FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY ADVISORY COMMITTEE (PSCP) MEETING

Virtual Meeting

Thursday, November 3, 2022

9:00 a.m. to 2:45 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

Department of Regulatory and Quality Sciences

School of Pharmacy, University of Southern California

Los Angeles, California

Eric V. Slud, PhD

(November 3rd only)

Area Chief for Mathematical Statistics

Center for Statistical Research and Methodology

Census Bureau

Washington, District of Columbia

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)

Gregory E. Amidon, PhD

(November 3rd only)

Research Professor Emeritus, Pharmaceutical Sciences

College of Pharmacy

University of Michigan

Ann Arbor, Michigan

Maureen Donovan, PhD

(November 3rd only)

Professor

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William Hancock, PhD

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Bradstreet Chair Emeritus

Barnett Institute

Department of Chemistry and Chemical Biology

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Tonglei Li, PhD

(November 3rd only)

Professor of Pharmaceutical Sciences

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FDA PARTICIPANTS (Non-Voting)

November 3rd FDA Participants

Lawrence Yu, PhD

Director

Office of New Drug Product (ONDP)

OPQ, CDER, FDA

Sau "Larry" Lee, PhD

Deputy Director of Science

OPQ, CDER, FDA

Stelios Tsinontides, PhD

Director

Office of Pharmaceutical Manufacturing

Assessment (OPMA)

OPQ, CDER, FDA

Larisa Wu, PhD

Associate Director of Science and Communication

ONDP, OPQ, CDER, FDA

Andre Raw, PhD

Associate Director of Science and Communication

Office of Lifecycle Drug Products (OLDP)

OPQ, CDER, FDA

Rakhi Shah, PhD

Associate Director of Science and Communication

OPMA, OPQ, CDER, FDA

Joel Welch, PhD

Associate Director for Science and Biosimilar Strategy

Office of Biotechnology Products (OBP)

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, everyone, and welcome. I'd first like to remind everyone to please mute your line when you're not speaking, and for media and press, the FDA press contact is Audra Harrison. Her email and phone number are being displayed as you can see now on the screen.

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

Rhea?

Introduction of Committee

MS. BHATT: Thank you, Dr. Morris.

Good morning everyone. My name is Rhea Bhatt, and I'm the designated federal officer for this meeting. When I call your name, please

introduce yourself by stating your name and affiliation.

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

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

MS. BHATT: Thank you.

Next, we have Dr. Finestone.

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

MS. BHATT: Thank you, Dr. Finestone.

Next, Dr. Kagan?

DR. KAGAN: Good morning, everyone. This is Leonid Kagan, Rutgers University.

MS. BHATT: Thank you.

Dr. Kraft?

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

MS. BHATT: Thank you.

Next, Dr. Lee?

DR. K. LEE: This is Kelvin Lee from the

University of Delaware.

MS. BHATT: Thank you.

Dr. Morris?

DR. MORRIS: This is Kenneth Morris, and I'm professor emeritus from the University of Hawaii at Hilo. Thank you.

MS. BHATT: Dr. Richmond?

DR. RICHMOND: Hi. This is Frances Richmond from the University of Southern California.

MS. BHATT: Thank you.

Dr. Zamboni?

DR. ZAMBONI: Bill Zamboni, University of North Carolina.

MS. BHATT: Thank you.

Next, Dr. Slud?

DR. SLUD: This is Eric Slud of the U.S. Census Bureau and University of Maryland.

MS. BHATT: Thank you, Dr. Slud.

Next we have our industry representative, starting with Dr. Rogge.

DR. ROGGE: Good morning. This is Mark Rogge. I'm with Sail Bio and the University of

Florida.

MS. BHATT: Thank you.

Mr. Rothe?

(No response.)

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

MR. ROTHE: Good morning, everyone. Can you hear me?

MS. BHATT: Yes, we can hear you.

MR. ROTHE: Pravin Rothe, industry representative within Novartis. Thank you.

