,15 401:7
analytically 226:7
analyze 376:16
analyzed 32:12 238:9 380:4 393:15,20
ANDA 274:7
ANDAs 190:4
and/or 13:19 179:17
animal 142:6
Anne 2:10 6:16
announce 353:13
announced 173:3 173:20 187:4 282:6
announcement 165:5 178:1
annual 189:6 372:20 383:14
anomaly 88:22
ANPR 298:20 299:2,7
answer 41:7 44:14

91:9 131:8 136:14 155:21 170:21 192:1 202:21 207:19 208:4 209:11
answered 45:16,16 131:19 171:3 200:22
answering 97:12 109:11
answers 31:21 32:5 45:18 148:18 192:14 207:19
antacid 297:17 300:9,10
anticipate 210:15 327:20 330:21
anticipated 190:14 360:3
anticipating 130:21
Antimicrobial 297:18
antiquated 283:17 283:17
anxious 9:2
anybody 75:16,17 201:15 240:19,20 266:5
anymore 157:20
anyway 15:11 207:16 254:18
apart 157:1 391:5
API 86:1 96:5 101:2,14 110:4 113:7,9,12,18 114:15 122:19 124:9 133:14 227:7 246:14,14 309:7,10,16 378:18
APIs 393:5
apologize 206:10 217:21 267:3
apparent 294:17
apparently 253:18
appear 46:2
appeared 381:16
applicability 12:6 151:7
applicable 24:13 29:16 35:16 47:2
applicant 190:2
applicants 39:1 148:6 154:6 156:17 175:3 189:13
application 40:8 56:3 65:20 66:1 70:21 76:15 77:1 105:13 127:12 135:22 162:15 165:18 173:10 183:7 185:1,8 188:13 192:17 193:3,22 194:12 209:2 210:18,20 211:4 213:9,14 219:5,7 222:11 237:7
applications 38:20 69:21 81:22 119:15 130:2 141:5 144:13 147:12,15,19 150:12 151:8 153:9 165:7,10 172:3 174:19 175:8,8 176:5,6 176:15,17,21 177:1,9 178:9 180:4 182:10 186:9 187:10,17 188:9 190:6,19,22 191:6,19 193:5,6 193:8 194:8,10 204:3 210:13 213:5 214:7,8 236:19,22 237:4,8 260:17
application-relat... 181:21
applied 32:6 71:5 81:1 155:13
applies 25:16,21 36:13 40:2 49:1 194:7
apply 109:8 117:22 131:14 155:6 180:4 387:1
applying 55:6 98:5 98:6 136:19,21 178:19
appreciate 16:2,14 94:5,7 233:1,10 234:4 315:7 403:2 403:8
appreciated 94:6
appreciation 134:14 185:17
approach 22:13,14 22:22 23:7 26:17 35:11 39:6,21 40:14 42:2,6 60:15,22 61:3 65:17 66:4,5,6 71:10 145:14 148:3,10 150:3 151:11 160:22 166:20 180:5 186:7 196:4,9 198:16 207:6 208:19 217:3 225:18 226:2 247:9 248:3,5 249:21 251:16 262:16,17 265:21 329:8 333:7 334:15 335:7 340:14 358:13 361:20 390:3
approached 305:5 371:21
approaches 22:12 22:20 24:13,20 27:8,20 28:10,16 29:15,20 30:18 32:19 34:4,11 36:6,7,8,11 37:10 37:16 38:21 39:9 44:9 49:6 51:15 52:4,8 54:20 61:3 78:10 148:7 173:13 174:21 176:16 182:9 184:9 187:8 190:20,21 196:13 196:17 197:21 199:17 207:2 211:10 212:8 215:10 223:11 252:4 259:8 261:5 262:12 263:2 265:2 305:6 322:9 328:18 358:9 375:11 382:15
approaching 21:1
appropriate 37:14 65:11 73:3 77:14 130:7 158:2 167:11 196:15 210:11 213:22 214:1 216:10,20 217:17 271:20 280:20 375:1 383:1 384:18
appropriately 91:6 255:2
approvable 107:5
approval 42:10 101:5 105:8 106:16 118:13 148:2 152:10 160:18 187:22 188:4 210:11 295:5 300:20 301:2,7
approvals 152:22
approve 42:21 77:1 219:5,12 222:13
approved 66:1 68:15 147:1 174:8 204:6 210:22 222:11,18 293:17 294:13 296:6 317:9
approximately 350:2
April 311:3 315:13
archaic 386:5,6
archive 397:9
archos 90:22
area 28:22 47:9 53:21 67:10 71:2 73:6 93:17,21 95:4,6 144:9 157:5,12,22 177:18 209:22 227:6,7 233:10,14 234:22 237:3 240:9 241:2 254:2 261:15 390:1
areas 31:15 59:12 59:12 73:20 144:18 157:18 215:2,18 216:10 250:8 262:16 332:18 370:3 371:19
argue 198:18 211:22
arising 167:7
arose 348:1
arrive 380:9
Art 7:8
ARTHUR 2:4
article 100:20 101:1,16 102:22 103:7 232:13 302:12
articles 273:8,15 281:12 358:18
article's 347:13
articulates 241:19
asbestos 289:22 351:21 352:2 354:9,18,20 357:6
Asia 50:2
aside 249:4 250:5
asked 34:21 50:7 96:22 132:18 245:13 379:2
asking 36:2 131:14 133:19 290:18 325:8
aspect 90:7 160:17

209:21 210:8 214:2 255:18 347:9 366:5
aspects 24:11 113:7 122:12 132:3 143:15 153:12 165:20 209:14 213:15,15 233:15 269:20 349:4
aspirin 309:16
assay 62:15 63:3 69:5 115:12 306:11 307:13 320:21 321:5 324:20 327:19 336:15,18 338:11 341:1 344:9,17 351:11 356:9,13 356:16 361:20 363:10,10 366:13 388:1
assays 363:20
assess 115:8 118:12 118:20 162:2 191:13 192:16 194:11 251:3 393:16
assessing 178:8
assessment 3:9,18 6:7 20:7 24:5,21 25:5 35:22 37:17 38:19 59:10,11 86:6 114:5 141:5 141:10 146:11 150:3 159:18 163:21 165:6 169:12 171:22 172:2 174:13 193:2 236:19 251:1 292:7,13,15 301:10 302:2 303:7 393:22
assessments 57:9 188:8 380:18 384:13 391:12
assessor 156:18
assessors 150:6,14 163:20 165:9 167:3,9 219:12
assign 194:9 370:1
assigned 179:13 193:6,8
assigning 194:11
assist 81:18 182:1 282:9
assisted 272:12
Associate 3:10 385:12
associated 57:22 354:9 366:17
association 2:15,20 14:6 87:20 96:12 304:16 367:18 368:4,9 383:21
associations 297:13
assume 203:16 360:16
assumptions 116:8 116:9
assurance 36:8 68:9 73:17 146:2 146:6 173:13 185:14 211:13 213:17 398:12
assure 41:16 117:6 198:21 199:16 214:4 218:15,18 219:17 362:18 375:16 400:1
assured 91:13 342:14
assures 23:21
assuring 351:20 390:4
ASTM 242:19 245:3
attack 114:2
attain 127:15
attained 133:8
attempt 150:18 159:3 161:13 257:7 259:14
attendees 15:6 140:21 268:12
attention 44:13 149:19 168:5 231:11,12 260:20 261:3 269:18 336:6
attracted 222:5
attribute 60:6 62:14 198:11,18 223:19 254:20,21
attributed 87:13 88:1
attributes 23:11,13 23:15 38:3 39:14 39:16 46:22 47:15 48:21 59:14,15 60:7,8,11 61:18 69:11 72:6 85:3 85:11,14 86:1,3,4 86:11,21 90:15,15 113:19 121:5 154:10 174:22 186:20 187:1,6 224:14 246:1 249:8,21 250:5 254:11,16
audience 13:18 140:8 373:11
Audio 18:17
August 354:4 355:3 357:8 372:2
authenticity 362:16
authorities 39:2 44:2 142:18 143:11 163:3
authority 9:15 266:5 362:21
authorization 142:14 147:2 161:19
authorizations 146:21 147:10
authorized 10:13 10:22 147:4
automated 243:8 244:1
automatic 74:12 244:8
avail 358:18
availability 314:22
available 29:13 33:17 98:15 99:20 102:15 108:22 109:7 110:7 113:22 114:18 122:4 139:20 145:11 179:1 188:19 189:11 209:6 291:3,10 304:20 333:16 387:1 391:4 394:4 397:6
average 89:3
avoid 365:3
aware 9:1 44:12 207:5 245:19 261:8 332:1 397:3 398:1,6
awareness 12:9 288:19,20 289:5 357:18 401:20
awful 74:22
A-F-T-E-R-N-O-... 268:1
a.m 1:21 5:2 140:14,15

B

B 2:9 73:6,7 88:4 216:14 308:19,21 345:11
back 15:12 29:3 47:7,9 58:12 71:6 79:4 82:17 84:15 86:18 89:7,18 108:13 110:17 125:20 140:12 156:4 158:14 160:22 161:10 166:17 168:13 170:14 197:6 201:13 222:4 223:8 225:3,4 227:19 233:21 238:22 251:19 259:13 265:19 266:10 267:14,18 268:3 272:2 277:15 279:3 284:19 286:12 294:11 296:6 297:14 305:21 317:21 364:8 403:9,14,21
background 82:10 87:5 172:10,20 221:8 230:9 291:1 348:14
bad 96:19 247:22
balance 98:4 110:15,21,22 111:2 123:1 134:22 159:16 164:17 264:14
balances 115:19
balancing 145:2
balloting 317:8
bar 212:21 213:2 258:20,20
bars 213:6
base 59:4 79:20 91:22
based 12:15 23:3 27:2 28:14 33:19 38:13,22 40:21 42:5 49:9 61:20 69:18 72:12 86:5 93:16 97:14 112:20 114:4 116:3 124:6 130:6 145:2,11 154:14 158:4 172:12 173:15 188:12 197:13 234:20 244:12,13 252:2 284:1 304:19 318:15,17 328:11 329:22 331:7 354:12 355:20 361:11 370:15 374:14,17 377:11 379:16

basic 22:12 36:7 88:3
basically 100:22 108:10 139:6 214:16 226:15 299:22 339:3 340:21 362:15
basis 47:11,20 70:19 71:1 144:15 157:20 202:9 235:22 273:3 276:1 291:11 319:19 330:1 335:21
batch 40:3 68:6,6 68:11 69:8,10 71:18 80:22 81:15 81:20 110:10 123:4 132:21 164:6 203:15,18 255:20,21 256:2,3
batches 63:21 64:11 73:2 75:7 87:11 130:22 203:20
beat 266:20
becoming 19:9 29:2 54:21 291:9
bed 118:1 130:14
beg 257:8
began 19:8 373:4
beginning 5:19 120:1 131:6 137:21 189:2 205:22 215:12 333:8 388:3
begins 22:22 131:6
behalf 13:7 368:6
behave 115:4
believe 21:21 29:12 35:9 47:1 65:21 66:10 89:22 165:21 169:3 203:4 211:9,11 244:18 272:19 278:21 335:1 337:3 374:4 384:1 384:7
believes 374:12
belong 215:7,8
belongs 215:7
beneficial 36:10 103:13 211:21 237:1,13
benefit 58:2,3 63:5 64:20 66:7 70:2 71:9 79:15 127:3 142:5 145:10 146:3,15 168:3 206:4 207:20 282:17 284:2 291:12,17
benefits 55:22 80:2 82:3 103:4 104:16 145:3,5 208:1 312:21
benefit-risk 146:6
best 30:22 76:11 99:17 109:4 194:11 205:19 257:13 265:22 356:1
better 19:3 24:1 42:4,12 56:5 63:11 66:3 68:22 93:18 133:17,21 145:19,20 146:2 156:14 157:21 160:4 161:2,4,7 163:21 164:10 165:22 167:21 168:1 198:3 199:21 204:21 207:13 211:11,11 213:17,18 226:9 232:12 234:6 239:20 248:22 251:15 254:22 255:1 261:20 264:13 280:3 362:18 403:1
beyond 98:19 190:22
beyond-use 400:18 401:1
biases 97:17
big 108:18 135:22 136:4 157:5 158:22 234:3 386:21 387:21 398:20 402:3,6
bigger 323:22
biggest 56:22 77:7 125:14 192:8,13 229:5 303:13 399:22
billion 101:20 102:12,20
bingo 390:15
bio 253:16 254:4
bioavailability 29:8 198:10,17,21 203:19 204:4 241:6
bioavailable 112:21
biodisposition 247:4
bioequivalence 29:8
biological 144:11 217:4 256:1
biologically 171:2
biologicals 147:8
biologics 262:22
biomarkers 238:20
biopharm 199:2
biopharmaceutics 179:14
bioreactors 253:18
biorelevant 170:19
Biosimilar 144:16
biostudy 101:11
biotech 16:20 28:18 29:18 46:13 46:16 47:3 78:5,6 78:14 79:11,17,18 79:22 187:14,22 210:17,18 238:6 245:9,20 255:15 261:5,12 262:1,2 262:9,14 263:5,13
biotechnique 322:17
biotechnology 3:6 6:9 44:10 46:4 78:8 79:6 172:19 178:2 186:16 187:13,13 207:3 266:15
bit 15:18 46:15 53:17 78:21 82:22 83:18 88:22 105:9 108:5 135:18 138:14 144:20 149:18 170:3 171:3 233:13 239:12 251:19 253:20 259:12 262:2 263:7 269:5 269:13,19 270:1 271:4 282:8 323:11 329:12 338:10 341:22 342:1 367:10 385:20 387:2,2 390:7 392:11,16 394:1
BlackBerrys 5:7
blend 69:2
blending 69:3 108:10
blocking 132:12
blue 79:18 175:16 176:4
board 68:16 214:19 314:13 388:16 403:10
Bob 327:2
body 54:5 213:22
boil 133:12
boils 104:11
bold 402:3
book 95:1 104:13 104:15 317:9 398:17,20 399:5
borderline 163:21 164:10
bore 56:19
boring 117:15,16 131:2
born 53:22
borrowed 25:19
boss 112:3,3 234:13
bottle 113:10
bottom 56:12
bought 221:12
bound 226:18
boundaries 155:7
box 148:12
bracketing 139:15
brain 16:20
branch 3:16,17 171:21,21 179:17
brand 113:4,6,7 121:20 122:7 125:11,13,19 139:10 368:14
branded 100:9 101:8 109:17 120:18 136:11 137:3 138:20 214:19 228:20
branding 124:2
break 140:5,7 248:10 385:8
breakdown 102:2
breaks 9:8
bridge 232:2
bridging 93:18
brief 21:20 26:9 172:12,20 177:12 304:22
briefly 32:10 40:7 123:15 257:7 269:12
bring 18:20 67:4 89:8 100:5 107:22 116:12 129:5,9 130:1 137:5 149:9 201:13 222:20 223:19 226:7 235:7 266:19 269:18 282:14 343:3 388:12

401:3 404:5
bringing 358:14
British 381:1
broader 16:16 177:8 191:4 262:15
broadly 72:16 85:12
broad-based 395:2
brought 197:6 229:12 370:12 386:1,8 387:7
budget 99:2 111:3
Buffalo 7:17
build 65:12 80:10 106:7 110:8 113:1 113:14 114:3 125:16 126:7 131:2 138:2 167:3
building 1:20 106:6 106:22 107:10 120:3 145:16 197:3,5 205:20
builds 62:11 251:18
built 107:4 332:1
bulk 310:22
bullet 390:19,21
bulletin 278:15 355:2,20 356:3
bunch 91:21 264:18 366:21
bunches 295:15
burden 164:18
business 52:17 54:11,13 79:5 104:17 105:1 125:11,16 126:8 131:16,17 132:6 133:12 220:22 221:3 226:16
buy 107:10
buying 72:16

C

C 2:12 64:9 73:7,8 88:4 308:18
cadre 176:21
calcium 300:12
calculation 224:3
call 4:2 5:15 59:10 59:21 71:22 75:9 101:1 180:18 201:2 273:14 279:1 281:7 284:6 313:11 314:3 315:17 317:17 320:5,5 333:7 334:15
called 149:4 179:20 180:19 338:5
calling 318:5
Campus 1:20
Canada 33:14
candidate 169:1 391:12
candidates 58:13 222:2 249:17 391:22 392:1
capabilities 182:11 259:17 365:1 380:6 381:1 382:21
capability 54:20 56:5 58:9 60:21 61:5,8,14,19,20 62:3 63:3 121:8 170:17 171:6 220:10 224:1,2,3 224:7,19,22 225:2 225:3,4 239:2,6 259:12 264:11,12 391:13
capable 62:2,4,6,10 71:8 176:19
capacity 65:9 112:11
capillary 278:9 349:8
capture 116:20 267:7
captures 275:6 355:1
capturing 75:6 177:3
car 386:18
carbon 365:11
carbonate 300:13
care 8:19 14:5 99:1 293:2 297:12 304:15 367:18 368:4 383:21
career 60:16 109:16
careers 387:4
careful 115:7
carefully 194:9
carry 114:19
case 33:21,22 34:8 34:10,17 35:4 54:11,13 78:17 93:5,8 104:17 105:1 116:4 125:16 126:8 129:7 131:16 153:7 154:19 155:17 188:18 250:1 291:11,11 291:15 294:4,5
cases 74:22 101:9 111:10 155:21 156:2 311:18 322:21 386:5
case-by-case 70:19 70:22 157:20
catalysts 343:10
categories 295:15 320:18 340:19
category 94:15 287:9 298:1,1,2,6 298:8 301:3 318:22
Catherine 2:22 14:1 270:16 275:7 285:5 340:5
causation 87:20
cause 221:19
caused 277:13
caveat 121:11
CA/PA 26:1
CDER 3:4,5,6,9,11 3:14,18,22 20:8 172:1 188:6 268:18 272:12,18 281:19 282:4 283:6 288:7 292:4 393:21
cell 5:6 263:10
cells 256:7,15 263:6
center 1:2,18 6:19 18:3 157:16 230:15 231:1 233:12 235:10 260:7 283:6
centralized 142:11 142:13,21 143:16 146:20 153:2
centric 236:5
century 173:3 196:15
certain 90:14 94:15 119:16 127:12 130:5 131:10 154:17 157:3 159:4 162:17 182:20 184:22 194:5 286:7 290:4 366:5 377:13 403:1
certainly 56:7 58:8 68:14 69:20 70:7 76:20 89:5 125:19 134:8,16 227:6 277:21 313:14 334:2 387:15,22 401:3 402:5
certificate 40:1 349:1
cetera 121:13 128:4 129:14 221:20 228:4 242:18 243:10,21 265:7 291:6
CFI 180:20
cGMPs 348:20
chain 25:18 30:6 36:15 42:1 349:4
Chair 1:22 2:2 5:3 5:13 7:3,20 8:4,15 15:1 20:1 44:16 45:20 47:5 49:19 50:5 52:11,15 53:3 74:1 75:12 77:15 80:5 82:5 85:8 87:6 89:20 92:12 93:22 96:6 120:11 125:2 127:18 128:22 131:21 134:10 135:10 136:7 140:2,16 168:6 169:19 171:11 191:7 192:3 194:15,18 200:11 201:12 206:7 207:12 212:11 214:10 217:1,19 219:22 227:13 232:7 234:11 236:13 237:15 239:9 240:1,13 242:12 244:3 245:7 250:11 252:5 254:6 255:3 256:21 263:18 264:16 265:11 267:2 268:3 288:16 290:11 291:21 308:7 309:1 310:7 336:7 338:18 340:2 360:9 363:6 366:14 367:6,14 385:2,5 395:18 399:7 401:16 404:4
chairman 7:8 94:6
challenge 42:18 43:5 92:4,5,5 110:6 125:14 154:2 159:1 194:1 217:13 222:8 225:12 237:21 247:17 248:10,13 248:17 250:4

256:4,8 314:15 347:10
challenges 4:7 17:7 17:18 20:4,15 21:7 22:5 32:14 40:16,19 41:2,3 44:12 49:17 76:1 76:2 78:17,21 103:21 105:14 106:3 109:13 110:19 125:9,13 141:21 151:19,20 156:22 163:5 166:7 195:18,19 207:4 218:2 226:22,22 227:3 232:14 237:18 240:10 241:7,21 242:4 245:18 261:6 262:4 264:3 312:4 350:8 355:7 359:22
challenging 126:22 187:2 328:3 339:6
chance 97:6 232:4
chances 359:9
change 17:13 26:1 28:8,12 37:6,11 39:7 42:13 58:1 60:17,18 61:6 77:5 82:20 83:2,5 83:6,10,12,14 84:5,14,18,20 85:2 104:12 108:11 113:19 119:22 120:6,7 137:15 159:22 160:2 161:8,15,21 162:3,8,11 188:2 196:21 225:2,3,11 247:10 278:16 335:18 396:19 397:11
changed 279:14 396:11 399:1,3
changes 42:14,21 43:2 48:6 56:9 80:11 83:21 84:7 84:9,11 118:1 119:9 159:4,19 160:18 162:17,18 171:7,7 246:20 247:2,6,14,22 248:2,6 250:17 270:22 299:3,5 315:9 328:19 330:3 361:12 384:9 396:6
changing 224:6
chapter 306:1 307:18 328:22,22 329:4,5,7 348:2 377:7
chapters 287:8 307:19
characteristic 223:18
characteristics 91:7 95:3 287:17 301:13
characterization 113:4 248:21,22 251:9,13 262:8 291:6
chartered 283:1
cheap 310:1
cheaper 275:16 342:19 362:3
check 125:3
checks 115:19
Cheese 104:13
chemical 6:15,17 91:3,4,14,17 146:21 246:16,17 246:20 247:10,18 247:19,22 250:18 277:20 351:19 355:16
chemist 104:19,19
chemistry 76:15 316:12 321:1 363:15 365:16
chief 3:16 171:21 179:17
children 11:11
China 277:16 362:13
Chinese 50:2
chipping 323:20
chlorinated 313:12
chloroform 325:3
choice 109:5
choose 50:18 215:14 225:16
choosing 380:16
chosen 65:19 387:9
CHPA 305:6 307:9 331:16 333:3 334:12 368:9,22 369:3,5,10,17 370:12 371:1,21 373:4,15 374:12 376:3,9 377:15,18 378:11 379:2,12 379:17 380:1 381:3,13,20 383:10,13 384:20 389:9
CHPA's 371:9 372:20 377:21
chromatographic 338:16
chromatography 306:13 321:11 347:16
chrondroitin 277:19
Cincinnati 38:7 39:13 40:15
circles 338:14
citations 102:13
cite 52:5 242:9,10
cities 50:1
citrate 330:5,9 382:6
civil 389:17
clarification 31:15 49:22 158:11 160:6 212:12 289:6 336:9
clarifications 367:8
clarified 43:10 157:21 160:4
clarify 16:7 48:1,12 119:2 157:4 166:1 219:9,10 220:16 318:16
clarifying 152:4
clarity 26:10 38:17 41:4,18 43:11 228:11 229:16 230:4 259:22 260:5
Clark 3:10 271:2 385:12,12,16,17 395:18 396:15,18 398:1 399:11,21 400:22
class 94:16 138:8,9 138:9,9,12 250:19 286:21
classification 298:11
classified 297:21 377:13
clear 26:18 51:13 76:13 106:19 107:4,18 117:11 120:2 156:16 213:2 253:5 292:17 355:11
clearer 402:14
clearly 26:13 55:22 67:9 71:5 155:9 215:6 252:22 349:4
clinical 1:7 5:14,17 9:14 93:19 98:12 175:22,22 204:11 237:19,22 238:19
clinically 166:16,18 170:2 187:5 239:7
clinicians 204:14 204:17 234:17
clock 183:8
close 52:11 96:6 227:20 234:6 236:8 257:2 267:8 288:3 308:22
closed 187:15
closely 142:17 143:6 222:1 276:20
closer 68:1
closing 167:19 195:8
CMC 16:16 19:18 42:3 48:6 174:2 174:10 177:19 179:13 182:21 183:14 199:2,9
coat 119:10
coated 69:9
code 167:6 243:20
codex 351:19 355:17
collaborate 56:20
collaboration 21:15 31:22 32:16 179:7 271:6 307:9 332:20 333:2 335:1 342:6 349:6 357:13 359:16 365:7 373:13 382:8 385:15,19 390:9 395:1,4,14
collaborations 331:15
collaborative 107:12 384:21
collaboratively 186:11 380:3
colleague 44:7 178:3 208:12 270:5 271:2 288:13
colleagues 20:21 21:5 27:19 34:19 35:22 37:1 44:2 97:15 103:15 121:2 126:15 181:1 200:8 235:16 236:6,7 237:11 313:3
collected 379:16

collecting 123:19
College 8:2
Collostre 130:14
coloring 97:17
colors 175:14
column 115:11 135:7 313:17 316:11 321:1,11 322:18
columns 313:19
combination 30:1 74:15,20 251:20 322:21 323:5 330:18 337:2
combinations 249:20 309:12 325:13 326:2
combinatorics 249:18
combustion 363:13
come 29:3 31:10 37:9 75:21 82:12 91:10 106:9 107:5 107:12 110:17 117:18 120:7 134:22 143:9 145:21 160:5 163:2 167:9 168:13 195:7 204:3 205:8,16 206:5 229:18 233:18,19 243:14 252:17 296:5,12 297:4 313:3 335:6 350:12 360:6 361:5 381:5 390:11 392:5 403:13,20
comes 60:3 107:2 124:15 193:22 231:19 283:2 285:17 289:12 338:2 371:2 379:21
coming 120:6 125:10 158:4 168:10 170:6 220:19 226:3 231:7 232:13 243:12 312:6 333:11,20 397:13 397:14
commend 205:21
comment 4:8,16 80:7 128:8,16 135:14,18 139:2 186:1 210:16 220:12,20 234:9 236:16 237:16 239:1 255:8 263:19,20,22 265:16 279:17 298:22 299:11 309:20 316:20 317:6 329:20 330:13 359:7
commented 220:21 259:1 260:14 261:9
comments 13:20 18:4,5 47:8 135:7 211:18 235:4 237:18 255:9 261:22 263:15 264:19 267:4 279:18 299:4,12 317:7 354:13
commercial 53:21 56:17 57:1,8,16 58:3 88:5 101:4 221:14 223:4
commercializable 253:2
commercialized 81:7
commercially 113:13
Commission 143:4
commitment 208:16,17,21 209:7 258:17,18 311:10,14 319:20 331:17 371:9 374:10 379:7
commitments 161:4 368:17 373:8,16 385:1
committed 165:15 319:22 369:6 377:4
committee 1:5 4:2 5:13,16 7:2,7 8:17 8:19 9:6,13,16,18 10:10 11:4,7,18 12:8,17,21 13:2 14:8,19 17:22 20:16 44:17 47:12 94:7,10 96:15 129:2 144:3,4 151:16 195:4 200:8,14 206:10 234:5 235:3 240:12 242:19 243:15 263:15 267:15 288:18 289:3 305:7 306:4 306:20 310:15 312:5 317:22 327:1 333:19 353:20,22 354:14 356:2 357:17,21 358:7 372:3 383:3 402:17 403:3,21 404:7
committees 143:12 143:22 317:6 326:16 331:22 332:3,16 364:5
Committee's 10:2 14:22 15:20 19:16
common 151:21 152:17 153:4,12 275:14,21 287:17 389:13 395:10
communicate 186:4 201:5 232:12 233:3 272:14 283:20,21 389:4
communicated 117:1 180:22
communicating 181:20 237:11
communication 24:6 25:1 185:22 186:12 191:2,20 232:10 333:5 358:12 375:1 403:1
community 230:12 231:9 253:10,13
companies 54:12 54:15 65:19 71:6 72:7 76:3,4 81:3 99:5,9 100:9 101:17 103:8 107:8 110:10 121:20 125:16 126:4,9 127:1 131:9,10 132:4,13 132:13,17 133:5 136:12 148:1 150:7 154:21 155:6 225:15 226:3 228:3,17 229:6 230:16 231:12 233:6,8 237:22 238:7 250:3 253:3 316:1 368:11,22 369:3 370:16,22 373:4 376:3,21 377:19 378:1,8,12 379:4 379:17 381:3,18 381:22
company 13:11 54:4 56:15 65:18 73:15 78:5 98:16 101:8 104:21 114:17 120:19 132:4 138:4 154:17 157:17 160:2 169:14 216:5 223:7 226:11,12 324:12 331:4 369:21 376:17 377:16 380:21
company's 83:7 164:8
comparability 178:12
compared 62:17 337:16 338:16
comparison 63:17 175:14
compelling 256:10
compendia 332:9 366:20
compendial 72:22 271:9 272:18 273:4 274:10 279:20 373:21 380:14 383:12 384:8,12 396:1
compendium 270:10 311:1
compete 225:16 226:9
competent 142:18 143:11 163:3
competition 110:11
competitors 99:11
compiled 32:12 318:13 380:4
complaints 119:1
complement 79:14 80:1
complete 38:9 41:7 68:6,7 103:16 174:6 279:11 330:11
completed 37:22 38:6 69:9 217:11 277:4 278:12
completely 45:16 50:9 223:15 250:20
completion 117:6
complex 29:16 101:14,15 145:6 148:7 182:8,9 184:9 187:1 219:20 250:9
complexities

