FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY ADVISORY COMMITTEE (PSCP) MEETING

Virtual Meeting

Wednesday, November 2, 2022

9:00 a.m. to 2:01 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Rhea Bhatt, MS

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY ADVISORY COMMITTEE MEMBERS (Voting)

Jeffery M. Carrico, PharmD, BCPS

Director, Research Pharmacy

Department of Pharmacy

Dana-Farber Cancer Institute

Boston, Massachusetts

Sandra Finestone, PsyD

(Consumer Representative)

Executive Director

Association of Cancer Patient Educators

Irvine, California

Leonid Kagan, PhD

Associate Professor

Department of Pharmaceutics, Ernest Mario School of Pharmacy

Rutgers, The State University of New Jersey

Piscataway, New Jersey

Walter K. Kraft, MD

Professor of Pharmacology, Medicine & Surgery

Department of Pharmacology, Physiology, & Cancer Biology

Thomas Jefferson University

Philadelphia, Pennsylvania

Kelvin H. Lee, PhD

Gore Professor of Chemical Engineering

Department of Chemical and Biomolecular Engineering

University of Delaware

Newark, Delaware

Kenneth R. Morris, PhD, FAAPS

(Chairperson, Pharmaceutical Science)

Professor Emeritus

University of Hawaii at Hilo

Hilo, Hawaii

Frances Richmond, PhD

Director, D K Kim International Center for Regulatory Science

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School of Pharmacy, University of Southern California

Los Angeles, California

William C. Zamboni, PharmD, PhD

Professor

Director, UNC Advanced Translational

Pharmacology and Analytical Chemistry Lab

UNC Eshelman School of Pharmacy

UNC Lineberger Comprehensive Cancer Center

Carolina Institute of Nanomedicine

University of North Carolina at Chapel Hill

Chapel Hill, North Carolina

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY ADVISORY COMMITTEE MEMBERS (Non-Voting)

Mark C. Rogge, PhD

(Industry Representative)

Chief Development Officer

Sail Bio, Inc.

Cambridge, Massachusetts

Pravin Rothe, MPharm

(Industry Representative)

Validation Lead, Manufacturing Sciences and Technology

Novartis

Wilson, North Carolina

T.G. Venkateshwaran, PhD

(Industry Representative)

Vice President and Global Head, Global Regulatory Affairs- CMC and Devices

Takeda

Cambridge, Massachusetts

TEMPORARY MEMBERS (Voting)

Mittal Sutaria, PharmD

(November 2nd only)

Senior Vice President, Contract and Program Services

Sourcing Ops – Pharmacy

Vizient

Irving, Texas

FDA PARTICIPANTS (Non-Voting)

November 2nd FDA Participants

Patrizia Cavazzoni, MD

Director

CDER, FDA

Michael Kopcha, PhD, RPh

Director

Office of Pharmaceutical Quality (OPQ)

CDER, FDA

Lucinda (Cindy) Buhse, PhD

Deputy Director, Operations

OPQ, CDER, FDA

Adam Fisher, PhD

Science Staff—Immediate Office

OPQ, CDER, FDA

Jennifer Maguire, PhD

Director

Office of Quality Surveillance (OQS)

OPQ, CDER, FDA

Ashley Boam, MSBE

Director

Office of Policy for Pharmaceutical Quality (OPPQ)

OPQ, CDER, FDA

Alex Viehmann

Director

Division of Quality Intelligence II

OQS, OPQ, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. MORRIS: Good morning, and welcome everyone. I'd first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Audra Harrison. Her email and phone number are displayed now.

(Pause.)

DR. MORRIS: I'm still getting echo. Okay. I think we've got it. Good. So hopefully everybody heard that, and we may proceed.

My name is Kenneth Morris, and I will be chairing this committee. I will now call the first day of the November 2 and 3, 2022 Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting to order. Rhea Bhatt is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

MS. BHATT: Good morning. My name is Rhea

Bhatt, and I'm the designed federal officer for the meeting. When I call your name, please introduce yourself by stating your name and affiliation.

We'll begin with the standing PSCP members, starting with Dr. Carrico.

(No response.)

MS. BHATT: Dr. Carrico, could you please unmute yourself and state your name and affiliation?

DR. CARRICO: Good morning. This is Jeff Carrico. I'm with the Dana-Farber Cancer Institute.

MS. BHATT: Thank you, Dr. Carrico.

Next, we have Dr. Finestone.

DR. FINESTONE: Good morning. Sandra Finestone, consumer representative.

MS. BHATT: Thank you, Dr. Finestone.

Next, we have Dr. Kagan.

DR. KAGAN: Good morning, everyone. Leonid Kagan. I'm at Rutgers University.

MS. BHATT: Thank you.

Next, we have Dr. Kraft.

DR. KRAFT: I'm Walter Kraft from Thomas Jefferson University.

MS. BHATT: Thank you, Dr. Kraft.

Next, we have Dr. Lee

DR. LEE: Good morning. This is Kelvin Lee with the University of Delaware.

MS. BHATT: Thank you.

Next, Dr. Morris?

DR. MORRIS: This is Ken Morris. I'm a professor emeritus at the University of Hawaii at Hilo, and formerly of the Lachman Institute for Pharmaceutical Analysis at Long Island University.

MS. BHATT: Thank you, Dr. Morris.

Next, we have Dr. Richmond.

DR. RICHMOND: Hi. This is Frances Richmond. I am at the University of Southern California.

MS. BHATT: Thank you.

Dr. Zamboni?

DR. ZAMBONI: Hi. This is Bill Zamboni. I'm from the University of North Carolina.

MS. BHATT: Thank you.

Next, we have our industry representative. We'll have Dr. Rogge introduce himself when he's connected.

Mr. Rothe?

(No response.)

MS. BHATT: Mr. Rothe, could you please introduce yourself and state your name and affiliation?

(No response.)

MS. BHATT: We'll come back to him.

Dr. Venkateshwaran?

(No response.)

MS. BHATT: Dr. Venkateshwaran, could you please unmute yourself and state your name and affiliation?

(No response.)

MS. BHATT: You may be double-muted. Would you be able to unmute yourself and introduce yourself to the committee?

(No response.)

MS. BHATT: We'll come back to him.

Next, we'll move on to temporary voting

members.

Dr. Sutaria?

DR. SUTARIA: Good morning. Mittal Sutaria from Vizient.

MS. BHATT: Thank you, Dr. Sutaria.

Dr. Venkateshwaran, if you're connected, could you please yourself for the committee?

DR. VENKATESHWARAN: Hi. This is T.G. Venkateshwaran from Takeda.

MS. BHATT: Thank you.

Next, we'll move on to FDA participants.

First, we have Dr. Cavazzoni.

DR. CAVAZZONI: Good morning. I am Patrizia Cavazzoni. I'm the director for the Center for Drug Evaluation and Research.

MS. BHATT: Thank you.

Next, we have Dr. Kopcha.

DR. KOPCHA: Yes. Good morning. I'm Mike Kopcha. I'm the director for the Office of Pharmaceutical Quality within CDER, which is part of the FDA. Thanks.

MS. BHATT: Thank you, Dr. Kopcha.

Next, we have Dr. Buhse.

(No response.)

MS. BHATT: Dr. Buhse, could you please unmute yourself and introduce yourself to the committee?

DR. BUHSE: Yes. I did unmute myself. I'll try again. This is Cindy Buhse, deputy director of operation in Office of Pharmaceutical Quality in CDER.

MS. BHATT: Thank you, Dr. Buhse.

Next, we have Dr. Fisher.

DR. FISHER: Hello. This is Adam Fisher, director of Science Staff, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, FDA.

MS. BHATT: Thank you, Dr. Fisher.

Dr. Maguire?

DR. MAGUIRE: Good morning. Jennifer Maguire. I'm the director of the Office of Quality Surveillance within OPQ, CDER, FDA.

MS. BHATT: Thank you.

Dr. Boam?

(No response.)

Dr. Boam, could you please unmute yourself and introduce yourself to the committee?

(No response.)

MS. BHATT: We can come back to Dr. Boam.

Next, we have Dr. Viehmann.

MR. VIEHMANN: Good morning, everybody. This is Alex Viehmann, and I'm a division director in the Office of Quality Surveillance within OPQ, CDER.

MS. BHATT: Thank you, Dr. Viehmann.

We'll go back.

Mr. Rothe, if you are able to unmute yourself, please introduce yourself to the committee.

MR. ROTHE: Hello. This is Pravin Rothe. I work with Novartis and representing industry.

MS. BHATT: Thank you.

And Dr. Boam, would you be able to introduce yourself to the committee?

MS. BOAM: Can you hear me, Rhea?

MS. BHATT: Yes, we can hear you well.

MS. BOAM: Hi. This is Ashley Boam. I'm the director of the Office of Policy for Pharmaceutical Quality in OPQ, in Center for Drugs. Thank you.

MS. BHATT: Thank you, Dr. Boam.

Dr. Morris?

DR. MORRIS: Thank you, Rhea.

For the topics such as those that are being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that the meeting will be a fair and open forum for discussion of these issues and that the individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson, but we look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask the advisory committee members to take care that their conversations about the topic at hand take place in the open forum of the meeting.

We're aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during break or lunch.

At this point, Rhea Bhatt will read the Conflict of Interest Statement for the meeting.

Rhea, if you could.

Conflict of Interest Statement

MS. BHATT: Thank you, Dr. Morris.

The Food and Drug Administration is convening today's meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws

and regulations.

The following information on the status of this committee's compliance --

DR. MORRIS: Thank you, Rhea.

MS. BHATT: -- with federal ethics and conflict of interest laws, covered --

DR. MORRIS: At this point, we'll proceed with the FDA presentations, beginning with introductory remarks from Dr. Cavazzoni.

Thank you, Dr. Cavazzoni.

MS. BHATT: Dr. Morris, are you able to hear me?

(No response.)

MS. BHATT: The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of

interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflicts of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them --

DR. MORRIS: Dr. Cavazzoni, are you ready?

MS. BHATT: -- including those of their spouses and minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants,

CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today, the committee will discuss the Center for Drug Evaluation and Research Quality Management Maturity, QMM, program. QMM is the state attained when drug manufacturers have consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement.

CDER has proposed the development of a rating system that will help incentivize drug manufacturers to adopt more mature quality management practices at their facilities. The committee will consider the impact that a QMM program would have on the pharmaceutical industry, drug shortages, and supply chain resiliency. FDA will seek input to determine if experts from academia and industry support the development of a CDER QMM program to incentivize investments in mature quality management practices.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial

interest reported by the committee members and temporary voting numbers, no conflict of interest waivers have been issued in connection with the meeting. To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Drs. Mark Rogge, Pravin Rothe, and T.G. Venkateshwaran are participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Drs. Rogge, Rothe, and Venkateshwaran's role at this meeting is to represent industry in general and not any particular company. Dr. Rogge is employed by Sail Bio, Dr. Rothe is employed by Novartis, and Dr. Venkateshwaran is employed by Takeda.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or

imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that could be affected by the committee's discussion. Thank you.

Over to you, Dr. Morris.

(Pause.)

DR. MORRIS: Sorry. I thought I had already read this. I may have been muted. But we will now proceed with the FDA presentations, beginning with introductory remarks from Dr. Cavazzoni. Sorry.

FDA Presentation - Patrizia Cavazzoni

DR. CAVAZZONI: Good morning. I am Dr. Patrizia Cavazzoni, director for the Center for Drugs. As we meet today to discuss the importance of incentivizing quality management in drug manufacturing, let's first reflect on our current supply chain vulnerabilities and their impact.

The 2021 White House 100-Day Report on Supply Chain eloquently states that, "Three pillars

of a secure and robust supply chain are quality, diversification, and redundancy." I don't think it is any coincidence that quality is listed first for reasons that I will soon explain.

Drug manufacturing remains a global enterprise that can be challenging to regulate. Over three-quarters of active pharmaceutical ingredient manufacturing sites are outside of the U.S. and over half of finished drug formulation sites are located outside the U.S. Many product launches are global events. Since it is not feasible to be omnipresent, regulatory strategies must be data-driven and risk based to deploy regulatory resources in a manner that provides the most benefit to patients and consumers.

Certainly, the COVID-19 public health emergency has changed how the pharmaceutical industry and regulators operate, and though some problems remain in the conduct of clinical trials, many other problems remain as well. We have a fragile supply chain to begin with, and COVID is not helping matters.

COVID is not entirely over, and we're still facing travel disruptions and limitations such as lockdowns in some parts of the world. The work required to avoid or mitigate drug shortages has greatly increased in volume and complexity during the pandemic. We continue to face the constant flow of information, at times updated by the minute, which challenges our science and risk-based decision making. COVID has also forced us to acknowledge and confront constraints of international supply chains, especially as related to supplies and services.

I ask you to consider this, the availability of medicines to treat COVID patients or avoid severe disease is impacted by the supply chain, but also impacts the supply chain. As we have witnessed over the past three years, COVID-19 has led to a sudden and dramatic increase in local demand of critical drug products such as IV, narcotics, and IV fluids. We've seen competition on manufacturing lines and in facilities to manufacture clinical drugs when there has been a

limited capacity to do so.

We've seen the problems created by short supplies of manufacturing components, services, and other commodities. One constant that has not changed is the importance of maintaining product quality. It is the foundation of safe and effective medicines and essential for drug availability.

Of course, drug shortages are not something new in the COVID era. Sadly, they have existed for decades. Let me explain a little bit more about the history of drug shortages and the contributing factors that lead to them.

Drug shortages have dropped significantly since 2011, with a dramatic drop occurring with the passage of FDASIA in 2012, which gave the agency new authorities to prevent and mitigate drug shortages. Still, in spite of the efforts of FDA and others, including industry, we see a consistent and persistent number of drug shortages every year, which posed a real threat to public health.

Make no mistake, shortages are not just

inconveniences for pharmacies. They impact the lives of patients. Many of you may be familiar with the story vincristine, the drug used to treat pediatric leukemia for almost 60 years that went into shortage a few years ago. It's stories like these that remind us that we need to do everything that we can to keep medicines available and to keep shortages from occurring, but even these data don't tell the whole story.

It takes a timed heroic effort to prevent drug shortages . Although the number of new shortages has decreased in recent years, the number of shortages we've worked to prevent has gone up, as you can see in this chart. COVID has made our job even more difficult. The highest number of shortages we prevented was 300 last year, but as you can see, we were preventing 100 to 200 shortages per year even prior to COVID.

Clearly in the COVID era, there has been an increase in the number of demand-driven shortages, but historical shortages have been largely supply driven. A team of economists examined the drugs

that first went into shortage between 2013 and 2016, and found that 62 percent went into shortage due to quality issues. As one can imagine, there are many factors that contribute to drug shortages, and there will need to be more than one solution.

A multiagency federal drug shortage task force released a drug shortage report in October 2019 that looked into the root causes and potential solutions for drug shortages. One of the three root causes was that the market does not reward manufacturers for mature quality systems, the focus on continual improvement, and early detection of supply chain issues.

This task force recommended an enduring solution to this problem, the development of a rating system to incentivize drug manufacturers to invest in quality management, QMM, for their facilities. Thus began our development of an innovative quality management maturity program in rewarding manufacturers that focus on continual improvement, business continuity plans, and early detection of supply chain issues.

Although with safe unprecedented challenges over the past few years [indiscernible], and continue to do, CDER is now even more dedicated to our mission of assuring drugs that are available in patients and consumers. To be clear, there is not any one solution that will solve all the problems plaguing drug availability, but we are prepared to do what we can as regulators. Simply put, the future of pharmaceutical equality requires proactive and rewarding regulation. Primarily, reactive impunity of regulatory standards will not be effective.

Companies are rapidly developing emerging manufacturing technologies, and we have CDER's Emerging Technology Program and FRAME Initiative to address related challenges. We're developing a holistic supply chain understanding, thanks to new technology and additional information such as drug amount reporting data and risk management plans.

Again, we know that manufacturing is a global enterprise, and we're seeking international regulatory conversion of standards and practice.

In fact, right now, CDER is part of two international pilot programs on collaborative international assessment and hybrid inspections, and of course there is the subject of today's meeting, a very proactive and forward-looking quality management maturity program that we'll hear a lot more about later today. You will also hear from the next speaker, OPQ director, Mike Kopcha, patients deserve quality medicines that are available when they need them.

Thank you to the advisory committee members who are here today, and to everyone participating or listening from around the world.

DR. KOPCHA: [Inaudible] -- to handle the ever-changing world.

COVID-19 is a virus that infects humans [inaudible] --

(Pause.)

DR. KOPCHA: There's a bit of an issue in terms of being able to hear me.

MS. BHATT: Good morning, everyone. We'll be taking a momentary break, and we'll be

reconnecting into audio. Thanks.

(Whereupon, at 9:29 a.m., a recess was taken.)

MS. BHATT: Dr. Kopcha?

FDA Presentation - Michael Kopcha

DR. KOPCHA: Hello, everyone. This is Mike Kopcha. As was done during the introductions, I'm the director for the Office of Pharmaceutical Quality. First, I want to apologize for some of the technical difficulties that we had. I do assure you if this virus has taught us anything, it's that it's in the midst of adversity where we shine. So hopefully we've gotten through this difficulty. so let me get back to my part of the presentation.