MS. BHATT: Thank you.

Dr. Venkateshwaran?

DR. VENKATESHWARAN: Hi. This is T.G. Venkateshwaran. I'm with Takeda.

MS. BHATT: Thank you.

Next, we'll move on to temporary voting members.

Dr. Amidon?

DR. AMIDON: Greg Amidon, University of Michigan.

MS. BHATT: Thank you, Dr. Amidon.

Next, we have Dr. Donovan.

DR. DONOVAN: Good morning. Maureen Donovan from the University of Iowa.

MS. BHATT: Thank you.

Next, we have Dr. Hancock.

DR. HANCOCK: Good morning. William Hancock, Northeastern University.

MS. BHATT: Thank you.

And next, Dr. Li.

DR. LI: Good morning. This is Tonglei Li from Purdue University.

MS. BHATT: Thank you, Dr. Li.

Next, we'll move on to our FDA participants. First, we have Dr. Lee.

DR. S. LEE: Hi. This is Sau Larry Lee. I am the deputy director of science from the Office of Pharmaceutical Quality.

MS. BHATT: Thank you, Dr. Lee.

Next, Dr. Yu?

DR. YU: Good morning. This is Dr. Lawrence Yu, director of New Drug Product.

MS. BHATT: Thank you.

Dr. Tsinontides?

DR. TSINONTIDES: Good morning. Stelios Tsinontides, director, Office of Pharmaceutical Manufacturing Assessment. Thank you.

MS. BHATT: Thank you.

Dr. Wu?

DR. WU: Good morning. This is Larisa Wu. I'm the associate director for Science and Communication in the Office of New Drug Products in OPQ.

MS. BHATT: Thank you.

Dr. Raw?

DR. RAW: Hello. I'm Dr. Raw, and I'm the associate director for Science and Communication in the Office of Lifecycle Drug Products, in the Office of Pharmaceutical Quality.

MS. BHATT: Thank you, Dr. Raw.

Next, we have Dr. Shah.

DR. SHAH: Hi. This is Rakhi Shah. I'm associate director of Science and Communication in the Office of Pharmaceutical Manufacturing

Assessment, OPQ, CDER.

MS. BHATT: Thank you.

And Dr. Welch?

DR. WELCH: Good morning. I'm Joel Welch, the associate director for Science and Biosimilar Strategy in the Office of Biotechnology Products, in OPQ, also in CDER. Thank you.

MS. BHATT: Thank you, Dr. Welch.

That concludes panel and FDA introductions.

Over to you, Dr. Morris.

DR. MORRIS: The statement to be read now is the following.

For topics such as those 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 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, and we'll look forward to a very exciting and

productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members 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 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 topic or topics during breaks or lunch. Thank you.

Now, Rhea Bhatt will read the Conflict of Interest Statement for the meeting.

Over to you.

Conflict of Interest Statement

MS. BHATT: Thanks, 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 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, including those of their spouses or 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, as part of CDER's continued effort to provide key updates on modernization of quality assessment, the committee will discuss the next stages of Knowledge-Aided Assessment and Structured Application, KASA. The concept of KASA was envisioned in 2016 and discussed at the

Pharmaceutical Science and Clinical Pharmacology Advisory Committee on September 20, 2018 as an IT system that modernizes FDA's assessment. Through the development, testing, and implementation of various KASA prototypes, the KASA system has been refined over the course of multiple years.

FDA will seek input on the vision and plan to expand KASA over the next five years to include drug substances, all generic dosage forms, new drug and biologics applications, and post-approval changes. Moreover, FDA will seek input regarding the need for advancing digitalization in KASA, including data standardization and mobilization of data from cloud-based servers.

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 this meeting. To ensure transparency, we encourage all standing committee members and temporary voting

members to disclose any public statements 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 non-voting industry representatives, acting on behalf of regulated industry. Drs. Rogge, Rothe, and Venkateshwaran's role at the 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 related 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.