253:22 383:9
complexity 38:22 115:5 124:15,16 149:13 186:21 254:10 328:3
compliance 3:14 10:2,11 173:14 180:1,10 181:2,21 185:21 186:2,3 188:6 191:21 204:19 205:3 268:18 276:5 312:2
complicated 100:15 101:11 164:20 186:21
complicating 96:5
complies 300:7,15
compliment 339:19
complimented 259:7 260:12
comply 299:15,17 302:5
component 25:6 29:7 181:3 263:12 310:2
components 175:15 175:17 178:9 179:4 199:9 266:22 276:14
composition 143:22 343:6 344:1,4,16 345:3 362:11,14,16 366:6,10
compound 394:13 394:15
compounded 393:11,14 394:3 394:10
compounding 390:21 391:2 392:14,15 393:8 395:6 400:13,16 400:21 401:6
compounds 345:17 363:20 393:19
compound's 101:22
comprehensive 33:21 35:13 46:2 54:6 90:1 147:19 148:1 190:12 371:15
comprehensively 307:16
compresses 124:12
compression 113:16 124:13
comprise 274:20
comprised 375:12
comprises 283:8 350:18
concentrate 373:1
concentrations 379:19
concept 70:13 291:13
concepts 22:18 165:11 174:4 175:5,7 176:22 189:8 199:11 244:9 249:13
conceptually 78:12
concern 103:17 136:14 208:22,22 211:3 271:20 289:18 290:2 304:15,16 305:22 306:3
concerned 116:17 233:17 273:18
concerning 13:2 157:13
concerns 36:20 105:2 113:2 216:14 273:3 313:2 321:2 351:13 356:13
concert 186:10
conclude 265:14 367:14 371:13
concludes 401:17
concluding 402:3
conclusion 9:5 191:3 334:19 359:12 383:20
conclusions 154:17 155:2,3
concrete 165:9 189:16
conditions 73:7,8,9 251:11 256:3 290:21 300:1 306:11 361:13
conduct 359:11 393:22
conducted 17:6 62:6 86:6 181:10 181:11 183:20 304:22
conducting 183:2
conference 1:18 12:2 179:8 372:21 383:14
conferences 188:17 358:17
confidence 124:3,4 131:18
confidential 169:15 300:22
conflict 4:4 9:10,21 10:12,19 12:18 384:11
conflicts 10:3,16 11:3,8
conformance 193:13
confused 270:10
congratulatory 258:8
Congress 10:13,22
conjugated 266:20
conjunction 353:21 366:9
connect 198:7 255:13
connection 12:19 243:18
consequences 84:20
conservative 379:13
consider 38:1,12 39:11 42:16 43:20 48:20 49:1 87:14 98:22 99:22 103:20 105:15 116:3 118:11 148:21 178:17 189:14 194:9 206:19 211:17 235:3 243:5 249:18 257:22 266:1,15 286:11 290:5 294:2 323:12 351:22 372:4,5 374:11 379:2 382:20
considerable 195:17 200:3
considerably 178:15 212:2
consideration 39:15 187:8 208:4 208:8 286:16 374:22 380:20 384:20
considerations 180:19 252:3 287:19
considered 62:2,4 290:6 321:6 338:15 347:12 380:17,18
considering 177:10 291:4
consist 155:8 179:11
consistency 173:17 313:22 314:5,13 329:6 331:8
consistent 105:12 215:20 280:20 346:21 351:3 354:10 361:19
consistently 369:17
consists 149:2 150:5 353:19
consortium 278:6
constantly 341:15
constitute 212:3
consultant 11:14 13:13
consultants 278:6
consume 390:5
consumer 2:3,19 3:12 7:1 14:5 268:16 304:15 367:17 368:4 374:14 376:6 383:20
consumers 297:12 299:15 302:20 368:21 375:22 390:5
contact 5:9 39:2 336:5 360:8
contacts 148:11
contain 141:11 279:21 301:22 351:21 354:8
containing 141:6 172:3 175:15,17 190:6 305:16 378:17
contains 271:11 300:12
contaminant 347:11
contamination 273:10
contaminations 388:2
contemporary 95:12
content 127:12 147:17,18 160:11 307:21 311:18 361:14
contents 182:2
context 364:6
continual 24:2 25:9 25:16 43:8 333:2 370:5

continually 272:1,5
continue 20:15 21:17 27:21 43:5 62:11 66:8 140:17 167:2,5,15 208:19 215:4 234:2,4 285:22 307:10 332:11 334:14 369:8 372:5 376:9 382:11 388:11 395:4
continued 191:1 375:4
continues 47:20 85:2 188:8
continuing 134:15 177:6 256:8 285:14 373:2 384:21
continuous 37:14 56:8 58:5,8,11 59:5 71:18 79:9 80:22 81:16,20 128:12 148:8,11 149:2,17 151:11 152:9 158:3 160:20 161:12 166:9 186:13 199:13,14,19 226:5
contracts 11:15
contrast 301:1
contribute 146:5
contributing 143:19
contribution 232:6 253:19
contributions 15:20
contributor 370:6
contributors 227:16
control 6:20 23:3 23:17,20 24:6,22 25:6,7,15 29:7 34:4 35:1 38:4 39:19,20 41:12,12 41:19,20 47:16 55:15 57:19,22 58:1 59:4 63:8 67:5,12,15 68:7 68:19 72:4 74:6 77:4,5 79:2 82:20 83:2,5,6,10 84:2,5 88:8 94:13 116:15 116:18 122:13 127:21 128:11,12 128:15 129:13,19 137:10 166:14 185:2 199:7,10,16 201:19 203:11,17 218:19,20 219:1,3 219:6,12 255:10 255:18 259:4 263:10
controlled 95:19 124:11 153:19 204:12,12 343:9 391:19
controlling 54:19 67:22 204:17 261:21
controls 89:12,13 146:13 157:17 161:6 170:22 182:5 301:17
convened 1:17
convening 9:12
convention 279:5,6 279:7,9,17 280:22 311:3 315:13
conventional 67:13 69:5 197:21
convergently 253:1
conversation 19:6 93:15 259:10,19
conversations 8:20 70:18 216:15 228:2
conversion 81:14 81:18
converted 103:8
converts 73:15
convey 35:7
convince 136:17 196:18 252:18
cooperate 388:13
cooperation 275:2 395:12
cooperative 389:11 391:9
coordinate 350:16 392:8,9
coordinating 386:15 393:2
coordination 173:17
copovidone 349:20 353:4
core 141:15 279:20 364:2
correct 48:2 153:1 309:8,18 339:1
corrections 263:14
correctly 171:13
correlate 60:9
correlation 87:19
correlations 60:5 86:9,19,22 87:2
correspond 155:14
corresponding 302:4 334:6 337:11
Cosmetic 10:6 271:17 293:5
cost 36:21 39:17 66:15 67:2,4 101:10,20 111:3 134:20 138:18 223:6 230:18
costing 101:17
costs 28:7 69:12,13 103:2 105:5 106:15 133:14 208:7 212:3 264:2
cost-effective 113:17
count 257:14 321:8
counter 293:1,11 377:3
Counterbalance 119:17
counting 22:2
counts 138:22
couple 15:13 64:14 78:4 93:3 125:22 215:2 229:5 258:7 297:20 312:19 320:7 330:17 366:16 385:22
coupled 67:13
course 55:12 66:6 70:3 81:8 96:4 121:11 145:7 146:3 149:16 152:11 153:10 155:4,9 156:9 160:7 163:4 165:2 166:8,22 167:5,11 167:14 168:1,2 173:3 175:17 179:4 200:14 221:22 241:11 282:11 290:20 312:3 315:12 318:9 319:20 331:13 389:11 390:5
COURT 397:15
cousin 277:20
cover 21:19 342:1
covered 10:4 40:7,7 46:4 264:20 296:2 296:16 297:1 390:10,10
covering 188:2
covers 85:14
Covidien 378:5
co-chair 269:7 288:14
co-chaired 283:4
CQA 113:21
cracked 79:17
CRADA 390:17 391:10,13,17 392:7,13
CRADAs 11:15
crazy 112:4
create 118:3 130:8 152:10 160:18 161:11 231:1 253:10 297:6 302:19 339:18 383:7
created 84:19 340:17
creating 55:10 230:14 253:1 298:14 340:16
creative 383:18
credo 91:2
criminal 273:14 310:1
criteria 154:14 158:8 160:11 244:15 281:10 311:20 314:17 350:7 360:3 372:16 380:17
critical 23:11,14 39:16,17 46:22 47:14 55:4,7 57:21 58:10 59:3 59:3 60:6,9 72:10 80:2 81:19 86:20 86:22 116:21 117:4 121:5 122:12 153:19 154:9 174:22 182:5,5 186:20 213:21 231:14 237:20 245:22 253:5,14 257:16 264:21 273:7 275:3 276:10 277:12 280:14 316:12,13 335:2 335:17 337:21 338:10 343:12,18 347:2
criticality 39:13
crospovidone 349:20 352:14
crudest 79:7
crystalline 124:10

cultural 129:11 132:3 137:15 193:10
culture 50:19 127:22 128:7,9,10 128:14 196:5 202:13 220:9 222:21 259:11,16
culture's 229:10
curiosity 119:8,13
curious 80:19 90:9 90:17 224:9 360:11
current 4:6 11:19 12:9 20:3 40:16 141:18 166:19 172:21 174:18 175:12,19 226:8 248:18 292:12 311:18,19,20 331:12 334:10 341:16 352:1 354:18 356:5,16 357:10 360:19 365:1 381:1 396:8 396:10 397:10,18 397:19 398:12
currently 38:8 40:11 81:14 100:17 162:5 182:7 190:4 242:20 285:22 313:11 327:10 348:12 356:10,17 376:20 381:8
currents 244:19,20
curve 108:14
customer 119:1
customers 100:11 102:16
cut 138:10 217:20 240:15 267:11
CVS 292:22
cycle 23:8 24:2,14 25:18,21 30:5,9 32:8 35:16 36:14 37:7 39:21 41:22 69:14 102:3 109:19 110:2 149:17 158:14 180:7 181:1 182:1 216:4 225:17 226:2 307:3 318:7 332:3 335:9,14,15 335:16 359:14 396:9
cycles 223:8
C-O-N-T-E-N-T-S 4:1

D

D 73:8
daggers 260:22
data 47:19 54:5,7 62:10 66:14 68:7 68:8 84:8 116:5,6 123:19 124:1,7 139:19 145:11 158:4 164:2 167:10 175:21 182:11 241:7 287:18 293:22 297:8,10,16,19 298:3,7,10,13 299:3,4,12 304:20 370:22 374:15 375:2 379:16,18 380:2,21
date 183:6 190:15 273:5 280:4 311:7 311:13 352:3 355:3 368:19 371:8 396:8
dates 181:15 279:3
dating 272:2 400:18 401:1
day 19:13 24:9 68:11 99:9 183:6 195:21 256:14,14 257:5 334:2,2 339:21 364:10 370:18 376:15
days 68:12 153:3 183:5,5 298:22 329:20 402:9 403:13 404:2
de 224:8
deadlines 180:16 193:13,15,16
deal 17:4 79:19 90:11 139:14 196:16 210:1,3 223:14 230:6 242:1 249:15 254:13 256:11
dealing 69:19 72:3 112:8 142:9
deamidation 247:1
dear 245:12
deaths 278:1
debatable 338:14
debate 99:2 136:4
debates 222:17
decade 98:20
decades 258:7 311:17 341:7 364:8
December 352:14 352:20
decentralized 142:7
decide 114:18 264:6
decided 33:21 295:12
decision 27:2 42:5 156:20 195:13 200:7 286:20
decisions 19:20 40:4 104:22 105:11 130:6 132:6 174:15
decision-making 403:7
dedicated 272:17 376:21 383:16 389:19 390:2
dedication 388:22 389:1
deemed 299:18
deep 50:17 227:11 248:21 262:1
deeper 227:10 233:13
default 293:8
defects 66:17
defer 208:12
deferred 47:7
deficiencies 364:20
deficiency 107:3
define 111:13 115:3 124:18 162:6 163:20 164:10 165:22 170:11,19 238:21 362:8
defined 22:21 23:1 24:18 57:16 155:9 219:2
defining 59:2 138:18 174:22 187:5 246:13 250:6 262:4
definite 199:15
definitely 100:2
definition 16:3 186:20 245:22 293:4 355:11 403:18
definitive 337:18 338:9
DEG 275:16 277:3
degradant 373:21 374:20 377:15,22 379:6,10,19 381:20 382:19,22 383:1
degradants 328:9 374:18 377:2,9 378:18,21 379:3 381:14 382:12
degradation 250:18
degradence 316:14 325:15 326:10,11 329:1
Delaware 6:18
delay 209:2 210:17 210:21
delaying 49:13
delays 152:22
deleted 324:22
deleting 316:15
deliberations 14:8
delineated 373:17
deliver 254:21
deliverables 180:15 183:11
delivered 394:10
demand 64:22 203:8 375:22
Deming 128:1
Deming's 242:21 243:16
demonstrate 77:3 85:1 161:6 223:2
demonstrated 29:9 55:21
demonstrating 92:6
demystify 253:20 262:22
depart 160:21
department 360:12
departure 223:15
depend 190:1 224:4 317:4
depending 99:19 101:11,13 401:12
depicts 379:18
deposits 354:8 355:12
depth 94:3 155:20
Deputy 3:4 6:4
derived 354:7
describe 22:14 25:20 32:10 100:21 144:21 162:7
described 24:18 26:16 34:7,11,17 36:18 130:3 162:15 303:5 357:12
describes 22:10

24:5 25:13 33:22 355:4
describing 159:1
description 31:18 40:11 141:14 159:8,10 182:4,4 182:4 351:19 354:12 355:16 357:3
descriptive 31:19
deserve 368:21
design 4:6 11:21 16:22 17:2,8,10 17:15 20:3 21:1,3 21:18,22 22:4,8 22:14,18,20 23:7 23:16,16 26:13,14 26:15,16 27:9,10 27:10,13,13,14 28:4,7,11,13,17 28:20 29:20 34:3 34:17 35:1 38:2 38:10,11 39:6 40:6,9,13,18 43:21 44:9 46:21 46:22 47:15 48:4 48:5,19,21 51:15 53:10 55:1,2,3,5,8 55:18,20 56:13 57:4,8,13,16,18 57:20 58:3 59:4,8 59:20 60:1 62:22 63:2,6,7,9 64:8,21 65:2,5,10 66:15 67:11 71:14 72:11 72:13 73:14 75:5 75:10 80:3 82:18 83:11 84:17,22 85:16 87:4 89:8 107:19,21 108:1,3 108:20 114:10 121:22 126:3 141:11,18,21 144:12 145:13 146:5,9 147:3,7 147:12,15,21 148:3,14 150:4,9 150:19 151:4 152:7,19 153:5,13 153:14,15 155:6,7 155:8,11,14,16 156:11,15 157:5,8 157:12,14 159:22 160:9 162:15 163:12 164:6,7 165:7,11,20 166:11,16 167:20 170:2,11,20 171:5 171:8,8 174:4,13 174:21 175:1 176:20 177:1 178:8 179:4 180:5 182:16 186:15 187:8 188:21 189:15 190:7,9,18 191:5,19 193:7 194:1 196:3 197:17 198:10 199:12 208:19 212:2 213:19 214:9,9 218:21 222:7 333:7 358:13
Designated 3:2 7:6
designed 91:7 145:4 254:20
designer 86:12,15 86:17
designing 58:19 214:1
designs 85:17
Design-based 192:17
Design-containing 186:8
desired 145:3,5
despite 106:2
detail 44:1 259:13 275:8 341:22 342:1 373:5 390:11 394:18
detailed 76:4 381:9
details 9:4 31:17 86:14 87:3 181:19 343:17
detect 347:16 356:19 387:18
detected 75:2 277:15
determination 23:9 23:10 39:19 327:14 348:4 356:11
determine 328:8 369:22
determined 10:9 10:17 13:15 71:7 266:22 344:19 374:2
determining 15:22 343:18 363:4
Detroit 128:3
develop 23:15,19 33:22 46:9 51:19 57:20 72:2 86:19 107:8 114:1 122:13 130:16 138:11 166:3 196:9,13 197:11 218:20 222:11 252:12,13 278:7 283:14 287:14 307:10 332:10 366:8 369:20 375:14 381:9 382:14
developed 31:2,16 32:8,16,22 33:5 33:17 34:2 41:21 49:5 59:9,21 86:15 107:18 109:2 112:9 114:1 117:12 122:20 137:20 155:12 157:8 158:4 177:14 181:6 190:7 226:13 228:18 243:10 295:20 304:17 311:17 349:8
developer 85:21
developing 33:1 37:20 47:15 59:3 72:11,11 81:9 123:12 124:18 136:16,22 137:22 149:21 163:15 175:1 224:18 259:8 286:3 324:7 333:9 377:6
development 3:21 22:10,11,12,15,22 24:15 25:5,7 26:17 27:12 28:21 29:15,19,22 30:14 31:9 33:20 34:8 35:12 38:21 41:19 44:11 46:11 58:12 61:12 78:7 84:17 100:22 101:3 105:5 110:18 111:13 112:16 114:2,4 122:8,8 124:6 130:1 133:14 137:10 143:20 145:15 149:15 155:1 158:5 175:9 176:13,17,21 189:13,21 196:2,5 196:11 202:18 207:3 209:18 212:10 222:1,6,10 223:1 226:6 263:1 292:3 391:10
developmental 34:4,11 36:5,11
developments 49:2 210:5
develops 212:16
deviate 347:7
deviation 64:3,12 89:6
deviations 63:22 66:18 67:3 164:7
devices 5:8 252:16 392:20 393:4
devise 166:13
devoted 334:3 339:22 369:1
devoting 324:3,6 334:21 359:15 383:4
dialogue 37:14 167:15 366:1
dialogues 216:2,16
dietary 393:6
diethylene 275:12 275:14 276:7,16 277:1,9 303:10 317:1 318:10 336:17 345:17,20 346:3,7,15 347:8 348:19 349:10
differ 186:19 189:21 262:2
difference 88:15 108:18 126:13 166:17 247:15,19
differences 31:5 78:15 88:4 249:14 300:18 301:5 355:12
different 32:7,7 34:3 37:6 39:22 49:6 57:5 61:16 70:16 96:4 115:9 125:12 146:8,9 154:8,8 163:2,3 169:4 175:20 193:20,21 212:8 212:10 233:2,15 238:12,13,17 246:10 250:3 309:11 389:13 399:1
differentiate 336:13
differing 389:14
difficult 94:16 105:7 192:16 208:13 246:15 254:4
difficulties 30:22
Difficulty 104:16

diffuses 119:10
dig 233:13 397:9
diligently 381:8
diphenhydramine 305:17,21 323:1 325:9 329:12,17 330:4,14,16 331:3 331:5 373:19 374:1 377:14 381:15,20 382:5,6 382:12
diphenhydramin... 382:2
direct 63:5 113:16 124:12 322:6 323:9 329:4,7
direction 70:8 88:9 105:15 201:18 206:3 265:3
directions 107:18 334:3
directly 44:14 314:22 370:19
director 2:19,22 3:3,4,5,6,8,10 6:1 6:4,6,9 20:6 179:18 281:20 304:1 308:18 340:5 367:16 368:2 385:13
Directorate 143:7
disclaimer 94:9 119:6
disclose 12:22 13:4
discontinue 264:6
discouraging 254:12
discrepancy 301:9
discriminatory 170:16
discuss 11:19 12:11 16:21 18:21 41:3 41:17 48:19 52:9 165:10 180:15,16 187:21 206:9 221:3 269:18 285:1 292:9 305:22 372:1
discussed 8:6 12:7 34:20 51:11 57:18 81:2 97:7 177:16 177:20 178:15 211:7 304:16 307:17 311:12 334:2 380:5
discussing 9:4,7 211:14 292:11 365:22
discussion 4:10 8:10 11:5 15:19 19:16,17 35:1,4 39:3 40:20 44:9 71:3 80:19 98:8 107:21 129:3,3 135:20 140:6 150:5,7 168:9 172:13 180:13 185:8 188:15 190:13 191:9 193:1 195:5,22 200:7,12 216:22 218:7,8 234:16 235:5 239:16 240:2 252:10 257:1,6,17 267:5 267:12,15 349:16 349:22 350:1 359:10 367:9
discussions 14:11 15:14,16,19 47:12 75:22 80:16 85:15 93:19 106:1 136:11 179:5 189:4 195:16 222:20 235:6 251:21 252:1 317:17 355:20 366:11 370:15 373:2 382:16 383:17 384:17
disintegrating 69:7
dispensing 69:1 115:13,20
display 90:5
disposal 364:15
dissertation 139:1
dissolution 90:11 170:7,12,15,18 171:1 198:12,13 203:17,19,21
distinct 78:15 176:8 180:3 182:16
distinguished 96:15
distribution 24:16 247:10
diverse 386:2
divided 294:12
division 3:17,20 171:21 175:22 179:17 191:14 292:2 304:1 308:18
division's 185:18
DNA-related 363:3
doable 127:8 365:17
doctor 293:2
document 37:20 180:21 352:8 371:17 397:6,20
documentation 38:2 40:5 209:17
documenting 176:16
documents 33:1 38:1,12 39:12 148:18 167:13 178:17 259:6 335:20
DOE 188:8
doing 18:15 27:5 42:4 50:10 51:6 67:21 69:2 71:20 90:12 96:18 102:8 104:9,9 110:11,11 116:13 117:21 122:7 123:17 131:18 137:13 198:12 201:18 205:15 209:18 215:3 216:6 217:16 221:3 226:14 229:6 238:5 254:3 269:6 295:13,16 314:2 316:8 321:21 327:15,18 328:21 342:14 388:12 400:2
dollar 126:19,20
dollars 101:20 102:12,20
domestic 369:18 380:21
doors 197:7
dosage 29:17 34:1 34:13 62:15 63:15 213:20 284:6 314:4 322:16 326:1,3,8,11,21 326:22 328:2,5,10 329:16 330:15 337:6,14,15 338:12 339:9 343:22 347:5 380:14
dose 69:5 178:12
dossier 147:21 154:13 157:2 159:17 164:11
dossiers 152:2 154:4,22 156:11 156:15 163:13 165:20
doubt 225:9
dozen 120:19
Dr 5:20 6:3,6,8 7:5 7:10,21 13:5,9,11 13:21 14:2,4 16:6 20:1,6,6,9,11 44:7 44:16,17,18,19 45:10,20 46:6,8 47:5,22 50:4,5 51:10 52:12,14,17 52:18,22 53:4,5 53:13,14 74:1,3,4 74:15 75:8,18 76:12 77:15 78:2 79:3 80:5 81:4 82:5 83:4 84:4 85:6,19 87:6,8 88:3 89:20 90:20 92:3,9,12 93:8,22 94:20 96:7,10,11 96:12,14,21 105:20 120:12 121:17 123:9 124:8 125:4,4,4,4 125:5,5,6 126:11 127:18,19 129:10 129:15 131:20,21 132:14 133:22 134:10 135:9,10 135:19 136:8 139:2,8 140:3 141:2,7,8 148:16 160:7 168:6,13,15 168:16,22 169:10 169:19 170:5 171:12,19,20 172:4,5 191:7,16 192:3,11 194:16 194:21,22 195:1 200:11 201:8,8,9 201:10,14,15,16 206:7 207:10,15 207:17 208:11 209:12 210:16 211:6,20 213:4 214:10 217:1,2,22 217:22 219:22 220:1 221:10 222:15,16 223:13 225:8,19,21,22 226:1,17,20 227:12,17 232:8 234:8,12 236:13 236:15 237:17 239:21 240:18,18 240:22 242:12,13 244:5,16 246:5 248:9 251:5 252:5 253:22 254:8

255:3,8 256:13 257:12 258:5,10 258:22 259:11,20 260:9,12 261:9,16 262:7,13,15 263:3 263:18,20,20 264:16,17 265:15 265:16,17 268:15 274:12 282:5 289:7 290:12,14 291:22 292:1,4,7 292:8 303:8 308:7 308:8,13,16 309:1 309:8,18 310:5,8 310:9,9,13,14 327:2 336:7,10 337:1 338:19 339:2,12 340:3,13 345:12 358:2 360:10 363:6 364:3 366:14 367:15,16,19,21 367:22 372:11 385:2 395:20,21 396:17 397:12,16 399:8,8 402:4,4
draft 161:14 166:6 178:11 328:22
dragged 205:17
dragging 205:18
dramatic 175:18 184:14
drawing 403:10
drawn 283:5 288:6
drive 370:14
driven 176:3 214:17
driver 311:11
drives 58:1,2
drop 99:11
drought 361:12
Drs 13:22
drug 1:1,2 3:8,17 3:21 6:7 9:12 10:6 19:4 20:7 25:16,17 29:14 30:2,4 113:3,4 119:10 138:7 171:22 173:18 176:5,9 179:10 191:17 193:4,5 198:21,22 204:3 208:15 209:1,9,9 213:12 238:11 245:11 264:7 270:21 271:12,12 271:16 272:6 274:20 276:11,12 276:15 277:17,22 278:1,11 284:20 284:20 286:13 287:21 292:3 293:5,18 294:4,15 295:15,18,20,22 296:3 298:1 300:21 301:3,15 302:6,9,13 303:16 305:2,14 308:1,5 314:4,10 322:15 327:7 329:18 330:5 338:13 339:6,7 373:19 374:13,16,21 377:3 378:2,4 382:6 384:2
drugs 3:5,22 16:1 16:19 51:20 172:11 174:20 176:11 177:22 178:14 203:6,6 204:13 270:7,8 274:2,4,6,7 280:5 280:16 282:20 284:10,12 287:15 292:4,18,20,21 293:6,7,8,13 294:20 295:6,17 305:1,13,16 306:2 311:8 403:19
drug's 286:17,20
drying 117:21
due 65:2 102:12 184:8 343:9 351:12 356:13 374:22 377:14
dump 204:19
duplicate 344:16
Durham-Humph... 293:4
dynamic 121:12

E

E 2:8,10
eager 381:3
earlier 23:19 30:8 37:8 39:5 41:15 48:13 59:18 98:5 98:8 100:16 111:15 165:5,13 166:7 184:15 216:12 217:21 221:13 280:10 322:22 339:12
early 30:14 96:17 122:19 127:3 129:17 133:16 156:3 173:8 180:7 180:22 182:1 183:13,16,21 192:22 216:3,15 267:4 272:3 327:21 333:11
easier 51:6 161:9 212:17
easily 102:18 290:17 291:3 330:10 363:22 391:4
easy 80:18 127:7 231:2 361:10 363:19 367:8
economic 273:15 391:16 392:18
economically 273:12 282:18,19 286:15 287:18 312:11 318:17 342:9,13 344:11 351:13 356:14
economically-mo... 356:20
economics 274:17
edge 369:7
edition 94:12
editor 94:11
EDQM 143:6 160:15
educate 373:11
effect 16:16 86:8 101:16 162:2,7 269:22 270:22 278:16 282:1 315:9 387:11
effective 55:3 72:9 188:5 195:10 298:5,8 300:1 369:3,9 376:2 384:6
effectively 77:4 85:4 98:7 117:1,2 135:6 222:6
effectiveness 138:19 294:1,7,10 295:7
effects 145:3,5 251:12
efficacy 23:21 41:16 134:22 197:15 218:15,19 295:4
efficiency 30:2 223:6 322:2 331:10 332:8
efficient 54:22 238:15 371:3 372:13 375:19 384:18
efficiently 98:6
effort 16:14 107:12 191:13 212:19 216:8 231:8 233:4 260:15 265:3,8 272:20 314:16,19 320:8 323:14 324:4,15 332:12 334:22 359:15 364:3,20 383:4 384:4 389:5 391:18
efforts 23:19 31:6 43:19 44:21 45:4 45:9 58:11 172:16 206:18 257:21 260:11 270:14 312:17 315:5 316:7 322:6 323:10 331:17 332:6,20 334:17 343:2 344:11 346:6 368:19 382:11 384:22 389:12 393:5
EFSA-related 362:20
egg 79:17
eight 63:22 87:17 88:21,22 89:1 130:17 304:6 309:10
either 50:19 78:17 132:8 149:10 230:9 233:17 248:14 293:16 298:1 302:18 304:3,11 343:9 375:9 377:5
elaborate 78:20 170:3 336:15,19
elaborating 28:22
electronic 5:7 84:5
electrophoresis 278:10
element 58:15 79:15 194:1
elements 25:22 60:22 141:6,12 147:16,20 150:19 172:3,14 174:1,13 176:17 177:7,8 182:16 190:7 191:5
eliminated 116:16 362:6
eliminating 67:18 67:19

Elizabeth 1:21 2:2 5:12
EMA 21:13 143:13 165:4 168:19 178:4 244:18 286:14
EMA/FDA 178:4 236:18 260:13
embrace 103:1
emerge 54:13
emergency 278:3
emerging 222:7
emphasis 23:1 30:13 136:20 184:10 269:16 272:6 284:9
emphasize 251:8 285:10 359:21 369:14 384:12
emphasized 282:21
employ 180:5
employed 221:11
employee 13:21 14:3,5
employees 9:19,20 10:14,15 11:1,2 14:1
employers 11:12
employing 227:8
employment 11:17
enable 174:3 248:3 248:4
enabled 174:16
enabler 48:3 71:19
enablers 26:6
enables 161:12
encapsulation 74:17
encompass 172:8
encourage 12:21 201:20 212:6,22 314:19 315:4 316:3
encouraged 39:2 90:4 350:13 360:7 380:7
encouragement 173:8,12
encourages 14:18
encouraging 254:9
ended 134:12
endless 119:8
endocrinology 176:10
endorsed 40:14
ends 329:20
energies 282:1
enforceable 317:14
enforced 220:18
enforcement 272:11 276:19,20 391:7 393:3,17
engage 195:15 334:8 359:9
engaging 334:16
engineering 6:12 6:15,17 121:2 199:8 244:1
enhance 19:17
enhanced 22:13 30:18 32:18 36:8 38:2 40:5 56:1,4,6 59:8 60:13 63:7 67:6,11 71:16
enhancement 29:19 173:16
enhances 73:16
enjoyed 92:14,15 125:8 290:14
enlisted 262:21
enormous 101:21 102:1 109:15 110:6,8 126:17 139:22
enrichment 75:9
ensure 12:20 19:3 31:13 152:13 157:9 163:6,9,18 164:22 166:15 171:4,8 279:21 292:13 302:2 349:2 352:2 364:18 366:3 369:2,9 376:1
ensuring 18:10,15 165:4 376:6
enter 286:19
enterprise 84:2
entire 24:14 35:16 41:22 71:7 93:11 180:8 181:12 183:15 185:10,19 317:3 326:6,17 383:16 389:21
entirely 213:14 269:15 389:16
entities 176:6 186:10 246:18
entitled 53:10 292:5 340:7
entity 246:16
environment 34:19 138:16 199:18 220:15 224:10,12 224:13
environmental 313:10
environments 363:12
envision 191:4
envisions 177:5
EP 329:22 350:19 351:6
equal 27:9
equally 26:19 29:16 158:15
equals 66:15 153:6 153:14
equipment 63:16 69:22,22 74:19 111:22 313:16
erroneous 116:4
especially 15:19 16:2 35:19 37:3 40:2 41:10 70:12 99:2 273:7 274:5 280:18 282:21
essence 219:5
essential 11:4 13:17 35:14 79:14 203:4
essentially 57:6 108:11 245:14 247:20 257:19 273:1 327:9 340:12 346:15 348:9 351:2 352:6 355:1 365:8
establish 31:12 60:13 117:11 144:14 154:14
established 30:20 60:1 81:11,15 150:1 160:10 244:14 295:6 353:18 359:10 372:16 373:15 376:20 381:13
establishing 23:12 27:14 39:16 193:11 214:3
establishment 25:14
estimate 145:10
estimated 115:14
estrogens 266:21
et 121:13 128:3 129:14 221:20 228:3 242:17 243:10,21 265:7 291:6
etcetera 57:14 59:21 75:7 84:9 90:16 138:7 251:14 252:14 311:21 316:12 335:20 361:10,13 361:14,20
ethics 10:3,11
ethylene 277:2 347:14,17,20 348:3,6 349:9
EU 143:5 260:16 260:18
Europe 33:8 68:16 148:22 150:2 152:12 162:22 164:21 167:1,16 169:3 229:2 244:17,20 362:20
European 2:16 141:3,6,10,16 142:2,6,7,15,16 142:20 143:2,4,4 143:6,8 144:19 149:14,20 163:8 167:20 236:7 362:21
evaluate 13:19 43:1 43:12 45:8 84:14 167:10 291:11 301:12,18,19,21 317:7 354:20 357:5
evaluated 32:12 34:16 162:5,9 382:3
evaluating 83:2
evaluation 1:2 3:21 44:21 84:1 142:4 143:18 149:6,7 150:12 163:13,16 188:3 292:3
evaporates 119:11
Evdokia 2:16 141:3
events 371:14
eventually 54:13 72:13 81:1 112:8 125:15 204:15 251:12,16 279:14 394:17
everybody 15:12 194:7 228:1 229:20 372:1
everyone's 16:14
evidence 218:17 249:5,10
evident 221:18,22 372:9
evolution 272:5
evolutionary 128:15
evolve 128:14
evolved 41:21
evolves 75:5

evolving 17:12 19:7
exact 291:19
exactly 72:19 127:17 136:6 172:6 204:13 263:8 313:21
example 23:6 24:17 29:7 42:9 43:10 60:3 68:21 80:20 87:17 144:10,16 144:19 162:14 170:6 185:22 238:7 246:19,22 250:16 253:17 259:5 265:7 275:4 277:12 287:17 300:5,6 304:5 309:9,15 321:11 322:17 324:19 329:2 331:5 337:5 337:8 342:19 343:21 344:7 396:14
examples 24:12 27:18 52:5 69:15 72:8 79:9 153:22 165:10 189:11,18 189:22 190:9 250:1,2 273:16 275:1,1 303:10 324:16 341:10 361:21
exceed 369:5
exceeding 376:5
excellence 54:17 98:4 142:4
excellent 19:13 47:6,22 96:21 192:12 206:8 232:9,19
excerpt 154:18
excessive 88:12 89:4
exchange 185:9
excipient 73:3 95:1 95:17 138:6 274:14 287:21 289:16 306:7 340:15,17,20 341:5,18 349:15 349:17 350:2 353:20 356:2 357:21 358:7 359:12 360:1 364:7,11 366:19
excipients 2:22 72:16,21 86:1 94:11,13 95:12,13 270:17 271:15 274:19 281:8 284:11,22 287:16 289:11,20 290:4 290:10 305:14 311:8 340:6,9 350:5 358:5 360:12,13 367:1
excited 236:17 237:13
exciting 255:17
exclude 14:15
exclusion 14:16
exclusivity 99:10 225:9 226:10,16
Excuse 225:19 251:7
exercising 54:2
exhaustive 319:6
exist 309:6 320:20 325:1 329:16 369:12,20 378:22 398:5
existent 308:19,19
existing 32:19 65:14 71:3 80:9 87:15,16 137:21 138:17 151:2 167:13 191:15 196:4 235:2 303:21 304:8 330:20 354:20 357:6 374:6 375:11 377:5
exists 66:22
expand 65:8,10 370:10
expanded 179:21 188:2
expect 60:19 62:11 90:22 120:5 163:22 368:21 375:22 397:19
expectation 41:5 219:10
expectations 218:3 228:11 243:5 260:1 302:21 311:19 355:13 369:1 376:6
expected 30:15 35:21 40:18
expecting 52:7
expects 50:20
expeditious 278:17
expeditiously 278:4
expenditure 101:7
expenses 114:20
expensive 28:5 342:17 362:2
experience 97:4 98:18 115:22 121:15 122:14 124:7,21 137:9 139:14 157:3,7 167:8 174:11 175:4 188:13 190:1 192:15 212:16 221:8
experiment 85:1
experimental 57:13 59:1,20 84:16 85:13
experiments 27:10 40:10 57:13 59:20 84:22 86:13,15,18 114:11,19 153:14 155:16 157:16 190:1
expert 11:14 78:14 87:4 149:11 297:15 298:12,17 305:19,20,22 312:4 317:6,22 326:16 327:1 328:13 331:22,22 332:3,13,15,16 333:19 353:18,20 353:21 354:2,13 354:16,19 356:1,2 357:1,17,17,19,21 359:10 375:12 376:11 378:10
expertise 11:4 112:1 114:17,18 130:8 137:20 144:8,17 163:6 167:11 184:11 185:7 192:9 193:21 194:12 196:15 228:19 288:7 374:5 376:12 404:2
experts 142:20 143:9,10 144:1 149:14 150:22 163:1 176:22 179:18 180:9 356:17 370:14,17 371:5 375:13 376:10,19 377:16 377:19,20,20 378:9 381:19
expires 99:10 394:5
explain 154:21 221:16,16 294:20 296:7
explained 280:14
explanations 154:16
explanatory 137:11
explicit 65:20 66:9
exploration 187:10
explore 250:15 332:21
exploring 148:6
exposed 238:16,16
exposure 374:15
express 8:11
extend 375:3
extended 190:22
extension 173:19
extensive 21:15 32:9 33:5,20 35:4 66:22 149:16 163:1,14 196:20 327:8
extensively 57:11 148:15
extent 46:4 50:22 168:20 197:9 227:22 265:1 318:22 336:20
external 178:22 179:6
extra 217:12,14 238:15
extracted 337:15
extremely 55:2 117:15 222:5 232:11
eye 239:11