I know we all keep hearing the phrase, "the new normal" that's associated with COVID-19, and many of us think of this as taking steps to protect yourself and others from COVID-19, to mask wearing, vaccination, as well as physical distancing. While this is all true and good, I'd like to talk today about how we can use innovation to better equip

ourselves to handle an ever-changing world.

COVID-19 is a virus that infects humans, but it affects nearly everything else, including pharmaceutical supply chains, consumer demand, decision making that's based on science, as well as risk. From one viewpoint, though, even prior to COVID, supply chain disruptions have been their own kind of contagion, so you see I'm building on this virus theme.

How common is this story? An issue, often a quality issue, forces the manufacturer to temporarily shut down operations. This issue then spreads as a virus to other manufacturers of their products, of course, to scale up to meet market demands; then this issue spreads to patients and consumers, who lose access to their drugs when the remaining manufacturers can't respond quickly enough, or in some cases they may not be able to respond at all.

We need to use the same type of innovative thinking that we've used to address COVID to realize a future where we are more immune to supply

chain disruptions. We're now at a point in history where challenges have created opportunities, and these opportunities will help us drive the future of pharmaceutical industry.

It's important to remember challenges spur innovation to drive us to do better, to be better, and to stay better, so let me start with a deceptively easy question. What is pharmaceutical quality?

Well, a quality product of any kind consistently meets the expectation of users, and I assure you that we treat drugs no differently, except our users are patients and consumers. Patients expect safe as well as effective medicine with every dose that they take. The pharmaceutical quality is assuring that every dose is safe and effective, and the quality pieces is free of contamination, as well as defects. It's what gives patients confidence in their next dose of medicine. That's kind of one of the easy ways me and OPQ think of quality overall.

So while this may be a relatively simple

explanation, I believe the pharmaceutical quality is, in fact, an array, with each element depending on higher elements. So let me explain what I mean by that.

The FDA assesses drug product quality in applications, and we monitor pharmaceuticals in the U.S. market to ensure that each dose is safe and effective and free of contamination and defects; so it's safety, efficacy, as well as quality. This then gives patients confidence in every dose that they take.

Process quality is controlling manufacturing risk in order to provide a quality drug product for raw materials all the way to the packaged product itself. The FDA assesses process quality in applications and we monitor and inspect facilities manufacturing through the U.S. market. This is then what gives manufacturers confidence in every batch that they then release to the market.

Mature quality management uses a performance and patient focus to identify areas of improvement and implement changes accordingly. This is then

what gives manufacturers confidence that every batch they make will be acceptable to release to the market now, or in years from now. Quality management, then, is an expectation in international guidelines, but the responsibility to this point has fallen on the manufacturer.

Let me explain a bit about what we do to give you U.S. patients and consumers confidence in their medicine. The mission of CDER's Office of Pharmaceutical Quality, or OPQ, is to assure quality medicines are available to the American public. The key point of delivering on this mission, though, is collaboration between OPQ's core functions of assessment, surveillance, inspection, research, as well as policy. Our assessment of drug marketing and licensing application employs a team of experts in drug substance, drug product, and drug manufacturing.

We continually monitor the state of quality of procedural regulated sites and products. We conduct some facility inspections, in particular, pre-approval or pre-license inspections, to ensure

that a facility can conform to current good manufacturing practice requirements or CGMPs. Further, our research program allows us to protect the public from standard products or substandard products and enables OPQ to make difficult science-based decisions and craft policies to support pharmaceutical quality.

OPQ's site and product catalog is daunting, and it's highlighted in this slide. It comprises 7,000 human drug manufacturing sites of obligation; 2,000 medical gas manufacturers; and 600 hand sanitizer sites that we added because of the pandemic. It covers active pharmaceutical ingredient, as well as finished dosage form sites.

The product comprises 170,000 finished dosage forms -- yes, you heard me right -- 19,000 APIs and 1500 medical gases. This includes products of all human drug user fee programs -- or our UFA programs as we call them -- for new drugs, biologics, generics, biosimilars, and over-the-counter drugs. Of course, as Dr. Cavazzoni explained in her presentation, there

are sometimes quality problems with sites and products that negatively impact patients, and then cause shortages.

To address these problems, the White House 100-day Report on Supply Chain challenged the FDA to develop a framework to measure a facility's quality management maturity, or what we like to call QMM. Yes, we're very fond of acronyms at the FDA, and we're no different here. The industry needs ratings that recognize and reward manufacturers for having mature quality systems that achieve sustainable compliance and focus on continual improvement. The bottom line is this; that we need to incentivize improvements to the pharma manufacturing infrastructure that enhance the reliability of manufacturing and supply.

Now, some have wondered if the QMM program falls within the FDA mission, and the short answer to that is yes. Let me be clear, though. The FDA's mission is to protect and promote public health by helping us to assure that safe, effective, quality drugs are available to patients.

Drugs are not available to patients if they are in shortage.

As I explained, OPQ has a surveillance function that monitors the state of quality procedural regulated sites and products. Now let me explain a bit about the data we currently use and how regulatory innovation is needed to address problems in the supply chain.

Of course we need to understand the indicators of quality issues in the supply chains. Data we use at the moment are largely lagging indicators of quality problems, things like defect reports; sampling; testing results; as well as external data that we make use of. These data tell us about a problem that has usually already occurred. Other data, such as that found in applications or from inspections straddles the line between being a leading and lagging indicator. To enable pragmatic, proactive regulation, we need leading indicators, data that tells us about potential problems before they occur. This is where quality management maturity now enters the

conversation.

QMM is the state attained when drug manufacturers have consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement. It's important to understand that QMM is not just one thing; it's an umbrella concept shown in this slide, and many elements fall under it.

For example, quality metrics are a key aspect of a mature pharmaceutical quality system, with data-driven approaches to reduce quality issues and to drive continual improvement. However, QMM is about much more than any one of these elements, and remember also that QMM is part of the bigger array of quality.

One thing that I want to be very clear about and emphasize is that quality management maturity is not the same thing as quality metrics. And as we've shown in the previous slide, QMM is an umbrella program; quality metrics, QM, is one piece of that. A lot of people confuse the two and think they're the same when in fact they are not. I just

want to be very clear about that and stress that because there is confusion around that. So for the sake of this presentation, or today's and tomorrow's advisory committee, it's important that you understand they are not one in the same.

Studies have shown that the effective use of quality metrics is one characteristic of a robust site QMM, as I mentioned previously. However, as the underlying science has evolved, there has been a shift to a more holistic approach that integrates metrics with other behaviors and attributes of effective PQS. What that stands for is pharmaceutical quality systems.

There is now a long history of benchmarking quality culture by the University of St. Gallen; the Parenteral Drug Association or PDA; McKinsey & Company, a consulting firm; as well as Dun & Bradstreet. Scientists have shown that sites with more mature quality practices are better able to anticipate and resist supply chain disruptions. These findings support the hypothesis that a high degree of QMM has a positive impact across an

organization.

What I want to do is I want to set expectations from what you will hear from the FDA side today. You will hear about our QMM pilot programs and the lessons we've learned from them. You will hear various stakeholder perspectives about a QMM program that we've heard throughout our engagements. You will also hear a high-level vision of QMM rating system and how it fits in the regulatory paradigm.

What you won't hear today, though, is specific details of QMM ratings or how the program will be deployed. I know that's of interest to many, but we're not there yet, and the reason we're having today's advisory committee is so that we can hear back from our advisors as we still continue to build this program.

In closing, let me just say how lucky we are to have a strong committee of advisors that we can turn to for input. I appreciate all your time and attention over the next two days, and I'm looking forward to the public dialogue.

So simply put, we cannot be proactive and pragmatic regulators by relying on lagging indicators; we need leading indicators. True regulatory innovation requires new data and science-based leading indicators. This will allow us to work together and avoid problems before they start. So I'd like to thank you for the privilege of your time this morning, and what I'd like to do is to turn it over to Dr. Jennifer Maguire.

Jennifer, it's all yours.

FDA Presentation - Jennifer Maguire

DR. MAGUIRE: Great. Thanks, Dr. Kopcha.

I've been looking forward to this advisory committee meeting for quite some time, and I'm excited to be able to speak with you all today about QMM lessons learned. I'm just going to pause for one second to make sure that you're hearing me. Someone just give me a thumbs up.

DR. MORRIS: Yes, we can hear you.

MALE VOICE: We hear you, Jennifer.

DR. MAGUIRE: Excellent.

In my talk, I will briefly introduce quality

management maturity, and then also give the remainder of the discussion on the lessons we've learned over the course of our QMM program development. These lessons come from our two pilot programs, an externally funded economic analysis and an internally conducted systems thinking activity to identify unanticipated consequences of the QMM program.

Understanding quality management maturity. As Dr. Cavazzoni mentioned in her opening, a multiagency report was published in October 2019 on drug shortages, root causes, and potential solutions. This report recommended a voluntary QMM program and a rating system to incentivize drug manufacturers to invest in quality management maturity as a comprehensive and enduring solution to drug shortages.

The COVID-19 public health emergency also exposed supply chain vulnerabilities and further motivated a consistent approach for both characterizing site quality and identifying continual improvement that can boost supply chain

resiliency. Dr. Fisher will talk after me about other stakeholders who echo these recommendations and support QMM program development.

Studies by the University of St. Gallen have demonstrated a positive correlation between pharmaceutical quality systems' effectiveness and the degree of implementation for numerous technical and cultural enablers. Drug manufacturers can achieve higher levels of quality management maturity when they successfully integrate business objectives and manufacturing operations with quality practices and technological advancements to optimize product quality, enhance supply chain resiliency, and drive continual improvement.

Sites with more effective and efficient quality systems and a strong culture of quality that permeates all levels of an organization will be higher on the spectrum of quality management maturity.

Now we're going to dive into the lessons learned from program development thus far. In fiscal year 2021, FDA executed two QMM pilot

programs, each by a separate contractor. The pilot participants all manufactured products for the U.S. market. The first pilot program included seven domestic sites that manufactured finished drugs, and the second pilot included eight foreign sites that produced APIs. We provided each contractor with a comprehensive but non-exhaustive list of practice areas for the assessments to cover.

The objectives of the pilot were to develop a QMM assessment framework that would enable FDA to establish what best practices are for quality management and to identify opportunities for proactive continual improvement at a site. We wanted the assessment protocols and the associated rubric used for scoring to maximize inter-rater reliability and to provide a quantitative overall rating that would distinguish between different levels of maturity. We also sought the development of an assessment protocol that would enable a cross-sectional comparison against industry peers.

The contractors developed assessment frameworks and scoring systems that assess practice

areas such as leadership and governance, workforce engagement, and quality culture. All pilot participants received a QMM score and a final report from the contractors.

So what was FDA's role in these pilot programs? During the pilot assessments, FDA participated as an off-camera spectator to observe and learn. In addition, FDA also met with the contractors both before and between the assessments to offer feedback, and this is especially important because QMM requires an understanding of above-the-bar behaviors that exceed CGMP requirements, and this type of novel assessment is distinctly different from a CGMP audit.

The pilots allowed us to learn about the challenges in developing assessment questions, evaluating responses to the questions, and creating a rubric that defines the criteria used to score the assessment. The pilots are also helpful in identifying important logistical and operational considerations when conducting the assessments, and provided examples of what scores on assessment

reports could look like. Lessons learned from these pilots will be used to help guide FDA in the development of a suitable assessment tool to identify indicators of mature quality systems to build a framework to evaluate QMM best practices and identify areas for continual improvement.

Next, I'm going to share some of the key learnings from the two pilot programs, beginning with the assessment itself. In terms of preparation, we learned that it would be useful to have a kickoff meeting prior to initiating the assessment to help orient the participating site and set expectations about the process. We determined it would be helpful to share the schedule of topics with the site so that they can schedule appropriate staff to be available when needed.

We're also considering if it might be beneficial to share the assessment protocol questions along with points to consider with the site ahead of time. Pilot participants stated that having this information at least 2 weeks in

advance, if not even sooner, is ideal to allow them to adequately prepare for the assessment.

Finally, we learned that we need to provide recommendations about the types of verifiable objective documentation, or examples, that could be used by the site to really substantiate and add context to their responses.

Moving on to the protocols, for the assessment protocol, we noted that some of the questions were really compound, complex, or unnecessarily used jargon, and this made the questions really hard to understand. Some of the content was also duplicated across topic areas.

To give you an example, when a site was asked about how they apply quality risk management principles, that our sponsors linked the application of quality risk management to their evaluation of CAPA effectiveness and change management; but then later when the site was asked about change management, they answered many questions by saying, "As we explained earlier." So there's definitely an opportunity to streamline the

assessment protocol to minimize duplicative discussions. We also noted that some of the questions may not apply equally well to an API manufacturer versus a finished dosage manufacturer, so we are considering if sector-specific questions are needed.

Some of the questions are best answered by corporate leadership with responsibilities across multiple sites, whereas some questions are best answered by site leadership. For this reason, questions really need to be grouped appropriately to facilitate the site's ability to arrange the participation of appropriate staff when needed.

Moving on to discussion, we found that the interactive assessments allowed for a deep dive into a site's quality management practices, but one thing that the assessors couldn't do, because the pandemic and associated travel restrictions prevented them from being on site, was to speak with management and staff separately. Both contractors stated that to truly get a sense of how the site functions and the strength of the quality

culture, it would be really beneficial to have these conversations separately with staff at different levels.

When it comes to time management, trying to apply a strict time limit per question was not effective because during the assessment, some topics were not fully covered in this time, while other topics had unused time, so managing time throughout the course of the assessment really needs to be dynamic. This will enable the assessment to be completed effectively within the time allocated for the overall assessment process without strict limits per question.

The next two slides discuss the rubrics used during the pilot programs and how that rubric was used to determine a final score for the QMM assessments. Just to provide clarity, when I think rubric, I'm talking about the level definitions used for each assessment question to best match the site's practices with the maturity level; and when I say scoring, I'm talking about how the site's performance and all the different practice areas is

considered to arrive at a final QMM score.

For the pilot programs, we had two contractors, so we had two independent rubrics, which were developed with different criteria to assign maturity levels. We had the benefit of learning from these two different approaches. For the API pilot, each response was scored and topic scores were aggregated to give a combined score for each practice area, as well as the final QMM score, but for the finished dosage pilot, scores for each question and the final score were determined using a rigorous consensus process between assessors.

So this process was a unique and deliberative process, where each of the outlier assessors have to make their case, one by one, to the assessment team for the reasons a particular score was selected, and a team continued to discuss until there was resolution on the assigned score.

From FDA's perspective, our rubric development will follow the development of the QMM assessment protocol and will be determined on both the practice areas and the underlying elements that

will be evaluated in the final QMM assessment protocol.

Both contractors signaled that multiple assessors will be needed to effectively execute a QMM assessment and minimize bias. A well-designed rubric will be absolutely critical to maximizing inter-rater reliability.

FDA will need to develop objective meaningful and reliable criteria to discern between the maturity levels. This will also allow QMM assessments to be scored in a consistent data-driven and scientific manner. This will allow sites to utilize their scores to benchmark themselves against their peers and to trend or track their own progress over time.

So moving on, one other thing about the scoring system I did want to mention, the scoring system will need to account for missing and outlier data. Just to give you an example, some questions in the assessment may not be applicable to all sites or some sites may choose not to respond to a given question. We are exploring different scoring

methodologies that will allow us to best handle these scenarios.

Now moving on to the assessor behaviors and our learnings, we've come to realize that, obviously, the assessors who performed the QMM assessments are critical to the success of the program. These assessors need to be well versed in the various practice areas that get covered during the assessment. They need to be familiar with quality management and best practices, and they need to have a strong background in CGMP regulations and the FDA compliance programs. This will enable them to correctly identify and evaluate behaviors and practices that go beyond regulatory requirements.

Making site personnel feel comfortable during the process is definitely a bit of an art, but we were able to identify some best practices. Strong interviewing skills are necessary to put the participants at ease and to facilitate efficient and productive discussions. Assessors must be trained to seize the opportunity to ask open-ended

follow-up questions to avoiding leading discussions off topic or limiting the discussions within their comfort zones, and they need to refrain from providing their opinions or lecturing the site on any given topic.

To ensure that participants get the most out of these assessments, the assessor should understand their audience. It can be confusing when questions are asked in very quick succession, so the assessors need to provide sufficient time for responses, and they should be able to repeat or rephrase the question as necessary, but being careful not to change the scope of the question.

Sometimes the site may misunderstand the intent of the question, so it's important that the assessor can clarify as needed and clear up any potential misconceptions. It's also key that the assessor seek supporting documentation or examples and doesn't just accept things at face value.

After the pilot program's concluded, the pilot participants have the opportunity to share their feedback directly with FDA. Here I'm sharing

some of the candid comments we received, and you can see that the overall sentiment for the program is positive. Participants discussed, among other things, examples of how they could use the results of their QMM assessments to improve processes and programs for communication within the corporate organization; reduce the frequency of and time spent on vendor audits; use the information to supplement the vendor audit process; and drive continual improvement by evaluating behaviors and actions; and striving to achieve even higher levels of quality management maturity. These are direct thoughts from the participants to the agency.