Dr. Morris?

DR. MORRIS: Thank you, Rhea.

At this point, we'll proceed with the FDA presentations, beginning with introductory remarks from Dr. Larry Lee.

Dr. Lee?

FDA Presentation - Larry Lee

DR. L. LEE: Thank you.

Good morning, everyone. I'm going to kick off the second day of this advisory meeting, talking about the vision and roadmap to advance our quality assessment. First, it is important to talk about the importance of pharmaceutical quality. In general, a quality product means that it consistently meets the expectations of the user. Drugs are no different.

To understand the importance of pharmaceutical quality it is necessary to relate pharmaceutical quality to a patient's perspective. Specifically, patients like you and me expect safe

and effective medicines with every dose they take. Pharmaceutical quality is consistently meeting standards that ensure every dose is safe and effective, free of contamination and defects. It is what gives confidence in their next dose of medicine.

The Office of Pharmaceutical Quality, the so-called OPQ within CDER, oversees the quality of many drug products, including new drugs, generic drugs, biologics, biosimilars, and over-the-counter drugs. All drug applications have a quality or the so-called chemistry manufacturing controls, CMC, section. One of the core functions of this office, OPQ, is to assess this section of all the drug applications.

Specifically, our assessors evaluate how a product is designed, how it is manufactured, and the manufacturing facilities to ensure a safe and effective drug is being delivered consistently to the intended patient population. OPQ also assesses product and manufacturing changes after a drug is approved as part of a continuous improvement to

ensure quality is maintained.

Although there have been noticeable improvement in the drug development and manufacturing arena, regulators like us are still facing challenges in assessing quality information in drug applications. The number and the complexity of the applications have increased dramatically in the last few years, and at the same time we are tasked to evaluate these applications in a shorter time frame with similar resources.

Let me just give you some idea. Every year at OPQ, we evaluate, on average, more than 3,000 INDs, more than 200 new drugs and biological applications, more than 900 generic applications, and more than 10,000 post-approval changes submissions. One problem is we receive all this information as unstructured information in PDF files.

As a result, our assessment of freestyle, unstructured narrative, in which a significant portion of the documents are pretty much a summarization of information or copy-and-paste data

from the submissions, such a system or approach can pose problems because the risk assessment and evaluation of the applicant's mitigation approach gets dispersed in lengthy narrative.

Oftentimes, there can be inconsistencies, and ineffectiveness, and encumbered ability to share knowledge and efficiently manage FDA's repertoire of approved drug products and facilities. Our decision-making capacity may not be optimized because assessors evaluate each application, or the information in each application, in relative isolation without fully assessing the wealth of information at FDA's disposal.

We should realize that good knowledge management is really essential. In the context of technology advancement, we cannot continue to assess quality through our traditional narrative-based evaluations, using unstructured text summarization of application information and copy-and-paste data tables.

I would like to point out that this practice

did not allow for easy knowledge sharing and management of quality across product lifecycles and overall modernization of assessment. Instead, in order to be most efficient, we want to take advantage of modern information technology tools and platforms that emphasize structured data and the ability to capture critical information. This will then move to highly specific -- stored in a predefined format -- structured data, which will enable us to achieve a systematic approach to risk assessment, resulting in much more consistent, high-quality evaluation and decision making. The idea here is based on efficient information exchange, knowledge management, and data analytics.

At OPQ, we recognize the need to modernize our quality regulatory assessment, and we are currently taking steps to transform our evaluation from narrative information to more structured data and a systematic approach for risk assessment powered by information technology, so we can best capture and manage knowledge.

This concept was envisioned in 2016 and

discussed at the Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting on September 20, 2018, as KASA, an IT system that modernizes FDA assessment. As part of the assessment modernization effort, we created KASA, a knowledge management system meant to modernize the assessment of drug applications.