F

face 110:6
faced 96:3 154:6 166:10 225:11
facilitate 17:17 18:2 21:8,17 22:3 26:6 27:11 30:17 30:20 32:2 38:18 43:20 44:8 51:22 141:20 148:13 149:1 151:3 152:6 152:9 159:4,19 160:17,19 162:12 177:11 179:3 193:1,12 195:12 195:22 206:19 257:22 260:8 263:1
facilitated 48:7 185:9 200:5 235:6
facilitates 25:13,15
facilitating 234:19 262:17
facilitation 173:10

facilitators 21:9
facilities 65:13,14 116:19 283:10
facility 63:16 219:15
facing 109:13,13 132:5,11 133:20 141:22 157:1 163:5
fact 31:1 48:5 56:15 70:10 91:2 124:7 152:15 205:10 210:19 214:17 222:19 230:5 364:14 380:7 386:14 392:7,12 397:4 400:9
facto 224:8
factor 96:5
factors 263:9 286:11,21 317:5 318:18 384:14
facts 66:13
faculty 33:7
Fadia 2:11 7:10
failed 88:17 171:15 198:13
failing 206:12
fails 198:14
failure 64:6 86:8 89:15
failures 118:21 303:12
fair 8:9 72:20 362:22
fairly 26:18 168:10 175:2 330:9
fall 190:13 284:19
fallacy 67:17
falls 183:20
familiar 82:1 177:16 309:5 361:12 398:16
families 138:6 322:12 323:7 325:17 375:10 377:8
family 314:3 326:6 326:18 328:19 329:13
fantastic 201:14
far 16:4 17:9 32:3 36:18 75:22 76:9 87:3 141:19 146:20 147:13 153:9 208:13 209:7 215:22 229:18 232:15 233:16 255:9,19 261:1 270:2 337:17 394:19 395:15 402:22
fashion 253:2
fast 110:5 132:21 206:2
faster 111:12 118:13 137:19 162:19
fatty 343:6 344:4 344:15 362:10,13
favorite 245:9
Fc 247:1
FCC 351:18 354:11 354:11 355:8 357:3
FDA 1:20 3:1 5:9 5:19 9:2,3 10:9,13 10:22 14:13,18 15:2,18 17:6,15 18:15 19:1,14 20:8 21:13 43:19 50:20 56:2 76:19 76:22 91:3 93:10 94:5 105:6 118:20 127:10 135:17 140:18 165:4 168:19 171:22 172:1,3 206:13,18 207:8 222:20,20 228:8 232:7,20 237:15 239:12 243:4,14 254:6 257:22 258:11,16 260:2,16,19 261:7 268:6,18,20 269:2 269:5 270:6 271:19 272:10,12 274:6 275:11 276:18 278:5 279:17 280:18 282:3,6 284:22 286:16 288:6 293:15 294:6 304:17 305:18 311:6 312:5 315:14,19 322:6 325:7 326:6,15,20 327:5 328:13 329:13 331:13 332:17,22 334:1,9 334:16 335:1 339:19 345:6 346:12,19 348:5 348:12,15,16 349:7,14 350:10 352:11 354:1,6 355:20 356:6,12 359:16 360:3 364:22 368:5 369:6 370:8 371:5 371:21 372:15,19 373:3,7 374:2,5 374:19 379:2 380:8,12 381:4 383:2,10 385:13 388:3 389:3,6 391:11,19 392:10 393:19,21,22 394:10 395:2,11 402:11
FDA's 11:19 12:9 13:3,14 18:8 173:17 257:8 282:11 305:9 315:2 335:4 352:18 365:8 374:12 375:2,6,7 377:12 381:16
FDA-USP 275:1 385:15
FDA-USP-CHPA 372:3
FDA/OTC 270:9
FD&C 10:21 271:18
fear 254:2
feasibility 393:4
feasible 295:9
feature 154:4 398:7
February 315:17 315:22 352:13 373:10
federal 3:2 7:6 8:17 9:16,19,21 10:3,6 10:11,15 11:2 241:12 243:21 297:9 298:16
feed 222:3
feedback 74:10 120:16 189:9 216:13 237:5 373:14 382:4 383:8
feel 132:2 204:6 240:9 241:13 315:2 335:4,9 376:18
feeling 100:11 128:8 134:19 261:1
feels 154:20
fellow 257:14
felt 15:17 260:15 260:19
fermentation 79:5 79:6
Fernando 2:9 6:14 51:10 121:1
Feuer 100:18
fewer 62:8
FID 349:8
field 127:11 179:10 283:9,9,10,11 392:21
figure 51:3 76:11 201:4 211:4 213:2 339:18
file 105:4 109:14,20 110:2,13 121:18 122:16 123:22 126:14,16 208:18 209:1,21 210:6 222:10
filed 65:11 124:2
filing 43:3 65:7 208:7 209:14 212:17,21 215:7 218:3 258:13 259:3,5
filings 62:22 76:7 215:18
fill 335:11
filled 99:8,15
final 52:18 57:15 119:19 178:13 298:14 299:9,13 299:13,16,17 300:3 352:15 355:21 375:20
finalize 40:12
finalized 39:12 46:10 181:13 190:10
finally 177:2 223:2 271:1 292:14 341:10 344:4 353:4 401:22
financial 10:16,19 11:2,8 12:16 14:14,20 64:19 212:1
find 62:21 63:9 90:3 98:4 136:6 230:12 232:12 233:3,15 234:22 235:19 286:8 313:17 320:11 323:22 331:2 350:20 396:2,4,8 397:17 400:5 403:17
finding 65:6 208:14 209:8 313:19
findings 36:16

fine 75:5 96:18 104:10 113:11 257:10
fingertips 139:21
finish 239:19 395:5
finished 67:18 86:5 86:21 93:10 153:21 156:1,6 158:20 159:6 162:3,8 276:14 390:13 395:7
finishes 304:13
firms 14:21 173:22
first 16:4,21 20:5 22:8,17 34:7 35:8 39:13 43:18 44:22 56:14 59:7 60:15 61:1,11 62:13 63:13,13,18 64:10 64:20 74:3 77:18 77:21 79:8 85:22 86:17 97:3 98:3 98:15 105:4 106:14 109:14,20 110:1,12 120:12 122:16 126:14,16 130:12 137:1 141:13 148:11 149:3 151:21 166:5 169:1 195:1 201:17 203:18 206:17 208:7,14 209:8,15,21 210:6 212:20 213:3 214:12 220:8,10 221:13 222:9,12 222:13 251:17 255:8 257:20 258:13 265:5 275:4 277:15 284:2 290:19 297:7 298:18 326:13 330:12 338:9 368:5,20 369:14 372:9 377:10 379:7 390:19 391:9 392:1 395:20 398:18,21 402:8
fiscal 184:15
fit 49:10
five 34:6,20 89:2 99:11 102:12 173:4 248:14 277:7,8 279:4,6 279:10
five-year 332:3 335:16
fix 110:16 387:5 388:14 400:10
fixed 55:17 60:16 72:5 73:14 342:5 342:11,16,17 361:22 362:9
flat 108:16
fleshed 175:2
flexibility 27:17 56:8 65:15,18,21 66:2,9 67:6 118:14 162:13 211:2
flexible 22:19 28:10 39:9 61:2 152:10 382:14
flow 113:9,11 186:12
flowing 118:2
flows 124:11
fluid 130:13
FMEA 57:10 86:8
focal 92:1,3
focus 40:20 42:7 59:12,12 67:10 115:10 119:7 122:5,11 128:18 144:20 149:18 164:4 215:4 218:12 219:1 227:7 249:7,7 258:10 279:20 280:15 282:1,16 283:16,16 286:12 289:13,15,18,19 297:5 307:3 325:9 341:15 371:20 377:2,8 382:11 392:19,19 395:13 401:4
focused 76:2 189:9 206:12 235:6 289:19 290:8,8 342:7 381:14 383:11
focuses 24:10 145:16
focusing 55:4 214:13 321:3 323:14 365:9
folks 102:20 118:10 131:17
follow 75:3 206:4 255:13 294:9 316:17
followed 20:20 21:12 60:15 162:2 172:11 278:18 346:18
following 10:1 13:17 23:18 35:7 146:10 149:3 277:5 280:22 284:22 298:12 313:20 401:5,6
follow-up 85:7 91:16 403:21
food 1:1 9:12 10:6 72:17 271:16 293:5 351:19 355:16 362:21 384:2 387:18
footing 226:9
force 216:11
forecast 65:1
forefront 81:9
forego 385:8,10
foreseeable 70:19
forever 51:7 158:12 247:13
forfeiting 210:10
forget 116:20
form 29:17 34:1,13 62:15 64:3 79:7 213:21 284:6 326:8 329:16 332:12 337:6,15 337:16 338:12 339:9 347:5 367:4 375:11
formal 45:7 251:22
format 190:5
formation 260:6 261:13,15 282:6 354:16
formats 384:12
formed 278:6 297:15 305:7 326:12 332:15 357:19 372:4 379:10 386:10
former 102:14 109:1 126:15
forms 63:15 314:5 322:16 326:1,3,11 326:21,22 328:2,5 328:10 343:22 380:14
formula 228:20
Formulary 271:13
formulation 95:22 101:2 108:22 109:1 114:15 124:6,13 245:11 300:3 301:16
formulations 95:2 95:5 106:7 309:11 328:6 373:22
formulation-dep... 94:22 95:14
formulator 104:18
forth 235:14 259:13 297:18
forum 8:9,21 150:5 150:6 218:11 233:2 316:6,19 324:18 398:13,15
forums 188:17 228:2 229:22 230:1 333:13 358:16
forward 8:16 15:21 16:4 17:19 19:12 19:15,18 56:19 68:17 176:12 214:22 220:14 221:7 233:9 234:19 240:11 242:11 287:14 328:16 330:12 334:9 340:1 368:16 371:3,19 372:6,14 373:4 384:17,21 389:14 390:22 403:22
forwarding 220:13
for-profit 235:10
foster 142:3
found 10:4 151:17 155:17 164:16 277:18 297:22 305:1 306:16 325:21
four 34:22 53:22 63:22 65:1 85:16 88:21 89:1 98:9 99:10 102:11 108:6 125:20 139:10 146:22 153:8 172:8 187:17 189:3 195:2 228:4 330:16
fourth 323:18
frames 209:19
framework 90:1 152:11 160:19 161:11
freely 95:9
frequency 184:6
frequently 110:4 225:11 341:8
friend 96:16
friends 236:8
front 201:3 205:13 386:21 389:2 395:9

fruit 91:1 120:18
fruitful 395:15
fulfill 373:16
fulfilling 369:1 385:1
full 54:11 56:19 90:5 190:15 324:13 375:18 381:5 399:4
fully 36:19 48:3 74:16,18 196:2 228:18 374:6
full-blown 392:22
full-time 230:22 272:19
function 392:5
functionality 91:12 289:11 290:2,7
functions 188:6
fundamental 88:14 177:10 365:5
funded 231:16
funding 241:11
Furness 304:1 308:17
further 18:2 31:15 39:3 41:17 46:9 49:5 65:8,9 142:1 153:18 156:12 158:11 166:2,4 187:12 190:13 200:6 257:1 278:20 359:20 402:22
future 19:20 29:4 37:4,10 52:10 58:12 70:19 73:22 92:21 103:22 104:3,7 166:8,21 214:12 235:5 270:2 288:1 334:3 371:12 374:7 379:15 389:15 395:15

G

gain 105:8 139:17 150:18 210:10 273:15
gained 15:18 124:22
gaining 17:12
gap 44:4 192:9,13 197:16 232:3 234:3
gaps 22:5 48:17 132:10 149:4,10 157:3 165:12 199:6 206:22 228:6 231:10,14 231:18 234:1,4,7 235:20 253:6 258:2 312:1 335:12 369:12,14 370:2 371:18
gas 347:16 349:8
gather 47:18 157:2 167:8 373:14 383:8
gathered 297:16
gathering 371:22
GC 313:17 316:11 347:15 364:9
general 12:5,6 13:10 16:17 19:4 35:5 46:18 94:4 119:4 132:4 141:14 201:18 204:20 205:4 287:7 292:19 295:1 297:8 306:1 307:18,19 312:7 326:10 329:14 338:6 377:6 382:9
generally 84:15 113:9 202:15 298:4 299:22
generate 116:6
generated 68:8
generations 206:4
generic 2:15 3:5 16:18 96:12 97:15 99:5,9,15 100:5 105:15,21 106:3 109:15 113:5 120:3,20 121:16 122:2 126:6 129:18 131:7 132:13,16 134:13 138:15 172:19 177:22 188:21,22 189:1 209:9 210:2 211:16,22 212:5,7 212:15,21 222:9 225:10,16 228:22 258:15
generics 98:1 100:9 101:9 106:13 109:8 120:18 128:9,17,18 129:12 132:13 147:12 189:8 237:12
generous 331:16
genetic 251:14
genetics 28:18
gentle 8:13
gentleman 220:2
Gerry 2:17 14:2 53:4 74:5 75:19 80:6 94:1 96:7 117:14 125:21 129:6 130:3 205:8 218:5 220:3
getting 56:22 73:4 110:12 213:21 214:7,8 224:22 251:13 255:20 314:16 318:7,8 324:9 338:14 363:2 389:8
giant 398:16
give 54:8 94:22 124:4 140:4 141:13 154:5,16 172:20 200:15 201:3 221:4 229:21 269:13 270:19 271:3 287:20 320:10 337:5 341:14 344:7 359:6 366:5 366:6,10 398:4
given 16:12 121:11 145:11 204:16 265:7 350:20 360:19
gives 64:16 100:14 123:20 124:3 340:14 348:9
giving 269:9 271:8 360:18 362:14
gizmo 253:7
glad 44:7
global 37:2 152:15 236:10 272:6 361:20 369:18 380:20 384:11
globalization 361:9
globally 152:16
glove 250:22 260:18
gluten 387:21
glycerin 275:5,12 275:15,17 277:7 342:2 345:9,18 346:3,12 347:1 349:2 358:19 359:1 365:4 388:2
glycerine 275:16 275:20
glycoform 248:14 250:16
glycoforms 238:12 247:2
glycol 275:13,14 276:7,17 277:1,2 277:10 303:10 317:1 318:11 336:17 345:17,20 346:4,7,15,21 347:8,14,17,20 348:3,6,20 349:9 349:10
glycolpyrrolate 324:19
glycol/ethylene 277:10
GMP 25:21 34:21 39:10
GMPs 41:20 347:4
go 5:18,20 47:14 58:17 60:12 67:8 70:8,20 71:6,16 75:6 79:4 82:16 84:15,21 86:18 87:9,18 89:7,7,12 89:18 91:1 94:19 95:1 103:10 108:21 110:5 111:12 118:7 120:2,5,9 135:14 155:20 162:5 164:1 170:14 180:21 186:2 187:12 202:7 214:14 218:16 225:10 230:1,3,17 233:21 238:22 247:13 260:17 265:22 269:10,20 270:12 273:16 274:22 275:8 279:1 281:3 284:16 291:16 292:21 296:6 298:18 317:2 320:11 337:17 341:21 343:17 375:17 386:19 388:18 393:10 394:14 395:12 396:3 398:19 399:4 403:9
goal 8:8 28:11,12 116:11 218:12,14 335:8 336:1 342:12 359:18 376:5 391:17
goals 111:13 279:10 374:7,7 388:14 389:13 395:13
goes 18:14 70:1 90:7 98:18 121:20

136:4 227:21 231:7 232:16 251:9 287:14 289:21 297:9 388:4
going 15:22 16:15 16:21 17:21 18:19 19:19 47:9 51:8 52:4 58:17 70:18 75:21 76:12 79:4 84:11 88:18 89:10 90:11 92:6,11,20 94:9 95:15 97:3 97:10,12,13,19 99:3 103:12 106:5 109:9,9,11 110:16 112:7,9,20,21 114:12,12 115:10 125:20 126:22 127:1,7 128:2 130:5 131:15 132:14 137:17 161:21 162:8 193:18 194:4 200:14 202:6,20 204:22 205:14 206:9 214:4,4 223:10 227:14,21 234:1 237:17 239:9,18 240:16 242:6 245:4,7 252:16,18 257:1,9 257:11 259:9,14 262:6 265:4 266:12 267:11 269:4 271:5 275:9 285:7 287:12 289:1,15,18 294:11,20 301:21 305:21 324:6 327:1,3 328:14 330:6 340:1,12 343:16 361:8 364:8 371:6 385:8 388:2 390:8,16 391:11 393:9 396:11 400:19 403:16
gold 205:14
good 5:3,22 8:4 9:11 20:11 22:10 23:3 27:7 28:15 28:15 36:22 40:21 45:11 50:8 51:11 52:9 53:14 62:17 66:13 75:14 93:1 96:15,16,17 108:9 117:13 118:5 120:3,4 122:13 124:19 125:17 127:2 131:15 132:2,7 133:9 134:6 137:18 160:5 172:5 181:14 182:14 193:14 195:5 196:10 197:18 203:19 204:17,18 207:11 213:7 214:9 218:22 233:8,12 234:20 242:10 250:4 254:17 261:2 265:4 276:11 287:11 289:2,9 310:4,14 363:21 368:1 387:9 390:15
Goozner 2:3 6:22 6:22 49:20,21 191:11,12
gotten 232:20,21 312:2
government 8:18 9:19 10:14 11:1
GPhA 97:4
GPHN 107:7 118:7
grant 10:14,22 118:8 235:8
granted 142:14
grants 11:15
Grant's 119:3
granulation 130:14
graph 175:11
grassroots 222:22
GRAS/GRAE 298:5
great 1:17 17:4 31:8 93:12 120:15 127:20 129:10 195:3 210:1,3 211:15 215:4 223:14 244:6 259:9 283:10 289:4,10 394:18
greater 275:8
greatest 307:4 314:15 322:10
greatly 67:6 211:21 272:7
grew 79:4
GRMB 208:20
group 30:20 31:13 32:4 33:4 37:19 41:7 78:7 93:10 108:8 138:6 148:20 154:19 156:13 165:3 167:18 178:16 188:16 222:1 223:1 241:18 242:3,21 245:10 261:14,15 268:21 269:7,8,21 282:6 282:8,9 283:1,3 283:13 285:3,22 287:5 288:4,8 291:4 304:17,22 305:10 315:15 322:5 325:8 331:15 333:3 342:4 349:16 350:1,1,17 357:13 365:8 377:3,22 378:3,11,15 379:12,18 381:8 381:14,21 382:3 382:19,19 386:2,8 386:11,17 387:8 387:14,15 392:10
groups 57:1 139:16 144:17 297:13 373:16 376:21 389:3 403:16
Group's 222:10
growing 256:14
growth 370:7
guarantee 135:2
guess 15:13 93:13 98:1 123:15,16 133:18 135:8 139:1 237:4 250:7 309:20 336:15 365:10
guesstimate 360:19
guest 2:14 13:14 14:7 140:18 268:6
guests 96:15
guidance 71:1 149:15,21 151:6 154:5 156:12 161:15 163:15 166:3,6,6 167:4 167:12 177:13 178:13 275:12 276:2,4 307:22,22 348:16 349:5
guidances 172:16 176:18 178:10,11
guideline 22:10,16 24:10 25:11 29:13 31:3 46:11 151:9 151:10
guidelines 21:21 22:6 26:10 30:7 31:2,14,16,19 32:6,17,20 34:7 35:14,15 38:15 107:9,18 143:20 148:17 151:1,2,13 369:18 380:21
gun 202:20
guy 109:1 130:15 130:15
guys 244:3 257:8

H

Haiti 345:7 346:4
half 109:18 120:19 247:4 324:5,5
hammer 296:17
hand 8:21 18:14,14 75:14 117:5 159:12 250:22 252:21 253:21 254:1 260:18 399:13
Handbook 94:10
handicap 134:4
handle 80:12 166:13 403:1
handled 160:1 164:8 356:1
hands-on 179:7
hand-held 393:4
happen 31:11 88:16 119:17 181:13 273:4 275:22
happened 205:1 258:6 260:10
happening 93:20 134:8 193:19
happens 186:5 261:11
happy 44:14 45:18 93:2 205:16 269:1
hard 136:17 137:14 237:20 238:6 251:5
harder 230:5 313:16
hardness 69:4
harmonization 12:2 37:2 66:7 164:20 352:12 353:3 370:3 384:9
harmonized 31:13 32:2 150:2 152:13 163:10 167:6 351:5,8 382:15
harmonizing 164:22 165:1
Harriet 2:9 6:11
hate 209:9 244:11

367:3
Hawaii 7:21 8:3
head 218:1
headed 327:2
heading 336:2
heads 272:17
health 14:5 18:11 98:22 142:6 278:3 282:12,14 284:2 290:1,9 291:12,17 293:2 297:12 304:15 307:5 311:14 322:11 367:17 368:4 383:21
Healthcare 2:19
hear 36:18,22 48:9 80:14 93:4 152:19 200:20 201:1 205:19 224:9 228:9 240:4 241:20 243:19 269:11 306:7
heard 111:15 113:21 195:20 200:2 207:20 208:3 211:17 220:19 228:2,15 385:20 403:12
hearing 194:19 205:12 220:12 245:3 385:8,10
heart 16:13 245:13
heavily 150:13 380:17
heavy 335:9 351:9 353:10
Heinicke 118:8
held 8:8 50:1 64:13 107:14 187:20 279:4 297:19 392:17 399:14
Helen 3:3 5:20 6:1 15:3 26:11 53:20 100:16 234:13 265:18 402:4
hello 52:22 127:19 141:8 220:1 242:13 395:21
help 42:19 43:18 93:6 134:9 184:22 203:13,14 208:10 219:9 230:6 239:20 241:15 258:12,12 262:22 263:1 266:17 280:10 282:15 283:16 322:6 333:1 362:5 364:21 369:8,22 369:22 388:18 392:8 394:12 395:8 402:13
helped 16:7 45:6 258:10 292:15
helpful 16:9 30:9 45:5 52:2 166:2 217:7 252:9 260:3 260:19 320:9
helping 15:21 288:14
helps 113:14 223:14 314:5 403:5
heparin 277:14,15 277:17,21,21 278:8,11 291:15 303:9 316:22 318:10 336:17
hesitant 233:9
heterogeneous 246:12
he'll 270:12
hi 136:9 399:10,11
high 106:17 115:14 115:20 116:12 258:4 259:10 274:20 281:12,13 282:3 284:21 306:19 315:19 325:11 342:2 345:4 348:7 359:2 359:4 376:7 387:21
higher 31:17 36:8 56:5 63:12 211:12 303:6 399:19
highest 167:22 283:22 284:8 286:2 368:21 375:22
highlight 275:9 346:4 371:11
highlighted 76:3
highly 204:11 260:13 275:17 350:4
hill 205:6
Hilo 8:3
hired 98:15
historical 79:20
historically 193:4 217:6 290:16
history 79:4 128:1 172:20 269:13 272:2 275:6,10,19 346:2
hit 258:4 400:11
hitting 218:1 364:2
hoc 144:15
hoc-ish 244:12
Holcomb 100:17
hold 45:12 168:12 211:4 264:14 358:16 400:7
holds 279:6
home 220:14 248:6 296:17 385:22 404:3
hook 257:12
hope 15:9 96:18 129:6 200:5 202:11 211:10 220:20 270:3 324:10 385:21
hopefully 44:1 117:13 118:18 185:11,16 223:9 231:16 299:2 323:11 329:9
hoping 321:18 332:20
host 383:13
hosted 373:10
hot 284:14 315:17 358:6,21
hour 385:6
hours 68:10 378:7 378:7 385:22
HPLC 324:20,22 341:3
huge 81:18 208:6
hugely 262:9
human 12:4 144:3 144:6 151:17
humbled 288:9
humor 220:20
hundred 126:18 339:8
hundreds 295:8,13
hurdles 56:10,14 56:22 60:18 68:17 70:9
hydrazine 351:8 352:9
hydrochloride 329:18 330:8 382:5
hydrogen-nitrogen 365:12
hydrolysis 112:19 114:9 379:11

I

IBD 266:2
ICH 20:9 21:21 22:2,6,9,21 24:4 24:18 25:11,19 26:9,16 29:11,20 30:10,19,22 32:4 32:8 33:8,17 35:9 36:6 37:3 46:10 93:1 148:17,19 152:12 154:18 165:1,2 167:17 174:17 178:19 189:17 219:2 307:21
ID 69:1 277:11 306:12 320:21 336:14,18 337:4,5 337:8,18,21 338:1 338:1 344:8 345:11,14 364:14 364:18 366:9 388:7
idea 100:14 116:15 169:17 215:9 232:19 233:11 237:19 238:4 241:17 263:4 295:1 307:16 310:4 371:21,22
ideal 202:5
ideally 231:21 239:6
ideas 32:18 49:3 128:2 185:9 328:17 333:9
identical 293:20
identification 46:21 245:22 273:8 276:8,13,17 340:21 343:5 344:2,15 345:11 346:10,13,14,16 347:3,5,13 348:7 363:9,9 382:9
identified 31:14 32:15 44:4 92:1 207:1 237:6 258:3 285:16 306:5 319:4,13 320:19 340:19
identify 5:8 21:7 32:13 114:14 116:11,20 149:4,7 231:9 235:10 247:13 253:13 283:13,14 307:10 361:11 364:20 365:2 371:18 374:13 376:9
identifying 242:4
identity 278:11

280:13 342:15 347:9 348:18 362:15
IED 363:20
if's?þ 135:5
IgG 247:1
illustrate 20:22 189:12,19
illustrates 21:14 389:22
illustrating 371:7
illustration 30:10 189:16
illustrative 23:6 25:4
imagine 66:20 83:20 99:8
imaging 91:3,4,14 91:17
immediate 90:21 189:19 190:8
immediately 373:5
impact 31:8 36:21 37:4,5 53:10,17 54:6,8 60:10 66:20 70:5 84:14 105:3 113:20 114:9 132:3 136:22 222:2 322:2,11 323:10 323:22 359:4
impacts 32:19 60:6 258:14
impart 329:5
impeding 43:7
imperative 384:1
implement 23:16 47:19 48:3,13 56:8 108:16 147:6 162:11,17 163:12 174:3 189:14 196:3 208:10 258:12,12 328:17 328:18 359:18 375:15
implementation 4:6 11:21 16:22 17:17,20 18:2 20:3 21:2,4,6,10 21:17,22 22:1,3,7 25:8 27:12 28:21 29:12 30:16,17,19 30:21 31:3,12,13 32:2,4 33:4 34:9 35:13 37:5,19,20 41:6 43:21 49:13 51:14 103:15 132:12 133:20 141:20 147:3 148:14,19 149:1 152:6,14 154:18 156:13 163:10 164:12 165:1,3 167:6,18 172:21 172:22 173:12 174:12 176:14 178:16 185:3 186:19 188:10,15 190:3,15,17 206:19 208:8 219:13,18 235:11 244:7 249:15 258:1 355:7
implemented 34:18 36:19 37:15 49:15 77:5,22 81:2 107:13 117:10 124:21 132:16 161:9,22 162:19 164:6 166:12 219:16
implementing 17:2 17:9,14 106:4,20 106:21 130:2 135:15 148:3 207:21 208:6 221:9 232:16
implication 42:15
implications 136:3 155:10
imply 369:15
import 86:10
importance 141:17 259:15 262:7 269:17 280:7 281:21 283:22
important 22:8 26:8,19,22 27:11 28:17,19 29:2 30:4 31:7 39:10 40:17 41:2,13 42:16,22 44:6 51:18 53:19 55:9 57:19 65:16 90:19 99:1,2,3 105:10 106:3 110:13 111:4 112:13 113:6 118:11 121:21 123:3 138:20 141:22 147:18 149:12 152:8 154:2 155:22 156:3,5 158:15 160:17 165:3 167:1 189:20 192:19,21 193:1 205:11 231:10 232:11 234:10 236:10 240:7 242:16 246:3 248:12 253:8,13 259:1 262:9 267:4,16 272:10 273:20 274:5,16,18 286:16 310:16 315:3 333:6 336:19 337:22 349:21 363:5 368:7 374:9 384:14
importantly 61:2 183:1 236:7 321:15
imported 277:16
impress 94:2
impression 290:15
impressive 74:8 80:8 90:3 134:16 192:7
improve 19:10 30:1 40:20 103:2,3 163:18 196:21 202:1
improved 54:19 66:17 152:3 277:9
improvement 25:10 43:8 56:9 58:5,9,11 59:6 128:13 152:9 160:20 161:12 251:13 277:13
improvements 61:4 65:9 102:4 271:1 307:2 370:5 375:17
improving 203:5 292:6,14 322:2 325:5 388:22 390:3
impurities 227:7 273:19,21 280:21 290:6 303:15 305:22 306:1,15 306:18 307:16 308:1,2,14 309:22 314:11 316:14 321:5 324:21 325:15 329:1,21 329:22 330:8,20 338:5 343:8 344:19 345:16,22 346:8 351:4 366:4 366:10 399:17
impurity 246:14 247:11,12 284:11 304:2,8,11 309:6 309:17 314:8 320:19 326:9 329:14,15 336:13 336:21 337:3 338:2 341:11 347:20
imputed 11:10 14:13
inactive 270:18 271:14 274:14
inadequate 73:1 273:6,19 304:3,7 304:12 308:20,21 308:21 309:6,16 338:4
incident 276:1 277:14 345:8 346:5
incidents 273:9,11 275:20,21 280:11
include 11:13 16:18 101:4 146:22 168:12 169:14 175:9 181:4 182:3 276:22 286:10 300:4 307:21 326:14 346:13 348:6
included 43:14 59:11 154:12 158:17 159:7 161:18 187:22 188:2 277:10 278:10 338:22 343:4,5,8 344:21 345:14,15 349:15 353:9 357:20 379:7,15
includes 24:11 179:22 301:15 308:2 348:19 352:8,16 380:14
including 11:10 28:18 68:7 172:15 174:13 178:11 179:4,17 180:9 189:3 221:18 300:2 326:17
inclusion 302:9,12 347:2
incoming 111:18
inconsistently 351:7
incorporate 12:1 36:1 183:14 231:3 403:11
incorporated 53:5