One important factor we seek to understand is the potential impact of QMM ratings on pharmaceutical manufacturers. To that act, OPQ's funded research through FDA's CERSI program to identify the effects of a quality rating system on the drug market structure, including both incentives and disincentives for manufacturers to strengthen their processes.

Dr. Clifford Rossi's published research

provides an economic analysis of the potential effects of the manufacturing quality rating on the pharmaceutical industry. This study examined the market structure conditions, including the degree of competitiveness among market participants when negotiating prescription drug product contracts. In addition, a machine-learning analysis for the duration of drug shortages was performed.

Alternative economic models and numerical analysis highlighted information asymmetries that prevent pharmaceutical buyers from differentiating between manufacturers of specific drug products by any criterion other than price. Examples of other criteria that would be useful for purchasing decisions include supply chain resiliency and reliability.

This analysis suggests that quality ratings can reduce the information asymmetry for buyers and increase transparency of a site's quality practices. This should then incentivize manufacturers to invest in quality processes, which could ultimately lead to a reduction of

quality-related drug shortage.

We also explored direct and indirect effects of a quality management maturity program on supply chain networks. This helped to characterize potential impacts that a QMM program may have on supply chain stakeholders. This initiative involved the collaboration of multiple FDA offices, including the Office of Regulatory Affairs; the Office of Quality Surveillance and the Office of Pharmaceutical Manufacturing Assessment, both within the Office of Pharmaceutical Quality; CDER's drug shortage staff; and the Office of Manufacturing Quality within the Office of Compliance.

This preliminary analysis increased FDA's awareness of the external factors that may affect stakeholders within complex supply chains and suggested that sector-specific incentives may be important for program success.

To just sum up my slides, the lessons learned from the QMM pilot program will help guide development and operational decisions, and this

will be done in conjunction with our findings from our research initiatives and our continued engagement with industry partners and stakeholders. And as you can see so far, the sentiment about the benefits of the QMM program, which is a voluntary program, has been overall positive.

With that, I'm going to turn the floor over to Dr. Fisher, who's going to share more about stakeholder perspectives.

FDA Presentation - Adam Fisher

DR. FISHER: Thank you, Jennifer.

I am Adam Fisher, the director of Science Staff in the Office of Pharmaceutical Quality. One thing thing that I thoroughly appreciate about the QMM program is how it affects so many different stakeholders.

As a person heading up outreach for the Office of Pharmaceutical Quality over the past few years, I know that the vast majority of our historical engagements have been with pharmaceutical manufacturers. However, the vast majority of our stakeholders are non-pharmaceutical

manufacturers, and this is not to minimize the importance of manufacturers in any way, but the development of the QMM program has been a catalyst for our engagements with other stakeholders in the supply chain, and more on those stakeholders in just a minute.

I know you've heard a few times about the 2019 cross-government report on drug shortages, and the root cause, and the potential enduring solution related to incentivizing drug manufacturers to invest in achieving QMM at their facilities, but since the publication of the drug shortage report, there has been a building consensus regarding the importance of the QMM program.

The conclusion of the 2020 CDER sponsored workshop held by the Duke Margolis Center, which included patients, healthcare providers, purchasers, pharmacies and pharmacists, and payors was that, "Stakeholders largely agreed on the need to develop and implement quality ratings to allow for differentiation by an attribute other than price," and that's a direct quote from the workshop

summary that's been published online.

Then last year, the White House's 100-Day Report charged FDA with leading the development of a framework to measure a facility's quality management maturity. Then earlier this year, the National Academies published a report with the recommendation to establish a quality rating system in collaboration with business partners and stakeholders, and I want to share some of what we've learned so far by engaging with stakeholders on the development of the QMM program.

We've taken the need to collaborate seriously as we've engaged stakeholders in building this program. I think it's clear to everyone that this is not the type of program that can be built in a vacuum. There is one important engagement you just heard about from Dr. Maguire. We held two QMM pilot programs that concluded earlier this year. One was for the domestic finished dosage form site and one was for the foreign API site. Of course, the goal of this program was to develop a framework to assess and rate these establishments.

Then in April of this year, we released a white paper that explains the importance of establishing a QMM program and also some of the key challenges and elements needed to successfully implement the program. After the release of that paper, we then hosted a two-day public workshop in May to discuss the development and impact of a QMM program with public stakeholders. And there's, of course, perhaps no bigger engagement than what we're doing here today, holding a public advisory committee meeting on the further development of the QMM program.

Based on these interactions, I will clearly state my personal bias. I believe that a QMM rating program is necessary to assure patients have consistent access to quality drugs. The way I see it, QMM information is the proven leading indicator of quality issues that Dr. Kopcha spoke about earlier. However, my role here today is not to share my personal opinions; it is to share what we've learned from these stakeholder engagements.

With that in mind, what I'm going to walk

through today are some of the key challenges we've identified as stakeholders, some of the key elements of the QMM program that we've identified with stakeholders, and finally, some of the feedback we received in our May workshop. All I think are important information for the committee and public to hear about today.

You'll see this slide a few times today, and I believe this emphasizes that stakeholder engagement has been a critical element in developing a QMM program. The stakeholders impacted by a QMM program comprise what we call the 6 Ps of the pharmaceutical supply chain: pharmaceutical manufacturers; purchasers; payors; pharmacies; providers; and patients, and there are ways that nearly everyone in the pharma supply chain can benefit from QMM ratings.

Without going through all of them in great detail because you will hear a bit more about this later, manufactures with high QMM get recognition in the market. Purchasers and payors get more insight and confidence in the supply chain for the

drug that they buy or reimburse. Patients, pharmacies, and healthcare professionals get medicines from stronger supply chains, and we at the FDA get to be better informed for resource allocation decisions such as inspection timing and frequency, and then also our use of regulatory flexibilities, for example, as related to making post-approval changes.

Now, all the challenges I'm about to discuss are shared in our white paper on QMM that you can find on our website. I will run through these challenges, but I encourage everyone to read the white paper for more detail.

The first identified challenge will be clearly defining the scope and meaning of QMM ratings. It will need to be clear to stakeholders that ratings reflect the QMM at a manufacturing site and not the quality of the product or the process used to make it. Again, these are not meant to be ratings of the quality of products. It is very important that consumers retain confidence in the quality of products.

As Dr. Kopcha addressed earlier, due to our regulatory processes, we have a high degree of confidence in the quality of products on the U.S. market. A high QMM rating will mean that the site has a history of quality management that goes above meeting minimum thresholds. And also, a rating is not absolute. It is not meant to be, and it will not be a guarantee of the availability of the site's products.

The second challenge will be convincing purchasers to consider QMM in decision making. It may be necessary for FDA to explain the value of using QMM ratings in purchasing decisions to stakeholders who do not regularly consider quality when making decisions. We have found that most drug purchasers do try to collect information on quality in the pharmaceutical supply chain, and they often have success in doing that proportional to the purchasing power of their organization. Purchasers generally have limited visibility in the site's pharmaceutical quality systems and will rely on FDA's public information or perhaps additional

information they can leverage from manufacturers.

FDA's engagement with purchasers have revealed that they do consider some form of supply chain information, or quality information, using pragmatic but somewhat limited indicators such as geographic location, historical fill rates, FDA's Form 483s, recalls and warning letters, and contract performance history; and still I think it's important to note that the driver of the decision is certainly still price.

In this challenge, CDER will need to clearly separate QMM appraisals from regulatory compliance. QMM assessments and ratings need to be surveillance functions separate from determining compliance with regulatory standards. This is another area in which transparency, engagement, and collaboration are critical.

Another challenge is that we'll need to rely on purchasers to understand their supply chain. It may be necessary for purchasers to have supply chain information to use the QMM rating of sites in their purchasing decisions. These site ratings may

be of limited value of purchasers who do not have insight into the specific facilities manufacturing the drugs or components they tend to purchase.

So QMM is a function of the establishment and not of the product, and we may not be able to disclose specific information about the drug product's supply chain, and we may have to rely on purchasers to ensure this information during the bidding or negotiation process. The good news, however, is that most purchasers already require supply chain site information as part of their decision-making process.

Another challenge is that we need to have faith that the market will reward products from facilities with higher QMM. The use of QMM ratings in purchasing decisions should incentivize continual improvement in the long term but not cause unintended consequences in the short term. Of course, there are cost savings to be realized by high QMM, and these include eliminating costs associated without specification batches or recalls and healthcare facilities costs to respond to

shortage.

Finally, we will need to address potential risks of using QMM ratings in decision making. There have been questions about using QMM in marketing materials. Some healthcare providers have also expressed their concerns about the responsibility or liability related to QMM ratings when prescribing. Basing our ratings on site rather than product does remove healthcare professionals one step from a decision-making process informed by QMM.

Now that I've run through some of the challenges that we've identified with stakeholders, let me share some of the elements we know our QMM program must have as we build it moving forward based on our engagements that we've had with stakeholders.

We know that the program must acknowledge that quality culture is the foundation for mature quality management. Quality culture is demonstrated by organizations in which their objectives drive quality and culture is led from

the top. These organizations are characterized by the linking of business and quality objectives.

Next, the QMM assessment tool must be objective and consistent across manufacturing sites and agnostic to the product or size of operations. It must be validated and standardized in order to be reliable and consistent between individuals conducting assessments, and this is true whether they are carried out by the FDA or by a contractor. And a QMM assessment, again, must be distinct from the determination of CGMP compliance. Again, it is a surveillance function.

Further, transparency is critical in establishing a QMM program. Raw communication is needed here. Understanding the intentions of the program, along with the ultimate impact, is important. Public awareness of a manufacturer's QMM could lead to uncertainty if the meaning of the rating is not very clearly defined. It must be clear that all drugs sold in the U.S. are of adequate quality and considered safe and effective when taken as directed. QMM is about supply chain

for the product. A universal understanding of what a QMM rating system means will be for the benefit of all stakeholders.

And finally, there must be clear incentives for industry to achieve QMM. Of course, there's an inherent incentive in avoiding the future cost of supply disruptions and shortages that impact the entire pharmaceutical supply chain. I note that public knowledge of facility issues and product recalls already have negative consequences to variables such as stock price.

When we look at regulatory incentives, things that we mentioned in our white paper include reduced inspection frequency, increased regulatory flexibility in making post-approval changes, and improved supply chain insight. As an example, an effective pharmaceutical quality system is necessary for firms desiring to use the tools described in ICH Q12 guidance on pharmaceutical product life cycle management, and I will share some surprising feedback on regulatory incentives in just a few minutes.

Also, as I mentioned, purchasers must be willing to consider QMM ratings in their decisions and select products from more robust supply chains. As healthcare professionals, pharmacies, and patients experience the most severe consequences from shortages, these stakeholders may need to advocate for purchasers to use QMM rating in decision making. Without their advocacy, there is a risk that purchasers may use QMM ratings to purchase drugs from lower rated sites, for lower prices, to realize short-term cost savings, but longer term thinking is required, and this is an outcome that we cannot let happen.

Again, those purchasers already use some form of supply chain or quality information in their decision making. The bottom line is that more robust and reliable supply chains are outcomes that benefit everyone, from pharmaceutical manufacturers to patients in the long term.

I've already referenced the workshop that we held in May on the QMM program, and I want to stress that this workshop was a two-way dialogue

between participants and CDER. The workshop was orchestrated with our CDER partners in the Small Business and Industry Assistance program, SBIA. We had nearly 2,000 virtual attendees over the two days from 106 countries around the world who came to discuss the program. Forty-six percent of the workshop registrants were pharmaceutical manufacturers, but the remaining were largely made up of consultants, researchers, other federal employees, contract manufacturers, academics, and and drug distributors.

We conducted polls of the attendees, and I want to share them with you because I think the results are valuable for today's proceedings. First we asked, should purchasers of drug products or APIs consider the QMM of their manufacturing facility? And the result was a resounding yes. Nearly 100 percent responded in the affirmative.

Our next poll then went a step beyond; should they consider, and asked if they believed that information on QMM would improve decision making in the the supply chain. Less resounding

than the first poll, but still an overwhelming 89 percent responded in the affirmative.

Then things got interesting. We established that attendees felt purchasers should use QMM information and that it would improve decision making. When we asked if the same information would reduce drug shortages in the long term, a slight majority said that it would. There are different ways to interpret this result, but what I believe makes the most sense is something that we've said all along and that you heard from Dr. Cavazzoni earlier. There is not just one solution to drug shortages. I think we all know that a QMM program is one potential solution, but alone it is not capable of solving every problem in the supply chain.

Then finally, we asked about which QMM ratings would most help prevent shortage, and it was pretty clear that the attendees felt that the program would need to cover both API and finished dosage form manufacturers.

Now, the next result that I'm about to share

is the most surprising result of our engagement, in my eyes. We are regularly pressed on the incentives FDA will offer related to a QMM program, so I was surprised to see that when we asked about the biggest potential benefit to participants in a program, FDA incentives came in a very distant third place. By far, the biggest benefit was believed to be identification of continuous improvement opportunities, and then second was improved supply chain insight.

For example, that might mean knowing the quality management maturity of your API supplier or contract manufacturer, and I note that this matches with the feedback from pilot program participants that Jennifer Maguire just shared. Many reported positive feelings about potential continuous improvement opportunities and improved supplier insight that they might get from participating in a program.

I want everyone who attended that May workshop understand that we did hear you, either through our polls or through our discussions, and

there are some key topics that we know folks are concerned about. So we heard your concerns about the timeline for program implementation; the regulatory incentives; cost to participate; these potential unintended consequences I mentioned; cost implications; feasibility of achieving QMM; the mazes of program success; and the transparency of ratings. Now, while we don't have a program built today, should we move forward with building it, please know that we are aware of these concerns, and we are taking them seriously.

So in closing, let me just say how lucky we are to have a strong committee of advisors that we can turn to for input on important programs like this. I appreciate all of your time and attention over the next two days, and I'm looking forward to the public dialogue later. As we wrote in the white paper back in April, we will continue to engage stakeholders during and after the development of a QMM program.

Thank you so much for your time. I'm very much looking forward to the rest of the proceedings

today, and I will pass things over to my colleague, Alex Viehmann, in the Office of Quality Surveillance.

Alex?

FDA Presentation - Alex Viehmann

MR. VIEHMANN: Thank you, Adam.

Hopefully everyone can hear me ok, and I want to thank the committee and those joining online and look forward to the robust discussion.

As mentioned earlier in the introduction, my name is Alex Viehmann. I'm a division director in the Office of Quality Surveillance, and I'm here today to talk to you about -- to give you a high-level vision for quality management maturity.

The extent of my talk is first I'm going to go through a little bit of background and the overall business case for QMM. What has FDA done? What have we looked at to further substantiate that this makes sense? Then moving forward, really getting into a little bit more detail around what some of the previous presenters have talked about and to the operational considerations. What are

the risks? What are the feasibility assessments that we need to consider? Then finally, to talk to you briefly about where we are within an assessment framework? What will this look like? What are the kinds of things that we are anticipating to assess and cover on a potential QMM assessment?

One of the quotes we like to use internally is, "QMM is nothing new." The core concepts of QMM really are nothing new. Quality gurus like Deming, Juran, and Shewhart -- looking back at the first Shewhart chart that was rolled out at Bell telephones in the 1920s -- have been speaking about the importance of technical excellence; culture; cost of quality; customer focus; integration of quality and business operations; quality planning; control; continual improvement; and more for, as I mentioned, a hundred years.

Yes, technology has drastically evolved and advanced in this time, but the overall foundation for QMM has been well researched and established, and when you think about things like culture, and you listen to more and more earnings calls, what

are the key things that we're hearing around the importance of culture?

So these things have been, obviously, well substantiated through time, and through these concepts, Deming was able to revolutionize and redefine quality in the auto industry by working with the Japanese auto industry, and these individuals were able to show in further studies since, and research, have substantiated that good quality doesn't always have to mean higher costs.

Yes, quality requires investment. For example, for better supply chain resiliency, this can mean inventory optimization decisions. This can mean additional supplier qualifications, which all cost money. Yes, we know that. But we know that organizations whose quality practices are the most sophisticated are not necessarily the ones that spend the most.

Now moving forward into what is the cost of quality, we think it can be broken down into poor quality costs, which are visible and invisible as demonstrated by this nice iceberg plot in the lower

right corner, and these things are costs related to failures; the line being down from planned maintenance or something related to that, which equals loss of production. This is a cost: time spent reworking, resources related to that; increase in scrap; excess inventory; and we get into fines; legal fees; image costs. The overall corporate image cost, which can lead to lost sales and loss of business. But we also know there are costs related to prevention and control; labor costs related to audits; costs related to establishing a preventive and predictive maintenance program; training, design improvements; implementation of advanced analytics and control strategies.

One of the things that we've seen here is that technology has evolved. Predictive is a key concept here, which ties into the overall technical excellence piece that I will address in a future slide. Advance companies are taking advantage of these technological advances and digitalization, and using data and analytics, things like AI and

machine learning, to be more proactive in their decision making. And we know that, overall, high levels of maturity can lead to increases in revenue, greater customer satisfaction, and operational efficiencies.

Now, the importance of advanced quality systems, and high maturity levels, and cultural excellence, quality culture has been further substantiated by many different companies and associations. As mentioned before, PDA has established work in assessing quality culture and developed a tool that rates, on an ordinal scale, attributes of a quality system; so things like staff empowerment engagement; CAPA robustness; utilization of new technologies; quality planning; amongst others.