174:17
increase 62:11 65:3 101:21 105:4 136:16 146:6 175:18 177:6 184:14 190:19 313:22 314:13 315:11 381:6
increased 38:15 56:7 65:15 102:14 184:8,10,20 185:17 272:7
increases 73:17 176:8
increasing 67:20 138:19 147:16 174:20 237:10
increasingly 272:9 313:18
incredible 110:1
incremental 61:4,5 101:20
incumbent 257:2,5
independent 13:12 143:22 392:17
indepth 185:8 235:1
index 398:20,21
Indian 50:2
indicate 170:8 354:7 358:4 370:2
indicated 347:19 348:22 349:5 351:10,17
indicates 17:8 348:17 356:12 400:5
indicating 170:13 356:15
indication 175:22 296:10,15 303:3 343:13
indicator 156:1 170:9
indifferent 250:20
individual 101:22 233:6 244:12 322:12 357:16 370:21 398:6
individually 375:9
individuals 8:11,14 10:18 18:20 376:14,16
indulgence 257:8
industrial 6:12 7:3 7:18 242:22 243:16
industries 72:17 97:16,16 137:12 152:15 370:4
industry 2:12 13:3 13:6,8,10,12 17:8 17:13,14 18:3,12 20:21 21:4,4,11 27:19 34:11,16 35:18 36:3 37:1 37:13,15 38:17 42:19,22 44:3 48:10 50:18 51:16 51:20 52:3 53:12 53:18 56:2 62:18 68:18 72:17 76:9 83:3 94:4 98:13 99:18 100:5 101:19 103:14 105:16,21 106:4 107:8,15,16 115:8 116:6 118:12 119:4,18 120:3 121:16 122:2 127:14 129:19 131:8 132:20 134:13 149:6 150:15 159:1,14 164:19 165:17 167:15 169:6 174:11 189:2,9 190:14 196:6 200:5 202:7 205:13 209:20 210:2,3 211:16,22 212:7,15 213:2 214:14,19 215:3 215:16,19,22 222:9 224:17 225:6 226:4 228:22 232:21 235:18 241:14,20 242:3,9 254:9 258:15 259:6 262:18 270:20,21 278:5 281:13 288:11 297:11 307:22 313:3 315:21 320:15 321:19 326:15 334:8,16 335:1,5 342:7 347:15 350:6,12 356:18 357:14 359:6,16 360:5 364:22 366:1 367:21 370:8 371:4 373:6 374:6 376:10 382:8,13 383:4 384:4 389:9 397:3
industry's 371:10 383:15
inferiority 301:9
inform 373:11 383:6
informal 45:8 308:17
information 10:1 13:16 26:20,22 27:6,7 33:10 34:15 36:3 40:8 41:9,11 42:21 43:14 56:3 105:10 113:22 116:21 117:1,5 118:17 122:3,5 135:20 136:2 139:17,20 152:1 154:3 155:15 156:9,15 157:2 159:16 163:19 169:15,16 175:9 181:6,9,21 209:16 215:6 216:21 217:9 219:6,8 222:3 236:1 237:8 259:1 259:2,4 284:17 285:17 308:5 318:16,20,21 319:2 322:9 336:5 350:21 353:1,2 355:5 360:8 366:20 380:4 382:20 403:4
informational 307:20
informative 194:16
informed 156:20 159:17 373:12 390:7
ingests 198:22
ingrained 50:19
ingredient 34:1,12 274:12 286:12 296:9,14 300:14 301:20 302:1,3,7 302:11,14,17 303:22 326:1 369:13 372:22 374:16,21
ingredients 46:13 46:17 270:18 271:15 274:4,15 295:16 297:22 298:2,3,6,9,9 300:2 301:3,19,21 303:3,17,18 304:10,21 328:4 370:19 374:2 381:16
inhalers 178:13
initial 113:8 161:19 183:6 256:3 267:3
initially 173:2 180:6 284:18 392:12
initiated 353:19
initiative 18:22 173:3,19 236:11 269:3 310:13 311:11 315:12 318:6,12 334:21 335:5 340:8 358:11 359:13 365:6 399:18
initiatives 4:14 177:13 217:7 268:8 271:5,7 367:21 401:19
injectable 343:22
injection 337:8
inkling 54:8
innovation 21:11 370:7
innovative 142:10
innovator 53:12 54:12,14 65:19 225:15 226:12
input 16:2,8 20:17 29:4 42:19 43:18 48:21 55:16 59:18 72:4 150:11 200:7 239:22 240:11 402:19
inputs 58:22 59:15 60:5,7 73:13
inquiry 353:5
inside 402:11
insights 375:5
inspect 202:8
inspection 34:21 38:19 43:12 77:2 150:3 153:7 163:22 164:16 173:14 179:21 180:20 183:19 184:18 185:10,12 217:5,8 218:5
inspectional 182:2 184:17 185:15
inspections 150:17 153:8 164:14 172:17 181:10,11 184:3,4,7 191:13
inspector 34:19 36:1 164:1
inspectors 43:9 150:6 163:20 164:4 167:4 202:3

215:8 219:11,15 230:7
instance 115:11 127:10 152:18 155:11 157:5 158:9 159:22 160:11 164:5 166:9
instances 362:9
institute 374:11
institutes 235:7
institution 177:2
instrumentation 262:21
instrumented 74:18
insufficient 31:17
integrated 186:7
integration 191:1 199:2
integrity 182:12
intelligence-based 55:13,19 71:22 73:21
intelligent 119:21
intend 38:8 210:17 390:1 391:21 396:19 397:11
intended 20:22 23:19 38:14,16 49:9,11 51:16 60:2 189:12 253:11 390:20
intending 327:17
intense 145:16
intensive 195:5
intent 353:12 386:12 394:17
intention 292:10
intentionally 397:9
interact 60:10
interacting 143:5
interaction 4:12,19 21:15 193:12 237:10 268:7 401:12,18
interactions 18:8 97:14 102:10 149:5 188:5
interactively 236:21
interdisciplinary 3:19 292:1
interest 4:4 9:10,21 10:3,12,20 12:18 14:14 99:17 127:20 168:4 169:5 190:19 239:10 245:5 256:22,22 265:12 265:12 313:14
interested 52:6 76:8 83:19 93:6 214:7 217:16 220:11 224:1 235:8 241:2 245:3 245:10 254:9 272:22 333:3 398:11
interesting 19:6 28:1 32:17 90:18 92:19 137:8 244:18,20 245:2 250:13,15 256:9
interests 11:9,13 12:16 13:17 386:2 395:10
interface 159:20
interfacing 269:22
interference 18:17
interject 239:9 257:15
internal 33:1 42:14 83:12,14 89:12,13 95:10,18 178:22 179:5 190:12 209:5 297:1 369:21 380:5
internally 21:8 193:2
international 12:1 21:16 66:7 242:20 380:20
internationally 275:22
Internet 397:5,13 397:18
interpretation 31:3 31:4
interruption 8:12
interruptions 100:12
intimate 86:13 349:3
intimately 82:1
introduce 5:19 20:19 38:15 52:20 269:2,4 346:6 371:9
introduced 22:17 61:11 62:13 344:14 345:10 362:7 364:16
introduction 4:2 20:9 26:9 206:8 268:15,20 271:9 368:1
Introduction/Bac... 4:5 15:8
introductory 229:6
inventory 70:3
invested 228:18
investigate 67:1 89:4
investigation 64:5 64:8 88:13,20 89:14
investigations 66:19,21 67:4
investigator 185:21 186:5
investment 45:9 56:16 69:16,20 133:13 137:16 207:21 212:1 223:3,10
investments 11:14
invitation 97:2 141:9 310:16
invite 235:17 236:6
invited 13:3 179:5 180:8 195:2 215:13
inviting 53:16 340:10
involve 188:4 327:1 390:6
involved 14:11 50:3 80:21 83:1 150:13,16 192:20 192:22 201:21 215:12 216:10 235:17 241:10 332:1 343:11 387:4 398:14 403:18
involvement 14:15 24:3 25:16 315:2 335:4 350:10 357:18 360:4 375:3
involves 191:20 193:22 358:13
involving 12:13 238:4 356:15
in-house 229:12
IPO 265:7
IR 189:18 306:12 337:16 366:22
irrelevant 247:21
isolated 72:7 73:11 116:4
isomer 325:1
issuance 18:11
issue 43:4 65:16 77:7 94:16 112:21 112:22 156:12 159:2 164:21 170:6 209:8,9,15 216:16 229:16 241:4,11 242:16 255:22,22 258:13 261:16 264:22 288:19,20 325:14 327:5 336:20 337:3 363:8 399:20
issued 12:19 181:6 275:11 276:3,5 348:16 353:11
issues 8:10 12:6 13:2 14:12 16:7 16:15 20:20 28:3 37:11 39:14 41:10 46:16 91:18 100:10 106:9 119:16 132:5 145:1 164:5 165:18 167:7,8 169:9,13 182:12 184:22 200:2 216:11 235:11 241:3 242:5,7 243:11 256:12 274:17,18 284:12 285:1 290:9 313:10 322:20 400:1 402:14
issuing 241:18
italics 341:21
Italy 130:13
item 52:16 194:20 396:7,14 401:22 402:1,2
items 306:9 319:15 319:16 321:8,9
iterative 57:8,15 86:16
IV 3:22 292:4
IVIVC 198:19 203:22 264:22 265:8

J

J 2:9
James 2:10 7:13
Janet 281:20
January 190:15 346:18 373:6
Japan 33:9 128:2,4 229:2,3
Jarred's 93:10
Jim 75:17
job 21:8 42:4 127:2 195:3 215:4

222:10 252:20 272:19 289:10 386:21 387:1 402:10,18
Johnston 16:6
join 52:18 402:13
joined 109:19
joint 117:7 164:14 260:15 305:6 306:4,19 353:18
jointly 374:5
Jon 3:10 271:2 385:12,12 399:10
Joseph 2:5 52:19 52:22
Joshi 2:15 13:21 96:10,11,13,14,21 105:20 121:17 123:9 124:8 126:11 129:15 132:14 133:22 135:9,19 139:2,8 140:3
Journal 365:16
journey 26:12 54:15
joys 220:17
JP 350:19
judged 303:13 304:7,11
judgments 254:17
July 1:13 173:20 187:4 380:11
June 278:12 354:3 356:4
justification 41:12 123:21 219:4
justifies 84:8
justify 133:13

K

Karen 2:21 13:22 270:14 285:4 310:9,17 340:12
keep 51:4 83:21 84:3 110:13,16,19 111:4 112:14 129:1 134:1 167:7 205:15,20 206:12 226:8 231:7 320:2 327:13 389:18 395:1,3,3
keeping 116:7 239:11 291:13
keeps 170:6
Keith 3:4 6:3 208:12 209:10
Ken 7:22,22 8:1,2 74:3,5,16 75:4,11 96:16,18,19 105:17 108:13 120:12,14 121:17 123:8,9,14 124:8 125:1 131:14 138:3 192:3,5 194:14 211:19,19 263:19 264:16,17 289:7,7,8 399:8 399:10,11,12,21 400:12 401:9
KENNETH 2:6
kept 205:13
keveldol 356:11
key 22:7 23:18 24:19 25:11,22 26:5,9 28:19 29:13 30:17 31:14 32:1 35:6,19 36:16 41:16 42:20 48:3 61:18 65:16 71:19 76:18 79:9 82:19 107:17 116:5 142:10 197:14,16 198:10 198:17,20 199:11 200:2 211:7 227:7 234:18 235:10,20 241:6 242:6 263:12 300:18 307:8 335:2 342:10 358:9 359:17 371:13
Kibbe 2:4 7:8,8 93:22 94:1 201:8 201:16,17 206:7 258:5 263:17,21 265:16,17,18 308:8,9,15 366:14 366:16
kicked 258:5
kickoff 180:6,7 183:12 354:2
kicks 58:8
kill 388:11
kind 51:5 54:3 77:18 78:9 89:16 89:18 94:17 106:6 122:6 125:15 126:6 180:5 206:6 212:17 228:14 231:1 260:17 262:5 266:2 269:12 271:3,19 277:20 279:15 290:15 345:12 363:10,16 365:5 367:9 371:10
kinds 119:5 121:22 127:15 247:18,19 256:15
knew 97:2 204:5
knock 295:14
know 40:17 42:11 45:5 50:9,9 58:6 58:18,19 69:1 70:5,17 71:17 72:15 73:16 75:6 75:9 76:19 77:9 78:21 79:12,13,20 80:17,20 81:1 82:17 88:10 90:12 91:1,20 92:9 93:1 94:14,20 95:21 96:2 99:3 102:5 103:18 104:1,6,10 104:13,18 105:9 107:11 109:1,12 109:16 111:14 112:19 113:7,12 114:9 115:3,16 116:14 117:19 122:7,17,18,22 124:1,9,20 125:19 126:7 127:10,10 129:20 132:17 133:4 134:1 135:1 135:6,17 136:13 136:21 137:1,11 138:4,7,8,12,22 139:1,10,15 157:7 173:6 191:18 200:21 201:2 203:1,14,21 204:2 204:10 205:16 210:9 215:14 216:15 217:17 218:9,9 221:2,11 222:22 224:8 225:2,17 226:2,13 227:3,8 228:1,8 228:15 229:7,17 229:17 230:18 231:2 232:2,4,5 233:7 234:21 236:17,20 237:4,9 239:1 241:20 242:2,17 243:7,20 245:16,17,21 249:17,22 251:2,2 252:9,16 253:12 254:4,5 255:12,17 256:15 258:14 265:6 267:5 270:9 271:10 272:2 275:13 278:4 282:18 285:6 289:9 290:1,3,4 291:10,15,18 293:12 308:22 309:21,22 320:7 333:10 341:5,7 361:16 363:2,11 363:17 364:9,9,13 364:21 366:4 367:2 379:21 386:20 388:21 396:1,7,9 397:9 397:14 399:1,15 400:14 401:13
knowledge 19:18 23:22 26:6,20 59:5,22 63:7 79:20 86:7 88:5,7 98:7 114:16 117:2 117:10 149:4,9,14 167:2 177:3 184:10 185:7 189:10 209:22 210:4 235:1 244:13 254:15 349:3
known 264:3 271:15 284:11 351:21 354:8
knows 173:7
Koch 2:5 6:19,19 47:5,6 75:15 80:5 80:6 125:4 134:10 134:11 201:15 251:6,7 262:7 360:10,11,16 361:1,8 362:19 365:10,15
Korakianiti 2:16 141:3,7,8 168:7 168:13,22 169:10 170:5 171:12,14
Korea 33:15
Kosler 2:5 52:19,22 53:1 75:16 125:4 127:18,19 129:10 131:20 201:9 217:1 219:22 220:1 222:15 223:13 225:19,22 226:17 227:12 240:18 242:12,13 244:16 259:11 261:16 263:18,20 395:20,21 396:17 397:12,16
Kozlowski 3:6 6:8 6:8 44:8 210:16 217:2 237:17 248:9 254:8

256:13

L

lab 69:12,12 155:12 157:8 327:15 328:2,15 330:11 330:21 331:10 332:21 349:7 363:15
label 300:10 368:14
labeled 303:4
labeling 300:2,5,15 300:16 303:4 343:17 344:10,21 351:17 354:6 355:8,14 357:4
labels 294:16,17
laboratories 283:9 324:7 392:9 393:20 394:11
laboratory 67:15 67:22 68:13 69:13 283:10 291:19 330:6 376:12 391:3,15,20 392:4 392:6,22 394:4,22 395:4
labs 324:14 327:16 332:12 370:17 376:15
lack 37:2 41:4 228:10 229:15 230:4 231:20 234:2 256:22 257:1 259:22 260:4 312:7 336:13,21 340:21
lady 244:17
language 41:18 209:8 300:15,16 355:21
languish 335:22
large 29:18 70:10 70:17 78:11 93:9 121:6 160:12 186:22 212:3 228:20 230:8 246:10 248:1 323:20 328:20 386:1,9 396:3 399:5
larger 131:13 246:12,12 283:2 285:13 323:6 394:22
large-scale 115:2
Larry 3:12 268:15 290:14 311:2 322:22 341:6 345:4 349:17
Larry's 336:16
lasting 189:2
late 169:2,3 345:7 388:19
laughable 387:3
launch 58:4 103:3 106:16 117:7 127:5
launched 63:19 64:9 109:22 315:16
laundry 344:10
Lawrence 96:22 97:1 106:1
laws 9:21 10:3,12
layer 306:13
lead 23:10 235:12 252:3 261:19 303:8 310:18 353:10
leaders 133:12 235:18
leadership 22:2 105:22 369:11
leading 25:6 79:15 116:9 183:2 242:20 368:10,13 369:7 378:4 379:4 382:1
leads 23:22 58:10 177:9
lean 54:22 55:6
leaner 66:14
learn 95:7 124:20 137:14 194:3 248:16,22
learned 33:13 95:7 95:8,9 169:12,18 195:10,16 232:22 233:20
learnings 72:12 174:16 186:17 188:12 222:4
leave 104:10 252:15 288:22 308:4 336:4
led 236:16 312:11
left 5:20 164:12 177:17 182:19 257:3 296:8,11 300:8 303:16 340:12
leg 64:17
legacy 50:12,16 224:18
legal 273:22
legally 280:5 293:13 300:11 311:8 317:14
lessons 33:12 169:11,17 232:22
less-than-high 369:15
letter 281:20 282:5 284:2,22 303:22 305:11,18 325:7 327:5 345:6 346:19 348:15 349:13 350:22 351:10,16 352:4 352:18,20 354:5 356:7 371:9 372:18 373:7,17 374:10 375:7,7 377:12 380:12
letters 107:3 348:9 348:11 402:3,6
let's 45:8 52:11 55:21 61:7 74:16 89:2 95:1 109:12 121:10 207:13 240:13
level 31:17 38:1 40:5 64:15 66:9 68:19 88:5,19 147:11 150:8 158:18 163:8 192:15 247:7,16 398:11
levels 127:11 379:1
leverage 329:10
leveraging 236:1
liaison 354:1
liaisons 317:22
lie 151:20
life 23:8 24:2,14 25:18,21 30:5,9 32:8 36:14 37:7 39:21 41:22 109:19 110:2 158:14 225:17 226:1 247:4 379:20 396:9
lifetime 101:22
lifting 335:10
light 176:4
liked 140:1
liken 279:8
limit 95:18 119:12 119:13 277:1,10 286:6 327:11,13 338:7 345:16,19 346:7,15 347:8 348:19,20 349:10 351:8,9 352:9,9 352:17 353:11 374:20 380:12,16 396:2
limitation 237:5
limitations 134:5 135:15 399:16
limited 10:4 110:4 158:4 159:10 163:7 182:3 286:6 324:12
limiting 287:1,8
limits 117:20 223:17 224:12,13 232:5 264:3 276:6 280:20 281:16 328:12 373:21 377:16 379:3,9,13 381:4 383:1
line 56:12 67:16 177:12 210:12 294:22 304:13 305:8 317:2 319:15 328:1 371:7,14
linear 185:22
lines 56:21 63:16 169:4 208:20 210:18 258:18
lingering 228:7
link 61:20,22 62:2 62:6 188:11 198:3 198:19 238:6,19 250:7,22 261:10 308:5
linked 35:10 314:22
linking 23:11 186:22 187:7 197:16 237:19 241:4
links 333:18
liquid 326:21 328:5
list 135:4 165:16,17 169:8,8 197:21 207:16 257:10 260:6 264:2 284:13,18 285:12 285:13 286:5 289:21 306:5,17 317:18 318:14 319:6,9 320:4,10 321:3,14,16 322:19 340:16,17 340:17 341:12,16 341:18 342:3 344:11 348:10 360:13 371:16 374:22 375:7,8 377:11 381:17 388:16,17

listed 113:3 115:10 185:6 277:7 281:6 284:4,5,13 327:5 385:9
listen 195:11 205:16 215:1
listening 136:10 227:22 308:6 395:17
listing 299:22
lists 250:9 281:1 286:1
literally 106:21
literature 332:10
little 46:15 52:16 53:17 54:2 78:5 78:20 82:22 83:18 105:9 108:5 133:7 138:14 170:3 201:21 217:3 233:13 239:11 241:7 246:15 251:19 253:9,20 263:7 269:5 271:4 278:18 282:8 323:11 329:12 338:10 341:22 342:1 367:10 385:20 387:2,2 390:7 392:16 394:1
lived 195:20
living 397:20
Liz 7:3 120:14 123:15 258:19 289:8
local 301:16
located 142:8
locked 123:4,6
LOEs 226:3
logic 136:20
logistical 394:15
logistics 394:2
London 142:8
long 15:11 103:10 115:3 120:2,9 121:9 133:4 134:1 216:18 227:5 230:3 256:16 272:2 275:19 294:9 307:15 336:1,3 388:20 397:3,14,18
longer 18:19 111:8 111:9,11 122:10 153:15 241:22 246:16
longer-term 335:8
long-term 104:16 359:18
look 8:16 17:18 19:12,15 51:2 57:6 60:21 61:15 86:3 91:3,4 92:20 100:10,12 109:19 115:11 130:5 133:6 137:9 156:5 171:1 176:12 203:10,16 214:17 215:1 233:2,13 234:4 251:22 254:19 264:2 299:3 314:12 319:16 321:4 322:8,15,19 325:16 356:18 362:4 368:16 384:20 386:22 387:2 389:14 396:1,8 398:10 403:10
looked 364:5 387:16
looking 62:12 91:13 92:10 125:8 126:6 135:3 151:1 161:22 162:1 200:6 213:9,16 248:20 249:1 256:14 294:16 322:1,10 325:17 326:5 332:8 335:13 336:12 363:7 365:19 391:11,18 396:10 398:19,21 399:17 399:20 400:16,20
looks 201:7 390:14
loop 58:12
lose 15:13 225:9 226:15
losing 130:17 210:9
loss 226:10
lost 97:7 105:17,20
lot 16:11,13 17:16 19:6 50:13 74:22 97:12 105:14,21 107:20 113:22 116:21 118:10 121:20 122:3 124:14,20 131:9 134:9 135:19 139:9,12 140:1 151:21 152:3 160:4 163:4 188:14 203:16 217:12 228:22 229:1 241:12 256:17 266:18 272:20 288:7 291:5 307:21 308:2 313:4 317:16 322:3 324:1,3 334:4 335:9,10,11 339:11 341:4 358:11,18 363:11 387:13 402:19,19
lots 139:13 217:14 247:13,14 249:19
louder 126:13 127:9
love 204:3 214:12 215:9 262:1 266:19
low 89:1 159:5
lower 87:12 119:13 138:21 147:8 212:21 213:6 223:6 230:18
lowering 138:18 258:20
low-hanging 91:1 120:17
lump 125:14
lunch 9:8 62:15 245:16 267:10,11 267:17

M

M 2:2
mAbs 250:19
machines 74:18
mag 95:2,4
main 150:4 151:16 159:2 289:19 366:20 401:4
maintain 210:6 280:4 311:7 358:5
maintained 100:8
maintaining 311:13
maintenance 25:14 177:2
major 172:8 199:3 310:2 320:18 321:4 327:5 328:18 334:20 340:19 359:13
majority 234:17 321:8,12,16 341:11 360:17 378:1
making 15:10 42:5 52:1 81:18 84:10 84:18,18 99:5,13 109:4 113:5,17 117:9 118:4 130:5 132:13 133:5,13 194:10 216:19 254:17 266:5 307:19 323:19 335:3
man 104:4
manage 24:1 111:3 111:18 116:18 130:8,10 145:20 168:12 388:14
manageable 89:9
managed 161:7 389:17
management 23:4 24:4,20 26:1,2,7,7 27:3,8 28:16 30:11 35:3 36:2 36:10 37:6,11 40:9,22 42:13 46:21 59:5 83:13 83:14 109:20 110:2 125:17 145:18 161:15 168:2 173:11 181:14 182:14 193:14 211:12 223:2 249:6 386:10 389:3
manager 179:16
managers 209:4
managing 118:6 123:13 127:2,6
mandatory 355:15
manner 278:17 384:19
manually 74:13,14 75:3
manufacture 51:19 101:4 196:14 343:11
manufactured 63:15
manufacturer 85:20 224:8 264:1 264:8 293:21 294:8 302:16 347:21 378:4
manufacturers 2:18 50:3 53:7 73:2 276:12,12 299:16 312:3 313:18 314:19 315:4 320:6 323:4 324:9,11 331:20 332:17 347:6,7 350:13 355:6 357:15 358:14

360:6 368:10,14 369:10,17 378:2 380:1 382:1
manufacturing 3:13 22:15 23:13 24:15 26:18 27:16 28:6 30:3,15 31:9 34:18 35:12 36:12 40:10 46:12 48:20 53:11 55:13,19 56:17 57:1 65:3 67:16 71:18,19,22 73:21 76:17 88:6 101:15 104:20 111:21 116:22 117:3,13 130:3 138:19 139:14 145:15 152:15 159:2,7,11 164:1 166:9 180:17 181:18 182:11 187:7,17 188:1 199:14 212:3 214:3 219:15 221:14 223:5 224:2,7 233:16 242:17 243:9 244:22 268:17 276:11 301:17 372:20 378:12,20 380:5 382:21 383:14
MaPPs 172:16 176:18 178:10,17
March 277:15 373:15
margins 138:21
Marilyn 2:8 7:15 7:15 44:18 45:20 45:22 46:7 125:5 135:10,12 168:16 169:19,21 236:13 236:15 260:12 338:20
markers 256:16
market 36:21 100:7 106:12 135:1 137:5 142:14 147:9 161:19 293:17 294:3,8,14 296:4 296:11,15 339:4 368:13 374:15 376:2 378:17
marketed 274:9 280:5 293:6,13,14 293:16 294:13 295:6 296:1,22 300:11 305:1 311:8
marketing 131:16 280:19
market's 134:17
marries 271:19
Maryland 1:21 7:12,14
mass 238:9 363:13
massive 83:20
master 318:14 340:16,16 341:12
match 351:18
material 23:13 32:9 33:8,16,19 48:21 80:11 110:7 113:11 124:10 343:14 344:18 347:6 362:12,16 365:3 400:2
materials 58:22 94:17 111:18 242:15 243:1 261:18 262:1 289:13 362:1 392:21 394:13
matrix 91:4
matter 12:5,13 48:5 68:18 100:3 115:2,15 140:14 243:12 246:21 247:2,3 248:14 249:11 250:17,20 267:20 362:11 370:16 375:12 376:18 404:9
mattered 121:6
matters 246:4
maximum 323:10
McKinsey 17:6 100:16 103:14 120:8 228:3
MD 3:6
MEA 151:18
mean 26:13 64:5 68:5 73:15 75:9 78:17 79:3,8 89:9 90:4,16 91:18 95:6 106:21 113:9 126:18 130:12 152:19 161:3,7 167:22 205:15 217:20 225:8 227:9 228:8 229:19 230:19 240:21 241:19 252:11 253:7 274:3 295:9 308:10 365:10,12 398:5
meaning 320:20
meaningful 118:13 166:18 239:8
means 29:10 64:3,6 67:18 68:5 108:16 153:6 167:20,22 202:19 319:7
meant 204:7 254:12
measure 33:3 88:17 90:14 102:10 108:10,12 108:13 134:21 232:1 253:7
measurement 47:20 49:11 91:11 108:17 243:6
measurements 50:12,16 51:3 78:19 79:1 198:5
measures 50:16 229:2
measuring 62:1
meat 46:15
mechanics 399:5
mechanism 118:3
mechanisms 77:6 216:13
media 9:2,5 251:10
medicated 339:14
medication 99:17
medications 99:19
medicinal 143:2 144:3 145:2 146:7 151:17 363:15 365:16
medicine 99:6,20 145:4 283:7 378:17
medicines 2:16 141:3 142:3,5,6 142:16 143:7,19 144:6 368:11,15 368:22 369:3,9,11 369:16 370:20 376:1,2,8,19 383:13 384:6
meet 39:9 62:9 208:19 209:6 224:14 258:17 305:3 369:5 376:6
meeting 1:17 5:15 8:6,9,16,22 9:4,7 9:13 10:7 11:6,18 12:16,19 13:6,9 15:4,5 29:5 38:7 40:15 72:5 118:7 118:10 140:7,20 140:20 144:2 180:6,8,12 183:12 195:8 205:12 215:13 225:12 243:15 268:10,11 273:2 326:13 340:11 354:2,3 357:8 372:10 376:4 404:6
meetings 107:14 149:11 176:3 181:4 183:14 187:19 189:1,6 217:12,14 285:7,8 297:20 333:12 358:16,17
meets 69:11 85:3 285:3
Mel 6:19 74:10
melamine 351:15 356:15 387:16
melting 316:16 324:22
MELVIN 2:5
member 2:2,4,4,5,5 2:6,8,9,9,10,10,11 2:12 6:11,14,16 6:19,22 7:8,13,15 7:18,21 8:1 45:22 46:7 47:6 49:21 50:6 52:18 74:5 75:4,11,19 77:17 78:16 80:4,6 82:7 83:17 85:6,9 89:21 91:16 92:8 92:13 93:12 94:1 96:19 108:7 120:14 123:8,14 125:1,7 132:1 133:18 134:11 135:12 136:9 139:5 142:18,19 144:1 163:2 168:17 169:7,21 191:12 192:5 194:14 201:17 214:11 227:18 236:15 241:1 251:7 252:7 255:6 256:19 263:17,21 265:18 289:8 308:9,15 309:3,15 309:20 336:11 338:20 360:11,16 361:1,8 362:19 363:7 365:10,15 366:16 369:3 373:4 376:3,21 377:15,18 378:11

379:4,17 381:3,18 382:7 399:10,12 400:12 401:9
members 8:19 9:1 9:17,18 10:9,10 11:6,7 12:17,18 12:21,22 14:10,10 140:5,8 143:12 181:5 195:4 200:14 206:11 211:18 239:12 257:14 267:14 283:5 288:3 312:5 318:1 350:17 371:1 378:6 380:7 383:22
membership 368:7
memo 180:17,18,20 181:18,20 183:16
memory 388:18
men 104:5
mention 148:17 255:12
mentioned 17:1,5 18:9 26:11 37:8 41:15 78:18 92:22 93:13 100:16 119:6 160:7,16 162:22 230:11 241:8 246:8 260:9 262:7 280:6 282:20 283:3 291:20 311:2 322:22 338:21 346:5
mentoring 179:6
mercury 313:12
merging 182:14
merited 299:5
Merrill 2:3 6:22
messages 35:6
met 208:16 285:1,5 379:13
metabolic 176:9
metabolism 256:16 378:21
metals 351:10 353:10
meter 178:12
method 49:2 278:9 278:10 291:2 341:3 347:16,16 349:8 351:12 356:11,16,16 364:17
methodologies 40:9 48:15 106:8 252:14 290:16 356:19 369:21 382:10
methodology 116:10 307:13 311:21
methods 50:16 51:2 69:5,6 84:16 117:4 166:12 224:18 226:8,19 243:10 248:18,19 252:13 261:20 272:11 273:7 278:7 280:13 291:9,13 301:16 306:11 307:13 343:4 354:18,21 354:22 357:6,7 359:7 364:22
metric 62:10
metrics 134:22
mic 201:14 206:6 397:12
Michelle 100:17
microbial 361:13
microbiological 287:3
microbiologist 179:20
microbiologists 287:5
microphone 52:20 201:3 397:15
middle 399:22
Midha 16:6
midst 217:11
mid-cycle 181:7 183:22
Migliaccio 2:17 14:2 53:4,5,13,14 74:2,15 75:8 76:12 78:2 79:3 81:4 83:4 84:4 85:19 88:3 90:20 92:3,9 93:8 94:20 96:7 160:8 218:6 220:3 221:10 222:16 225:8,21 226:1,20
Miksinski 3:16 171:20 172:4,5 191:8,16 192:11 194:16
mile 308:21
milestones 371:8
million 126:19,20 327:12
millions 249:20
mind 15:9 71:21 96:3 110:14,20 111:5 112:14 116:8 129:20 131:5 170:21 198:9 223:22 242:14 389:18 396:7
minds 245:17
mine 236:8
mines 351:21
minimal 273:22
mining 139:19
minor 11:11 162:10,19 330:2 399:3
minute 75:13 140:3 140:5 239:10 266:9
minutes 5:4 140:11 239:18 240:8 246:6 267:10,11
misbranded 299:18
misconception 153:5
misconceptions 151:22 152:17 153:11
mispronounced 14:3
missed 75:17 263:16
missing 125:6 156:8 267:3 273:19 283:17,18 306:14 314:7 320:19 321:4 325:15
mission 142:2 339:2,5
mistake 116:4
mistakes 116:1,2
misunderstand 133:19
misunderstanding 153:13
misunderstandin... 153:22
mitigation 59:2
mix 238:11
mixed 95:15
mixture 248:15 342:20
MMTG 268:21 283:4 306:20 307:8
mobilized 163:2
mock 150:16,17 188:18
mode 86:8 250:14
model 35:10 73:5 155:22 156:6 158:1,3,6,12,13 158:20 185:20 196:11 287:13 291:19 381:11 387:15
modeling 38:11 40:13 116:13 157:22 197:1,12 235:20,21 250:22 252:12 262:19
models 55:14 72:2 72:12 155:16 158:9,15,17 164:2 166:13,14 185:4 198:19 215:17
modern 51:15 173:10 272:8,10 279:2 280:12 281:16 334:11 343:7 344:1,5
modernization 4:13 12:12 18:9 18:22 268:8,21 269:3,6,14 270:1 270:17 271:10 273:1 279:3 280:9 281:2,8,22 282:2 282:7,11 283:1 284:7,15 285:2 288:4 289:15 305:10 306:10,21 306:22 310:12 312:13,15,21 313:5 314:21 315:15,22 316:2,9 318:2,5 319:5,13 320:8 323:14,18 324:3 325:8 331:21 332:2 333:1 334:1,18 340:8,20 341:17 346:20 349:14 350:9 357:16,20 357:22 358:5,10 358:10 359:13,20 364:3,19 365:7,8 367:20 368:8,18 370:3,9 371:2,8 371:17 372:2,8 373:12 374:14 375:4,14,17 376:22 378:8 381:12 383:17 384:1,7 386:11,16 387:17 389:19 392:10 401:18
modernizations 311:15 323:3

341:19 360:1
modernize 270:15 275:2 286:2 307:12 317:20 335:18 343:2 346:12 381:17 386:13 388:6
modernized 282:17 286:9 379:8
modernizing 280:7 283:16 285:15 292:15 374:9 384:15 386:19 390:3
modifications 247:18,20
modified 90:10 189:18 190:9 213:20 276:22 277:9 279:14
modify 207:17
Moheb 3:8 6:6 20:6 50:6 56:11 57:4 57:18 58:18 67:8 71:5 92:20,20 105:8 115:6 118:16 135:21 194:22 230:11 232:13 249:12 264:20
Moheb's 75:20
moisture 69:7 108:12,13 114:10 114:11 115:1,3
molecular 176:6
molecule 29:17 47:3 77:20 78:1,4 78:11,11 112:17 112:18,18,20 114:8 186:18 188:11 246:7 247:4,9 255:21 281:7 306:6 310:19
molecules 2:21 29:18 46:13 79:21 245:10,20 246:7 246:10,11,13,20 247:11,22 248:1,5 248:21 250:19 262:2,3,5 270:15 306:6 310:10,13 318:14 319:4 323:17
moment 82:22 85:12 107:22 147:9 149:22 151:5 160:14 161:21 171:16 274:22 288:2 317:18
momentum 17:12 126:5
money 223:7 265:9
monitor 121:5 134:7 359:19
monitoring 26:3 58:10 79:9 143:18 146:12 185:3
monograph 4:12 12:12 18:8 268:7 268:20 269:3,6,13 269:22 270:9 271:1,10 272:14 272:22 273:9 274:11 275:5 276:9,18,22 277:13 278:8,21 279:2 280:17 281:22 282:7,22 283:22 284:15 287:20 288:4 289:16 290:20 291:20 292:10,12 293:18 294:5 296:3 297:1,2,5 298:14 299:1,6,8 299:9,13,13,16,17 299:21 300:7,9,10 300:17,19 301:1,8 301:10,18 302:4,5 302:7,9,10,13,16 302:18,19 303:17 303:19 304:3 305:2,9 308:5,12 310:12 314:3,10 315:14 319:17 322:12 323:2,15 323:16 324:19 325:8,17,18 326:6 326:17,18 327:8,9 327:18 329:16,18 330:1,5 331:21 334:7 335:15,16 337:4,21 339:19 340:8,20 341:19 342:2 343:1 345:9 345:19 346:1,9,17 347:1 352:8 353:17,20 355:9 355:17 357:5 358:10 359:13,19 364:16 367:20 368:8 370:9 371:7 372:2 373:12,19 375:10,17 377:7 377:10 378:7 383:17,22 386:11 391:14 392:3,6,10 392:15 393:14,15 393:16 398:2 400:16 401:5,18
monographed 18:22 304:19
monographs 270:11,15,17 271:11,12,14 272:4,8,13 273:4 274:2,14 275:3 277:6,8 280:8 281:2,7,9 282:10 282:15 283:17 284:7 285:12,13 285:15 286:1,4,7 286:8 287:4 288:1 292:6,16 294:15 295:21 296:16 300:14 303:21 304:6,19 305:12 305:12,15,15 306:6,7,17 307:4 307:12,14 309:10 309:13 310:20,21 310:22 311:16 312:8 313:5,15 314:1,6,8,18 315:19 316:9 317:1,21 318:1 319:3,5,7,12,14 320:17 322:13 324:2 325:6,10,21 326:9 328:12 329:3,6 330:15 331:3,9,14 332:4 334:4 335:11 337:7 339:7,8,13 339:14,18 340:15 341:5 342:5,6,8 342:11,16,17 344:3 345:4 347:18,22 348:8 348:15 349:15,17 350:3,4,9,18 351:6 353:3,5 357:11,21,22 360:1 361:5 364:6 364:7,12 366:19 368:18 369:13 371:16 372:7,17 372:22 374:10 375:8 377:1,6,14 379:8 381:2 384:5 384:15 386:3,4,13 390:22 391:2,6 392:14 393:8 394:7 395:6 400:21
monograph's 351:19 354:12
monograph-spec... 323:5
monomers 352:17 353:11
month 33:14 38:6 39:12 40:15 181:15,15 210:14 218:11 232:14 280:22 326:14 328:15
monthly 281:4,18 285:21 319:19 333:17 358:3
months 19:8 62:20 69:17 109:21 122:9,9 216:3 229:5 297:20 317:11
morning 5:3,11,22 8:4 9:11 20:5,8,12 21:20 26:11 35:9 36:19 42:17 43:17 44:5 45:14 48:9 51:14 53:4,9,15 96:10,16,17 141:2 141:4 168:9 171:14,19 172:2,6 172:7 177:11 191:10 200:2,17 211:8,18 214:18 218:6 220:11 245:16 257:17 389:22
morning's 265:14 267:9
Morris 2:6,8 7:15 7:16,22 8:1,2 44:18 45:21,22 46:7 74:4,4,5 75:4 75:11 96:17,19 120:13,14 123:8 123:14 125:1,5 135:11,12 168:16 169:20,21 192:4,5 194:14 211:19 236:14,15 260:12 263:19,20 264:16 264:17 289:7,8 338:19,20 399:8,9 399:10,12 400:12 401:9
motivated 264:1 273:12 282:19 286:15 287:19 312:12 318:18 342:9,13 344:12

351:13 356:14
motivating 264:11
mountain 323:21
mouthful 187:14
mouthwashes 339:15
move 15:21 17:19 19:18 20:2 30:15 49:7 52:15 62:7 63:1,8 68:20 71:17 83:11 125:20 126:3 141:16 172:18 183:8 191:9 194:21 196:22 199:11 200:9 216:18 227:14 233:9 234:15 236:2 242:11 244:6 328:16 330:12 334:9 345:3 371:3,19 384:17 393:7 403:22
moved 104:13 206:1,3
moves 387:12
moving 54:21 56:19 68:17 70:7 108:16 129:1 157:18 177:17 178:1 182:19 183:8 188:20 199:13 200:12 214:22 220:14 221:7 234:19 240:10 276:16 307:17 312:22 372:5,14
MPH 2:11
multiple 60:10,11 95:9 108:2 187:19 188:3 189:1,5 286:11 309:13
multiply 326:4
multivariant 57:14 60:4 87:1
multi-active 328:4
multi-phase 204:4
multi-step 58:14
Muzzio 2:9 6:14,14 50:5,6 75:16 89:20,21 91:16 92:8 125:5 136:8 136:9 139:5 201:15 211:20 227:17,18 252:5,7 259:20 262:13,15
Muzzio's 255:9
mystery 263:7

N

N 3:3 70:10,17
nail 218:1
name 5:12 137:11 171:17 172:6 295:19 310:17 368:14
names 207:14
name's 368:2
naproxin 296:20 297:3
narrow 94:18 95:6 239:3
narrowed 55:9 94:21 239:4
narrowing 96:2 239:1
Nasr 3:8 6:6,6 20:6 20:6,10,11 44:16 45:10 46:6,8 47:22 50:4 51:10 52:12,14,17 148:16 194:22,22 195:1 200:11 201:10 207:10 208:11 211:6 217:22 234:8,12 236:15 239:21 244:5
national 53:1 142:17 143:10 163:7 271:13 280:4 311:7 368:9
natural 266:15 360:14
Naturally 360:15
naturally-occurr... 362:1
NDA 161:19 274:7 286:19 293:17,19 293:20 295:10 296:6 297:4 300:19,20 301:7 301:11 305:3
NDAs 174:7 175:15 175:16 294:13 296:8,12
near 89:15 245:12 288:1 371:12 390:12
nearly 205:1,11
near-IR 69:3
necessarily 153:6 291:5 400:3
necessary 11:3 69:2 76:22 291:8 332:13 384:17
necessity 291:17
need 10:17 14:14 17:17 29:2,8 32:14 37:9,12,13 41:17 42:7,9,18 42:19 43:6,6,10 43:10,11 48:18,22 49:5,17 51:1 52:6 68:10 69:10 72:19 73:12 79:1 80:14 91:10 99:20 102:16 105:9 106:6 110:5,6 111:14,18 112:10 112:11,22 114:9 114:19 121:2 122:11 124:13,16 125:18 130:7,8 132:20 133:3,13 136:5 138:13 149:3 150:22 151:2,22 153:16 154:1,5 155:18,18 155:19,20 156:4 156:11,17 157:4 158:6,10,15 159:12,13 160:21 160:22 161:10 163:14,17,20 164:10 166:5,22 167:2,14,15 170:14,15 194:8 194:13 196:1,6,7 196:11,18,22 197:10,19 198:2 198:18 199:1,6 201:10 203:10 208:9 212:9 215:4 216:2,22 218:4,9 219:4 230:17,21 231:8 232:17,18 233:2,12 235:1,14 237:21 239:4 244:6 249:3 252:19,22 253:3,7 253:20 254:12,16 256:10 265:16 267:6 272:7,22 281:2,8,15 282:10 284:7 286:8 293:1 302:17,18 317:20 318:11 319:5,13 320:8 323:21 328:7 329:14 330:19 335:17 337:13,14 350:16 367:6 371:16 372:7 374:14 376:22 383:22 395:7 400:1
needed 27:22 42:10 43:3 112:1 175:4 179:16,19 180:9 181:5 191:2 216:1 237:8 287:13 306:17 316:21 318:2 320:16 329:16 377:17 396:1
needing 126:7 170:22
needs 92:21 112:10 131:13 132:11 136:1 141:22 152:2,4 157:20 159:16 160:3 166:4 167:10 170:1 218:4 219:21 243:19 249:21 253:6,14 311:15 320:10 327:8 329:11 359:20 387:16 392:6
negative 37:4 136:3 248:15
neither 119:20
Nembhard 2:9 6:11,12 75:16 82:6,7 83:17 85:6 85:9
nephrotoxic 326:9
nerd 250:14
network 143:2,2,3 149:13 150:22 163:1 167:3
never 102:10 208:20 239:6 254:14 266:21
new 3:8,17,22 6:7 18:11,21 19:7 20:7 22:17 32:16 32:18 35:15 36:17 38:14,15 70:12 80:20,21 81:12 121:9 137:15 167:10 171:22 172:11 173:9 174:3,19 176:5,6 176:11 179:10 187:15 191:17 193:4,5,21 194:1 196:2 203:6 204:3 208:14 209:1,9 213:12 215:17 217:6 222:2 223:10,11 224:10

224:18 225:12 227:4 243:6,7,8 244:1 247:12 261:19 269:15,16 278:7 282:6 292:4 308:1 361:5 377:6 386:18 392:19
newer 81:21 82:3,3
newly 243:10
news 345:8 387:20
NF 271:13,21,22 273:15 274:13 279:21 280:7 284:7 314:20 341:15 342:5 348:13 349:15,20 349:20 355:14 360:20 361:6
NF-23 342:22 344:7
NF-25 344:14
nice 20:12 42:11 100:19 104:15 122:21 124:10 169:22 204:2 218:9 242:8 258:5 404:3
NIH 231:15 394:15 394:16
nine 122:9 174:6 283:5 394:8,9
NIPDE 260:10
NIR 69:6 151:6,7 178:20
nitrogen 351:11 356:9,10 365:20
NMR 278:9 290:18 290:19,22 291:18 337:16 363:13
nodding 260:21
nominated 142:20 143:10 144:1
non 149:16 205:2 283:18 286:18 292:20 308:18 316:15 338:10,15 351:2
Nonprescription 3:20
non-chemical 287:2
non-clinical 98:15
non-CMC 174:9
non-destructively 231:21
non-existent 304:4 304:12
non-ICH 31:22
non-mandatory 355:17
non-prescription 270:7 292:2 293:10
non-QbD 202:12 254:18
non-specific 306:12 312:10 313:1 320:21 336:14,14 336:18,18 337:4,5 340:22 341:2 345:1 351:11 356:9,16 362:6 363:9,10 365:20
non-voting 2:12 13:6
normal 95:17 238:8
normally 389:4
note 189:20 198:12 273:6 308:20 334:20 345:21
noted 14:16 318:1
notes 195:11 266:10
notice 129:1 183:4 289:20 296:9 297:10 298:19 353:12 397:21 398:2,17
noticed 50:1 312:3
noting 318:5
notion 264:1
novel 238:18,19 328:17,17 375:11
November 284:3 325:7 327:6 349:13 350:22 352:4,19 354:5 356:6 372:17
NSF 231:15
NTI 15:19 16:1,4 403:18
number 50:12,18 66:21 67:3,3 73:22 89:9 96:3 121:7,18 133:6 138:2 174:19 175:11 176:1 177:15 178:22 179:12 184:16 186:22 189:22 192:20 220:4 226:3 227:15 228:15 229:9 230:8 303:21 360:14
numbers 89:16 102:1 147:8,14,17 175:21 182:20 184:12
numerous 184:20 185:5 402:12 403:16
nutrients 251:10

O

Oak 1:18,20 219:14
objective 221:2,5
objectively 13:19
objectives 23:1 114:5 173:4,21 187:5 270:3
OBP 187:3 188:8
observation 15:5 140:21 184:12 186:1,4 268:11
observations 147:14
observers 15:4 140:19 268:10
obsolete 281:15
obstacle 132:22 220:13 221:6,6
obstacles 133:20
obtaining 350:6 360:2
obvious 251:11 311:16
obviously 58:10 62:8 66:3,15 67:5 69:12,17 70:9 71:15 74:8,16 78:9 81:13,17 134:6 193:15 207:21 227:3 272:3 312:1
occasionally 397:1
occur 68:13 116:22 131:13 136:1 216:3 399:14
occurring 108:12 360:15
occurs 56:16 109:20 135:20 183:12 215:15 398:2
October 33:15 169:3 281:19 334:14 383:13
odd 60:16 71:11 225:13
offer 185:15 191:16 191:22 234:5 354:21 357:6
offering 374:20
offers 217:11
office 3:3,5,6,8,13 3:14,21,22 6:2,4,7 6:9 11:20 20:7 177:22 178:2 180:1,1,11 181:2 187:12 188:22 190:11 191:3 193:20 199:4 268:17,18 270:6 272:16 276:5 283:7 292:3,4 305:4 390:17
officer 3:2,12 7:6 186:3,3 268:16
offices 11:22 51:1
official 183:3 271:17 302:10,13 310:21 317:3,10 317:13 352:13,20 355:3 399:2
officialed 348:13
officially 5:5
officials 243:14
offline 51:12
offset 207:22
offsets 207:22
oftentimes 179:16 179:19 181:11
OGD 3:5 106:19 107:6 188:22 190:7
oh 54:16 104:9 120:14 289:1 290:12 395:21 397:16
oil 342:5,11,16,17 342:20,20,22 343:15 344:8 362:9
oils 342:19 361:22 362:3
okay 44:19 58:20 59:16 61:21 62:17 63:4 69:17 75:17 75:17 76:12 79:15 80:4 83:4,7,16 85:19 88:6 89:14 89:21 92:14 93:12 95:6 96:21 125:6 129:10 131:21 135:9 140:16 192:11 201:7,16 207:13 221:10,15 221:17 222:4,12 222:14 227:6,18 240:13 255:6 263:19,21 265:11 266:11 268:3,22 293:7,11,19

296:18 298:12 310:7 361:1 385:5 401:16
old 53:20,22 96:16 98:9 203:6 266:16 266:18,18 386:17
older 281:14 316:15 364:12
oldest 95:1
once 26:22 31:2 34:5 35:8 58:4 65:22 68:5 99:9 116:15 123:3 125:22 126:1 137:17,17,20 142:12 162:9 181:8 212:15 229:19 253:4,11 299:13 317:8 382:7
oncology 176:9
ONDQA 3:9,18 173:20 176:12 177:5,19 179:11 179:15 180:9 181:19 184:6 188:12 199:4 217:11
ones 103:5 167:13 250:17 280:17,18 285:16 321:4 323:6 370:17,18
one's 57:2,2
one-size-fits-all 160:21
ongoing 19:2 70:17 160:14 312:14 331:14 356:8,22 366:11 395:14 397:2
online 46:3 67:13 67:21 68:8 69:5,7 74:11,19 78:19 79:2,7,13,22 91:10 185:3
open 8:9,21 15:5 140:20 194:19 205:12 222:19 268:11 320:5 321:10 383:19 385:7,10
opening 15:2
openness 128:17 129:14
opens 298:21 299:10
operation 154:9
operational 54:16 192:15
operations 59:13 80:21 187:9 272:18 334:13 383:12,15
operator 75:1,2 130:4
operators 131:1
opinion 120:1 228:5
opinions 8:7 144:5 145:1 389:14,15
opportunities 4:7 17:18 20:4 21:7 22:19 23:22 24:1 25:9 28:9 36:9 39:8 73:22 179:1 211:16 232:15 359:9 383:5,7
opportunity 20:13 23:15 46:14 111:1 113:15 173:22 184:2 208:6 217:12 221:5 359:7 370:10 385:18 400:18
opposed 337:18 361:2
OPS 3:4,4,6,9,11 3:18 16:16 271:2 385:13
optimization 84:12 332:7
optimize 45:4
optimizing 65:4 102:7
option 48:7 106:5 106:11,12,20 107:2 139:7 264:8
optional 107:19 108:4,21
options 70:16 322:1,21 332:7
ORA 191:21 390:18 391:10 393:22
oral 314:11 326:21 326:22 328:5 337:7 380:15,15
order 4:2 5:17 42:11 43:20 45:2 148:22 150:2 151:3,6,10 152:5 162:2 170:11 179:2 198:2,9 200:8 210:5 211:8 256:11 278:16 280:3,16 342:8
ordinary 324:21 338:5
organization 32:1 68:9 108:7 136:17 137:6,18 150:14 374:8
organizational 56:21 104:22
organizations 76:20 102:22 372:10,14 375:14 389:6 402:13
organize 249:6
organized 107:16 318:8,12
organizing 150:13
oriented 101:9
origin 343:10
original 84:17 170:10 174:6 187:10,16 207:18 319:14 386:12
originally 319:10 320:4 357:2
orthogonal 366:8
OSCS 277:19,20
Osterberg 327:2
OTC 270:8,20 274:2,4,7 282:20 284:10,12,20 286:18 292:9,20 293:13,17,18,19 294:4,14 295:6,15 295:17,18,20,22 296:2,11 298:14 299:21 300:8 301:1,3 302:6,9 302:16 303:16 305:1,2 306:2 308:5 309:5 325:11,12 333:20 334:4,5 339:7,19 367:21 368:12,15 370:8 373:6,21 374:13 378:16 380:13 382:8 383:4,12,14
OTCs 334:18 338:21
Ouderkirk 3:12 268:15,16,22 288:22 289:17 291:7 303:9
ought 203:6
outcome 142:13 165:14,15 380:9 382:16
outdated 312:9 316:10 335:22 341:4,9 343:4 345:1
outline 22:12 33:6
outlined 30:7 36:6
outlines 26:5
outlining 373:7
output 55:17 59:17 72:5 73:14
outputs 59:1,16 60:5 86:10
outreach 243:13 333:5 358:12
outside 16:5 19:15 29:20 37:3 89:12 171:7 188:9 217:14 402:12
outstanding 165:17 169:9 356:7
outweighs 10:18
overall 101:7 172:9 174:10 175:6 177:5 185:16 188:10 203:5 204:7 238:11 271:3 325:6 373:14 376:5 384:8 386:16
overburden 159:13
overcome 56:15 117:19 229:14
overhauling 386:19
overlooked 274:13
oversee 306:20
overview 141:12 269:10
over-sulfated 277:18
over-the 377:2
over-the-counter 292:6,18 293:8 368:11 376:7
owns 14:4
oxidation 112:18
oxidized 343:14

P

package 98:14
packed 313:17,19 316:11 321:1 322:18
page 216:7 284:15 284:15 315:14,17 333:16,17 358:3,6 358:21
pain 220:22 296:19 296:22
panel 15:7 52:18 74:3 120:12 125:3 129:3 133:21 140:5 141:1 168:8

168:15 191:11 206:11 212:14 235:16 257:14 268:13 288:18 290:12 297:17,18 298:17 305:20,20 305:22 308:8 326:12,14,16,20 327:4 328:13 336:9 338:19 353:18 354:2,16 354:20 356:1 357:1,18,19 360:10 367:7 376:11 378:10 385:3 395:20
panels 297:15,17 297:21 331:22 332:13,15 333:19 359:11 375:12
panel's 298:16
paper 70:15 396:20 396:22
para 326:7 327:10 328:8
paradigm 36:17 192:18
parallel 165:6 181:12 236:18
parameter 23:14 48:22 102:8 108:2 108:3 153:18
parameters 38:4 39:17 59:14,15 60:8,10 65:5 79:10 85:11,14,22 86:2 110:15 155:8 159:5 198:20 203:2 246:2,3
para-aminophenol 326:19 327:15
Pardon 396:17
Parliament 143:4
part 24:18 76:14,16 82:19 83:7 91:2 107:9 143:1 193:2 196:5 202:17 203:5 208:12 210:21 212:19 214:16 220:21 221:3 234:16 245:4 259:3,18 319:19 338:2 347:12,14 349:21 349:22 350:15 358:19 359:1 364:19 365:22 378:19,20,21 379:17 384:8 392:3 396:21 400:20
partial 71:14 275:6
partially 45:15
participant 14:13
participants 3:1 10:7 14:14,19 187:15,20 316:1
participate 14:8 15:6 140:22 184:2 268:12 315:5 327:4 333:11 376:10 378:13
participated 150:17 372:19
participating 2:6 13:5 164:15 167:17 173:22 184:7 378:9
participation 172:17 179:8 183:19 184:5 188:17 316:3 334:12 378:3
particle 73:5 95:4 119:11 124:11 361:14
particular 10:18 12:5,13 13:11 37:5 135:2 178:10 211:2 212:16 223:17,18 250:19 261:10 262:22 264:7 387:20 398:7
particularly 258:14 260:3 265:6 272:12 289:10 301:6 306:14 395:6
parties 12:14 143:13 144:8,14 144:15,16 149:21 151:15 333:4
partly 207:19
partner 179:22 384:4
partnered 107:7
partnering 12:10 19:2
parts 143:3 165:18 250:18 327:11 386:18
Party 144:11,11 151:14
party's 279:8
pass 342:21
passed 342:22
passes 203:15
passion 17:12
Pat 7:18 57:11 67:13 69:20,21 70:20 74:19 79:13 80:22 81:5,13,22 95:7 107:19,21 108:4,9,21 134:1 144:20 147:15 149:20 150:1,21 151:8 221:18 243:7,22 253:18 399:17
patents 11:16
path 256:16,17 387:9
paths 372:4,5 373:3
patient 103:3 141:18 146:4 168:3 198:22 204:18 232:1 238:15
patients 73:18 99:18,19 106:18 204:10,18 208:1 248:8
Patricia 2:12 13:5
PAT-2s 90:13
Paul 269:7 272:17 283:3 288:14
pay 231:11,12 239:5,6
payback 56:17 69:16 70:5 223:4 223:11
paying 57:2
PDG 350:16,17,18 352:5,15 353:2,6
PDUFA 176:2 193:15 208:20
peak 337:10,11
Pedro 130:14
peer 163:15
peer-reviewed 189:7 235:13
penetration 191:14
Penn 6:13
penny 138:22
people 15:13 50:18 52:7 93:1,5 111:8 115:16 118:6 125:19 179:12 192:20,22 193:20 194:5,6,11 197:4 202:7,8 205:7,8 216:10,19 229:22 230:8,20 234:17 241:20 242:10 246:8 252:3,12,13 256:14 262:19 333:10 335:19 386:2 387:4 388:8 388:11,13 389:1 389:12 393:3,21 402:12
perceived 43:7 138:1
percent 62:5,9 63:21 64:1,1,10 64:11 65:4 87:17 88:21,22 89:1,3,6 89:17 99:12 100:7 101:7,10,17,18 102:1 106:12 130:17,21,22 134:17 138:13 173:6 214:18,20 214:21 248:14 326:20,21 338:7 348:21 349:11 360:22 361:4 368:12 378:16
percentage 64:13 87:10 135:1 306:19
percolating 193:19
perform 203:15 276:13 348:18
performance 25:15 26:3 170:9 171:9 197:18 214:5 231:20 234:3 235:22 237:19 238:6 241:5 246:21 247:21 255:14 261:10,11
performance-bas... 197:20
performance-pre... 203:12
performed 331:10
performing 182:21
period 85:16 298:22 299:11 316:20 317:6 329:20 330:14
periodic 181:4 183:13 286:1
periodically 283:21 285:3
peripherally 240:3
permanent 144:13
peroxide 343:12 345:2
peroxides 351:9 352:10,17
persic 342:20
person 104:20

400:2
personal 14:13 245:9
perspective 18:21 22:4 36:22 45:19 53:12 76:9 82:12 82:13 97:18 98:10 100:3 107:16 110:13,18 115:6 115:15 116:7 119:4,7 126:5 134:2 141:7,10,17 172:4 183:11 196:7 208:5 213:5 248:4 256:1 270:20 282:11,13 282:15 310:12
perspectives 4:6 20:4 111:4 340:7
pertinent 220:4 223:20
PF 316:20 320:2 323:17 330:13 331:1 353:13 359:5,8 398:10,11
Pfizer 2:17 14:4,4 53:5 58:16 78:3 220:3,18 221:11 228:16 230:19
Pfizer's 59:7 79:5
PF-37-3 329:19
pharma 97:16 229:1 262:18
pharmaceutical 1:6 2:15,18 3:4 5:14,16 6:2,5 7:9 7:16 9:14 11:20 13:12 21:11 22:9 22:11 25:12,22 29:15 30:2 31:8 34:1,12 35:2 36:12 41:19 43:13 46:12,17,20 53:7 94:11 96:12 145:15 173:15 191:4 196:14 199:4 270:18 271:14 274:3,11 274:15 281:13 283:2 286:12 305:4 350:5 363:15 384:4
pharmaceuticals 12:4 13:22 97:21 197:10 242:18 245:1,6
Pharmacoepide... 7:11
pharmacognocist 266:17
pharmacokinetics 238:10
Pharmacology 1:7 5:15,17 9:15
pharmacopeia 2:21 12:11 14:2 80:15 143:8 316:19 324:18 381:2 384:3 398:13,15
pharmacopeial 349:16,22 350:1
pharmacopeias 350:19
pharmacy 7:4,12 8:3 115:13,20 390:21 391:1 392:14,15 393:8 400:14
PharmD 3:2
phase 57:7 58:5,9 86:17,19 134:15 279:2,2 333:7 358:13 379:8
phased 204:10
phases 57:6
PhD 2:2,4,5,5,6,8,9 2:9,10,10,11,12 2:15,16,17,19,21 3:4,8,16,19
philosophy 104:21
phones 5:6
phone-in 7:21
phoning 7:21
PhRMA 53:16 73:15 237:12
physical 7:4 243:9 246:20 247:18,20 289:12 353:21
pick 126:10 340:12 391:5
picked 126:4
picking 387:9
picture 141:15 146:4,18 175:10 182:13 294:11 296:6 303:1 402:14
piece 57:21 238:18 397:17
pieces 198:7 230:17 248:11
pilot 59:8 63:13,13 64:8,21 86:14 155:12 157:8 158:6 165:6,19,21 168:19 173:20 174:5,10 177:19 178:2,4 187:3,14 187:14,22 188:9 188:12 217:10,15 236:18 260:13
pilots 68:14
pivotal 110:5,10 123:4 132:21
PK 238:8
PKs 238:13
place 8:21 51:6 74:7 77:6 80:13 128:1 161:6 172:14 204:9 219:13,14,17 230:15 291:1 343:18
placement 355:22
places 228:9 229:1 229:10 233:22 288:6
plan 20:18 59:11 59:22 122:21 130:11 169:7,11 287:22 306:10 307:15 327:13 330:19 357:20 382:11 383:11
planned 273:13 371:12 396:6
planning 90:13 182:2,22 217:8 272:11 329:9 372:3 392:11
plans 57:13 59:1 228:19 285:22 306:20 332:2 358:7 394:19
plant 112:9,9 120:20
plants 117:3
plasticizer 119:11
plate 17:9
platform 196:12,13 211:21 279:9 392:13
platforming 138:3
play 28:19 234:18
player 78:6 252:11
playing 104:6 127:11
plays 374:8
please 5:6 9:6 87:9 140:5 168:12 200:21 201:1,5 236:5 248:8
pleased 53:15 234:15 239:21 333:22 402:18
plug 253:4
plus 401:11
podium 15:11
point 23:18 37:1,22 38:12 39:4,11 42:16 51:1 52:1 53:19 76:13 80:18 90:17 92:1,4 100:4 107:4 123:16 124:19 145:12 146:19 152:8 157:16 158:22 160:6 163:17 177:17 186:14 187:16 189:8 204:16 206:15 216:14,14 231:8 247:8 257:4 258:5 262:11 287:11 291:8 296:17 310:6 318:6 321:22 323:11,21 330:14 336:3 345:15,18 346:8 348:5 363:4 385:21 386:17 390:20,21
pointed 47:16 103:14 364:3
points 88:8 98:22 99:22 103:20 118:9,11 123:19 148:21 158:11 178:16 213:22 251:17 259:10 265:19 316:16 328:10 342:10 371:13
policies 173:14
policy 3:11 176:14 385:13
political 279:8
Polli 2:10 7:13,13 92:12,13 93:12 168:16,17 169:7 290:13,14 309:2,3 309:15,20 336:10 336:11 363:6,7
polydispersed 246:9
polymer 361:6
polymeric 94:17
polymers 360:21
polymorph 119:9
polyol 358:19
pooling 374:4
poorly 247:8 263:5
POPE 3:16
Pope-Miksinski 171:20

population 246:17
portable 392:20
portion 93:9 212:4 247:1 319:9
pose 45:2 248:7
posed 45:1 239:14
posing 153:20
position 210:10
positive 142:12 354:13
positively 248:15
possible 55:1,18 144:14 146:1 169:10 255:19 332:21 356:19
Possibly 158:18
post 147:1 152:9 160:17 226:10 229:20 278:14 320:9 327:22 353:3
posted 281:1,9 284:13 285:21 319:10 320:4 352:12 353:7,13 354:14 355:2 356:4 358:8 371:15
posting 319:14
postponed 356:2
postponement 355:19
post-approval 159:4,19 161:12 161:15 162:12,17 162:20 210:7
post-launch 62:20
potential 10:16,19 11:2,8 32:15 36:21 44:11 86:9 87:11 101:18 102:11,12 180:13 207:4 210:9 245:18 249:16,20 254:19,21 262:16 284:1 286:14 287:18 303:8,11 303:14 318:17 344:18 354:21 356:20 357:7 370:2
potentially 87:1 113:19 381:10
pound 130:15
povidone 349:19 352:5,5 353:4 388:1
povidones 351:1,2 356:8 357:11 365:21 366:13
power 121:8 278:14
PPD 101:1,16,19 101:21 103:1,13
PpK 62:14,15
PQM 180:18 183:16
practical 313:2 322:13 380:11
practicality 38:3 339:5
practically 266:13
practice 27:20 50:11 53:21 61:8 181:14 276:11
practices 22:11 107:13 182:15 193:15
practicing 171:13 171:17
pre 22:22 147:10 150:7 295:4 358:21 359:3
preapproval 77:2
precedents 177:4 180:14
precisely 227:20
predates 387:14
predetermined 72:6
predict 86:9 103:22 104:4,7 231:20,22 234:3
predictability 232:6
predicting 104:3
prediction 121:3
predictive 55:14 72:2,12 73:5 121:8 196:22 197:12
preempted 265:17
prefer 154:15 351:12 356:12 397:7
preference 207:8
preliminary 34:6
preparation 38:18 101:3 183:16
prepare 144:5 150:2 179:2 288:15
prepared 17:16 148:19 181:20,22 182:7 195:8 225:17,19,20,21 225:22 398:7
preparedness 128:17
preparing 209:16 383:5 393:19
prescription 99:7 274:6 292:21 293:1,7,10,20 316:6 325:14
prescriptions 99:14
Prescription/Non 316:5
presence 289:22 343:19
present 2:1 5:6 20:13 29:3 37:9 94:2 97:13 141:9 307:4 341:1 371:9 379:1 398:7 401:2
presentation 12:9 13:19 20:22 21:20 34:6,10 47:7 51:13 52:13 53:9 82:8 92:14,15 96:8 97:1,10 98:6 118:8 134:12,16 136:10 141:4,13 144:22 157:1 160:8 165:13 169:22 172:1,7 194:17 228:16 268:19 292:5 306:8 310:11 336:16 340:3,6 367:12 385:11,14
presentations 16:12 19:13 21:13 45:13,13 140:18 189:6 253:16 268:6 269:11 401:17
presented 27:1 33:7 34:14 35:20 44:1 93:9 111:2 118:16,17,18 124:17 148:15 152:2 154:3 155:3 165:13 166:7 177:15 178:4 186:18 192:7 218:11 279:16 372:21 401:20
presenters 402:9 402:11
presenting 43:17 90:2 97:11,20 109:10 175:20 195:19
President 2:21 310:10
presiding 1:22
press 5:9
pressed 209:20
pretty 62:17 81:5 81:10 93:2 132:2 175:18 192:7 264:19 265:2 340:13 363:21 389:16 401:11
prevailing 131:7
prevent 280:10 342:9 344:11 362:5
prevention 362:18
previous 103:16 108:6 111:16 128:20 130:18 132:9 146:16 186:17 188:13 342:3 346:6 357:12
previously 180:19
previously-menti... 190:8
pre-approval 153:6 153:8 184:4 274:8 280:19 295:3
pre-defined 114:4
pre-determined 23:14
pre-market 300:20 301:2,6
pre-PF 327:22
pre-reviewed 286:18
pre-submission 182:21
price 99:9,11 212:4 239:5,7
primarily 77:19 102:2 179:12 325:12
primary 11:17 220:13 221:6 311:11 325:14 342:11 343:13 370:6 391:17
principally 12:11
principles 11:22 24:12 27:4 46:19 54:22 55:6 71:12 147:4 148:4 163:12 189:17,19 202:19
prior 33:13 86:7 98:7 114:3 189:10 209:22 210:4 296:15 345:5 354:15 381:4