ISPE Advancing Pharmaceutical Quality program has collaborated with stakeholders to publish a series of guides that enable assessments of attributes like change management; CAPA; management review and responsibilities; process performance; and product quality monitoring. We

know that the University of St. Gallen has done extensive benchmarking and research into the importance of behaviors and quality management practices in how they correlate to performance measures, so that's a little bit unique.

So not only are they assessing maturity levels of these quality management practices, but they're also collecting data related to performance measures that measure delivery performance; things like [indiscernible], et cetera, to really substantiate the relationship that exists between certain quality management practices, and output measures, and performance.

CDRH has initiated the Case for Quality program with industry, and Dun & Bradstreet recently executed a quality benchmarking study to characterize the state of quality management practices and, again, look at their relationship to different performance metrics. All of these efforts are a clear indicator of the importance of advanced quality management practices.

As Jennifer pointed out earlier, Dr. Rossi's

research identified market imperfections related to information asymmetry. He studied other industries and how ratings reduce this asymmetry problem and contributed to more objective and data-driven decisions. The first thing is CARFAX. The used car market was the epitome of information asymmetry. Buyers were completely disadvantaged by lack of information, odometer fraud [indiscernible] and things like that. So Dr. Rossi explored the used car market before and after advances in IT, which enabled car buyers with data on a car's history, and this revolutionized the used car buying experience for consumers by reducing these information asymmetries that had disadvantage them.

It has become so important and critical in decision making that other competitors have entered the market. And we know that it's not only benefiting buyers, but sellers. It provides them with an estimate of what they can expect to receive for their car.

Now, we know CMS has a rating system for nursing homes, and they introduced this 5-star

rating system on nursing homes, which considers things like health inspection; complaints; staffing; and facility quality. These ratings are publicly available and enable consumers with information to make more informed decisions.

We also know that there is a development of ratings for U.S. depository institutions. Regulators of U.S. depository institutions -- things like commercial banks, thrifts, credit unions, and things like that -- have used a 1 to 5 rating system to determine the strength of an institution's financial condition and operations, known as the CAMELS rating, where quality is defined by financial performance and risk.

These ratings are not publicly disclosed, but they are made available to bank management and their boards, and these ratings have a significant implication for a bank's operating plans. For example, banks may be restricted from growing their asset base. It may be required to suspend dividends. It may be required to seek approval for acquisition or mergers. So these ratings are very

important and have many implications.

All of these things are further substantiating the motivations for pursuing a quality rating. First, if increasing quality reduces cost, a manufacturer would be economically incented to make quality improvements. Also, from a market standpoint, if a higher rating meant landing on a preferred tier, that would incent manufacturers to invest. A third motivating factor would be the potential regulatory relief or flexibility that we've spoken about.

It is important that we clarify what a QMM assessment is and what it is not. First, a QMM assessment is not intended to be used in lieu of, or as a surrogate, or establishment inspections, and does not evaluate compliance with CGMP. It is also not a reflection of product quality. Adam already pointed out that all products approved by FDA and the associated establishments are approved to manufacture and meet certain quality standards. A QMM assessment is an evaluation of an establishment's quality practices.

What is a QMM assessment? As previously stated, it is an evaluation of the establishment's quality practices which will identify and assess above-the-bar behaviors and attributes of an advanced quality system. It will also promote continual improvement by identifying opportunities for growth. Where are there critical gaps in our system, and how do we compare against our peers? It also promotes a challenge to the establishment systems by addressing things that aren't typically assessed. The assessment will also allow participants to become eligible for incentives, which will be discussed in a few slides.

The agency understands that incentives are critical to promote participation, drive continual improvement, and provide more transparency in the marketplace to facilitate more risk-based and objective decisions. As mentioned earlier, it will also promote benefits from investments in quality and continual improvement, reducing availability risks, reducing costs through less rework/ reprocessing, line down time, amongst others.

Now we will discuss important operational considerations the FDA is discussing internally. First, who's going to conduct the assessments? Will it be managed by FDA staff, a third-party, a hybrid? For example, will FDA develop the protocol and a third party executes the assessment? We're currently weighing the pros and cons and the feasibility of both because we know operationalizing a QMM program requires budget, logistical, mechanical, mathematical, and communication considerations.

Second, will this be done on site or virtually? As Jennifer mentioned in her talk, the lessons learned were strictly from a virtual perspective due to the pandemic, however, she also mentioned the value that the contractor said and the advantages in conducting face-to-face engagements.

Third, the reassessment period and shelf life; what do we mean by shelf life? For example, if there are certain incentives associated with participating in the program, and I, Alex, am

assessed 6 months ago and Adam is assessed 12 months ago, does Adam's incentives degrade over time? Do we have to consider some type of time since last assessment waiting when connecting to particular incentives?

Also, what would drive reassessment? Is it solely based on time? Would other factors we observe in the postmarket space drive reassessment needs? Would it be based upon demand? Would there be scope considerations based on the reason for reassessment? And also, would any engagement happen between assessments, and what would the parameters be?

Next, the QMM assessment results in an overall score that we've already discussed, which is a function of multiple different scores to assess each different area. But when considering a, quote/unquote, "final rating," what does that mean? We are currently discussing whether to consider additional information in an overall rating, and what would be the pros and the cons for doing so?

Lastly, very important is the communication. How would the scores or ratings be communicated to the necessary stakeholders? As previous speakers have talked about, one of the goals is to reduce this information asymmetry. So how do we best facilitate that? What information would be communicated? Who would communicate it? Obviously, the establishment would be able to communicate their involvement and scores with their business partners, but what role would FDA play in the communication aspects?

Now, to get through potential incentives that we're discussing, and that previous speakers like Adam have already teed up, the first thing that QMM ratings could inform is regulatory flexibility decisions. If ICH Q12 is implemented, and more and more submissions are containing established conditions, it's imperative that we use these data from the assessments to complement the current PQS assessment because one of the key components of a regulatory flexibility decision is the effectiveness of the pharmaceutical quality

system where the EC is being proposed. These data will improve our confidence in an establishment to PQS, and therefore promote more regulatory flexibility.

Inspections. We all know that there are valuable tools the agency has to assure high-quality standards, and our current surveillance selection model and pre-approval process for inspections are risk-based and utilize intelligence and data related to the establishments and the products that they make.

For example, our surveillance site selection model uses inputs like previous inspection history; the type of product the establishment is manufacturing; how long has it been since the last inspection; how many different types of products are being manufactured here; amongst others.

It will be imperative that we utilized QMM scores and ratings to improve our inspection decision algorithms and improve our ability to make more risk-based and data-driven decisions related to inspections both from a pre-approval and

surveillance perspective. But we also understand we have a diverse industry, and not all incentives hold the same weight for all segments. It is our duty to better understand what incentives are truly meaningful for these different industry sectors, and then convert those into actionable things the agency can implement.

What will this look like? What is the FDA's current thinking on assessment framework? Jennifer alluded to our learnings through the pilot, and we are also able to leverage what PDA, ISPE, St. Gallen, and the other partners have been doing, and it became clear on a lot of intersections. This is a draft assessment framework outline that I'm showing you here, which reflects our current thinking on certain practice areas and a few examples, to be clear; just a couple examples of elements within those practice areas.

To start, leadership and its commitment to quality, how do you assess leadership on a QMM assessment? Some of the items we were thinking about and learning from other entities are

management's responsibilities, review, and overall resource management, addressing things like quality planning and looking at how objectives are holistically tied to the management review process and tracked.

Are mechanisms in place to routinely communicate with suppliers, customers, amongst others, as well as internally for staff to bring up issues? Technical excellence and addressing things like data governance and process optimization; do they have systems and governance structures in place that promote this digital framework to enable advanced analytics and predictive modeling or proactive processes? Do they use these data to optimize processes and are they leveraging advanced technologies?

Addressing how advanced the quality system is, things like CAPA activities and change management, but we're not addressing these things in the same way as a routine GMP inspection but looking at the behaviors, habits, and attitudes in managing these activities at the manufacturing

site; utilizing patient-focused priorities; looking at things like is the firm proactive and predictive through signal detection and trending, at implementing, prioritizing, based on risk rather than responding to out-of-control situations? Do they embrace attitudes in their actions throughout the product life cycle?

Looking at employee engagement, do operators and staff understand how the product is used by patients and the overall impact on outcomes? Do they have opportunities for engagement with patients, advocacy groups to better understand impacts? Are employees rewarded and recognized? For example, do they get rewarded for alerting management to potential issues?

Finally, but very important, business continuity and supply chain resilience; how resilient is the establishment? How are they minimizing availability risks? The pandemic has showed us how vital the supply chain is and the need for resiliency. How are establishments performing supply planning? Do they work with

sales and perform market research to better forecast demand? Do they use appropriate statistical methods that build in uncertainty? How is it manufacturing strategy operations connected to that? Again, these are currently in draft and only a subset of the particular elements we were thinking about addressing through QMM assessment.

Next steps. What do we have to do? Well, first is we have to continue our development of a protocol for the QMM assessment, then very important, and as Jennifer talked about the lessons learned from rubric and scoring, we need to develop a rubric for scoring the assessments. This has to consider mathematical considerations, as was previously mentioned, around missing data. How are certain things weighed? If we're going to bring in additional inputs, how are they going to be brought in?

Weighing the pros and cons to those operational considerations and determining the feasibility of the optimum path forward; what will the final ratings look like? What will be and how

will it be communicated to our business partners? Should it consider all the relevant data about the establishment? And finally, coordinating with our government partners and others to enable more informed and data-driven reimbursement and procurement decisions.

With that, I want to thank you, and I will pass it to Dr. Buhse to discuss further.

FDA Presentation - Lucinda Buhse

DR. BUHSE: Thank you, Alex, for giving us that insight.

I am the last speaker here, and I know we've heard a lot about how this program was rooted originally in drug shortage, and what we've done with our pilots, and our research, and some of our engagement activity, and some of our thinking moving forward, as we've just heard from Alex.

I just want to go through -- and we've heard a lot of potential benefits as we've gone through the previous discussion, but I'm just going to try to pull it all together here to kind of show you in one place where benefits could potentially affect

not only us as FDA, but also everybody in the supply chain as outlined by Adam.

I'm going to start with industry because I think they actually, potentially could have the best benefit of this program. In fact, I think I even have more than one slide on benefits to industry. The first thing on this list is ICH Q12. Some call this established conditions. The official title is Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. This is really an opportunity for industry to get regulatory flexibilities on changes they make after approval and allow them to make changes without waiting for us to say yes or no.

This program is already going. We have applications that we're approving, and part of our approval is our need to assess the pharmaceutical quality system of the facilities that are in an application. So already having a rating that potentially links into ICH Q10 and ICH Q12 would really help make these assessments easier, but it also would help industry in the sense that they

would have confidence going into a regulatory flexibility discussion that their facilities are already in really great shape. And as we do the PQS assessment, they would only expect a positive outcome because they've already engaged in our QMM program.

Then, of course, another thing to mention about industry is they're also a purchaser. Many of them purchase supplies, including the API, active pharmaceutical ingredient, from another industry partner. They have contract manufacturing, a huge industry in pharmaceutics, and as they're deciding which contractor to go to, they can decide which one of these manufacturers to go with. If you have a better QMM, more maturity, then potentially, you're not going to be worried about supply chain issues for whatever it is that you're asking this particular manufacturer to do.

So I'm not necessarily going to read everything on these slides, but I did want to point those two out for sure. The last one I think is the point that Adam made, which was very

interesting to us as we did the workshop back in May, which is that the biggest benefit of this program is the ability for industry to do continuous improvement, kind of an outside assessment coming in and telling them this looks really great, but potentially here's an area where you might want to put a little bit more effort, et cetera. And it's always valuable to get feedback, no matter what industry you are or what it is that you're trying to do.

Of course, recalls is another area that I wanted to make sure I mentioned because that is not good for corporate image. Some of you must be watching the Jeopardy Tournament of Champions. Last night, one of the answers was, what is infant formula? So you can imagine what the question was. But the question was about a manufacturing facility that had to shut down a site that resulted in infant formula shortage. I'll just say that everybody seemed to know the answer to that, and I know that people don't want their name on Jeopardy in this kind of a context. So hopefully that would

be another way to prevent that from happening.

I think Dr. Kopcha talked about lost leaders, versus lagging indicators, versus losing indicators. A QMM can give you a really leading vision on where you're going with your efficiencies and your cost savings as well. I talked about the supply chain, your own supply chain as a manufacturer, and also then your ability to have the insight and talk about your supply chain when you're talking to the purchasers that are buying your own product as well.

The last two are kind of interesting because not only in this pilot program that we did with QMM, but we've done pilot programs of quality metrics. We've done other pilot programs with site engagement where we've reached out and talked to industry, and it's not in, I'm going to say, a compliance way or GMP way, which people are used to interacting with us, either in that way or when we're talking to you about your application.

In both those cases, we're usually telling you about things that you're doing wrong, and in

our quality metrics pilot, in this QMM pilot, we really had a great chance to talk with industry in a back-and-forth dialogue way, and industry really fed back to us -- and all of these programs that we've done in a pilot way -- that they really liked that. They really liked hearing from us and really liked interacting with us in this, I would call, more positive way, getting positive performance acknowledged from us, which is not something they would get necessarily from an inspection when we walk in the door.

So I think that that's something that we've heard, and it's good to hear that we can have good dialogue back and forth. We think this QMM program is another great opportunity for us to have those kinds of dialogues.

Purchasers and payors, I think the success of this program is really getting some of these purchasers and payors on board. As Adam said, a lot of them already do kind of their own, I would say, rating of the pharmaceutical manufacturers that they're buying from, and they're using their

own either surveys with the people that they're doing interactions with or they're pulling data off of our website.

Potentially, if we do this ourselves and we can give them even more information that they can use in these decisions, then hopefully that will drive, as Alex talked about, other industries that might drive the opportunity to have quality be valued by purchasers and payors. It doesn't have to be potentially the cheapest price, but maybe it's a good value, which includes the value of knowing that you're going to get the supply you need and when you need it. Of course, then that would hopefully lead to less drug shortages as well, which is good for all.

I think a study done by Vizient in 2018 showed that 8.6 million labor hours, $359 million was the cost of shortages for hospitals in a study that they did. So you can imagine the value of not having a drug shortage or at least reducing them as much as we can. Sixty percent are due to quality issues. If we can really drive that down, that's

really going to reduce the cost of shortage across the board.

Healthcare professionals, and pharmacies as well, I think also hear a lot of complaints from their patients when they can't get the drugs they need. I think a couple of years ago, two of the drugs my parents were taking were on shortage. They're in their 80s, so they have quite a pharmaceutical array that they take every day. And every time I called my mom, I had to hear about the drugs that were on shortage for her.

So I'm sure the healthcare professionals and the pharmacies also are getting the same litany of complaints from their patients, so anything we can do to reduce drug shortages is only going to reduce the noise that healthcare professionals and pharmacies have to hear as well. Then as they prescribe drugs, they can hopefully have more confidence in the supply that they are prescribing or dispensing to their patients.

Pharmacies themselves, a lot of them are also buyers with increased supply chain

transparency. For something like a QMM program, they can be assured that they'll have the drugs they need when they need them, and be able to meet that demand, and not have their patients at their windows complaining about the lack of drugs that they need. Then also, as part of that, a study I mentioned earlier, 38 percent of hospitals reported medication errors that related to shortage as well. So hopefully by reducing shortage, we can also have an impact on medication errors.

I've talked a lot about the patients already as I talked about physicians and pharmacies as well. But as you can hear from my own parents, patients do not like it when their drugs are on back order. If they have to switch to a new drug, often they don't take them or they're uncomfortable taking them. So really, the more we can do to make them feel confident in the drug supply can only be to everybody's benefit.

Obviously, recalls have a huge impact on consumers as well. They don't know what to do. Should they stop taking their drug right away?

Often that can have very bad consequences, so reducing this uncertainty will be a great benefit to patients and consumers.

Obviously, I just wanted to show this because this was right back there where we started this whole discussion at the beginning of the day, but our goal is for patients to have greater confidence in their next dose of medicine and not have to worry about it being recalled later, and not have to worry about whether they'll be able to refill it the next time they go to the pharmacy.

Let's talk a little bit about ourselves, as well here, in the benefits to FDA. Alex mentioned some of this as well. The more information we might have about a site, the more we can feed that into our risk assessment. Our current information is all about meeting the current regulations. And we've talked about above-the-bar behavior, but we have a lot of pharmaceutical industry that really are trying to improve and do continuous improvement. We've seen some fairly high QMM scores in our pilots, so how do we reward them?

How can we be informed about who's doing what? If we know that, we can help use that to feed into our current risk assessment systems.

In addition to that, we're still learning about what causes supply disruption. We did the report back in 2019 and looked at a lot of things, but there's a lot more to learn. Certainly with this pandemic, we've learned also a lot about the supply chain and what are all the different factors that go into making a pharmaceutical product. It's not just about the API and the finished dose. There's everything else that goes into it.

If we have confidence in a pharmaceutical manufacturer's ability to monitor and know its own supply chain for everything else, all those components and excipients, et cetera, that's really going to give us better information and better confidence in supply as well.