priorities 371:2 374:3 387:10
prioritization 283:15 286:10 287:13,15 304:18 306:21,22 307:11 318:15 322:4,7 332:8 364:4 374:22 377:11
prioritize 249:4 251:15 286:4,20 318:19 374:13
prioritized 305:11 305:12 306:17 318:15 340:15 375:8 379:3 396:12 397:22
prioritizing 123:12 282:10 350:11 360:4 371:19 372:16
priority 282:3 284:8 285:11 286:2 288:1 315:19 342:2 345:4 348:7 359:2 375:7 377:14 381:17
private 368:14
proactive 24:2 369:4 376:4
probability 242:22 243:6,22 245:5
probability-based 242:14 244:21 261:17,19
probably 50:8 56:21 68:22 80:13 134:20 223:8 239:17 246:22 275:13 287:14 338:10 339:8 360:22 363:12 364:9
problem 108:8 114:7 117:12 118:4 138:11 155:5 209:12 210:12,15 275:17 303:14,14 386:7 386:10 387:5,16 387:21 400:6 401:2
problematic 216:11
problems 94:13 112:19 116:22 117:18 160:5 205:2 221:14 303:8 312:11 388:15 389:21 397:8
procedural 143:15 152:18
procedure 49:8 142:12,13,22 143:16 146:20 153:11 313:17 324:22 327:14,17 328:7 329:15 330:8 331:2,7 337:6 338:12,17 357:8 388:6 401:6 401:7,13
procedures 49:9 176:14 178:20 306:12,14 311:20 312:1 313:1,11,20 313:21 314:17 315:1 316:10,11 320:6,12,21,22 321:7,10,18,20 322:18 324:8 325:6 329:15 332:9 338:11 341:5,9 350:6 354:22 360:2 370:12,18 376:17 382:9
proceed 15:2 268:5 371:18
proceeded 318:3
proceedings 9:3
process 6:20 17:2 19:19 21:3 23:2,2 24:5 25:2,5,15 26:2,6 27:15 32:22 33:11 34:16 37:20 38:4,10 40:10 45:7 47:12 47:17 48:2,6,11 48:13 49:13,15 51:5 54:20 55:10 56:1,4,5,7 57:7,8 57:9,12,15,16 58:2,7,9,14 59:9 59:10,13,18,19,22 60:4,13,13,17,21 61:1,5,6,8,13,13 61:17,18,20 62:3 63:3,6,12 64:4,17 65:5 66:16 67:5 67:12 68:2,19 71:7,9,13,15,16 72:2,14 74:17 75:3 77:19,20,22 78:14 80:12 81:20 81:21 82:18 83:6 84:11,13 86:2,4 95:15 100:22 101:2,15 104:19 111:9 113:1,14 114:15 116:10 117:4,9,11,14,20 118:5 121:6 122:12 123:6 127:21 128:10,11 128:12 129:12,19 130:11,16 131:1,3 133:10 134:8 137:10 145:6,17 145:22 146:11,13 146:14 148:8,9 149:2 151:9,12 158:3 159:2,5,7 159:11 160:20 161:3 167:21 170:17 171:1,6 180:3,14 181:3,12 182:3,17 184:21 185:2 187:7 193:11 197:17 199:7,8,10,16 201:20 202:2,11 202:18 203:3,5,7 205:5 213:17 214:9,22 218:13 218:14 220:9 224:1,3,7 226:6 231:4 237:7 239:2 239:5 241:4 242:11 243:3,4 246:2 251:8,11 254:20 255:14 256:6,6 259:4,12 259:17 261:9,11 262:8 264:5 266:8 292:10,11,12 293:19,21 295:18 295:19 296:1 297:5 298:14 300:19,19,20,21 301:1,4,12,17 302:22 312:18 316:22 317:3,8 333:9 352:7,16 353:2,6 359:19 373:14 374:19 375:4,18 378:20 380:5,22 381:7,10 382:21 383:6,9 384:8
processes 16:17 19:11 36:12 37:7 39:1 40:3 42:14 55:14 61:9 72:1,8 73:11 78:1 80:9 81:15 106:8 107:1 111:19 124:20 139:16 182:8 187:1 196:8 214:3 226:7 261:21 262:20 263:6 293:15 294:18,19 294:21 316:18 319:21 403:7
processing 81:16 148:11 182:22 199:14,19
process-related 115:9 182:6 347:20
produce 54:4 85:2
produced 91:5
product 3:13 23:1 23:8,9 24:2,14,15 25:17,17,20 26:3 27:15 29:6 30:5,9 32:8 35:16 36:14 36:14 37:7 41:22 44:10 49:4,5 53:11 56:6 58:4 58:18 61:19 62:13 64:17,21 65:1 66:16 67:19 69:18 70:1,4 71:12 83:9 85:2 92:17 100:22 107:4 109:3,4,22 111:20 112:8 113:17,20 114:10 115:4 116:10 117:4,13 118:21 118:22 121:9 122:4,12 123:6,11 123:17 124:14,17 126:19,20,20 127:5 130:10,12 130:14,18 131:3 131:15 133:10 136:15 137:4,10 138:11 145:16,22 146:3,7 153:21 156:1,7 158:7,9 158:14,20 159:6 162:3,8 167:21 168:1 169:1 170:10 171:9 180:13,17 181:17 182:4,6 184:21 185:14 186:21 189:21 196:10 197:12 198:13 203:13 204:5,8,22 207:3 208:2 209:18 211:9

212:4,5 213:7,18 213:19 214:2,4,9 223:18 224:4 225:14 226:13 227:5 247:12,21 259:17 266:18 268:17 274:21 276:12,15 286:13 286:19 294:2,3,9 295:10,10,14 296:1 299:18,20 300:6,11,21 301:12,13,20 302:16 303:2,6,7 305:15 309:7 331:6,7 334:4,13 374:16,21 375:20 378:2,18 379:6,10 379:20 381:2 383:15 394:3
production 155:13 157:11 242:17 243:8 244:22 264:5,7
productive 8:16 185:11 395:12
productivity 65:4 204:8 263:10
products 2:20 3:6 6:10 14:6,11 16:5 16:20 18:13 19:4 28:18 29:14 30:5 39:1 46:4 61:11 62:8 63:14,18 64:2,16 67:2 71:4 71:10 78:8 81:7 81:15 87:15,16 88:4,16 89:2 90:10 99:15 100:1 100:6,8,13 102:15 102:18 103:2 104:2 106:7,17,22 107:1 109:2,20 110:3,4 120:4,19 120:21 121:7,18 123:18 131:7,10 133:5 136:21 137:21 138:5,17 139:9,12,15 142:10 143:3 144:3 145:2 146:21 147:4,7 148:5 151:17 172:19,22 178:2 182:8 186:16 187:6,13,13 188:3 188:21,22 191:15 198:1 206:5 210:2 210:5 217:4 224:19 225:10 245:12 255:15 261:5,7,12 263:13 266:15,16 271:13 278:1 284:21 292:19 293:15,22 294:5,7,12,14 295:9,11,14 296:7 296:10,13 297:22 301:22 302:21 304:15,19 305:2,4 305:13 329:2 334:5,6,11 360:14 367:18 368:4 374:13 377:3 378:12 382:3 383:21 387:22 390:4 393:11,12
product-based 61:13
professional 36:5 189:6
professionals 297:12
Professor 6:12,17 7:10 8:2
profile 23:10 49:4,5 58:19 90:16 374:17 380:19
profiles 377:15
profit 32:1 138:21
profitable 126:21
profits 101:18
profound 102:21 103:4
program 3:10 4:13 12:12 33:5,6 173:20 177:19 178:3,5 187:3 188:10 268:8 281:22 350:16 385:13 386:16 388:20 389:22 390:8,12,18 391:5 392:4,15,18 396:21 397:2 401:18
programs 173:18 262:19 361:19 389:1,20
progress 17:4,16 20:14 22:1 105:21 107:15 146:12 178:18 195:17 200:3,4,6 231:17 234:20 256:11,18 281:17 285:7 323:3,19 324:1 332:5 352:3 353:16 358:1,6 368:19 371:10 381:7 384:16
progressed 168:21 229:4
progressing 109:3 190:18 285:2
project 112:2 179:15 236:18 260:13,14 277:13 282:3 287:13 288:10 394:6
projects 199:21 390:16
promise 29:1
promising 91:17
promote 93:7 280:12
promotions 235:13
prompted 276:2
prone 112:18 114:8 342:18
proper 170:22 273:20
properly 77:5 91:22 118:18
properties 58:21 289:13
proportion 274:20
proposal 283:12 327:21 329:19 353:14 354:15 379:8
proposals 231:15 235:9 314:20 316:19 319:22 323:16,16 324:8 324:17 331:21 350:14 357:16 358:1 360:7 371:1 378:14
propose 327:18 375:6 382:22
proposed 187:21 272:15 279:13 298:19 299:1,6,7 299:8 302:11 328:12 355:8,22 357:3 373:20 374:11 379:14 380:12 381:5 382:4
proposing 83:10 175:1 328:14 377:4 379:3
proposition 66:11
proprietary 80:18
propylene 346:21
protect 342:12
protective 235:21 235:22
protein 187:6 245:11 387:18,21
protocol 75:2 84:13 188:2 304:9 308:14
protocols 161:16 161:17,18,20 162:6,18 178:12 187:11 304:2,11
proton 278:9 291:18
proud 333:22
proudly 373:18
prove 294:1 372:13
proven 91:14
provide 24:1 26:10 27:16 35:10 36:8 38:17 39:8 41:18 42:20 43:11 46:15 57:11 106:16 144:4,8,17 150:8 150:10 154:5 174:11 185:7 211:12 236:21,21 237:4 262:19 280:3,19 286:1 307:5 311:6 375:4 375:19 376:10,12 377:16 384:6
provided 10:7 13:16 65:22 100:6 107:17 198:6 208:1 372:18 377:19 381:18 382:4
provider 293:2
providers 252:11 262:18
provides 25:9 28:9
providing 102:15 119:4 143:17 173:22 384:22 403:5
proxy 87:11
public 4:8,16 10:8 13:1,18 15:4,5,6 18:11 27:21 28:2 94:5 140:19,21,21 142:5 169:17 194:19 204:20 205:11 218:11 268:9,11,11 278:3 279:22 282:12,14 282:17 284:1 285:8 290:9 291:12,17 297:10

297:19 298:21 299:1,11 301:4 307:5 311:14 312:22 317:14 319:4 322:11 333:13 339:3,20 358:16 373:10 375:18 383:6,19 385:8,10 394:18
publication 31:21 298:15,19,21 299:10 327:20 330:13,22 353:14 358:22 359:4,5 372:6
publications 141:11 149:8 189:7 235:13
publish 166:5 169:8,11 299:7 316:18 365:15
published 32:5 70:15 161:14 165:5 169:14 178:18 287:10 299:6,14 317:9 324:17 329:19 353:8 378:14
publishing 299:12
pull 216:19
PUP 59:10 85:10
purchasing 361:9
Purdue 7:4
Purdue-MIT 108:7
pure 363:20
Purities 307:18
purity 271:18 274:1,17 289:10 310:2 326:10 342:15 344:18 362:8,15
purple 175:14 176:3
purpose 49:10 283:13
purposely 273:14
purposes 11:11 25:4 73:1 142:21 353:1 401:8
push 87:16
put 16:11,13 27:20 31:6 51:5 66:13 74:7 76:5 113:10 130:4 133:1,16 135:21 201:19 206:13,15 207:22 209:10,13 215:17 216:20 226:9 232:18 233:22 240:19 264:9 265:3 272:19 276:7 278:7 284:9 335:14 391:5
puts 67:1
putting 60:22 164:18 241:17,18 242:2 324:13 386:18 388:7 390:22
P-R-O-C-E-E-D-... 5:1
p.m 267:20,21 268:2 404:9

Q

QbD 4:6 17:11 18:2 47:10,11,21 50:10 53:11,17 54:6,9 54:14 56:16,19 60:4,21 61:1,11 71:5,9,12,19 72:2 76:5 78:7,14 79:14 81:7,17 87:13,14,15,21 88:2 92:16,21 97:6,22 98:9,10 98:18,21 100:1,4 102:4 103:8,12,15 103:19,21 105:2,4 106:4,5,13,20 107:9 109:8 111:7 118:12 120:5 122:6 125:9 129:18 133:21 134:14 135:16 137:5 141:6 172:3 172:10,11,14 174:1,14 175:6,11 175:15,17 176:2 176:15,16 177:6,8 178:4 180:3 183:11,12 187:11 187:21 188:1 189:3,4,8,11,17 189:19 190:12,22 191:14 193:19 202:19 206:20 207:2,21 208:6,8 208:10 209:1,15 210:5,7,13,19,20 212:16,21 213:10 213:10,14,15 214:7,19 220:14 221:7,9,12 228:14 229:17 232:15,16 233:16 236:19 238:2 243:20 251:16,22 252:4 253:18 258:1,6,13 260:8,16 261:4 262:17 263:1 264:6 266:7 389:22
QbD-containing 174:19 179:9
QbD-developed 62:7
QTPP 111:15 113:21
qualifications 347:6
qualified 117:21 144:12
qualifier 191:17
qualify 85:21 114:12 132:15
quality 3:9,14,17 4:6 6:7 11:21 16:22 17:2,7,9,14 18:13,16 19:3 20:3,7 21:1,2,18 21:22 22:3,7,14 22:20 23:3,6,9,11 23:15,21 24:4,7 24:11,19 25:12,22 26:3,7,13,14,15 26:15 27:3,8,9,12 28:4,7,11,13,15 28:17,20 29:19 30:2,4,11,16 32:4 32:20 33:4 34:3 34:17 35:2,3,15 36:1,9,10,13 38:2 38:3,11 39:6,14 39:16 40:6,17,19 40:21,21 41:6,16 41:20 43:13,21 44:9 46:19,20,20 46:22 47:15 48:3 48:5,22 49:4 51:14,21 53:10,12 55:1,2,3,4,5,7,8 55:18,20 56:6,12 57:4 58:3 59:8 60:6,7,11 61:18 62:14 63:6,11 64:8,18,21 67:11 68:8 69:11 72:6 72:10 73:14,16 76:16 77:3,11 80:2 81:19 82:18 83:5,8 85:3 86:11 86:21,21 87:12 88:17 89:8 99:20 100:1,6,8 102:4 102:15 106:17,22 107:5 111:20 119:8 120:4 121:5 128:2,15 134:21 135:3 141:11,17 141:20 143:7 144:10 145:13,18 146:2,5,8 147:3,6 147:12,15,21 148:2,14 150:4,9 150:19 151:3,14 152:6,19 153:5,21 154:9 156:2,7,11 156:14 158:21 159:6,21,21 160:1 160:9 162:3,8,14 163:12 164:8 165:7,11,19 166:11 167:20 168:1 171:22 173:11 174:4,12 174:21,22 176:20 177:1 178:8 179:3 180:5,17 181:17 182:16 185:14 186:8,15,20,22 187:8 188:20 189:14 190:7,9,17 191:5,19 192:17 193:7 194:1 196:3 196:21,21 197:1 197:15 198:3,11 198:17 199:12 203:11,17 206:5 208:2,18 211:8,9 211:12,13 212:2 213:7,17 218:15 218:18,21 219:16 222:6 246:1 258:20,20 268:17 271:18 274:1 283:2 292:7,13,14 301:9,14 302:2,21 303:6,8,12,14 305:3 334:13 342:15 349:2 362:15 368:22 369:16 370:13 376:1,7 377:20 381:19 383:15 384:5
quality-related 177:13
quantitation 346:14
quantities 290:5
question 37:21 44:20,22 45:11,12 46:1 48:1 49:22 50:7 51:11 71:4

74:3,6 75:20 77:12,21 80:7,17 84:3 85:7 87:14 89:22 90:6 98:2 109:6 129:11,16 131:19 132:18 136:8 139:3,4,18 154:13 155:18 156:10 159:15 161:1 168:18 169:22 171:4,4 177:10 192:1,6,12 192:13 206:17,21 207:1,14,18,19 211:7 212:11 220:4 223:14,16 225:6 227:10,17 228:12 239:12,16 240:2,4,5,5,8,17 245:8,13,17 251:19 252:1 258:11,11 260:21 261:3,4 265:5,6 289:7 309:1,4 351:14 366:15 374:16 396:16 399:8 400:13
questionable 182:10
questioning 52:12 96:7 195:5
questions 18:5 31:21 32:5 34:20 38:13 41:8 43:16 44:15,17,22 74:2 77:18 82:9,9,12 82:14 96:9 97:11 103:11 105:6 109:10 112:3 118:15 120:12 128:19 129:7 135:13 139:6 148:18 152:21 155:4 158:1 159:10 165:16 168:8,11,14,15 169:8,13 191:9,10 200:22 202:15,17 203:3,7 206:12 220:2,5,7 227:15 227:16,19 239:14 239:16 240:15 252:3 257:18,19 257:21 263:22 264:11 266:6 288:17,20 289:3,6 290:12 308:8 336:8,9 338:19 360:10 367:7 385:3,5 395:19 399:13
question-based 177:22 190:5 262:12
queue 75:13 125:3 200:15 201:7 240:14 395:19
quick 49:21 162:10 192:6 255:7 366:15 393:10 399:12
quickly 148:3 173:5 216:17 234:9 244:5 264:17 363:4
quite 8:7 15:18 64:17 106:21 119:3 122:17 139:11 152:18 154:6,20 155:1,5 156:3,8 159:3 160:4 164:9 214:14 241:2 245:12 258:8 259:12 262:2,10 311:16 341:8
quote-unquote 34:2
Q&A 161:14
Q10 25:11,19 58:8 178:19 219:2
Q11 46:10 188:16
Q3A 307:21
Q8 22:9,21 26:16 29:11,22 30:13 36:6 58:6 174:17 178:19 188:16 189:17
Q9 24:4,18 30:11 58:7

R

R 2:6
race 109:14,15 110:1,3,12 132:19
RACHAEL 2:19
Rachel 14:4 270:19 367:15 368:2
radically 247:3
raise 75:14 156:9 158:10
raised 37:21 38:13 41:8 121:12 218:5 264:21
raises 155:4 159:9
raising 152:21 158:1
Ralph 68:21
ramman 366:22
range 95:3,6 114:12 115:3 168:1 286:7 324:22
ranged 63:22
ranges 155:13 157:10 379:18
ranging 184:13
rank 249:4 250:3
ranking 249:15 250:5
rapidly 120:7
rarely 193:8 213:13
rate 89:6 134:17 314:20
rates 121:12
rating 304:1 308:17,18
ratio 146:7 342:21
rationale 124:5 347:2 372:18
rationally 248:5
raw 80:11 347:6
reach 151:1 243:2 290:17 332:17
reached 155:4 352:5,15
reaching 154:17
react 138:16
reaction 139:6
read 5:4 9:9 59:12 60:2 75:13 100:20 104:12,14,15 173:5 206:16
readiness 129:14 224:17 225:6
reading 100:21 245:15
ready 79:21 214:14 318:7
reagents 313:15
real 34:18 64:20 73:10 74:20 100:10 123:15 132:10 151:8 165:10 170:22 189:21 192:6 198:10 249:14 256:4 264:17
reality 244:12
realization 80:11
realize 48:16
realized 195:9 386:9
realizing 197:13
really 16:3,14 17:17 19:8,12 47:18 57:21 67:19 78:18,21 89:4 90:6 92:13,15,18 94:21 97:13,20 99:12 100:4 103:8 104:11 106:5,11 107:6 108:21 110:8 113:10 114:21 115:7 116:5,17 121:6 122:11,13,14,19 122:20 125:17 127:1,9 128:6,14 129:3,11,13,17 131:5 132:7,21 133:9,12,19 134:3 134:5 135:22 139:9,13 163:17 170:15 186:12 194:9 203:4 205:5 207:20 213:16 216:8 218:1,9 228:8,13 229:3 232:2 233:1,8,12 235:12,14 236:16 237:2,20 238:20 239:18 240:1,3,12 241:12 245:17 246:4 249:22 250:6 251:3,5 255:10 256:17 258:7,16 260:16 261:1,2,4,20 263:5,11 264:21 265:9 289:21 311:9,12 312:14 312:18 314:16,18 315:18,20 318:4 321:7,18 322:4 323:8,15,21 324:10 326:3 334:20 336:21 337:1 338:1 368:7 370:6 374:4 381:6 401:14 403:2,5
real-time 40:2 67:9 67:17 68:4,20 70:6,20 73:20 74:9,12 78:19 79:16,17 90:9 126:2 146:22 148:7 158:2 175:6 203:2 244:7
reaping 57:2 221:1
reason 137:7 145:9 163:14 164:3 165:8,9 167:12 239:4 309:9

320:13 347:19 364:2 394:15
reasonably 62:4,10 71:8
reasoning 365:6
reasons 174:9 198:7 218:10 260:6 280:8 355:10
recalls 133:7,7
recap 258:6
receive 12:8 220:20 355:18 376:7
received 146:20 147:5,9,11 148:2 153:9 181:9 239:22 320:1 345:6 346:11,19 348:11 349:13 355:5
receiving 190:6 396:22 397:1
recently-published 148:20
recite 195:21
recognize 125:10 320:7 383:22
recognized 8:15 271:16 273:22 298:4 300:1 302:12 317:20
recommend 76:1 230:2 375:2
recommendation 305:19
recommendations 14:22 298:17 307:6 322:5 323:9 402:20 403:12,22
recommended 45:4 262:11 326:19 351:5,22
recommends 261:13 349:3
reconvene 267:13
record 8:15 14:17 52:21 68:6 140:14 164:6 267:20 404:9
recorded 278:2
red 183:4 396:3 398:17,20
redesign 71:6,14 80:10
redesigned 71:11
redevelop 89:8
redevelopment 93:11
reduce 28:6,8 67:2 67:3 69:13 103:1 103:3 106:15 145:21
reduced 66:17,18 69:12,12,14 102:13
reduces 239:2
reducing 54:21 66:21
reduction 102:3 118:21,22,22 296:19
reevaluating 379:5 382:12
refer 283:8 312:17 314:3 398:18
reference 173:2 290:19 309:7 319:1 337:17 366:18 391:12,18 391:20,21
referenced 113:3
referred 56:11 67:8 298:5
referring 345:12
refine 287:12 322:6
refined 278:20
refining 343:10
reflect 47:7 311:19
reflects 171:5
refocus 83:18 239:15
reformulate 92:17
refrain 9:3,6 245:15
regard 13:14 147:7 152:4 213:6,10 245:19 259:21 261:7 262:15 286:2
regarding 181:19 243:22 368:17
regardless 29:14 36:11 43:2 51:17 302:21
regards 135:15,16 135:18 172:22 213:11 356:22
region 165:2
regional 39:7
regions 29:21 31:1 33:8 37:3 152:13 363:1
Register 297:9 298:16
registered 194:19 385:7
registration 12:3
regular 9:19 10:15 11:1 202:9 318:4 335:21 359:19
regularly 307:6
regulate 16:20 390:4
regulated 13:7 302:22
regulating 294:19
regulation 3:20 16:1 28:12,14 242:7 292:2 302:6
regulations 9:22 243:21 276:11 302:8
regulator 34:14 37:13 38:18
regulatorily 391:7
regulators 21:16 27:1,19 35:18 37:15 42:4 43:7 48:10 50:3 51:16 51:19 68:16 148:13 358:14
regulatory 19:10 19:19 21:3,13 22:19 26:21 27:2 27:16 28:7,8,10 31:4 35:22 37:6 38:16 39:2,7 40:3 40:6 41:5,10 42:15,18 43:2 44:2,4 48:17 49:17 60:18 61:2 62:22 65:7 67:6 83:15 101:5 102:13 118:14,14 136:16 141:5 148:12 152:5,11 152:20 153:12 155:10 157:13 158:16,18,19 160:10,19 161:3 166:1 172:2,15 173:13,18 174:2 174:15 177:7 180:2,11 181:2,22 182:8 184:9 196:8 206:22 218:3,13 218:14 224:16 228:11 235:18 248:4 256:12 258:2 259:22 283:7 286:17 293:3 355:13 390:18 393:12 401:8 403:7
rehash 307:7
reinvent 367:3
rejections 66:18
related 11:5 21:21 35:4 37:11 38:1 38:19 40:8 41:11 41:11 46:16 48:17 48:22 75:20 77:18 164:5 185:1,4 197:15 209:15 218:2 219:3 241:16 303:21 314:4 321:2 345:17 347:11 348:3 377:2
relating 144:6 153:11
relationship 23:12 23:12 39:18,22 107:9 224:15 227:20 259:16 280:3 311:5
relationships 14:20
relative 184:15 321:6
relatively 91:18 182:1 231:2 312:10 338:15 388:19 393:10
release 40:2,4 67:9 67:18 68:4,20 70:6,20 73:20 79:16,18 90:9,10 90:16,22 91:6,12 138:7 146:22 148:7 151:9 153:16 158:2 166:13,15 175:6 189:18,19 190:8,9 197:12 203:2 213:20,22 224:14 244:8,9
released 68:11
relevance 144:2
relevant 28:2 144:12 158:19 166:16 170:2 171:2 187:6 197:22 279:22 359:11
Relevantly 159:20
reliance 50:15 348:22
relief 296:22
relief/fever 296:19
reluctance 41:9 76:10 77:8,9
reluctant 76:5
rely 210:1,3 274:10 358:11 384:15
relying 198:19

199:11
remain 263:6
remaining 22:5 36:20 195:18 356:6 366:12
remains 41:13 171:9 258:21
remark 167:19 220:17
remarks 4:22 15:2 195:9,14 267:6 402:3
remember 59:17 79:5,12 88:15 121:1 130:12 140:5 201:6 212:13 395:22
remembering 228:1
remind 5:5 14:9 15:3 140:19 151:14 200:13,16 267:14 268:9 288:18 289:4 367:6
reminded 9:6 41:3 128:1 136:10 258:19
reminder 8:13
reminds 362:19 363:11
remiss 206:11
remove 313:5
render 273:8
repair 401:3
repeated 35:8 228:10
repeatedly 249:13
repeating 33:12 39:5
replace 306:12 365:20
replaced 281:16 324:20,21 325:2
replacement 356:8
replacing 316:10
report 17:11 100:17 228:3 229:17 232:19 241:19 260:2
reported 12:16 107:15,17
REPORTER 397:15
repository 84:7
represent 13:10 53:16 101:19 183:5 270:20 310:18 368:13 378:1 382:1
representative 2:3 2:12 7:1,19 13:4,7 114:22 301:22 380:22
representativeness 91:20
representatives 179:22 180:10 285:4 288:11 326:15 389:9
represented 303:20
representing 2:15 2:18 53:6 96:11 134:13 175:11 368:10
represents 97:20 311:10 378:15
request 15:7 141:1 150:11 157:17 181:6,9 268:13 297:8,8 327:3 329:13 346:11 347:17 348:1 352:4,10,19 355:19
requested 167:9 276:6 281:22 299:5 326:7 348:8 351:1
requesting 346:20 350:11 360:4
requests 147:6 297:11 356:6 361:16
require 31:15 95:5 135:7 375:9
required 27:13 64:4,7,7,12 65:7 66:22 69:11 70:12 101:12 127:22 209:17 213:7 276:13 293:9 295:3,4 300:16 301:7 307:20
requirement 38:16 39:8 83:15 347:11
requirements 12:3 28:8 39:10 69:14 152:5 157:4,13 166:1 299:15 300:3
requires 88:13 89:14 128:6 298:15 302:9
requiring 42:15
research 1:2 2:18 53:7 101:8 199:21 223:8 233:14 271:5 391:9
reside 259:2,5
resides 288:8
residual 178:14 343:10 348:2
residues 343:9
resistance 104:11 388:5
resolution 117:12 158:9 279:20 280:1 311:4 315:13
resolutions 118:4 279:12,16,18 307:3
resolve 184:22 216:16
resolved 76:18,20 389:15
resonance 121:15
resource 55:11 230:15 231:1 233:11 260:7 391:20
resources 123:13 133:1,15,16 163:7 178:21 209:5 217:13 229:11 233:18 313:8 324:4,14,15 334:22 359:15 386:22 387:11
respect 13:3 63:11 74:11 103:19 121:12 351:3 352:11 399:13
respective 233:22
respectively 181:16
respond 217:2 225:5,6 254:7 396:15
responded 258:16
responding 44:22 361:16
response 105:19 181:8 217:20 232:8 244:3 385:4
responses 96:9
responsibilities 185:18
responsibility 117:7,8
responsible 51:21 143:8,14 208:14 209:5 310:19
responsive 119:22
restrains 254:3
restrictions 343:20
result 56:6 61:5 108:18 152:21 349:6 355:18 400:5
resulted 348:10
resulting 173:16 185:11,16
results 32:11 74:8 107:17 126:12 127:9 133:17 162:4 380:3 394:18 395:11
resume 140:9,17
resumed 140:15 267:21
retention 177:3 337:9,19 345:13
retire 387:6
retreated 208:21
retrospective 121:3
return 45:8 69:16 206:14 245:8
returned 263:4
revealed 355:6
review 11:22 16:16 24:6,22 25:8 26:2 42:3 48:6 76:15 76:15,17 86:7 101:5 105:12 110:18 119:7 142:11,13,21 143:16 153:2 163:15 164:2 172:11,14,17 173:14 176:16,20 178:1,19 179:3,11 179:21 180:3,7,8 180:14,15 181:1,3 181:12,13,14 182:1,14,17,21 183:1,2,8,13,14 183:15,17,21 184:22 188:5 190:5 191:18,21 193:14 196:16 199:9 202:8,11,16 203:2 213:5 215:9 216:4 242:21 243:15 252:2 274:7,8 295:18,22 297:15,15,17 298:12 300:21 301:2 335:15,17 335:20 359:19 371:6 375:18 378:13 400:20
reviewed 77:2 181:10 228:13 243:17 297:19

318:1
reviewer 105:13 183:19 184:4,17 184:18,19 185:6 185:13,21 186:1,2 192:9 193:9,17 219:11
reviewers 43:9 115:8 116:7 164:15 175:3 176:18 178:7 179:2,13 184:1,7 193:7 202:2,14 217:5 219:12 230:7
reviewer/inspector 251:20
reviewing 150:16 176:15 210:18 265:21 313:14 332:7
reviews 179:6,10 181:15 210:13 236:22 254:19 295:10,14,16
revise 167:13 272:7 353:12
revised 151:3,13 243:17 272:1,4 299:5,7 342:6 345:9 351:18 357:2
revising 149:21 151:5,8 272:13 342:8 352:1
revision 143:20 242:21 278:15 312:14 316:21 323:16 327:8 329:10 330:2 341:7 344:13 347:17 348:14 350:8 353:8 354:14,15 355:1 355:19 356:3 359:14 366:12,12 396:13 397:22 398:3
revisions 272:14 278:18,19,22 281:17 283:22 285:20 318:4 328:21 333:10 341:16,19 342:2,4 342:10 348:10 358:20 359:4 373:19 377:5,10 382:4
reward 212:1
rewards 57:3 221:1
Reynold 3:19 270:6 291:22
re-queue 240:17
richest 104:4,5
rid 51:4 221:17 343:3 344:22
right 27:5 28:5,13 45:10 50:11,16,22 61:9,12 77:6,7 78:16,16 81:6 88:8 90:21 91:18 98:2 106:14 111:7 113:14 114:1 115:18,19 117:8 118:5,15 121:22 123:12,14,19,19 123:20 127:5 131:6,9,10 132:18 136:18 137:18 139:3,8 156:18 171:10,15,15 172:6 177:18,21 182:19 183:9 198:15 203:9 205:6 206:3 222:12,15 227:2 227:12 228:5 229:1,7,13 230:9 230:10 231:17 239:4 248:19 251:1 252:2,12,19 255:19,20 257:3,3 265:4 289:1 292:9 296:13,21 300:9 303:20 309:19 310:20 324:5 328:1 387:5 390:16 392:2 393:18 396:19 399:22 400:10,11 400:12 401:9,9
rigorous 401:13
risk 23:4 24:4,7,11 24:20,21,21,22,22 25:4,6,8 26:7 27:3 27:8 28:15 30:11 35:3,11 36:1,10 40:9,21 46:20 57:9 59:1 86:5 103:3 111:1,2 114:5 115:9,14,21 116:12,12 127:2,6 127:15 136:16 145:10,18 146:10 153:20,20 154:14 158:20 159:5 161:3,5,7 166:13 188:8 189:10 197:14,14 211:12 248:7 249:6,21 250:5 251:1 254:22 255:1 264:2,13 307:5 370:14 380:18 384:13
risks 114:6,14 116:14,17 145:4,6 145:19 154:8 168:2 180:14 182:6 249:16 251:3
risky 138:1
risk-based 25:7 42:2,5 161:11 173:12 174:14 254:16 283:14 286:3 307:1,11
risk-benefit 24:7
road 336:3
roadblocks 228:6
Robinson 2:10 6:16 6:16 75:15 77:16 77:17 78:16 80:4 125:4 131:22 132:1 133:18 240:18,22 241:1 246:5 255:3,6 256:19 261:9 263:3
robust 30:16 43:1 63:7 72:11 116:10 158:5 370:11 391:3
robustness 42:13 66:16
rocket 364:10
Roehrig 2:19 14:5 270:19 367:15,16 367:19,21,22 368:2 385:2
role 13:9 18:10,14 21:9 27:22 28:20 38:10 43:9 51:21 149:20 150:4 156:5 219:11 234:18 369:12 373:5 374:9,12 379:4
roles 185:18
rolling 205:6 214:20 390:12
room 1:18 5:18 173:6
root 221:19
roughly 324:5
round 189:4 235:6
routine 316:17 378:19
row 115:12
royalties 11:17
RTR 68:15
rule 210:14 299:8
Rulemaking 298:20
run 128:20 133:4 210:14 226:17 227:1 397:8
running 255:4 392:16
Russo 2:21 13:22 270:14 285:4 310:9,9,13,14,17 336:7 337:1 339:2 340:3,13 345:12 358:2 364:3 372:11
Rutgers 6:15
R&D 56:16,22 101:7 121:21 139:14
R2 22:9,21 36:6 174:17 189:17

S

S 2:5,10
safe 298:4,7 300:1 369:2,9 376:1 379:1 380:11 384:6 404:7
safety 3:12 18:13 19:4 23:21 41:16 73:17 143:18 197:15 218:15,18 268:16 294:1,6,10 295:3,6 313:9 321:1 322:19 362:21 374:17 376:16 380:2,18 382:22
sake 58:16 148:16
Salerenol 63:14
sales 102:14 252:19 286:13 287:17 304:20
salts 313:13
sample 70:21 91:22 160:13 337:11
samples 113:8 238:9
sampling 50:17 70:10,11 242:14 242:22 243:6,9,22 244:22 245:5 261:17,19,20 316:8

Sandy 5:9
Sarah 3:16 171:20
satisfied 45:18 352:10
satisfies 352:18
satisfying 68:18
saved 223:7
savings 66:16 102:4,11,12
saw 103:16 108:14 120:8 126:1 214:18 222:2 224:21 388:1,16 389:10
saying 49:14 88:19 131:1 135:21 171:17 218:8 226:15 258:16
says 73:5 99:7 130:16 140:11 257:12 302:6,8 338:6 397:21 398:2 402:2
scale 114:20,21,21 131:14 155:12,14 157:9,11 199:18 241:22 394:6
scaled 185:2
scales 39:22 115:18
scan 400:2,4
scene 256:2
schedule 335:19
scheduled 353:14 354:4
scheme 286:3 304:18
schemes 283:15 307:11
scholarship 82:11
School 7:12
science 1:6 3:4 5:14 5:17 6:2,5 9:14 11:20 21:10 27:7 28:15 40:21 65:21 66:10 76:6,6,21 77:10,11 98:6 106:6 107:1 110:9 111:7 120:3 145:18 173:16 191:4 197:11 198:3 199:5 201:19 211:11 233:16 250:6,14 264:4 305:5 306:22 307:10 364:10 370:14 384:13 385:18 390:9 403:6
Sciences 7:9,16
science-based 35:11
scientific 2:19 27:3 29:22 41:11 42:12 44:12 76:4 84:8 142:3 143:12,17 143:17,21 144:9 145:14 147:5 150:11 207:4 218:10 231:10,14 231:18 234:1 237:18 242:4,14 244:14 245:18 247:7,16 248:13 249:5 253:6,15 254:15 261:6,17 261:18 317:22 367:17 368:3 370:11 375:2 382:16 385:15
scientifically 90:18 211:3 256:9
scientifically-bas... 380:10
scientifically-det... 378:22
scientist 3:19 104:20 292:1
scientists 95:22 124:5 283:11
scope 326:16 354:4
Scott 304:1 308:17
scratch 196:10
screen 206:16 392:20 400:3
screened 11:7
screening 156:4 400:4
scrutiny 152:20 158:16,19
scurry 266:10
se 336:22
search 227:10,11
seated 201:11,12
second 18:7 39:20 43:22 85:7 97:4,5 115:11,12 133:2 200:15 220:9 266:4 277:12 280:1 299:10 344:14 346:19 353:15 354:3 381:15 390:20 400:13
secondly 402:16
seconds 261:14
secret 169:15
Secretariat 143:13
section 10:5,5,13 10:21 11:12 168:9 200:12 276:17 307:20,20 345:16 345:22 346:9,10 346:13,16 347:3 354:12 355:9,14 355:16 357:4 388:7
sections 174:2 176:10 300:8
see 15:13 21:9 23:5 24:17 27:18 32:17 58:6 61:7 62:5 63:18 64:14 68:2 68:17 77:7 87:16 88:10 103:6,7,22 104:16 109:2,12 118:1 129:2 130:15 132:10,11 139:2,7 140:12 146:9 153:22 154:15 155:1 156:10 157:3 158:22 159:10 161:10 175:13,18 176:8 177:1,19,21 178:2 182:19 183:11,13,18 184:14 188:8 194:8 198:20 202:15 204:3 205:7 221:6 223:9 223:9,11 227:20 236:17 237:5,13 257:18 267:17 276:21 277:7 278:9 284:13,16 284:19 285:1 288:5 297:5 300:12 304:9 310:2 319:16 324:18 330:7 331:1 340:18 344:8 361:15,17 363:18 367:3 377:18 378:11 381:17,22 387:10 389:12 390:2 391:6 393:3 394:7 395:16 397:13,18 398:14
seeing 19:9 82:2 90:4 100:9 103:5 114:22 260:22 303:15 318:11
seek 20:16 29:3,4
seeking 43:17 383:17
seen 46:3 66:13 69:15 75:1 93:11 98:5 119:15 128:11 188:14 192:10 215:2 232:22 233:7 253:16 290:19 387:13 389:2 395:9
segment 228:20
select 281:10,11
selected 63:14 137:4
selling 99:8
semi 74:13
seminar 304:16
semi-regular 275:22
send 284:2 287:22
sense 50:13 70:14 121:4 132:8 136:19 208:10 340:13 341:2,14 344:17 357:18
sensitive 170:16 208:9 394:1
sensitivity 399:16
sensors 69:21 74:11 121:13
sent 169:16 279:18 281:20 284:19 373:6
Seo 269:8 272:17 283:4 288:14
Seoul 33:15
separate 211:5 223:16
separately 287:15 300:22 312:17,19 372:14
September 33:14 169:2 333:21,21 383:11
sequence 20:21
series 86:12,14
serious 48:4 276:1 290:1,9
serve 19:17 143:11 235:9 381:10 385:19
services 10:18 53:2
session 28:1 29:1 265:13,14 267:9 268:5 271:3
sessions 120:17
set 47:11 89:11 129:20 130:9 131:5 141:15 166:18 167:2

225:12 242:4 279:10 287:22 334:10 387:15
sets 262:5
setting 146:4
seven 17:3 26:12 45:5 47:10 53:20 54:1 59:12,12,13 59:13 98:10 99:14 216:3 229:17 342:4 344:3 347:21
shampoos 339:15
shape 311:10
shaping 31:8
share 20:13 21:5 36:3 41:9 43:6 45:19 94:4 100:7 106:12 138:6,7 149:13 169:17 174:1 195:12,15 230:13 287:16 374:19 381:4 382:15 383:8
shared 26:21 27:1 33:10 48:13 117:8 163:19 184:10 260:8 380:1,2 382:20
sharing 27:6 56:2 217:9 368:16 404:2
Shaya 2:11 7:10,10 44:18,19 75:16 87:7,8 201:9 207:16,17 258:10
Sheehan 2:22 14:1 270:16 275:7 285:5 340:5,5,9 340:10 360:9,15 360:18 361:2,21 364:1 365:13,18 367:11,13
shelf 379:20
shift 16:15 67:14 172:18 186:14 193:10 222:21
shipment 400:7
shore 338:1
short 69:17 100:13 122:9 267:11 277:19 307:8
shorten 103:2 106:15
shortly 32:10 33:6 180:22 181:7 190:10 282:22
show 27:14 30:10 54:5,7 87:10,12 126:9 154:7 170:17 211:8 215:14 238:12 292:11 293:22 295:2 319:22 320:15
showed 339:12
showing 54:14 108:11 294:21 298:3,7 304:14
shown 50:14 301:11 394:7
shut 251:4
shy 216:5
side 5:19 36:1 81:5 109:17 125:11,13 125:19 137:3 138:21 164:1 186:18 191:18,21 208:15 209:1 210:17 237:22 238:19 255:16,22 257:4 301:7,8,10 301:18 315:9 324:6 371:4,4
Siemens 253:17
sight 335:8
sigma 54:20 55:6 60:20 61:4 62:16 62:19 63:4 221:19 224:22
signal 75:1
signals 130:5,6
significant 15:21 50:12 92:7 132:22 240:2 262:3 355:7 379:22
significantly 99:6 103:1 105:5 121:19 138:10
signs 23:3
silence 5:6
silenced 160:9
silos 389:3
Silver 1:20
similar 49:4 78:15 100:10 119:5 120:21 121:7,10 123:18 125:12 136:19 137:2 222:9 236:22 277:3,5,6 303:4 340:14 382:18 386:2 388:14
similarities 186:17
simple 84:22 117:15 219:19 266:6 364:14
simplest 113:16
simply 264:6 386:12 398:5
simultaneously 285:18
single 60:11 193:7 193:9 194:2,3 238:15 246:16 325:22 328:4
sir 220:6
sister 389:6
site 65:3,3 76:17 111:21 164:13 215:8 359:5
sites 188:3
site's 83:8
sitting 239:13
situation 88:12 124:2 365:4
situations 32:7 204:12 321:14 403:2
six 54:20 55:6 61:4 62:20 89:2 122:9 143:21 147:1 174:20 181:15 187:16 221:19 224:22 304:7 317:10 357:22
size 70:21 73:5 95:4 119:11 124:11 138:10 174:5 361:14
sizes 160:13
skeleton 197:5
skepticism 103:17 228:7 229:15 230:4 259:22 260:4
skip 146:15
sky 79:18
slide 23:5 82:15,16 82:17 85:10 87:9 87:10,17 103:16 120:8 122:22 125:8 146:15 168:18 170:1 176:1,7 177:18 178:6,10 182:18 183:9 185:6 272:21 275:5 301:11 307:7 309:4,5 336:12 339:11 340:13,18 346:6 349:21 355:4 363:8 394:8
slides 58:15 75:21 82:10 214:18 249:19 288:15 357:12
slightly 172:18 186:15 389:13
slow 91:19 105:3
slowly 125:20 147:20
small 2:21 29:16,17 46:13 47:3 77:20 78:1,4,11 79:20 104:15 114:21,21 130:15 186:18 188:11 199:18 212:1 246:11,13 247:9,21 255:21 255:22 262:3 270:15 281:7 290:4 306:5 310:10,13,19 318:13 319:4 323:17
smaller 228:22 329:13
small-scale 115:2
smart 399:21
snapshot 345:5 352:22
snowball 205:6
societies 370:4
sodium 278:8,11
software 84:1 98:14
sold 238:2 303:19
sole 156:1 256:2
solely 383:11
solicit 18:1
solid 74:17 90:22 326:22 328:5
solids 380:15
soluble 112:22
solution 29:9 136:5 231:22 314:11 337:8,10,11 346:20
solutions 380:15 383:18
solvable 227:2
solve 40:19 43:4 221:14 389:20
solved 386:8 387:17
solvents 313:12 348:2
solving 118:3
somebody 115:16 361:17
somewhat 182:9 233:9 279:7 287:15
soon 168:10 195:9

226:15 372:15
sophisticated 264:5 363:2
SOPs 335:20
sorbitol 346:20
sorry 14:3 108:4 119:14 132:14 140:4 176:5 240:16 353:8 397:16
sort 83:18 85:17 93:16,18 110:19 118:1 121:3,14 122:4 129:20 130:1 132:5,9,11 209:22 212:20 236:2 237:6,9 238:18 250:22 254:2 261:14 279:8 290:21 313:13 329:8 339:10
sorts 158:17
soul 16:13
sound 121:13 364:18 403:6
source 68:1 266:16 361:11
sourced 351:20 362:11,12
sources 312:6
South 33:15
space 22:18 23:16 27:10,13,14 35:1 38:10 40:13 46:21 46:22 47:15 48:19 48:21 56:16 57:17 57:18,20 60:1 62:22 63:2,7,9 65:2,5,10 69:13 72:13 75:5,10 81:13 83:11 84:18 107:19,21 108:1,3 108:20 126:3 153:14,15 155:6,7 155:8,11,14 157:6 157:8,12,14 164:6 164:7 166:16 170:3,12,20 171:5 171:8 197:17 198:10 225:16
spaces 71:14 72:11 175:1
speak 8:14 9:2 85:12 126:12 127:9 193:5 200:18,19 310:16 335:10 349:14 367:19 368:6 369:15 385:18
speaker 20:5 52:16 53:4 96:10 97:3,5 102:14 111:16 128:20 132:9 141:2 171:18,19 288:21 291:22 310:8 340:4 367:15
speakers 2:14 13:15,16,20 14:7 16:6,11 44:5 129:8 140:18 146:17 179:5 194:18 195:3,20 200:17 207:1 237:6 258:3 268:6 270:13,13 385:7 401:20
speaking 11:16 52:17
spec 227:4 238:9
special 9:18 10:14 11:1 130:8 217:15 284:9 290:21 315:16 318:6 345:21
specialized 144:18
species 119:20
specific 12:13 15:7 46:16 48:19 52:5 62:14 82:9 83:22 85:15 90:7 94:13 140:22 164:3 169:13 173:4,21 183:10 185:7 187:5 191:22 268:13 283:18,19 297:11 313:1 320:16,16 321:6 325:4 332:14 334:17 337:13 338:11,16 343:3 344:1,12,15 348:3 348:18 350:18 351:12 354:19 356:13 357:11 364:17 373:20 377:1,7,8 379:5 396:6
specifically 62:12 87:9 211:17 269:5 270:8 280:6,15 293:7,9 312:16 326:6 348:17 401:1
specification 40:1 64:5 70:22 88:18 89:15 95:11 197:19 235:22
specifications 72:22 86:4 153:16 153:17 166:19 197:20 224:4,6,16 225:10,13 239:1,2 259:18 351:4 370:1
specificity 38:22 308:2 312:8 352:2 363:21
specifics 48:11
specified 374:17
specify 221:5 379:9
specs 74:6,12 225:4 238:21 241:5 248:19 255:14
specter 367:1
spectographic 280:12
spectrometry 363:13
spectrophotomet... 338:12
spectroscopy 306:13
speed 98:4 134:16 135:1 231:4
spend 313:7 317:18
spending 233:5
spent 265:9,10
spirit 8:17 207:13 373:9
Spironolctone 325:2
spite 388:21
split 207:7
spoke 100:18,19 349:18
sponsored 334:1
sponsors 331:20 357:15
spot 62:21 63:3,10 65:6 209:10,13 400:11
spouses 11:11
spread 194:4
spreads 387:22
spreadsheet 319:16 319:18
spring 1:21 279:3
SQC 82:10
stability 245:11 301:18 343:15 380:2 401:14
stable 124:9
staff 19:14 66:22 143:14 188:16 196:16 230:20 272:18 312:5
staffs 364:5
stage 103:9 262:6 278:17,19,21 320:2 352:6,7 353:3,5 392:12
stages 24:19 28:21 30:14 32:7 69:3 242:16
stakeholder 316:6 354:13 375:13
stakeholders 35:17 311:6 321:19 335:2 349:7 356:18 357:14 358:15 359:17 366:1 384:10 403:17,17
stand 402:5
standard 28:2 108:14 153:2 161:20 205:14 242:22 243:16 273:22 302:11 303:6 319:1 337:10,18 339:3 364:13 369:19,20 391:12,18
standardized 65:17 66:4,5,6
standards 18:12 27:21 94:19 160:10 271:17,21 271:22 272:8 280:1,4 283:3 292:7 294:7,10 295:7 305:3 311:7 311:13 312:22 317:15 334:10,11 339:20 369:5,7,19 370:12 376:5 383:12 386:3 391:21 395:3
standard-setting 316:18 319:21
standing 12:21 146:19
standpoint 83:19 188:11 190:3
stands 226:11,12
start 15:12 76:13 93:1 112:15,16 121:9 129:17 136:13,15 137:14 148:6 159:12 195:2 196:1,11 197:11,19 198:18 199:6,13 201:15

204:11 212:7,9 218:7,8,16 240:21 269:9 270:5 271:8 292:17 297:7 328:15 386:18 400:20
started 64:15,22 79:8,10 88:6,7 98:21 147:20 168:20 199:8 221:13 222:19,21 255:11 295:21 296:1 312:15 317:20 321:17
starting 23:8 24:21 54:18 58:17 66:14 112:2 139:21 205:7 287:11 327:9 328:10 333:8
starts 326:4
state 6:13 25:14 256:15 292:12 343:13 373:18 375:21
stated 17:11 374:8
statement 4:4 9:10 102:22 103:4 228:10 230:3 231:13 351:17,18 354:7 355:8,15,22 357:3
statements 13:1 253:5 354:11 355:14
states 2:21 12:10 14:2 142:18,19 144:2 163:3 261:4 275:21 277:17 278:2 384:3
state-of-the-art 173:15
statistical 87:3 137:9 146:11 155:15 199:10 244:14
statistically-based 251:1
statistician 98:16 127:20 179:19
statisticians 98:13 102:7 215:21,22
statistics 53:1 82:16 107:22 116:13 155:19 215:18 243:14,16
status 10:2 141:19 172:21 174:18 188:7 286:17 394:8
stay 15:10 73:19
steadily 147:16
steady 64:13 190:18
steal 45:17
stearate 95:2,4
Steering 94:10
stemmed 348:16
step 16:4 59:18,19 128:16 156:4 160:22 161:10 162:10 166:17 183:1 236:3,12 251:21 299:9 352:7,15 400:6
stepping 17:8 158:14
steps 24:19 27:5 45:3 59:13 61:16 61:17 71:9,14 73:11 149:3 182:5 182:20 298:15 307:8 343:10 394:21,21
Stepwise 84:12
sterile 343:22 345:3
Steve 6:8
Steven 3:6 44:7 241:3
stick 129:6
Sticking 305:8
stimulate 202:22 237:3 260:16
stimulating 204:18
stimuli 358:18
stimulus 202:14 266:12
stock 104:6
stocks 14:4
stood 396:2
stool 334:15 372:11
stop 51:6 149:17 235:19
stops 153:19,20
storage 306:11
stories 126:1
story 156:18
straightforward 145:8
strategic 228:19
strategically 90:19
strategies 11:19 67:12 70:12 83:3 162:16 187:21 196:2,4 238:18 250:5 358:9 375:15,15
strategy 23:17,20 23:20 25:7 29:7 34:4 35:2 38:5 39:19,20 41:12,13 41:19,21 47:16 55:15 57:19,22 58:1 59:4,20 63:8 72:4 77:4 82:20 83:5,10 85:13 88:8 89:11 90:2 114:1,3 122:13 150:9 162:1,7 212:10 218:20,21 219:2,3,6,13
stratify 175:21
strength 271:18 342:15
strengthen 280:2 280:16 312:22
strengthened 278:20
strengthening 311:5
strengths 63:19
stretches 265:4
strictly 335:7
strides 258:9
strike 159:15
string 107:3
strive 370:5
strong 104:22 126:8 224:2,21 230:2
strongest 119:20
strongly 8:8 47:1
structure 57:5 156:14
structured 90:15 97:9
struggle 42:6 400:15
struggling 366:7
students 400:15
studies 61:16 62:1 62:5,8 93:5 155:2 156:4 162:4 188:18 189:13 376:17 382:22
study 17:6 33:21,22 34:9,10,18 35:4 93:8 154:19 156:6 204:4 238:8 250:1 380:3
stuff 47:1 90:13 197:18 204:1 218:22 229:7 366:21 367:3
style 303:4
subject 9:20 20:19 31:4 165:19 370:16 375:12 376:18
submission 26:21 38:3 40:6 41:10 65:11 83:15 110:22 147:11 150:8 158:18 172:10 174:14 182:22 183:6,7 266:3,6 379:15 381:5,9
submissions 43:15 68:15 135:17 150:4,16 172:12 172:15 174:2 175:12 177:7 179:9 187:11 202:10 251:22 350:11 360:5,20 361:5 378:14 379:22
submit 139:10,11 174:1 235:8 297:10 314:20 350:14 360:7 370:22
submitted 34:15 43:11 161:20 169:2 176:7 190:4 219:4 323:4,17 347:15 373:18
submitters 202:20
submitting 377:4
subscriber 398:13
subscribing 396:21
subsequent 59:19 330:22 381:11,11
subset 312:14 342:3
substance 25:17 36:13 275:18 277:3,17,22 278:12 301:15 305:14 314:4 322:16 327:7 329:18 330:5 338:13 339:6 378:4
substances 271:12 277:6 284:20 305:13 308:1 339:7 362:2 373:20 382:6 391:19
substitute 275:15
substituted 102:18 275:20

substitution 274:17 342:18
success 47:21 103:22 119:18 126:1 128:4 323:12
successes 126:9 199:12 200:9 205:9 233:7
successful 117:5 335:3
successfully 133:6 190:20 374:9
sudden 161:8
suffer 399:16
sufficient 43:22 54:5 77:10 211:10 308:12 349:1
sugar 347:18,22
suggest 45:11 46:8 96:2 202:13 243:1 287:6 294:18
suggested 212:13 212:15 246:6 260:2,5 262:13
suggesting 49:12 214:16
suggestion 233:10 235:2,15 241:15 262:14
suggestions 201:22 232:10 250:8 259:21 402:21
suitability 39:21 343:20 393:13
suitable 373:3 391:7 393:17
sulfate 277:19
summarize 257:6 259:14 269:12 306:9
summarized 234:14
summarizes 272:21
summary 4:22 154:7,20 156:10 167:7 182:6 200:1 235:15 265:20 271:4 368:19
summer 305:7
summit 78:10
Sunshine 8:18
supervision 142:4
supervisors 179:16
supplement 160:3 187:9 188:1,4 317:10 344:14 353:15 399:2
supplemental 174:7 175:16
supplements 176:4 187:18 393:6 396:22 398:18,21
supplied 113:13
suppliers 72:18 95:9
supply 25:18 30:6 36:15 42:1 99:16 100:11,14 106:17 272:6 349:3
support 50:10 128:10 143:17 217:18 241:12 299:3 311:14 314:19 315:3,7 324:11 331:16 332:12,19,21 376:12 392:7
supported 144:7 241:13 280:2 386:3 391:3
supporting 151:16
supportive 219:7 260:14
supposed 204:14
sure 31:10 78:10 84:18 95:19 107:11 111:19 112:10,12 114:11 117:9 118:4 123:5 133:15 176:19 192:21 194:10 203:21 209:6 214:14 215:11 216:9,19 219:16 234:11 302:17 306:21 327:16 330:7 365:3 394:2
surface 73:6 95:4,6
surprised 205:2
surrogate 170:7
survey 305:1
survive 119:22
suspect 182:11
suspensions 380:15
sustained 91:12
sweet 62:21 63:9 65:6 400:11
switching 331:6
swords 260:22
Symposium 306:2
synchronize 140:10
synthesis 301:16 378:19
synthesize 101:14
synthetic 360:20 361:6
system 25:12,13,22 26:2 30:16 35:2 36:13 41:20 43:1 43:13 46:20 77:3 77:11 83:6,7,8 84:6 85:5 137:19 160:1 164:4,8 270:9 339:19
systematic 22:21 24:5 26:17 35:10 145:14 146:10
systems 26:4 76:16 79:2 84:1,1,2 106:9 159:21 177:3 185:4 219:17 243:8,9 244:2
S-E-S-S-I-O-N 268:1

T

T 2:11
table 5:21 15:10 153:3 154:11,15 184:13 189:4 235:6 239:13 240:5 303:16 335:6 350:13 360:6 366:2 372:1 372:12 380:8
tables 154:7
tablet 74:17 232:5 314:10 337:7
tableted 69:9
tablets 70:11 339:10
tackling 304:18
tag 398:4
take 8:19,21 54:10 73:13 74:2 92:11 111:9,10 120:12 127:22 140:3,4 151:6,10 168:8 191:8 195:11 207:14 220:5 233:18 236:11 247:9 264:13 274:22 276:6 288:2,17 299:19 317:12 349:21 369:17 385:22
taken 269:16 286:14 369:11 379:4
takes 68:10 80:13 111:8 219:13,14
talc 289:20,22 349:19 351:16,20 353:17,17,18 354:2,6,7,11,11 354:19 355:6,9,12 355:19 356:1,3 357:1,4,11,19
talk 16:19 17:21 18:19 19:1 46:19 53:17 55:21 56:10 59:7 68:22 74:16 82:22 96:1 98:21 108:1,3 110:17 120:15 129:17 132:8 170:2 172:7 186:15 202:8 220:11 229:22 233:19 240:8,17 269:4 270:1,7,8 270:12,14,16 271:4 273:17 274:12,13 275:7 282:8 288:3 289:9 289:14 292:14 311:2
talked 48:8 67:7 77:19,20 79:2 85:10 102:14 111:17 115:6 118:16 122:22 127:16 134:3 248:12 249:22 252:10 253:22 285:6,8 303:9 305:9,10 317:16 372:11 403:11
talking 42:3 74:10 90:8 92:21 97:6 98:11 103:18 104:14,17,21 115:12 118:10 120:5 122:1 136:12 202:4 232:19 233:6 246:16,17 254:10 298:18 308:13 370:20
talks 229:21 311:5 395:22
Tan 3:19 270:6 274:12 291:22 292:1,7,8 308:7 308:13,16 309:8 309:18 310:5,8 339:12
Tan's 292:5
target 23:9 49:3,4 63:2 72:18 190:15 315:20
targeted 400:22
targeting 73:2 90:21 393:5

task 127:8 197:4 242:20 268:21 269:7,8,21 282:6 282:7,9 283:1,12 285:3,22 287:5 288:4,8 305:10 315:15 322:5 325:8 331:15 333:3 357:13 365:8 386:11 392:10
tasks 199:3 313:6 374:11
teaching 11:16
team 144:20,21 149:20 150:1,10 150:15,21 172:16 179:6,11,20,22 181:3,4,5,5 183:14,15 184:17 185:5,10,15,19 192:18,20 194:11 202:11 215:9,12 216:8 217:3 259:7 265:21 310:18 376:11 393:21
teamed 383:10
teams 375:11 376:13
team-based 179:10 182:17 190:20
technical 2:19 12:2 44:3 48:17 49:17 132:10,11 133:20 134:2,5 144:8 179:4,18 199:5 206:22 235:10,20 258:2 324:14 367:16 368:3 369:7 370:13
technique 343:7 344:5
techniques 69:4 73:4 81:6 102:5 108:15 173:11 382:9
technological 173:9 253:15
technologies 48:7 83:22 231:3 243:7 291:4
technology 47:13 47:18 48:2,12,14 49:14,16 80:21 81:13 82:4,15 83:1 112:12 196:12 211:21 227:9 252:10 262:18 392:19
Ted 100:18
teleconference 2:7
tell 52:3,7 91:5,11 105:6 112:4 113:6 122:6 126:13 156:17,18 205:9 240:6 252:21 317:19 363:1 390:13 392:1 393:9 396:13 398:22
telling 112:17 265:15
tells 257:5 398:18
temporary 2:2,4,5 2:5,6,8,10 9:17 10:10 11:6 12:17 12:22 14:10
ten 19:8 70:11 99:14 140:3 146:21 181:15 239:18 244:21 284:5 394:7,9,10
tend 50:18 219:20
tentative 210:11 299:8
term 298:5 307:8 307:15 312:15 336:1 341:17 355:12
terms 75:7 132:5 132:22 172:10 174:18 178:8 192:9,10 193:17 203:11 218:16 221:5 242:7,7 245:5 246:21 251:18 271:19 291:6 325:21 341:12 343:21 351:1 352:4 353:16 356:7 401:14
test 170:12,15,18 171:1 197:6 198:14,14 203:15 203:18 224:18 226:18 231:2 273:6 276:6,8,14 276:16,22 277:10 277:11 278:7,11 278:20 280:13 291:2 308:10,11 308:11 314:8,11 316:12 319:12 320:19 325:1,15 326:7,11 327:10 329:21,21,22 330:20 337:3,8,21 337:22 338:1,2,2 338:5,6 340:21 343:5,6,12 344:2 344:5,9,15,21 345:2,11,11,14,16 345:17 346:7,14 346:16 348:3,7,19 348:19 351:11 352:1 353:10,11 356:9,10 362:14 362:17 364:12,14 364:18 365:12 366:13 388:6 391:20,22 394:4 400:2,3,4,4
tested 388:8 393:12
testimony 11:15
testing 18:13 28:19 29:6,9 37:8 40:3 48:18 67:19,20,20 68:13 69:1 70:13 126:2 147:1 151:9 158:2,6,7 166:15 170:7,10 175:6 196:20 197:8,21 198:12,13 199:17 203:11 244:8 275:12 300:4 304:11 306:15,18 308:3,14 309:6 310:2 312:9 313:4 316:14 331:11 336:14,21 339:20 347:5 388:22 389:19,20 391:21 392:4,21 393:1 394:22
tests 203:12 273:7 273:19,21 280:17 281:15,16 283:18 283:19 287:2,3,7 313:8 316:13,15 316:16 320:16 321:12 325:18 338:3 341:11 344:7,12,20 345:1 351:7 352:8,17 354:19 362:4,6,7 363:3 365:14,19 365:21 366:8 386:6
Teva 2:15 13:22 96:11 97:20,21 100:18 109:17 138:4
text 366:18,21 399:4
thank 9:8 14:22 15:1,15 16:5,10 19:21 20:1,11 44:13,16,19 45:20 47:5 49:19 50:5 52:11,12,14 53:3 53:14,15 73:22 74:1 75:12 77:15 80:4,5 82:5,7 85:9 87:6,8 89:20 92:12 93:22 96:6 96:8,14,19 97:1 120:9,11 123:8 125:1,2,7 127:18 131:21 132:1 134:10 135:9,10 136:7 140:2,2 141:8 168:4,6,17 169:19,21 171:11 171:12,14 172:5 191:6,7 192:3,11 194:14,15,15 195:4 200:10,11 206:6,7 214:10,11 217:1,19 219:22 220:5 223:13 227:13,13 232:7 236:13 237:15 242:12 244:2 245:7 252:5 256:21 264:14 265:11,18 267:2 267:17 268:22 288:13,15,16 290:11 291:21 292:8 308:6,7 310:7,7,15 336:5 336:7,11 338:18 340:2,3,10 360:9 363:6 366:14 367:11,13,22 368:5 384:19 385:1,2,6,17 394:11,16 395:16 395:17,18,21 399:7 401:16,19 402:8,16 404:1,4 404:5
thanking 195:2
thanks 74:5 75:11 104:10 105:22 120:14,15 192:5 194:17 237:14 241:1 289:8 401:15
therapeutic 286:20 296:10,14 318:22
thereof 224:17
the-counter 280:16 369:11 382:2