Then inspection, I know people don't like inspections, but we want them to be as most effective as possible. If we're walking into a facility and we know something about that facility

ahead of time because of an assessment that might have been done, potentially we can just focus on one or two areas while we're there, and be in and out faster, which I think everyone would love to see as well.

I think Alex talked about a lot of these surveillance tools, our site selection model; how do we allocate our resources when it comes to surveillance tools? There are a lot of sites that we oversee, a lot of products that we oversee, thousands and thousands; and if we can really be focused on where the issues are, then hopefully that's going to be better for everybody.

Finally, for FDA, additional information, as I said, for quantitative and objective insight into these facilities as well, move us more towards performance-based regulation, and be able to change the balance between us as a regulator and the pharmaceutical industry as well.

Then, of course, the last two are, once again, about streamlining post-approval changes. As an agency, we spend a lot of time approving

supplements and changes to an initially approved drug. That's not surprising in the sense that when a drug is first approved, there's not a lot of experience manufacturing it. The facility's going to learn a lot as they start to make this drug, and they're going to learn that there are better ways of doing it.

We want to really give them the opportunity and ability to make improvements that improve not only potentially the cost of making the drug, and efficiency of making the drug, but that also leaves the facility open to maybe make other drugs that might be needed by the marketplace if they can improve the way they make drug A, et cetera. So there are a lot of benefits, as I said, of being able to change that balance when it comes to post-approval changes and a great benefit to all.

So I guess in closing, I talked about all of these different segments. We think quality management maturity is important to all, and if we can really drive the industry to think about this and start moving toward it, we think it could

potentially improve all of these elements in the supply chain, including reputation, keeping yourself off of Jeopardy, I would say, when necessary, and only be there for what I would call positive questions.

So that is the end of my talk. I'm going to turn it back to Ken, I believe.

DR. MORRIS: Thanks, Cindy.

Actually, Rhea has one item to cover first, and then back to me.

Rhea?

MS. BHATT: Thank you, Dr. Morris, and thank you Dr. Buhse, and thank you to all of the FDA presenters.

Before we move to break, I'd like to ask Dr. Mark Rogge to please introduce himself.

Dr. Rogge, would you be able to state your name and affiliation?

DR. ROGGE: Good morning. Yes. Thank you. My name is Mark Rogge. I'm with Sail Bio, and also on the faculty at the University of Florida.

MS. BHATT: Thank you, Dr. Rogge.

Over to you, Dr. Morris.

DR. MORRIS: Thank you, Rhea, and thanks to the presenters.

We'll now take a quick 10-minute break. Panel members, please remember there should be no chatting or discussion of the meeting topics with the other panel members during the break. It's 8:06 now, so we'll reconvene at about 8:15 or 16, to be accurate, and we'll then take up clarifying questions. Thank you.

(Whereupon, at 11:06 a.m., a recess was taken.)

Clarifying Questions to the Presenters

DR. MORRIS: Hello, everyone. We should be back from break now.

At this point, we will now take clarifying questions for FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When you're acknowledged, please remember to state your name for the record before you speak, and if

possible, direct your questions to a specific presenter. If you wish a specific slide to be displayed, please let us know the slide number, if you have it.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of any follow-up question with, "That's all for my questions," so we can move on to the next panel member.

At this point, we'll take questions from the panel. I might start by way of example. My name is Kenneth Morris, and this question is really to Jennifer, I guess -- or, sorry, Adam, I should say; and not necessarily slide 67, but certainly slide 67 discusses it.

Is my understanding correct that the QMM concept is really about anticipating availability as opposed to an individual product's quality issue? Is that a correct statement?

DR. FISHER: This is Adam Fisher. I'm going back to slide 67. This is where I talked about how transparency is critical. I think this is an

important message, and this goes back to what Dr. Kopcha talked about in his earlier remarks; that pharmaceutical quality is made up of this array of product quality, process quality, and then quality management.

I think it's very important when we talk about QMM ratings that we do not interpret them to be ratings of the quality of the product because that is not what they are. They're about ratings of the quality management of the establishment, and that influences, as you heard from Alex, the quality of the supply chain and the reliability of supply.

So I think you characterized it pretty correctly. The QMM rating is about the establishment and not about the quality of the product.

DR. MORRIS: Okay. Thank you.

Next, I believe Dr. Zamboni has a question.

DR. ZAMBONI: Yes. This is a Bill Zamboni. Thank you for those presentations. My question is related to has a QMM program ever been implemented

for other healthcare products or other products in general? And if so, did that actually impact supply chain issues, and were their benefits to the manufacturers? Thank you.

DR. FISHER: Yes. That maybe could have been directed to a Cindy Buhse as somebody to answer that. Sorry.

MR. VIEHMANN: Cindy, this is Alex --

DR. BUHSE: Sorry. I had to do all the unmuting.

Are you good, Alex?

MR. VIEHMANN: Yes. Cindy, I can start -- this is Alex Viehmann -- and you can go from there if I miss anything. But thank you for the question. It's a great question.

Within the healthcare industry, one of the very relevant cases that we've learned all of this -- actually, internally to FDA and CDRH's Case for Quality program -- is now the mechanics work a little bit different. They work with a third party, again, CMMI, to do these types of assessments, but the overall model is very, very

similar.

They're looking at these advanced quality management practices, promoting continual improvement, and through that, the participating establishments get certain incentives that have turned out to be great, number one, from an overall business, and number two, from an economic perspective; things like, again, considerations into reduced inspections, things like faster turnaround times, and post-approval changes.

So yes, that is the one very relevant business model that we've been able to learn from, is CDRH's Case for Quality program.

DR. BUHSE: Thanks, Alex.

Yes, that was the one I was going to bring up as well, and we are learning from that. Devices obviously have different regulations than drugs, so the ability for different incentives is very different. The model that they use may not be one that we want to use in terms of the third party administering it, including cost to industry. So we're considering all that as we move forward with

our own program, but we had positive feedback from industry about the device program.

DR. ZAMBONI: Great. Thank you very much.

DR. MORRIS: Thank you, guys.

Next, Dr. Kraft has a question.

DR. KRAFT: This is Walter Kraft. This is not directed at any particular speaker, but one of the nominal goals of QMM is addressing drug shortages, which would mean broadening the base of manufacturers from 1 to greater than 1.

Has there been any thought about quantifying the burden on manufacturers, with the concern about potentially concentrating rather than expanding the numbers? In a similar vein, is there thought that this would disadvantage old versus new entrants into the market? Thank you.

DR. MORRIS: Yes. Cindy, maybe you can respond or turn it over?

DR. MAGUIRE: Yes. This is Jennifer, actually. If you can hear me ok, I can go ahead and start, and then I'd invite other FDA folks if they want to join in.

I mean, certainly supply chain redundancy in terms of having multiple manufacturers for some of these products that chronically go into shortage would be beneficial, but that's not only the solution. Quality management maturity would also allow one site that manufactures the product to take a look at their supply chain and relationships with the supplier and build redundancy into their own supply chain; so that if something happened to one of their suppliers, they would have the option to quickly change over to another supplier.

So I wouldn't say it's necessarily encouraging multiple manufacturers -- that that's not the only solution or benefit of quality management maturity -- but I would invite other FDA folks, if you want to --

MR. VIEHMANN: Yes. Jennifer, this is Alex, if it's ok if I also add on to some of the things that you say, and thank you for the question.

I think the latter half of the question related to maybe disincentivizing older versus newer, and that's really not what we're trying to

do. The core concepts, as discussed with quality management maturity, are applicable to old/new sites. They're really agnostic to facility age or the age of the product.

But we also understand, as we talked about, that when it comes to increasing supply chain resiliency, and when we talk about, as Jennifer just mentioned, qualifying additional suppliers, caring and being confident in your stock and inventory, these things come at a cost. However, we also recognize that these costs outweigh the potential downstream impacts of not having these resiliency measures in place. And that's really what we're trying to do here, is to measure and calibrate one of the areas, how resilient, and what are the business continuity measures that establishments have in place to ensure reliable supply.

However, we also understand that there are certain things that are completely out of the establishment's control: the Suez Canal gets blocked; workers go on strike at the LA port.

Obviously, there are things that -- but this speaks to more and more about the resiliency of the supply chain with the unknown implications in the market.

DR. BUHSE: Yes. This is Cindy Buhse. I only talked about old versus new manufacturers, but I think in our pilot, we really had a wide variety of facilities engaged with us, some of them very sophisticated, some of them just entering the U.S. market and just starting to understand our regulations, and I think everybody learned something from being in that pilot.

So to your point about older manufacturers, being part of this program may give them some of the leverage they need to convince their owners, or whoever is making the financial decisions, that maybe it's time to invest in their plants, et cetera.

So I think that there can be benefits for older or newer facilities. And for facilities just entering the marketplace here in the U.S., as well as ones that have been here a long time, I think there's something to be had. I think all of the

different elements that might go into a QMM assessment that Alex showed, shows there's a lot of different areas, and that it would be great to get the outside feedback and determine where you really need to focus your improvement efforts. And if you have limited resources, maybe it's where you need to focus your resources in terms of making yourself a more reliable supplier.

DR. MORRIS: Thank you.

Any follow-up, Dr. Kraft?

DR. KRAFT: No. Thank you. Those are excellent.

DR. MORRIS: Thank you.

I believe Dr. Richmond is next.

DR. RICHMOND: Hi. Thank you, and it's a pleasure to hear such passion around a program. It sounds like many people there are on board. I have a few questions, but a question that intrigues me and, to some extent, worries me a little bit is more about the C ratings. Even though there are other programs that in the past have done maturity ratings on companies, typically they aren't in a

position to another similar rating system.

Now, I know that this is supposed to measure capabilities and the other rating system, which is the GMP system, is supposed to measure safety and efficacy, or safety primarily, but what happens if, for example, a company gets an A rating from you and fails an audit? Or if it's a voluntary program, what happens if those most likely to fail an audit don't even apply for the voluntary program?

I don't have anybody I want to direct that specifically to.

DR. MORRIS: I don't know -- Alex, is this your area to respond to, or somebody else?

MR. VIEHMANN: Thanks, Ken, and thank you for the question. This is Alex. I can start, and others can chime in. Related to the question, it sounds like the question's related to what will happen if the ratings conflict with CGMP audit outcomes --

DR. RICHMOND: Right.

MR. VIEHMANN: -- and how will that do?

Well, I think it is possible that we could see this, but as we develop more and more our measurement system to better understand what QMM is, and how it is, and how you measure it, I think the likelihood that you would have a very robust rating from QMM and then in three months if you were to be inspected have an OAI inspection, it's probably going to be very, very low.

But if these things do happen, then I think that's a reflection on potentially how we're measuring QMM, and we would need to tune our system. But there are things that we are thinking about right now, and putting in plans, and thinking about contingency plans because we know that would be a serious concern, is if a facility has a very robust QMM rating, and then three months later they get inspected and have an OAI inspection.

Hopefully that addressed a little bit of your question, but I invite others to respond as well.

DR. MAGUIRE: Yes. This is Jennifer. I can add on to that, and thank you for the question. It

is definitely something that we're considering, and I do agree with Alex.

I think during implementation of this program, there will be a learning period, but I think the occurrence of that would be quite rare. But if it does happen, if we're finding that we're assessing sites highly in terms of maturity, and then their GMP inspection is non-compliant, yes, I think that would trigger us to take a look at our tool and make sure that the sensitivity is there, and we're asking the questions appropriately.

So we are having these questions internally, and it ties into figuring out what is the shelf life of the QMM assessment and how do we handle it when we've granted incentives. Then we have additional information about a site that would cause us to consider if they're still mature and performing the way that we would want them to.

The other part of your question was touching on disincentivizing sites that might be a bit lagging relative to their industry peers of joining the program. We were carefully considering that,

as well, as we consider how to implement this program because we do recognize that there are sites that will likely score high and have high maturity. And while that's wonderful, I think we can be most influential in driving behaviors and getting sites that are actually a bit lower on the spectrum to a better place.

So we do want to be very mindful when we implement a program that we are not inadvertently offering incentives or sharing information publicly that would disincentivize sites from participating. So that's something that's at the front of our minds at this point.

MR. VIEHMANN: Jennifer, this is Alex.

To also the committee's question, I think the other thing we're really focused on is not driving bad behaviors by setting up this program. So if we do a quality management maturity assessment, we don't want to promote bad behaviors of then companies feeling like they're going to be severely penalized in a program if they submit a field alert report or if they recall because these

might be indicators of a very robust quality system that's detecting issues quickly, and being proactive, and addressing them, and putting improper mechanisms in place to correct it and prevent it from happening again.

So we want to promote those behaviors of being transparent with the agency as well. So it will require additional context, too, like is this actually a robust system that's being proactive or is it an indicator of potentially the quality system degrading since the last assessment? So these types of considerations will have to be thought through because the state of quality is always evolving, and as a surveillance organization, we're constantly receiving information related to the sites and products.

DR. MORRIS: Is that sufficient, Dr. Richmond?

DR. RICHMOND: Yes, I think so. Thank you for your help.

DR. MORRIS: I think Dr. Carrico is next, if you would like to weigh in.

DR. CARRICO: Yes. Thank you. This is Jeff Carrico with the Dana-Farber Cancer Institute. I suppose the question could be for Dr. Kopcha, but whoever would like to step in and take it.

In order to fully implement a successful QMM program, it would take investments by FDA, and personnel, and additional support of the program. No one can fully tell the funding future. Does it appear there's an appetite to support the funding required for a program of this nature? Thank you.

(Pause.)

DR. MORRIS: I'm not sure -- Dr. Kopcha?

Mike, are you on?

DR. KOPCHA: Yes. I'm sorry.

Can you all hear me?

DR. MORRIS: Yes. You're fine now. Thanks.

DR. KOPCHA: Okay. Thanks. I had to unmute on a couple things.

Yes, there is definitely agency support for this. I guess the question is, for success of QMM, there will need to be an investment, and do we have that appetite? So the appetite is yes. The

details of that, depending upon what the final program looks like, still need to be worked out.

Oh. The other thing I did want to mention as well is based on the White House report, there is definitely, even at that level, an appetite for this type of a program being put in place. So again, once we're defining in more detail, then we can determine what that cost may look like and where that funding may come from.

DR. MORRIS: Is there any follow-up, Dr. Carrico?

DR. CARRICO: No. Excellent point. Thank you.

DR. KOPCHA: Thank you.

DR. MORRIS: Thank you.

I believe next is Dr. Sutaria.

DR. SUTARIA: Thank you. First of all, thank you so much for a great presentation this morning and really great insight.

One of the questions I had was it was mentioned that the ratings are based on the manufacturing sites and not the products

themselves. And my question would be that if the manufacturing site or facility is the one that has the rating, one of the things asked was that a provider or a purchaser could then utilize a decision-making process based on that QMM rating to purchase the product, and mentioning earlier that if there's an oversight for 7,000 facilities or it's 170,000 finished dosage forms and presentations, what visibility or insights would the providers have available to make those decisions, based on the rating that's provided at a manufacturing or a facility's site and correlate that to a product?

DR. MORRIS: Jennifer, maybe this is a topic for you, but if not, please identify someone.

DR. FISHER: This is Adam Fisher.

DR. MORRIS: Or Adam.

(Crosstalk.)

DR. FISHER: I'm happy to -- thank you, because I think I did talk about this somewhat in my presentation on some of the key challenges as we build the program, and the idea that we may have to

rely on purchasers to understand the supply chain for the product that they purchase. The reality is that we may not be able to disclose specific information about the drug product's supply chain, and we might have to rely on purchasers to procure this information during the bidding or negotiation process.

I think I've mentioned that based on our engagements with purchasers, we have found that most of them require supply chain site information already as part of their decision-making process. The information that they use is just not optimized, so they're making decisions based on geographical location sometimes, or maybe on, again, some public reports like FDA Form 483s and whatnot. We think that more -- as Mike put it -- of this information are what we would call these leading indicators to help them make better decisions.

I'm not sure if someone else had something that they wanted to share there.

DR. MAGUIRE: Yes. I can take a stab at

this, Adam, and then, obviously, if anyone else wants to also jump in. This is Jennifer.

Yes. You raise an interesting point because we do, as Adam was saying, have to be careful with proprietary and company confidential information, but it's possible that the construct might look like the sites participate voluntarily in the agency's program. We give them a rating, and then it would be up to them to disclose their rating in those supply chain relationships between the sites and products with the purchasers and other stakeholders that they engage with during the contracting process.

DR. SUTARIA: Thank you.

DR. MORRIS: I think Dr. Venkateshwaran, you're next.

DR. VENKATESHWARAN: Hi. This is T.G. Venkateshwaran from Takeda. Many thanks for the overview on QMM. It was very, very interesting.

I'm actually going to build on a thread that you're seeing. In a number of the presentations, it was alluded to there being three levels for a

site, one at the product level, one at the manufacturing process level, and then QMM, which is at the site level. In another place, we also alluded to regulatory flexibility and use of Q12 and established conditions.

Established conditions, typically when you're establishing it for a product, involve multiple sites in there. So could you help me understand how one would use it when we have multiple sites, which may have different QMM ratings, and how do you kind of bring the two together? Has the agency thought through that?

MR. VIEHMANN: This is Alex, and a great question. The current construct, the current state of established conditions is you're exactly right. When we get the PLC in and the established conditions, we have multiple sites that are referenced as part of the submission that are impacted by these established conditions, and therefore may be requesting some regulatory flexibility in reporting categories or things that are non-ECs.

Our current model is that a PQS assessment is done for all of those facilities, and one of the things that we recognize is that we have a blind spot when doing these PQS assessments because if you look at things like ICH Q10, Q9, and these principles, or robust [indiscernible], is that we may not typically cover above-the-bar behaviors and above-the-bar indicators, as defined in these constructs of an effective PQS, so our level of uncertainty is high.

So what we would like to do is facilitate that gap and fill that gap with information from a QMM program because it will be addressing things like when we talk about change management, not that they just have procedures in place and have an effective change management, but asking questions like do they have retrospective evaluation criteria or are they using multidisciplinary teams to evaluate risk; these very peculiar questions that give us more insight into the effectiveness of their change management program to then better promote and provide us confidence in, yes, this

site has an effective PQS, and therefore we're comfortable with providing them regulatory flexibility.

So others want to join in, but hopefully that answered the question.

MS. BOAM: Hi, Alex. This is Ashley Boam with FDA. I wanted to just add to that very briefly for those on the committee who may not be as familiar with the concept of established conditions raised in the question.

Essentially, an applicant for a particular product requests a certain amount of regulatory flexibility in the area of making post-approval changes based on two things in our assessment. Part of it is the scientific knowledge and understanding that the firm has and is able to demonstrate about their particular product and the manufacturing process that they will be using, and the second piece is what Alex just spoke about in terms of the effectiveness of a pharmaceutical quality system at those manufacturing establishments where the product will be made.

So to your question, as you heard from Alex, we will look at the facilities that are identified in the application for that particular product, look at the information we have about the PQS, which would certainly be much enhanced by the availability of QMM information, and we use those two pieces together to then make a decision about whether the amount of flexibility requested by the applicant is acceptable and can be approved. Thank you.

DR. MORRIS: So if that's sufficient, we'll go on. I'm trying to let everybody who's got a question get in, and then come back and cycle around to those who've already asked questions. I hope that's fine.

Next would be Dr. Lee.

DR. LEE: Thank you. This is Kelvin Lee. I have a question. I think it can be for Dr. Fisher, but it can be actually for any of the agency staff. And I'll preface the question by first acknowledging I'm aware this is a CDER Center for Drugs advisory committee meeting and understand the

sphere of responsibility there.

I'm curious. As part of the stakeholder engagement, and outreach, and communications, some number of the establishment that would potentially be rated under the proposed program would also be making products that would be regulated under the oversight of Center for Biologics.

So I'm curious, as there has been stakeholder engagement, the extent to which there has been companies that have had questions, or perhaps even confusion, or maybe wanted clarification on how a CDER potential rating might impact or benefit CBER-related products, and to what extent has there been those kinds of questions that have come up, and does this just reinforce, obviously, the need for clear communication going forward? Thank you very much.

DR. FISHER: Hi. This is Adam Fisher. Acknowledging the sphere of responsibility here, I can't speak for CBER. One thing that I will say, though, is that, as was mentioned a few questions back, CDRH already had their Case for Quality

program, and certainly there are combination products that overlap the CDRH and CDER jurisdictions, so we work effectively with them now.

So I believe in the future that cross-center collaboration would look similar to that. But in terms of CBER's direct engagement in the program, I can't comment on that directly, though I do appreciate the question.

DR. LEE: Thank you.

DR. MORRIS: Next would be Dr. Finestone.

DR. FINESTONE: Yes. Thank you. Can you hear me?

DR. MORRIS: Yes, we can.

DR. FINESTONE: This is probably a naive question, and I apologize up front for asking it, but I just had a concern. If you have a site or an entity that is producing above the bar and you have one that's not, my assumption is that you as an agency would go to the site that's below the bar and perhaps give them some suggestions from the site -- or not from the site, but how the site is

performing well; that they could utilize those in there.

Is there some concern from the sites that are producing above the bar, that by sharing that kind of information or [inaudible - low volume] a below-the-bar producer, that you would be [inaudible] assisting someone as a competitor.

DR. MORRIS: I'm not sure who -- go ahead.

DR. MAGUIRE: I can start.

DR. MORRIS: I was going to pick on you.

DR. MAGUIRE: This is Jennifer.

From the agency's perspective, we have no intention of sharing best practice and information about one site with another site, so we would not do that. But I will say that from my interactions with PDA, and ISPE, and PhRMA, and AAM, and other trade associations, the members of those groups do tend to share and learn from each other, is what I've observed. So there might be an opportunity there for best practices to be shared based on different companies' experience with our QMM program, but the agency would not disclose

information from one site to another to help them grow.

But I will say also that each site that goes through a QMM assessment, regardless of where they score in terms of their rating, they will get a report after the assessment that identifies continual improvement opportunities, so they won't be left in a lurch trying to figure out how to improve by themselves. They will get recommendations and identification of the areas where they're a little bit weaker, along with the areas where they're a little bit stronger.

I hope that helps address your question a little bit, and then open it up to others if they want to add on.

DR. FINESTONE: Yes. I wasn't intimating that you would assist them or you would share proprietary information, but I guess I was asking is there apprehension on the part of those that have performed well. But I thank you for clarifying that.

DR. MORRIS: Very good.

Next, I believe Dr. Zamboni has a question.

DR. ZAMBONI: Hi. This is Bill Zamboni. This is also another question about the scoring, so maybe Dr. Maguire or Dr. Viehmann would be the one to answer this.

My question, obviously, this is a new program, and you may initially want to prevent the bad image of low scores, so I'm wondering if there's a way to implement a pre-testing program, where you go and give the site a pre-test, you give them feedback, and they then prepare for the re-test or final test, and then give them a score, rather than -- I think maybe the sites may be more open to that so that they can get some feedback before getting a final score. Thank you.

DR. MORRIS: I'm not sure who is best to address that, but --

(Crosstalk.)

MR. VIEHMANN: Ken, this is Alex.

DR. MORRIS: Yes?

MR. VIEHMANN: Can you hear me ok? I can take the first stab.

DR. MORRIS: That's just fine. Sure.

MR. VIEHMANN: Thank you, Dr. Zamboni, for the question.

Your question really gets into overall implementation and are we going to stage it, and what will those stages look like. Those are currently under consideration, and learning about the different models used in the pilot programs, as well as some of these other learnings with PDA and others around, and would it also incorporate things like a self-assessment, then followed by on-site engagement and a facilitated discussion. Would the stage approach look like you said, to start with kind of this predetermination, provide feedback, and then follow up with a a more intimate engagement?

I think all those are under consideration and trying to weigh the pros and cons of them, but also considering the budget, the logistical, the demand, and all these other considerations. But it's definitely something that we're talking about and trying to better leverage what we learned

through the pilots, as well as what CDRH is learning from PDA and these other organizations around the overall model for how you do this, whether it be a self-assessment followed by something else; whether it be, like you said, start small and then go into more intimate details.

So those are all under consideration at this point in time, but I invite others if they have additional thoughts.

DR. MAGUIRE: Thanks, Alex. I agree with with what you said. Just to reiterate what I said previously, very aware that we don't want to set up a program and inadvertently disincentivize voluntary participation. So we do intend to continue engaging with industry around this idea of information that could be made public because I know there are a lot of thoughts on that point.

But it's something that we actually would also welcome the advisory committee's recommendations on if you have thoughts about how we might incentivize people to participate in the voluntary program and how we might make sure that

we don't disincentivize the sites that might be poor performers because we really want to drive their behaviors in a better direction. So it is a topic that we would welcome any insights that you may have.

DR. ZAMBONI: Great. Thank you.

DR. MORRIS: Actually, Dr. Sutaria, do you have a question or is your hand still up from your previous question?

DR. SUTARIA: I apologize. I'll take my hand down. Thank you.

DR. MORRIS: Okay. No problem. No problem.

Dr. Kraft, I believe you're next.

DR. KRAFT: This is Walter Kraft. I can speak from a local health system that the shortages are very disruptive and that the health system would clearly pay a premium for manufacturers or products that would be less likely to go into shortage, and presumably quality measure would be a predictor; not 100 percent, as has been pointed out, but a predictor.

I think the challenge is that this market

signal may not funnel back because there's a distributor between that, and it's not linked to a specific drug product but a site. So the question, and I think probably best addressed by Dr. Viehmann, is with the goal of reducing information asymmetry to allow this market signal, is there thought of maybe bringing transparency to specific drug lots to link them to specific sites? Thank you.

MR. VIEHMANN: This is Alex. Thank you, Dr. Kraft, for the question. I think it's very relevant, and it's something that we hear a lot about, the first part of your question related to if QMM ratings are an establishment, but people take products, how would that look?

Through our engagement process with purchasers, and distributors, and these other entities that we typically haven't discussed with, we've learned, in very intimate details, their due diligence process, and they do require or request supply chain information: how many API suppliers do you have; in certain cases, metrics; in certain

cases, looking at what's available through the FDA website around warning letters, inspection outcomes, and things like that.

So we know that this information will complement that in their decision making, and we've heard that, but to the latter half of your question around linking it directly to a specific lot, and that lot at a manufacturing site, it's a great question, but it's something we would need to consider around scope, within scope of the current QMM vision. So it's definitely a good point that we would have to take back and consider within the realm of the scope.

But related to the product and site differentiation, these distributors and purchasers, what we've learned through them is that they do have a due diligence process at the site level to better understand the supply chain and better understand the performance. But again, it's limited, so we're trying to better inform that.

DR. FISHER: This is Adam. I --

DR. MAGUIRE: Yes --

DR. FISHER: -- I'm sorry.

DR. MAGUIRE: I'll go first, and then you can also add on.

I would just say thank you for that question. I think the tricky thing, though, is we need to be very, very careful not to conflate quality management maturity, which is done at the site level and describes best practices and behaviors of the site, with the public understanding this to be about the quality of the product because from the agency's perspective, every lot that's released is supposed to conform to safety, efficacy, and quality standards. So if we were to start differentiating between lots, that could open up the perception that we're inferring one lot would be of higher quality than another.

So we need to be very mindful and careful that everybody understands that this is about the site and the site's behavior and performance, and not a question of the quality of the product.

Adam, please go ahead of you had something else.

DR. FISHER: Right. That's a key point, Jennifer. I only wanted to add a point that I'd made during my talk that these healthcare systems, the healthcare providers, the pharmacists, may need to advocate to the purchasers and to the distributors to use QMM ratings in their decision making because those stakeholders are the ones that feel the biggest impact of drug shortage. So they would really need to be advocates for using this in decision making wherever it happens along chain. Thank you.

DR. KRAFT: Okay. Thank you.

DR. MORRIS: Thank you.

I think there was another question, and I just lost you, Dr. Richmond, I believe.

DR. RICHMOND: Sure. Thank you very much.

I'm actually circling back to another aspect of the question of cost and budget, and [indiscernible]. My sense is that this will be a voluntary program; correct me if I'm wrong. If it were a mandatory program, the back of the envelope would suggest you need a thousand-plus evaluators,

which would be a pretty big workforce because it would be a bigger program as your current inspectional program.

But even notwithstanding a voluntary program, one of the things that you've pointed out is the level of capability of the assessors. Currently, there is a very big timeline [indiscernible] shortage in this area, and notified bodies are sort of groaning under the inability to meet the needs on the device side because of the inability to staff the notified bodies, and the regulators sort of didn't really understand that, I think, when they they put their timelines in place.

Do you have concerns about your ability, or your contractors' ability, to get the kind of, really, capable people who will keep you from having constant grievances about the ratings that companies might have received or even litigation over those ratings? Thank you.

MS. BOAM: Hi. This is Ashley Boam with FDA. I can start and invite my colleagues to add on. Thank you for the question.

For those who may not be familiar, the notified bodies system in Europe for medical devices is a system in which third parties provide assessments of medical device applications as part of gaining approval to go to market. I do think this is a bit different, but I take the sense of your question, which is noting appropriately that we want to make sure that whoever's doing these assessments are well trained and have a good understanding of what we're looking for here. You heard Dr. Maguire talk about having the ability and wherewithal to ask open-ended follow-up questions. Obviously, we'll need to have folks with the right training to do that.

So, yes. Part of our implementation would be to ensure that we have appropriate training and that we have folks with the right types of capabilities, not only technical but also in their engagement with firms on the ground. And that will take some time to build, but I think we are looking to that as a factor for how we would initiate implementation of the program once established.

I don't know, Jennifer, if you would like to add anything else, but thank you for the question.

DR. MAGUIRE: Yes. No, I think you covered it well, Ashley. The only thing I might add is that it's really no different than our colleagues in the Office of Regulatory Affairs having a trained workforce that's capable of executing surveillance inspections each fiscal year, so they've built those skills up over time and are adequately trained for the intended audits that they perform.

So it's the same thing here. We would need to build up over time and make sure that our staff, or the contractor, depending on how we go in the future, is adequately trained in executing these assessments.

DR. RICHMOND: Thank you.

DR. MORRIS: Alright.

We have Dr. Kagan, who's next.

DR. KAGAN: Thank you. Leonid Kagan, and I want to thank all the presenters for an informative presentation today. My question is mainly for

clarification of the main question asked from the committee, the QMM program, should it be established or not?

Given the multiple challenges presented, what is the final form of this QMM program that is going to be established? What are the main things that will go in it? Is it something that is a clear way to implement questions that were asked in pilots? How do you see this implementation to be? Thank you.

MR. VIEHMANN: This is Alex, and hopefully you can hear me.

DR. KAGAN: Yes.

MR. VIEHMANN: I think the crux of the question gets down to implementation considerations. What are some of the main themes that will be addressed on these assessments? I think there are considerations and challenges we're going to need to consider when implementing this.

We spoke about when it comes to the budget considerations, logistical, and the mathematical communication piece, as others have brought up, how

will this be communicated? These are certain things that we are weighing -- pros, cons, feasibility -- and we would love to hear the committee's thoughts around what would be the optimum way for implementation related to these operational considerations.

Then the themes -- if I understood the question correctly, and I apologize if I didn't -- we've looked at what the contractors came up with through the pilot, and then we did a cross-sectional comparison across what PDA, ISPE, and all these industry associations are doing, St. Gallen, Dun & Bradstreet, and we identified a lot of intersection and things like how to measure management's commitment to quality; how to measure technical excellence; how to measure employee engagement; supply chain resiliency and business continuity; and advanced indicators of PQS.

That's really where we're starting the focus and the development because we've recognized -- and we don't want to recreate the wheel. There's been a lot of work and research done over the years in

this space, and we really want to leverage that.

Hopefully, that answers the question, Ken.

DR. MORRIS: Yes. And I think, Dr. Kagan, you could clarify, but I thought you were saying what would be the first steps. But correct me if I'm wrong, and otherwise please let Alex know.

DR. KAGAN: Yes. This is Leonid Kagan. Yes. I think my question was, what will be the first steps and what will be the final form of the program? The question is should we establish this program, basically? Should we still keep working on this and redefine it, and keep talking to each other? Thank you.

MR. VIEHMANN: I apologize. I think the first steps is to really continue and finalize the assessment protocol, the scoring rubric, how this will be assessed, the different elements, and really throughout that process, parallels that continue to get stakeholder feedback, understanding that we have a very diverse industry and not all incentives hold the same weight for the different sectors.

So we need to better understand FDA incentives, but also the end goal here is to promote more supply chain resiliency; put more transparency into the marketplace; drive continual improvement and promote continual improvement within the industry to obtain all the benefits that Dr. Buhse spoke about across all the stakeholders. But what the final form will look like, I think that's it's going to evolve as we continue the development work, and as we continue our engagement with stakeholders, and continue learning from these parallel efforts.

DR. MORRIS: Thank you, Dr. Kagan.

DR. KAGAN: Thank you.

DR. MORRIS: Dr. Sutaria?

DR. SUTARIA: Yes. Thank you.

This is Mittal Sutaria. I had a question on, as we implement, or look to implement, the QMM rating for each of the various suppliers' or manufacturers' sites, is there consideration as to how cumbersome it might be to provide that information or submit that information on a

periodic basis to maintain that QMM rating? This would be a volunteer program, and certainly the manufacturers that see the benefit of having that rating would lead to, hopefully, better purchases and purchasers as well. But I guess my question is, is there a consideration for that?

Then another question I wanted to also ask, and thus a follow-up for my previous question is, since there is not a direct correlation between the manufacturing site to the products or presentations that might be produced at that manufacturing site, and since those could change on a periodic basis, is there a consideration for potentially asking for that information during that periodic monitoring of all this information that might be required for the QMM rating evaluations as well? Thank you.

DR. FISHER: This is Adam Fisher. I can certainly start out here. We've had some questions about the burden to participate in the QMM, and the highest level, I just want to say, it came to our pilot program, or how we would envision the future of this program, and there was and will be no

direct cost to participate to be in the program. Another great part about the pilot program was that it gave us an opportunity to directly engage with the folks that went through this process and get a feel for the burden on their side.

I can just give you a rough estimate. From the pilot program participants, their total effort across the site for the entire program was estimated to be somewhere around 100 hours, although I want to be clear here that this varies considerably, and the actual level of effort for a QMM assessment really depends on the breadth of participation in the assessment meetings and what type of staff participate in those meetings. So is it more executive level staff, which obviously has the higher hourly cost, or is it more direct manufacturing staff, which comes with a lower cost to the company? So again, that was the nice part of the pilot program because we were able to get a little bit of a feel for this.