thin 306:13
thing 28:13 85:17 93:4 94:18 95:13 121:21 123:3 127:4 154:12 206:6 217:7 223:1 228:14 230:14 231:6 241:8 264:20 279:15 293:12 313:13 339:10 358:22 365:11,17 390:14 398:22 401:11
things 50:17 51:7 97:13 112:13 115:9 119:5 122:1 122:16 127:16 130:9 133:1 137:22 164:9 176:2 191:18,22 201:22 205:3 210:19,21 216:5 219:20 224:12 225:1 228:1,4 233:20 236:2 237:21 241:12,21 242:6 243:20 247:5 250:13,15 250:18 251:14 252:8 254:3,11 255:13 263:15 264:4,10 273:3 278:15 282:18 314:2 315:10 325:4 335:22 339:13 361:10,18 362:20 366:17 387:18 400:9,14 402:7 403:11,20
think 16:3 17:3,13 18:14 19:5,13,16 20:12 21:14 26:8 28:5 30:3 33:2 35:19 37:9 39:4,5 40:17 41:2 42:6,9 45:3,10,15 47:9 47:11,16 50:7,20 51:12,17 52:2,8 54:12 56:10 66:12 72:7 73:19 75:21 77:8,12 79:21 90:17,19 92:1,22 93:5,17,20 100:2 100:3,21 101:8 103:4 105:6 111:6 112:1,6,16 115:7 120:2 121:21 123:7 126:12 127:1,8,16 129:18 129:22 131:12 132:2,19 133:11 133:22 134:1,11 135:12,19 136:5 138:2 139:8 166:18 177:10 191:22 192:12,13 192:16,19,21,22 193:18 194:2,6 195:3,16 196:1,9 196:18,22 197:2,3 197:10 198:4,15 199:5 200:2 201:17 203:8 205:5,22 206:8 209:4,14,21,22 210:1,3,12,13,19 211:15,17 212:9 213:4,8,11 214:20 215:2,3,10,11,16 216:2,18 217:3,10 217:13,15,22 218:1,8 219:9,19 220:3,13,17 221:2 221:12 223:20 224:10,11 225:5 225:15 226:11 227:1 228:5,17 229:3,9 230:5,12 230:13,14 231:5 232:10,17,18,19 233:1,5,11 234:9 234:14,15,18,19 234:22 236:9,19 237:2,12,21 238:1 238:14 240:7,9,11 241:3,6,8 242:8 242:11,15 244:5,6 244:9 245:21 247:8,16 248:3,9 248:11 249:3,12 249:14 250:4,11 250:12,21 251:12 251:21 253:4,12 254:1,8 255:15,18 256:8,13,17 264:18,19,21 265:2 266:4 275:7 276:1 281:5 282:16 284:4 289:17 290:7,8 291:2,10 299:4 310:1,3,5 316:13 319:6 330:15 336:20 337:2 338:9 363:11 387:8 396:4 402:9 402:17 403:4,9
thinking 87:20 93:14 111:9 113:1 196:1,11 197:19 199:6 212:10 250:8 328:20 336:16 399:15 402:22
third 25:11 44:6 94:12 97:7 265:6
thorough 335:17
thought 15:16 31:6 31:20 110:19 119:3 122:19 133:3 220:12 235:18 244:19,20 252:8 265:20 392:12
thoughts 51:8 119:2,19 195:12
thousands 271:11 295:8,13
three 22:6 26:9 27:5 29:13 30:7 33:8 35:14 37:22 38:7 39:11 40:7 43:16 45:1 53:22 57:6 60:20 63:14 63:14 88:15 103:20 109:18 130:22 139:10 174:6 186:10 187:4 189:3 228:15 257:17 349:4 350:19 366:20 372:10,13 375:13
three-legged 334:15 372:11
three-step 298:13
threshold 399:19
thresholds 379:1
throwing 227:4 260:22
thunder 45:17
tight 87:19 89:11
tighten 224:5
tightening 94:19 223:17 224:12,13 224:17
time 16:14 19:22 22:17 26:8 36:21 37:10 50:8 51:12 51:18 58:16 69:8 69:14 74:20 75:14 94:1 97:5 98:3,3 98:12 102:3,8 103:2 104:1,6 106:14,14,15 109:18 122:8,8,15 123:20 128:20 129:5 130:19 133:15 134:20 135:7 140:17 145:12 146:13,14 146:15,19 148:16 151:9 153:2 159:18 163:6 169:4 170:22 171:7,15 175:19 177:12 202:1 207:7,10,12 208:20 209:18 210:11,18 213:3 222:7,12,13 227:4 227:6 229:16 231:22 233:5 238:8 239:11 241:22 255:5 256:22 257:20 258:17 260:3 265:9,12,13 268:4 290:19 294:22 304:13 305:8 311:4 313:7 317:2 318:9 328:1 336:8 337:9,19 345:5,8 345:13 347:13,15 364:15 371:6,14 372:19 383:4 384:19 388:8 390:11 394:4 402:18
timely 117:7 279:22
times 65:1 78:18 91:21 102:5 116:21 198:6 214:1 219:20 285:6 341:4 364:8
timing 180:15 394:1
title 20:8 268:19
titration 321:5 324:20 341:2
titrations 338:15
TLC 316:11 324:21 338:4,6
today 15:12 16:15 16:21 17:21 18:7 18:19 27:21 53:6 54:7 98:9 102:17 109:19 120:6 202:4 206:9 231:19 239:19 246:8 273:2 343:7 360:21 361:4 368:7,17 369:15 370:20 371:6

373:17 388:4 389:2 390:10 396:14,16 403:11
today's 8:6,8 9:13 10:7 11:6,18 12:15 29:1 349:12 383:2
TOFF 367:14
told 109:9 130:19 205:10 320:6
tolerance 70:14
tool 81:5 148:12 272:10 276:19,20
tools 24:12,13,20 27:11 50:20 57:9 80:22 86:7 89:19 108:9,22 109:6 134:7 137:15,19 137:22 146:10,11 146:12 172:13 178:7 221:11,17 221:18,19,19,21 221:22 222:3,6,17 223:10 230:10,13 238:20 253:2,10 256:13 260:7 363:16
toothpaste 339:12
toothpastes 339:15
top 128:7 144:13 165:4 183:4 281:5 281:7,8 284:4,6 285:19 286:5,5 287:9 317:17 319:10 321:3 322:18 340:17 358:4
topi 268:14
topic 4:6,9,12,18 8:20 9:7 12:5,12 16:21 18:7 20:2,5 20:9 41:14 129:4 160:14 194:21 200:13 212:12 242:13 263:4 265:14 267:9 268:7,20 269:2,4 269:10,15 271:9 288:19 310:17 368:8 401:17,20
topics 8:5 15:16 32:15 35:1 40:7 107:17 140:7 149:7 172:8 267:16 270:4 284:14 289:5 315:17 332:14,18 333:17 358:6,21
Topp 1:22 2:2 5:3 5:12 7:3,3,20 8:4 15:1 20:1 44:16 45:20 47:5 49:19 50:5 52:11,15 53:3 74:1 75:12 77:15 80:5 82:5 85:6,8 87:6 89:20 92:12 93:22 96:6 120:11 125:2 127:18 128:22 131:21 134:10 135:10 136:7 140:2,16 168:6 169:19 171:11 191:7 192:3 194:15,18 200:11 201:12 206:7 207:12 212:11 214:10 217:1,19 219:22 227:13 232:7 234:11 236:13 237:15 239:9 240:1,13 242:12 244:3 245:7 250:11 252:5 253:22 254:6 255:3 256:21 263:18 264:16 265:11 267:2 268:3 288:16 290:11 291:21 308:7 309:1 310:7 336:7 338:18 340:2 360:9 363:6 366:14 367:6 385:2,5 395:18 399:7 401:16 404:4
top-selling 303:18 304:10
totally 214:19 250:14,14 390:2
touch 108:5
touched 105:8 241:3 280:9
toxic 275:18 277:2
toxicogenomics 362:22
toxicologists 377:21 381:19
toxicology 304:20 327:2 370:14
track 83:21 84:3 285:20 383:16
tracked 85:4
tracking 83:2 84:6 312:16,19 323:15
tracks 281:17
Trackwise 84:6 85:4
trade 169:15 297:13 368:9
traditional 29:18 52:4 60:14 61:9 61:12 148:9 185:20 199:17 211:9 248:19 291:13
traditionally 184:3
trained 115:17 204:15
training 31:21 32:9 32:9,11 33:2,3,5 33:12,13,16,19 34:5 35:20 36:17 37:12,21 38:13 92:22 93:2 130:7 149:16 150:13 163:14 167:4 172:16 176:18 179:7 188:18 190:12 229:13
trainings 33:11 179:1
transdermals 178:14
Transfer 117:2
transferred 130:13
transformation 127:21 128:6,9 129:12 131:13 220:8,18 259:11 259:15
transition 135:22
translate 375:6
translates 131:4 331:9
transparency 12:20 319:20 320:14 373:9 381:7 384:22
transparent 156:16 375:1
travels 404:7
treat 70:16,21
treated 289:14
treatise 245:14
tremendous 191:20
trend 66:14 75:1 88:10,11 116:3
trends 54:7 68:3 166:8,10,21
trials 204:11
tried 35:6 41:5 250:3 362:3 388:6
tries 290:16
trigger 253:9
trip 404:3
trouble 313:19
true 121:17 213:11 390:8
truly 61:3 86:20 203:12
trusting 197:11
try 60:17 149:9 165:12,16 195:18 202:1 207:15 218:7 227:19 247:17 250:15 252:18 257:11 258:4 259:9 322:17 361:19 391:6 401:3
trying 128:22 167:12 215:16,17 233:3 315:6,8 328:16 403:16
Tums 300:10,12
turn 322:20 369:8
turned 260:20 261:3
Tway 2:12 7:18,18 13:5,11 75:15,18 75:19 125:4,6,7 214:10,11 217:22 258:22
Tway's 13:9
two 20:20 21:12 33:11 39:14 40:11 45:13 58:15 60:20 61:11 63:18,19 77:13,17 82:14 91:17 138:2 168:8 168:15 173:21 189:17 191:8 192:14 198:7 209:14 211:17 220:2,7 227:15 231:7 243:13 248:10 257:20 265:19 267:3 270:13 288:17 289:3 293:14 294:18,19,21 304:6 305:13 317:4,13 321:14 323:13 326:2 336:8 338:7,9 344:19 349:17 359:9 381:16 389:6 390:16 399:12 402:9 403:13 404:2
Tylenol 296:18,20 303:1,7

type 43:14 85:13 93:19 121:10 252:2 361:4,7 365:4
types 64:19 85:17 139:16 167:10 189:12 361:22
typical 317:2
typically 298:22 299:14 370:21

U

ultimate 55:12,17 71:21 72:9
ultimately 335:13
uncertain 249:10
uncertainties 145:9 145:21
unchanged 258:18
undergo 274:8
underlying 90:2
underpin 403:5
understand 57:1 76:21 86:20 114:5 124:16 133:21 145:19 156:19 168:19 194:5,6 203:13 247:7,17 250:16 256:6 262:10 263:5,11 307:17
understandable 159:13
understanding 17:7 23:2 27:15 42:12 54:18 56:1 56:4,7 57:7,12 58:7,21,22 59:9 59:11,22 60:14 61:1 63:12 67:12 71:16 72:10 76:14 81:19 82:19 94:3 113:18 128:12 133:9 136:1 145:17 150:18 161:2,4 163:11 167:21 184:21 185:2,14,17 193:17 197:17 199:22 202:6 213:18 248:2 251:9 255:1 262:8 263:9,13 292:20 309:13
understandings 204:21
understood 261:13
underway 392:2 394:16
unending 186:12
unequivocally 368:20
unfortunately 72:15 78:13 192:2
uniformity 69:2,6 70:13 92:6 160:12
unintended 84:19
unintentional 303:11
uninterrupted 99:16 106:16
Union 141:6 142:8 142:15 167:20
uniquely 125:12
unit 59:13 80:21 154:8 187:9
United 2:21 12:10 14:1 275:21 277:17 278:2 384:3
univariant 85:1
universal 369:20 383:1
universe 250:13
university 6:15,17 6:20 7:4,9,11,14 7:16 8:3 363:12
unknown 93:16
unknowns 135:16 237:7
unnecessary 313:4 313:6 345:1
upcoming 334:14
update 4:18 12:1 17:22 20:9 188:7 287:6 306:10,11 314:16 316:4 319:19 329:3 330:20 354:6 358:2,3,6 392:6 398:15
updated 18:12 239:5 281:4,18 287:4 319:21 320:22 325:18 329:17 397:1
updates 172:10 333:17 391:14 392:3 395:3
updating 327:14 341:15 375:9
upfront 69:19
upper 61:9,12 119:12
UPS 353:13
upstream 198:20
urge 284:16
urgency 282:2
USA 2:15
usable 401:8
USDA 53:2
use 12:4 18:12 33:18 36:9 73:1,4 73:6,7,9,12 84:2,6 86:7 89:7,18 114:16 121:7 137:21 144:4,6 146:10 151:7 170:12 186:8 187:11 189:9,13 199:17 203:17 215:10,17 222:17 231:13 232:1 233:21,22 249:5 263:8 280:12 290:16 313:12 316:21 318:21 330:7 332:11 333:15 343:21 347:4 358:21 367:4 375:10 391:19 392:7,13 397:7,15
useful 27:14 30:8 52:3 164:17 217:9 250:10 252:9 260:12 332:19 367:2 386:14 401:11
uses 300:14
USP 2:22,23 4:12 18:8,10,20 19:3,9 243:21 268:7 269:3,21 270:14 270:22 271:6,10 271:19,21,22 272:2,13,14 273:15,21 274:2 275:4 276:6,20 278:5,14 279:4,6 279:11,17,18,21 280:7 281:1,3,11 281:17,21 282:1,9 282:15,16 283:16 283:20,21 284:3,7 284:13,19,22 285:4,10,10,14,17 288:1,11 289:9 290:16 291:13 292:15 302:4,7,10 302:13,18,19 303:21 304:2,8,10 305:5,5,11,11,12 305:15,18 306:2,5 307:1,2,6,9,18 310:10,11,12,18 310:20 314:20 316:5 318:16 319:1 321:21 324:3,6 325:20 326:15 327:1 330:21 332:6,11 334:5,7,17,21 338:22 339:7,18 340:6,7,8 341:15 342:5 345:8,18 346:22 347:18,22 348:13 349:7,15 349:19,19 350:14 350:19 351:6,16 351:22 353:1,17 354:21 355:9,14 355:18 357:4,6 358:8 359:14 360:7,20 361:6 363:18 365:6 367:20 368:8,18 369:6,13 370:9,9 371:1,5,7,15,16 371:22 372:1,7,16 372:19 373:3,7,10 373:11 374:5,10 375:6,10,16 376:11 377:1,5,12 378:15 379:15,21 380:8,12 381:1,4 382:17 383:3,10 383:16 384:5,15 386:4,16 389:5 390:17,22 392:8 393:18 394:11 395:2,11 396:2,4 396:13 398:8,9 401:17
USP's 279:19 287:10 306:1 311:10 315:9 341:14 358:21 378:9 382:4
USP-FDA 280:2
USP-related 304:6
USP-35 353:15
usual 312:18 316:17
usually 84:12 183:20,22 248:20 252:15 282:12 300:4
utilities 29:11 172:13
utilization 177:6,8 191:5
utilize 209:5
utilized 25:1 28:14 30:11 35:17 175:7

190:21
utilizing 98:7 122:5 212:7
U.S 1:1 33:9 68:15 99:15 169:2 229:2 236:5 362:13 368:12 378:16 384:2
U.S.C 10:5,12 11:12

V

valid 142:15 157:10,10 158:12 310:6 322:10
validated 349:9
validating 324:8
validation 38:10 101:3 117:6 148:10 151:10
validity 155:15 158:13
valuable 44:10 174:11 207:2 217:4 261:5
value 54:14 55:10 56:12 66:11 70:3 70:4,6 101:22 139:22 184:19 185:5 221:17,21 316:16 343:12,16 379:14
valued 240:12
value-added 71:15 344:6 362:4
variability 54:19 55:16 64:4,7,11 68:1 71:13 72:20 86:10 88:12,19 89:13,17 92:18 93:14,16,17 95:17 95:20 96:4 108:17 163:4 204:5 221:15 255:21
variable 69:18 72:3 73:13 110:16
variables 85:18
variant 238:16 248:14
variation 87:11,12 87:18 88:1 160:3 162:10
variations 111:17 147:2 162:20
variety 8:7 80:13
various 193:18 250:2 303:11 331:20 389:3
vast 378:1
vendors 252:15
venue 217:14
venues 77:14
verification 148:8 151:12 157:14 158:3
verified 158:13
version 357:2 396:9,10 397:5,7 397:10,19,20 399:2
versus 42:10 80:22 81:20 87:20 105:9 126:19 145:4 212:5 218:4,9 287:16 291:12 296:18 303:1 322:16 341:3 355:15
Veterinary 283:7
vetting 378:13
viability 256:2 263:10
viable 139:7 265:2
Vice 2:21 310:9
vice-versa 186:5
view 80:18 224:15 363:16 385:6
views 8:11 97:19 218:10,19 370:9
virtually 291:3
Viscosity 119:13
visibility 315:11 320:14
vision 35:15 214:12
vitro 212:5 232:3
vivo 170:8,9 171:9 197:18 198:5 232:3 236:1 241:5 246:21 255:14 261:12
volume 69:18 89:1 117:22 281:12 284:21 287:18 304:20 325:11 396:4,20
volumes 281:13 286:13 374:15 396:22 397:1
volunteered 394:12
vote 14:9 223:21
voted 223:16 279:13 356:2
voting 2:2,4,5,5,6,8 2:10 9:17 10:10 11:6 12:17,22 14:10
vulnerability 282:19
vulnerable 273:9

W

wait 68:12 392:22
waivers 10:14,22 12:18
Walgreens 292:22
walk 15:11 182:17
Walsh 5:9,10
Wal-Mart 99:7
want 15:11,15 16:10 18:18 31:10 45:17 51:4,4 89:22 98:2 103:11 106:13,15 108:15 111:12,14,16,21 113:12 114:6 118:7 123:11 127:4 128:18 133:2 135:14,17 138:2 140:10 170:18 176:13 177:17 207:17 224:20 227:18 228:14 231:6 239:3,12 240:4,5 244:4 255:7,11 284:16 285:10 288:2 299:2 310:15 313:21 314:9,12,18 350:20 366:7 368:5,20 382:14 383:6 390:6 393:5 393:7,11 394:16 395:1,13,16 402:8 402:16 403:6 404:1
wanted 16:5 82:16 119:2 120:16 128:19 236:16 251:8 264:9 265:19 269:17 276:18 317:18 323:10 334:19 337:17 373:13 385:21 388:21 390:13
wants 279:11
Waples 3:2 7:5,5 9:9,11
Washington 6:21
wasn't 222:18 295:2,3 308:12
waste 54:21
watch 140:10 239:11
watches 140:10
way 25:20 40:19 47:18 51:2 57:6 94:18 97:10,21 98:1 100:1,10 102:9 103:6,10 104:2,4 108:21 109:4 112:6 113:16 120:2,4,9 123:13 134:11,20 145:13,19,20 146:1 152:1 162:12,19 163:19 171:2 175:20 192:8 195:10,19 199:15 201:4 202:6 204:13 207:6,22,22 211:5 222:13 230:3,7,13 242:10 251:10 254:13,16 257:9 265:5,22 287:2 291:16 302:2 310:1 315:20 320:2,15 322:13 323:22 339:18 359:6 371:3 387:3 390:14 392:17 402:6
ways 21:14 25:1,20 162:21 186:6 205:19 212:8 216:9,18 232:11 234:5 261:20 287:11 318:19 322:8 333:14 334:9 403:1
weakest 61:20,22 62:2,6
web 315:14,17 316:11 320:22 333:12,16 358:3 358:16 359:5 398:10
Webber 3:4 6:3,3 208:13 209:12 213:4
webinar 315:21 373:10
website 33:17 151:18 278:15 281:1,3,18 284:14 287:10 319:11 327:22 350:20 352:13 353:1,13 358:8 398:3,8
WEDNESDAY 1:12
week 378:7
weeks 68:12 109:21

109:21,22
weigh 115:17 299:11
weighed 258:22
weighs 299:1
weight 69:4 145:5
welcome 8:5 108:13 268:3 322:4 323:8
welcoming 15:12
well-behaved 88:16
well-developed 65:2 81:6
well-received 15:17 18:6
well-verified 157:18
went 59:19 128:4 140:14 260:18 267:20 291:16 389:21 404:9
weren't 128:3 216:7 249:1 318:4
we'll 18:19 20:2 66:12 80:13 96:6 105:3 120:11 139:11 140:4 165:22 168:13 191:8 201:2,4,13 207:15 210:1 235:3 240:21 251:15 267:8 270:13,19 273:6 287:14 291:11 330:12,21 367:14 403:15
we're 15:22 16:15 16:21 17:21 18:15 18:19 19:19 36:2 50:10 51:8 54:3 56:3 58:5,19 62:1 67:18,19,20,21,22 70:7 79:21 81:5 82:2 84:10,18 88:18 90:21 91:8 91:8 103:18 104:9 104:17,20 112:7 115:12 116:17 120:5 130:17 154:6 177:10 193:10 194:10 200:14 201:18 205:6 206:9 213:8 214:6 215:16,17 217:10 221:22 240:10 246:15,17 248:19 255:4,9 258:19 267:10,17 269:6,21 272:21 273:1,2,18 286:6 287:1,8,12 289:19 290:7,8 294:5 314:2,7 315:14 321:18 322:1,10 323:19 324:6,9,11 324:12 325:17 326:5,22 327:3,8 327:15,17,18 328:14,14,16,20 329:8 330:5 331:13,19 332:6,8 333:6,8,9,21 334:16,21 335:13 336:2 338:14 341:17 349:12 357:14 365:9,19 366:7 370:20 380:9 389:8,18 393:2 399:17,18 399:20 400:10
we've 17:1,3,15 51:7 54:1 62:8 64:15 69:15 79:12 91:1 92:10 95:7,8 95:9,19 96:3 98:21 104:1,2 106:1 107:7,14 115:14 119:15 147:5 148:10,22 153:7 178:15 188:14 215:1 226:21,22 227:1 232:15,21,22 233:7 257:16 272:19 285:6,7,16 304:14 305:8 312:1,3 315:10 316:8 323:2,13 331:16 353:7,9,11 353:17 367:9 385:20 403:12
whatsoever 209:3
wheat 387:21
White 1:18,20 219:14
wholeheartedly 250:12
wide 150:22 170:19 194:4 363:14
widely 291:10,14 319:2 375:19
widely-used 284:10
widespread 363:17
wide-ranging 257:16
wild 15:14
Wilkes 7:9
willing 205:8 220:5
willingness 94:3 129:13
win 122:16
window 183:20
Winkle 3:3 5:20,22 6:1 15:3,9 18:18 20:2 232:8,9 240:7 257:12 260:9 265:15 402:4,4,5
Winkle's 257:3
wish 208:15 235:9
withdrawals 118:22
withdrawn 174:8
witness 11:14
wonder 103:5 128:7,16 136:20 138:16 253:19
wondered 78:20 400:19
wonderful 5:7 201:20 205:4 228:16 241:9 255:16 267:16 402:10,18
wondering 45:7 46:3 82:21 224:15 361:15 396:5 399:18
Woodcock 281:20 282:5
word 240:21 255:4 263:3,8 316:2 333:6,14
words 211:1 302:15
work 16:11 58:6,7 76:4 82:11 90:13 91:2 92:11 93:18 102:6 104:8 107:15 114:4 144:4,7 151:16 152:3 160:14 163:18 165:2 167:12 179:5 186:10 202:3 204:8 220:14 236:9 238:1 245:9 253:1,11 254:3 263:6 266:22 267:1 285:14,18 285:19 288:9,10 307:1 312:15 317:7 318:3 321:16,19 322:3 324:1,2,3 327:16 327:19 328:2,15 329:9 330:6,11,21 331:2 332:2,19 341:11 350:16 356:8 357:20 358:7 359:17 376:15 387:13 390:15 391:3,14 391:15 394:2 395:5,7,9
worked 61:7 98:17 108:8 118:13,21 249:22 276:20 358:20 378:6
working 30:19 32:4 33:4 37:19 38:8 40:11 41:6 81:14 102:6 107:10 142:17 143:13 144:7,11,11,14,15 144:16,17 148:19 149:20 151:14,15 154:19 156:13,13 167:5,18 178:16 188:15 193:11 202:12 215:19 222:1 225:1 241:18 242:3 261:14,15 266:1,2 269:21 270:21 275:2 283:3 285:11 302:19 304:17,22 306:4 306:19 315:14 322:11 323:1 331:13,19 356:17 357:2,14 369:6 370:17,19 371:4 373:16 374:5 376:21 377:3,22 379:12,18 380:9 381:8,13,20 382:3 382:19,19 389:5 396:14,20 400:10
workload 350:2
works 73:14,16 123:7 278:22 327:17 390:14 399:6
workshop 32:11 34:6 333:20 334:13 339:22 383:11,16
workshops 35:7,21 36:17 37:22 38:14 46:1,5,9 49:22 107:16 149:10 150:15 189:3 333:13 358:17 359:11 383:18
world 73:10 79:11

79:22 210:7 213:12 238:1 245:4 362:12 388:4
worried 115:1
worth 39:5 223:3
worthwhile 100:21
wouldn't 81:12
wound 386:15
wrap 239:17 271:2
wrap-up 4:9,18 194:21 385:19
write 202:15 229:19 231:14 294:6 376:17
writing 11:16
written 230:3 294:9 313:21 388:17
wrong 239:3
wrote 245:14
Wyeth 78:3

Y

Yatindra 2:15 13:21 96:10 120:15
yeah 255:9
year 33:16 38:9 40:12 61:10 63:13 64:10 130:18 139:10 165:5 175:13 184:15 190:13 226:4,4 278:19 279:4,4 281:19 299:14 315:18 319:11 326:13 335:15 391:22 396:11
years 17:3 26:12 31:9 42:3 45:5 47:10 48:8 50:15 53:18,20 54:1,10 54:16 55:22 60:16 63:21 64:14 66:12 78:4 81:10 93:3 94:14 97:15 98:9 98:10 100:6 108:6 109:18,21 122:7 125:20 136:12 137:13 163:16 174:21 184:15 195:7 196:6 197:4 201:21 206:1 224:11 226:14 229:18 244:21 272:1,12 279:7,10 295:5 311:17 312:4,20 315:11 317:4,13 320:7 323:13 361:3
year-old 64:2,16 71:11 92:17 98:11 225:13
yesterday 15:14,18 16:12 17:1,5 18:10 85:16 93:20 223:16,19 231:19
yesterday's 15:16 93:15
yield 91:6 102:3 130:20
Yvette 3:2 7:5

Z

zero 64:1 70:13 183:6 197:13

Þ

ÞWhat 135:5

$

$20 365:12
$4 99:8

0

0.10 348:21 349:11
0.7 64:10
01 326:21
09 277:4

1

1 4:6 20:2 138:8 171:22 182:20 207:14 227:21 240:15 251:19 257:19 258:11 265:15 267:9 278:17 298:1,2 334:2
1st 352:14,20 355:2 355:3
1,000 307:19
1,800 61:17
1-1/2 64:1
1.2 62:16
1.8 63:4
1:30 267:13,14,18
1:33 267:21 268:2
10 29:12 30:1,8,21 31:7 35:9 54:16 284:4,7 285:19 394:9
10-15 50:14
10:27 140:14
10:30 140:11
10:43 140:15
10:45 140:9,12
100 120:20 123:17 316:1
103rd 138:11
1086 306:1 307:18
11 125:8 174:8 303:18
12 69:17 87:9
12:48 267:20
13 305:12,14
142 306:16
15 4:5 54:16 101:6 140:4,4,11 189:7 267:11 305:12 326:20
15th 354:4 357:9
150 61:15,16,22
16 309:4,5
16th 349:13 350:22 352:4,19 354:5 356:6
17 297:16
18 10:5,12 11:12
180 99:9
1800's 272:3
190 59:14 85:11,22
1938 295:2
194 4:8
195 4:9
1951 293:4
1962 295:4
1972 9:16 295:19
1986 98:16
1990's 345:7
1991 63:20
1992 63:20

2

2 3:17 4:12 138:9 171:21 206:21 227:21 240:4,15 257:20 268:7 269:2 278:19 279:2 288:19 298:1,6 299:9 334:2 339:22 363:8 401:17
2nd 187:4
2-1/2 62:18
20 4:7 63:21 64:1 64:15 101:17,18 101:20 102:19 137:13 147:9 201:21 225:13 226:13 361:2
20th 175:12
20-some 60:15
200 4:10 281:5,6,7 285:12 286:5 287:9 306:5 317:18 319:10,14 321:3 322:19
2000 348:11
2004 173:4
2005 173:21 175:12 177:18 317:21 341:20
2006 70:15 177:18 177:21
2007 61:10 63:22 64:9 184:13 275:11 276:2 345:6 346:11 348:11,17
2008 178:3 187:4 277:15 278:13 304:17
2009 178:3 189:2 276:21 312:16 341:18 346:19
2010 184:14,15 279:16 284:3 305:5,6,7,19 311:3 315:13 318:7 371:15 372:3 373:15
2010-2015 307:3 359:14
2011 1:13 33:14 306:2 352:14,21 353:19 355:2 356:4 357:9 383:15
2012 190:14 327:21
2013 190:16
208 10:5,13 11:12
21st 173:3 196:14 354:3
210 153:3
22 214:18,20
25 98:11
25th 352:13
26 168:18
27 1:13 142:19 170:1
270 4:14
28 391:1 394:9
297 247:1

3

3 138:9,12 207:1 240:2,5,6,8,17 245:8 260:21 261:4,4 278:22 298:2,8
3,600 310:21
3-1/2 62:16
3:56 404:9
30 92:17 101:6,20

101:22 102:20 137:13 210:14 249:7 353:19
30th 356:4
30-some 71:11
300 130:15 138:5 319:15
31 1:20
37 325:21 328:21
37-4 353:9
385 4:16
386 4:19

4

4 82:15,17 138:9 183:1 379:13
4-aminophenol 379:9 380:13,19
40 137:13 391:22
40-50 360:22
400 138:5
401 4:22
42nd 372:20
43rd 383:14
45 32:5 267:10
467 348:2 356:10

5

5 4:2
5,000 142:20
5-1/2 63:4
50 89:5,17 102:1 214:21 249:7 327:11
500 70:11
52 59:14 85:11

6

6 182:20 352:6,7 353:3
60 350:2
66 65:4
67 341:18

7

7 82:16 85:10
70 316:1 332:4
70's 296:2,5,12,16 296:22 297:14
70-80 361:4
700 319:5
71 324:2
712 10:5,21
72 100:7 106:11 134:17

8

8 30:8,21 31:7 35:9 340:13
8th 333:21
8:00 1:21 5:2
80 62:5
80-90 101:10
81 62:5 278:1

9

9 4:4 29:12 30:1,8 30:21 31:7 35:9 336:12
9th 333:21
9/30/2010 187:15
90 99:12 138:12 298:22 368:12 378:15
90-day 316:20 330:13
92 62:9
96 281:8 286:5 306:6 340:17 358:4
98 130:21
99 173:6
99.1 130:22

C E R T I F I C A T E

This is to certify that the foregoing transcript

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Before: U.S. Food and Drug Administration

Date: 07-27-11

Place: Silver Spring, MD

was duly recorded and accurately transcribed under my direction; further, that said transcript is a true and accurate record of the proceedings.

Court Reporter