DR. SUTARIA: Thank you. That's very helpful.

DR. MAGUIRE: Yes. I think there was a second question you had. I was wondering if you could repeat your second question.

DR. SUTARIA: Sure. My question was related to an earlier question where you had indicated that since QMM ratings are really at the manufacturing site or facility levels and not the product levels, the purchasers have some insight on correlating the product to the manufacturing site, but that could change on a periodic basis; so unless that information is required and provided on a consistent basis every time that change occurs, it may be potentially challenging for a provider to assess if that product is certainly produced at the site or facility that that rating is available at.

So I guess my question was, is there consideration for potentially making that information a requirement of that so that there's more visibility, ability to even correlate?

(No response.)

DR. MORRIS: Was that clear, Jen? Dr. Maguire?

MR. VIEHMANN: This is Alex. I can try to take a stab here. I think it's really related to similar conversations about how do we draw linkages between the sites and the product from a purchaser's perspective, because you're right; that can constantly evolve. New sites are brought in and backups are done as these are put in place.

Really, as we learn more, it speaks to the need for transparency in the agreements to be aware of these supply chain changes so that the purchasers can be as informed as possible around who is actually providing these products and what does that supply chain look like. But again, I think we've learned that there is a hefty due diligence from the people we've met with around assessing sites.

I'm not sure, Ken. Was the question also related to -- I remember there was a question that the committee spoke to about the assessment is about a point in time and what information will be submitted to maintain a rating.

DR. MORRIS: I thought you answered it --

MR. VIEHMANN: Okay.

DR. MORRIS: -- but as the last clarifying question, I'll go back and see, Dr. Sutaria, if you have any follow-up.

DR. SUTARIA: No, that was great. Thank you so much.

DR. MORRIS: Thank you. Good.

Alright. Well, we're a little bit over, but not bad, and we'll now break for lunch. We'll reconvene at 1:15 Eastern Standard Time. And again, panel members, please remember there should be no chatting or discussion of the meeting topics with other panel members during lunch.

Sorry, not 1:15, 1:00. We'll reconvene at 1:00. Sorry. I was just adding an hour. But you should have no discussion with other panel members during lunch. And additionally, you should plan to join at about 12:45 to ensure you're connected before we reconvene at 1:00.

With that, I'll suspend us for lunch, reconvening at 1:00, and logging in at 12:45 Eastern Standard Time. Thank you.

(Whereupon, at 12:16 p.m., a lunch recess was taken.)

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

(1:00 p.m.)

Open Public Hearing

DR. MORRIS: We're now at the open public hearing section of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting. We are now beginning the session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of the individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses

in connection with your participation in this meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson, and thank you for your cooperation.

I believe speaker number 1 should be connected now. Your audio is connected. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record. Thank you.

MR. RANDAZZO: Hi. Thank you. My name is Giuseppe Randazzo. Can you hear me?

DR. MORRIS: We can.

MR. RANDAZZO: Thank you.

Hi. My name is Giuseppe Randazzo, and I'm the vice president of Scientists and Regulatory Affairs at the Association for Accessible Medicines or AAM. Before I begin, I would like to take a moment to thank the agency for holding this important public meeting, as well as thank all the FDA staff for their presentations, and the committee for their attendance here today, and their insightful questions and dialogue.

The Association for Accessible Medicines, or AAM, represents the manufacturers and distributors of finished generic pharmaceutical products; manufacturers and distributors of bulk active

pharmaceutical chemicals; biosimilar manufacturers; and suppliers of other goods and services to the generic pharmaceutical industry. AAM consists of 25 generic manufacturer members, along with 17 associate members, the Biosimilars Council, which is a division of AAM and represents 10 biosimilar manufacturers.

Generics represent 91 percent of all prescriptions dispensed in the U.S., totaling 18 percent of expenditures on prescription drugs, and AAM is the sole association representing America's generic pharmaceutical sector. We appreciate the opportunity to speak here today, as well as submit comments and questions to the docket.

In listening to the meeting, it appears that many of our members' comments, questions, and concerns align with earlier presentations, as well as some of the very good questions from the committee previously submitted. We start our specific comments by emphasizing that AAM agrees with the FDA in that delivering high-quality, safe,

and effective drugs is of paramount importance to ensure patients have access to needed medicines.

To fulfill this objective of delivering high-quality, safe, and effective drugs, and as this relates to the QMM Initiative, AAM has questions and would appreciate more details around the specific goals trying to be accomplished with the QMM program; what precisely FDA is attempting to measure; and what the relevance of those measurements are to the goals of the respective QMM program and to pharmaceutical quality in general.

AAM is an organization that represents companies of different sizes, corporate structures, and types of supply chains, not to mention different jurisdictions. With this, we have concerns about whether QMM can be accurately measured, normalized, and applied in a meaningful and consistent manner across this diverse global industry to satisfy all these differences.

If FDA's QMM assessments and ratings will be used by the FDA, as well as made public, then these ratings could be used to make important public

health decisions that may impact patients, the pharmaceutical industry, insurers, and other stakeholders in the pharmaceutical ecosystem. With this, the assessments and ratings must be accurate, validated, meaningful, normalized across companies and products, and relevant to establish goals of the QMM program.

AAM is concerned that this will be difficult to achieve for many QMM assessment topics discussed by the FDA in the context of the QMM pilot program, such as quality culture, customer experience, continual improvement, planning, among other topics.

As was hinted earlier today, implementing a QMM program will add operational costs and complexity, and AAM members are concerned that this additional cost will not have commensurate return, thereby potentially jeopardizing patient access to medicines by driving companies away from manufacturing certain drugs, and potentially resulting in an unintended consequence of additional drug shortages.

CDER's publicly available QMM white paper, as well as what was stressed here today on numerous occasions, is that the agency will need to clearly communicate to stakeholders that ratings reflect the QMM of a manufacturing site and not the quality of a product or the process used to make the product.

As you are well aware, and has been discussed here today, there are many stakeholders in the pharmaceutical ecosystem such as purchasers, pharmacies, payors, and most importantly, patients, and all these stakeholders have a different level of education and understanding of quality and quality management maturity. With this, we believe it is imperative for the FDA to articulate a clear and specific communication plan for how it intends to educate stakeholders on the distinction between QMM and the quality of a product.

AAM remains concerned that stakeholders tend to confuse a QMM rating with the rating of a drug's quality to the detriment of patients. The QMM white paper also notes that CDER will need to

clearly separate QMM appraisals from regulatory compliance, and AAM agrees with this. AAM requests that FDA further details how they plan to do this.

The FDA and the committee should consider that QMM data, metrics, indicators, and ratings, though different than quality metrics, will likely be even more difficult to standardize and validate than quality metrics alone. Many human assessment topics such as quality culture and workforce management are generally less amenable to objective assessments, and standardization, and QMM assessment topics.

Finally, AAM recommends FDA not make QMM ratings public. As mentioned previously, stakeholders have different levels of education and understanding of quality and quality management maturity. Public QMM ratings could cause confusion not only to insurers or payors and the like, but also for patients.

Again, AAM is grateful for the opportunity to comment here today, and we wish to continue working with the agency on all programs that will

help ensure manufacturers are delivering high-quality, safe, and effective drugs to patients. This concludes our comments here today, and thank you.

DR. MORRIS: Thank you very much.

At this point, speaker number 2, I believe your audio is about to be connected. Speaker number 2, please begin an introduce yourself, and please state your name and any organization you are representing for the record. Keep in mind we have a 10-minute time slot for each speaker. The last speaker did fine, but just a friendly reminder.

Speaker number 2, please proceed.

MS. BAKER: Thank you.

Good afternoon. My name is Denyse Baker. I see that the time alarm -- oh, there it goes; now it's reset. I'm senior director and team lead for Global Regulatory Policy at AstraZeneca. I'm speaking today on behalf of the Parenteral Drug Association.

PDA is an international, nonprofit, professional association made up of more than

10,000 individual members from regulated industry, academia, health facilities, equipment, and service providers. Since the organization's founding more than 75 years ago, PDA volunteers have been committed to the advancement of science and regulation in our industry. Working collaboratively, PDA members deliver science-based, technical information through publication, education programs, conferences, workshops, and research, with the ultimate goal of enabling members and organizations to better serve patients.

I currently serve as the vice chair of the PDA Regulatory and Quality Advisory Committee and co-chair of the PDA Quality Management Maturity Task Force, and I have no financial conflicts of interest for the subject of today's meeting.

PDA has been engaged with the topic of quality maturity, including quality metrics and quality culture, since early 2013 when the FDA's Federal Register Notice for metrics was issued. I would like to start by highlighting several positive elements in the current CDER OPQ proposal

for a QMM rating program from PDA's perspective.

First, PDA strongly supports the view that a positive quality culture is foundational for mature quality management system, and metrics alone are not sufficient to evaluate a quality system. PDA is pleased that the FDA recognizes this concept in their program [inaudible]. PDA also proposes to differentiate and recognize sites that demonstrate mature approaches to quality systems, have invested in sustainable quality, and emphasize continuous improvement from other sites, which may be focused primarily on basic GMP compliance and cost minimization. Another positive point is FDA's use of external research and pilot program experiences in developing the QMM program.

PDA also find FDA's aspiration to create a market incentive, which could bring more investments in pharmaceutical quality systems by bringing transparency to the evaluation of system maturity as a positive goal to the program, albeit one that may be difficult to achieve.

PDA would also like to point out some areas

in the proposed program that would benefit from additional clarity. I would like to acknowledge the FDA speakers for addressing many of these points, which PDA submitted to the docket already in their remarks earlier today.

Given that this has been described as a voluntary program, PDA would like to see FDA provide more details about the incentives for participation. As mentioned earlier, and also by the previous speaker, there are time and resources consumed by hosting an on-site assessment or submitting data and information to FDA. For industry, especially those manufacturers who may not already be focused on quality maturity, to accept this burden, there should be a clear benefit.

For sites to demonstrate mature quality systems, PDA does support FDA providing inspection frequency or regulatory flexibility for post-approval changes. Although the survey results presented by Dr. Fisher earlier showed the opportunity for continuous improvement as the most

highly rated incentive, I would like to respectfully challenge whether those survey participants were presented a broad spectrum of industry or just sites and companies who have self-selected to engage with FDA in this area.

PDA is also asking that FDA exercise caution when identifying attributes to be assessed by the QMM program. Establishing [inaudible - audio gap] changes behavior. It is critical that CDER's OPQ select attributes that will result in positive behaviors, drive increased maturity of systems, and avoid unintended consequences. PDA recommends that FDA continue to work with academic and industry experts and their research findings in this area.

PDA launched a quality culture maturity assessment program in 2017, and since that time has trained hundreds of assessors and collected data from more than 50 sites. PDA would like to highlight for FDA's consideration three keys to executing a successful assessment.

First, it's important to ensure that any site evaluation include feedback from the shop

floor and not just site leaders. Our research has shown that leaders have a more positive bias as compared to that of staff at lower levels in the organization.

Secondly, making an assessment of culture and maturity attributes requires a different approach than a traditional compliance audit. Both participants and investors need to be fully aware and prepared to ensure meaningful outcomes. And I did note that Dr. Maguire addressed this earlier in her remarks.

It is important to understand the limitations with quantifying culture maturity, which are assessments of behaviors of people and not machines. PDA is concerned that an overemphasis on scoring precision or a narrow scale of differentiation in the FDA model could create the risk of driving the QMM program toward a compliance check rather than a meaningful understanding of maturity.

Finally, PDA believes it will be challenging for several stakeholders, in the group of 6 P

mentioned earlier, to understand the distinctions made in the FDA QMM program, the product quality, process quality, and quality management system maturity, to be able to use this information to make informed purchasing decisions. As noted earlier in the discussion today, more work is needed to ensure that stakeholders can make the connection between a product they select and the applicable site QMM rating such that informs the purchase and then creates the market incentive that FDA desires.

PDA remains ready and willing to further collaborate with FDA and others to increase the quality management maturity within our industry to better serve patients. We'd like to acknowledge these comments have been prepared by members of the Quality Management Maturity Task Force and endorsed by the PDA Board of Directors. Thank you very much for the opportunity to present today.

DR. MORRIS: Thank you.

Speaker number 3, your audio is now connected. Will speaker number 3 begin and

introduce yourself? Please state your name and organization you're representing for the record.

Speaker number 3?

MS. FREDERICK: Good afternoon. My name is Tami Frederick. I'm senior director of Corporate Quality Systems and Cultural Excellence at Perrigo. I'm also the chair of ISPE's Advancing Pharmaceutical Quality program, which is a QMM program. I have no financial relation or conflict of interest in presenting today, and I do thank FDA for this opportunity to speak on the topic of QMM.

ISPE is aligned with FDA's vision on the value of QMM and has initiated the ISPE Advancing Pharmaceutical Quality, APQ, program in 2018 as an industry-led approach to advance pharmaceutical quality. The basic framework of the APQ program is to assess, aspire, act, and advance quality maturity, and was outlined in ISPE's comments to the FDA docket in 2018.

The APQ program, which is scheduled for completion in 2022, provides a framework for assessing and enhancing the effectiveness of the

pharmaceutical quality system, the PQS, as described in ICH Q10. The program consists of five good practice guides, which I'll describe in detail in this presentation. The APQ program recognizes that the ability to advance quality management maturity lies within industry itself, developed by industry representatives for use by industry. It builds upon the ICH Q10 model and enhances PQS elements with aspects of cultural excellence, operational excellence, knowledge management, and continual improvement. It provides a comprehensive approach for assessing and improving an organization's quality management maturity to advance the state of quality within the organization.

The APQ program focuses on eight overarching goals: 1) to integrate quality management maturity, culture, and operational excellence, principles, tools, and approaches; 2) support and incentivize continual improvement; 3) foster industry ownership and quality beyond compliance; 4) promote effective and efficient use of

resources; 5) encourage self-improvement and supplier improvement; 6) enable structured benchmarking, knowledge sharing, and learning amongst organizations; 7) increase the reliability of supply of quality products; and 8) offer routes to delivering sustainable competitive advantage.

At the core of the APQ program is the Assess, Aspire, Act, Advance framework, which provides a set of tools, resources, and systematic approaches for organizations to advance their maturity and the effectiveness of their PQS.

The ISPE Advancing Pharmaceutical Quality Management Maturity program includes five guidance documents. The first ISPE APQ guide is corrective and preventive action, CAPA. ICH Q10 demonstrates defined requirements for a robust corrective action and preventive action system throughout the product life cycle.

The ISPE CAPA guide covers the practical application of the APQ framework for each CAPA system requirement by evaluating the following elements: CAPA documentation; problem

identification; root cause identification; corrective and/or preventive actions; CAPA effectiveness; CAPA metrics; governance; management oversight; and CAPA prioritization.

The second APQ guide is change management system. ICH Q10 establishes clear guidance for the effective management of change throughout the product life cycle, which enables quality improvement and is critical to patient safety, supply reliability, as well as operational effectiveness and efficiency.

The ISPE Change Management Guide provides a quality management framework for assessing and advancing change management system maturity level by evaluating change management documentation; change scope and identification; change rationale; impact; level and risk; change plan and execution; post-change evaluation; change management metrics; governance; management oversight; and change management prioritization.

The third ISPE guide is management responsibilities and management review. The

ICH Q10 clearly states a clear expectation regarding the role of strong leadership in terms of demonstrating and communicating strong and visible support for the pharmaceutical quality system. The ISPE MRR guide provides a quality management framework for assessing and advancing leadership systems. It provides a systematic and proactive approach to evaluating management responsibilities and key leadership components by evaluating the following elements: patient and consumer focus; management commitment; quality planning; internal communication; management of outsourced activities and purchased materials; management of change and product ownership; and regulatory and industry awareness.

The fourth ISPE guide is process performance and product quality monitoring system, or PP and PQMS. The ICH Q10 establishes an expectation for pharmaceutical companies to plan and execute a system for the monitoring of process performance and product quality to ensure a state of controls maintained.

This guide provides a quality management framework for assessing and advancing an organization's PP and PQMS maturity level by evaluating the following elements: establishing a control strategy; determining tools for measurement and analysis of parameters and attributes; analyzing parameters and attributes; identifying sources of variation, including feedback on product quality from internal and external sources; and providing knowledge for enhanced process understanding.

The fifth ISPE guide is cultural excellence. The cultural excellence guide shares insights on quality culture improvement across six key dimensions and outlines practical and powerful approaches, practices, and tools, to support the implementation of cultural excellence framework, and promotes behavioral change that will ultimately benefit the patient and the business.

It's based upon the 2017 ISPE Cultural Excellence Report with enhanced features supporting key behavioral assessment at employee and

management levels, a robust recognition and reward program, and third-party contract evaluation. It provides quality management framework for assessing and advancing cultural excellence maturity through leadership and vision, mind-sets and attitudes; Gemba and employee engagement; leading quality indicators with metrics that matter; proactive management oversight review and reporting; and cultural enablers.

Recommendations. ISPE aligns with FDA's vision of the value of quality management maturity for FDA, industry, and patience. ISPE recommends a voluntary industry-led program for QMM to achieve this vision. This approach would align with CDRH's voluntary improvement program VIP, which is primarily facilitated by industry. As described in the CDRH guidance, the VIP program offers a participating manufacturing site potential benefits, including enhanced risk-based inspection decisions, reduced review timelines, and/or reduced submission content for changes.

Clearly articulated, potential benefits are

essential for a successful QMM program for drugs, as was indicated in the 2022 OPQ white paper. Incentives described by FDA could include reduced inspection frequency, increased regulatory flexibility in making post-approval changes, and improve supply chain insight.

The ISPE APQ program is a voluntary industry-led program for QMM, whereby industry can assess, aspire, act, and advance their level of quality management maturity and share it independently with their patients, consumers, customers, and help authorities globally, based upon ICH Q10 standards.

Any QMM program should entail quality system assessment, performance measures, improvement tools for advancement, and case studies for robust application. Any public rating system for QMM should be avoided, as it may negatively impact the availability of drug products due, in part, to the potential public misperceptions relating quality management maturity to product quality, as we've heard from other speakers today. Further, any QMM

program should include tangible incentives to achieve higher QMM, such as those promoted within FDA's CDRH program.

Achieving a successful QMM program could help fulfill FDA's vision of pharmaceutical quality for the 21st century, of a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight. Thank you for your time today.

DR. MORRIS: Thank you.

We have one more OPH speaker, open public hearing speaker. Your audio is now connected, so speaker number 4, if you could begin and introduce yourself, and please state your name and any organization you are representing for the record.

Speaker number 4?

DR. PANNALA: Good afternoon. Am I on?

DR. MORRIS: Yes. We can hear you. Thank you.

DR. PANNALA: My name is Raghuran Pannala. I'm senior vice president for regulatory affairs,

pharmacovigilance, and corporate quality compliance at ScienGen Pharmaceuticals. I don't have any financial commitments to disclose.

Thanks for providing me an opportunity to speak at the advisory committee meeting on QMM. I appreciate FDA and the QMM schedule and guidance. The white paper, research articles, and seminars on this topic are knowledgeable, thought-provoking, and highly appreciated.

I would like to make a few comments for the agency review. As you are aware, product quality, compliance, lifecyle management, leadership commitment of product are interdependent and comes as a package. QMM is a combination of product quality and site compliance and continuous improvement. It may be difficult to separate regulatory compliance from QMM.

Where two QMM are interested firms and they establish a level playing field, firms may need more guidance, an elaboration of guidance, and model case studies. For example, FDA has released several guidance and revisions for user fee related

guidance. Along the same lines, inspectional guidance and other facility guidance needs updating to the current expectations and happenings like concerns of [indiscernible], where multiple products are being manufactured. Model documents of case studies are expectations from the agency to be provided by ICH Q10 and Q12.

Human factor variations in inspections on both site, either on auditor [indiscernible] site or [indiscernible] site, may affect the inspection outcome. This may be reduced by introducing or increasing the automated process utilization and related guidance revisions. A supply chain risk assessment and vendor management are really a challenge and a more tough job [indiscernible] creating a small business entity, and the pandemic has posed more challenges.

The supply chain risk assessment guidance is to be elaborated [indiscernible], and I expect FDA to act as a mediator or a bridge in exchange of information for both the parties involved, [indiscernible] manufacturers and drug product

manufacturers.

To conclude, I see QMM as a great institute [indiscernible], but it should be noted that if implemented, it may not only denote the product quality or affect quality rating, but represent the firm's image as a whole. Thereby, I request the agency to evaluate all related items listed under the illustrated QMM umbrella for updating to current thinking and scenarios. I appreciate, again, a great institute [indiscernible], and I think the success of a quality management maturity program is mutually beneficial and also beneficial to patients and other stakeholders. Thank you very much for providing me an opportunity.

Clarifying Questions to the Presenters (continued)

DR. MORRIS: Thank you for your presentation.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, which is the careful consideration of the

data before the committee, as well as the public comments.

Since we have a little time, we do have a few minutes, until 2:00, to entertain any other -- we can return to the clarifying question session from this morning if any panel members have any additional clarifying questions for FDA.

Let me just scroll down. I believe there was one question still pending from this morning. Bear with me one moment.

(Pause.)

DR. MORRIS: I'm sorry, Rhea. I can't see the questions still remaining. I actually have one myself. Let me pose that first, and then the other panel members can identify themselves.

My question actually would go to to Alex, I believe, and it has to do with sort of the question I asked earlier, which is the distinction between the QMM and product quality, being that you're really talking about anticipating accessibility of the product as the ultimate goal, which includes shortages.

But my point was that it's not just the site itself that you are talking about any longer; now we're talking about, when I say the overall availability, including the other stakeholders that you outlined in your white paper. In particular, I wanted to focus on the example of CARFAX being a game changer for information asymmetry, and wondered if there are any ideas of how that asymmetry between the patient and the provider can be addressed; because as was stated in the paper, that could have impacts on the patient's willingness to look at the advantages of one product over another.

MR. VIEHMANN: Hi, Ken. This is Alex. Hopefully you can hear me ok.

DR. MORRIS: Yes, you're fine.

MR. VIEHMANN: I think the first part of your question, you're absolutely correct. Overall availability for a given product is a function of all sites in the supply chain. When sites are performing risk assessments related to availability, it's not just about manufacturing

either. Now you also have to think about logistical considerations, get moving products, shipping, and all these other things.

But when it comes to information asymmetry to the patients, that is -- and again, I think that might be a little bit out of scope because the patients are not the buyers, and we're really not trying to impact at the patient level because patients really, also in lot of cases, don't have a choice when you go to the pharmacy; it's what's there.

We wouldn't be able to provide patients with this meaningful information, but what we're trying to do is to reduce the gap of this information asymmetry between the people that are making the purchasing decisions and getting the product to the patient, and so forth. So I think talking about it at the patient level might be a stretch because I think, as others mentioned in the public forum, there might be -- if that was tried, to happen, it might cause confusion and such.

It's really trying to provide information

and reduce that gap with the people making the purchasing decisions and having better supply chain transparency in the products that they're buying, ensuring that their agreements have these transparencies and have the information that they would need. But I'd welcome others from the FDA to also chime in.

DR. FISHER: This is Adam. I would just say that I do think there are differences in the relatively linear car-buying market example that you asked about, Ken, and then in the drug supply chain, which is highly non-linear. I think Alex's point is exactly right. It's about the people that are making the decisions in the supply chain having access to the information that they need to make the best decisions for their customers.

Questions to the Committee and Discussion

DR. MORRIS: No, that's fine. That's the clarification I was looking for because of the complications you raised, so thank you.

So if there are no other lingering clarification questions, we can move on to the

panel discussion questions.

As we said just a few minutes ago, the committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the question to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. After I read each question, we'll pause for any questions or comments concerning its wording, and then we'll open the question to discussion.

We'll start with question 1, which is a voting question, and Rhea Bhatt will provide the instructions for voting.

MS. BHATT: Thank you, Dr. Morris.

Question 1 is a voting question. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After the

chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved into a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you only need to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the

chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, however, you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

MS. BHATT: If not, I'll hand it over to you, Dr. Morris, to read the voting question.

DR. MORRIS: Alright, and we just have to pull it up.

The voting question is quality management maturity, and the vote is, should CDER establish a QMM program to incentivize investments in mature quality management practices?

That's the question, and so we're now open for any issues or questions about the wording of the question, so it's open now to the panel. You should raise your hand if you have a question or comment.

(Pause.)

DR. MORRIS: The question is now on the screen, by the way.

(Pause.)

DR. MORRIS: Sorry. I got dropped. Can you hear me now, Rhea?

MS. BHATT: Yes, Dr. Morris, we can hear you now.

DR. MORRIS: Sorry. My phone cut out.

I was about to say Dr. Lee has a question.

Please, Dr. Lee?

DR. LEE: Thank you. This is Kelvin Lee.

I just want to make sure that I understand. I understand the question to be about establishing a QMM program, but in light of the discussion, I also understand we do not have details on how such a program would be operationalized at this time. So the question is really independent of any operational details.

Is that a fair understanding of the question?

(Pause.)

DR. MORRIS: Sorry. I'm back.

DR. KOPCHA: Hi. This is Mike Kopcha. Yes, that is correct.

DR. LEE: Thank you.

DR. MORRIS: Dr. Kagan, you have a question? Please go ahead.

DR. KAGAN: Yes. This is Leonid Kagan.

To follow up on my previous question and Dr. Lee's, for me it wasn't very clear what establishing the QMM program means, as some of these parameters of the QMM system are still fluid; and then what, really, establishing means, if it's establishing a group at FDA working on this or already trying to implement it with certain industry partners. Thank you.

DR. KOPCHA: Yes. This is Mike Kopcha. Thanks for that clarifying question. Yes, by established, we mean to develop, implement, and operate, and obviously as you correctly pointed out, that would be with continued engagement with the industry, and I'll leave it at that.

DR. KAGAN: Thank you.

DR. KOPCHA: You're welcome.

DR. MORRIS: Are there any other questions?

If I can just ask a follow-up on that to Dr. Kopcha, so you're that implicit in established means developing as well as implementing and sourcing from the stakeholder.

DR. KOPCHA: Yes, it would include all of those three pieces because, by doing that, we need to know what the resources would be, the resource commitment from our end, because obviously we're working in this area right now, and it's the reason why we're bringing it to the advisory committee; because we want to see if we can get the support to establish, as I defined previously, so that we can continue looking at this in more detail on developing it, implementing it, and then eventually operationalizing it at the appropriate time and with the appropriate continued input.

DR. MORRIS: Thank you.

Are there any other questions?

DR. KOPCHA: Ken, this is Mike Kopcha again. Sorry. If I may?

DR. MORRIS: Yes, please.

DR. KOPCHA: I just wanted to add that we would also put details in a guidance for stakeholder feedback; so that would be part of the definition of establishing. Thank you.

DR. MORRIS: Oh, I see; the details for the stakeholders in the guidance.

DR. KOPCHA: Right, the draft guidance, and then we'd ask for stakeholder feedback, as we typically do. So I wanted to clarify that piece of it more specifically.

DR. MORRIS: That's helpful, yes.

DR. KOPCHA: Thank you.

(Pause.)

DR. MORRIS: Sorry. I'm just making some notes. We can begin voting on question 1 if there are no more questions, so I'll turn it over to Rhea.

MS. BHATT: Thank you.

We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

MS. BHATT: Voting has closed and is now complete. Once the results display, I will read the vote results into the record.

(Pause.)

MS. BHATT: The vote results are displayed. I will read the vote totals into the record. The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you wish to. However, you should also address any subparts of the question, if any.

There are 9 yeses, zero noes, and zero abstentions.

Dr. Morris?

DR. MORRIS: Sorry. I was on mute. Thank you.

We'll now go down the list of everyone who voted to state their name and vote into the record. And as I said, you may also provide justification of your vote, if you wish to.

We'll start with the first person on the

list. And, Rhea, I'm assuming I'm starting with the list as shown in my panel here, so that would be Dr. Richmond.

MS. BHATT: Yes.

DR. RICHMOND: Thank you. My vote is yes. I want to just state, though, that the vote probably is to encourage more exploration, knowing that we really need that exploration to amplify and harden the operational parameters and the stakeholders' concerns. So, in a sense, it is not a complete yes in that I think that it needs quite a bit more development. Thank you.

DR. MORRIS: Thank you, Dr. Richmond.

Dr. Carrico?

DR. CARRICO: Yes. This is Jeff Carrico. I voted yes. I agree with the supporting factors that have been presented for this program, and agree that it has the potential to affect drug shortages and supply chain issues in a positive manner. Thank you.

DR. MORRIS: Thank you.

Dr. Lee?

DR. LEE: This is Kelvin Lee. I voted yes. I voted yes with the understanding the definition of "established" included understanding resource commitments and developing the concept further, and operationalizing it only at the appropriate time with continued input; and I also took literally the purpose being to incentivize investments and mature quality management practices. Thank you.

DR. MORRIS: Thank you.

This is Kenneth Morris. I also voted yes. This is, to me, a logical direction to go from the early days of the ICH guidances and quality-by-design initiatives. I do fully agree, as Dr. Kopcha had mentioned as well, and as Dr. Lee just mentioned, that this has to be a careful development and be also at the right time. But with the inclusion of the stakeholders, this is the sort of task that could probably only be addressed by the agency with a lot of careful implementation and hardening of the parameters, as Dr. Richmond mentioned. Thank you.

Next would Dr. Kagan.

DR. KAGAN: Yes. This is Leonid Kagan. I voted yes. And from my perspective, it's an interesting initiative, but it will require a lot of funding and further evaluation as we go. Thank you.

DR. MORRIS: Thank you.

Dr. Rogge?

(No response.)

DR. MORRIS: Sorry. Dr. Rogge, can you hear me?

MS. BHATT: Dr. Morris, Dr. Rogge is an industry representatives, so the next panel member is Dr. --

DR. MORRIS: Oh, oh, oh. I didn't realize he was on mute there. Then I should go to Dr. Sutaria. Sorry.

DR. SUTARIA: Thank you. This is Mittal Sutaria. I voted yes. I would just say that I applaud FDA's efforts, and I certainly believe this is a step in the right direction for addressing drug shortages and ensuring long-term supply chain resiliency. Certainly, the operational and

development details are still to be worked out, but this is a great effort in the right direction.

DR. MORRIS: Thank you.

I thought IR stood for infrared spectroscopy, so I'm thinking that it's not the case. With that in mind, I'd go to Dr. Finestone.

DR. FINESTONE: Sandra Finestone. I voted yes with the understanding that the project will be further developed, and that we'll be advised of that development. I do have a concern about the word "incentivize," that it may be misunderstood to mean monetary.

DR. MORRIS: Would you say that again? Your concern is what?

DR. FINESTONE: I'm concerned that it might be misconstrued as a monetary incentivization.

DR. MORRIS: Oh. Yes, I see your point.

Dr. Kraft?

DR. KRAFT: This is Walter Kraft. I voted yes. There's clearly broad agreement in the value of quality improvement programs such as this. I think the comments and the questions that have been

raised have focused primarily on specific implementation details and not the larger value. I think the FDA has also been thoughtful in outreach to stakeholders, bringing in multidisciplinary expertise and the use of pilot approaches. And I think that they are being responsive to societal needs in terms of drug shortages, as well as overall quality.

I think the approach so far, for me, has provided confidence that the final guidance and the details will ultimately lead to improved drug manufacturing in multiple domains. Thank you.

DR. MORRIS: Thank you.

Dr. Zamboni?

DR. ZAMBONI: Yes. This is Bill Zamboni. I voted yes, based on the clear need to address supply chain issues with medication, and especially with the experience with similar plans in other areas of medicine such as devices. I do agree with the other comments that additional input and work will be needed to finalize and implement the plan. Thank you.

DR. MORRIS: Thank you.

Adam, Alex, and the FDA, is that the list?

Have I missed anybody that you can see, Rhea?

MS. BHATT: No, Dr. Morris. I think we've been down the list of panel members. Thanks.

DR. MORRIS: Okay. Good.

So I'll try to summarize if I can. I was taking notes as we went along, of course, but I think the sentiment of the committee and the opinion of the committee is that the actual implementation -- or I should say the actual concept of drug shortage and supply chain being hot issues that require this sort of more global approach to address -- that is including all the stakeholders and recognizing both the technical and logistical aspects of the problem -- really needs to be addressed.

The rest of the statement would be, though, that there's an awful lot that needs to go into the development of not just the rubrics and the assessments, but how those are managed and how you

interface with the other stakeholders, particularly as complicated a system as we have to deal with. And implicit, at least in a couple of these statements, was that we'd assume that FDA would want to, at intervals, get back with the committee to look at progress on this. And then ultimately, as Dr. Kopcha said, coming up with a guidance might be a goal and a way to start the process of interacting.

So implementation is the key, although the the actual topic itself is agreed upon by all stakeholders from the pilot studies that we saw, as well as our open hearing guests.

With that, therefore, if there's nothing else, Rhea, I think we're on the cusp of the journey; is that correct?

MS. BHATT: Yes, that's correct. If there are any additional last comments from the FDA, or if you have any additional comments, Dr. Morris, please feel free to make them now.

DR. MORRIS: Well, thank you. No, I've made mine in the summary. I hope I have not missed

anybody's main concerns.

Are there any comments from FDA that they'd like to -- I see somebody's active, but I can't see it. It's a phone number.

(No response.)

DR. MORRIS: No, I guess not.

DR. KOPCHA: I --

DR. MORRIS: Alright. Well, if there are no additional questions -- oh, sorry. Go ahead.

DR. KOPCHA: Sorry, Ken. This is Mike. Sorry. I was trying to get my phone off mute.

I just want to thank you, Ken, for chairing this advisory committee, and also all of the participants on the comments that we've had and the public statements that were made. I really appreciate the time and attention individuals put in, in sharing their perspectives with us, and really giving us some meaningful feedback. It was what we were hoping to get out of this advisory committee, and we got so much more than what I expected.

So again, I just want to thank everyone for

their time to be here with us today and really provide honest, candid feedback, so thank you.

Adjournment

DR. MORRIS: Yes. Thank you.

If there are no other questions, we'll now adjourn the meeting. Thank you.

(Whereupon, at 2:01 p.m., the meeting was adjourned.).