KASA stands for knowledge-aided assessment and structured application, which is really the IT platform internal to FDA. It is a database platform for structured quality assessments and applications that support knowledge management. We already have a fundamental knowledge base of the products, manufacturing processes, and facilities. As new information comes to us in the application, we want to be able to assess that information in conjunction with our existing knowledge and achieve knowledge management throughout the lifecycle of the drug product we evaluate.

While KASA is a key driver, to fully achieve our vision of advancing quality assessment powered by IT and multidisciplinary approaches, we must

integrate KASA with other key OPQ initiatives for our program I'm going to briefly describe here, although the focus of this advisory committee is on KASA. These initiatives and programs include QSD, IQA, M4Q, and PQ/CMC, and in the next few slides, I will highlight what they are and explain how they relate or connect to KASA to provide a comprehensive framework or approach, enabling more effective and efficient quality assessment.

KASA, the focus of this AC meeting, is a system that takes advantage of IT technology and innovation to modernize regulatory submission, assessments, and registration using structured data, advanced analytics, and knowledge management. KASA captures and manages knowledge and incorporates rules and algorithms for risk assessments, and enables the assessor to perform advanced analytics, resulting in a comprehensive and science risk-based structured assessment.

To maximize the benefit of KASA, we will need information and data that are well structured and organized. This is where I think M4Q and

PQ/CMC come into play. ICH M4Q is currently under revision. It will reflect advancements in technology and regulatory approaches so it can continue to provide harmonized guidelines or guidance on the content and organization of the quality information in an application across regulatory agencies.

KASA will use information from M4Q for quality assessment to really facilitate approval and lifecycle management and accelerate patient and consumer access to critical medicine. For KASA to effectively use information from M4Q, it links to PQ/CMC, which stands for pharmaceutical quality, chemistry, manufacturing, and controls.

PQ/CMC is still under development. It provides standard data elements and data exchange standards to the industry so the future submission will contain structured quality information to be used by the KASA system. It is a critical enabler for M4Q implementation and long-term effective knowledge management, therefore to enable an effective and efficient quality assessment and

fully take advantage of KASA, we need an application that incorporates both organizations as defined by M4Q and data standards as defined by PQ/CMC.

To assure seamless integration of all the relevant quality disciplines in assessment of applications using KASA, we have integrated quality assessment teams and processes. In this context, the assessment is done by a multidisciplinary team following a defined business process with clear roles and responsibilities, and this figure shows the relationship of integrated quality assessment with respect to KASA, M4Q, and PQ/CMC.

An assessment of an approved product should leverage relevant information available about the product and how and where it will be made. The Quality Surveillance Dashboard, another IT system, the so-called QSD, will augment KASA and allow us to use current and historical information about both the facilities, as well as the applicants, in one place. Together, with the information from the application, using this IT platform, we will be

able to conduct a comprehensive assessment of the application by considering all relevant risks.

I want to emphasize these advanced tools or systems are expected to enable us to do our quality assessment more effectively and efficiently, applying the same quality standard. Let me just emphasize one more time, we are going to apply the same quality standard regarding using this IT platform or using the traditional way we do it. At the same time, using this IT platform will really help us to improve the consistency of our quality assessment.

Among these tools, process certainly plays an important role in ensuring the quality and consistency of our assessment. In this context, some key features of KASA worthwhile highlighting here are: captures and manages knowledge across lifecycle of a product; establishes rules, algorithms and analyses to inform regulatory decision making; focuses on structural regulator quality assessment; and provides data integration with other FDA systems. My colleagues will

elaborate more about these key features of KASA in their presentation later today.

OPQ is focused on continuing process development following the release of KASA for generic solid oral dosage forms. Our vision over the next five years includes expanding KASA to drug substance, including DMF; new and generic applications; all generic dosage forms; INDs; new drugs; and biologics applications, as well as post-approval changes.

In conclusion, KASA is one of the approaches we are working on to drive innovation in our quality assessment by utilizing 21st century information technology. I would like to thank our OPQ and CDER staff, as well as CDER leadership for their support of KASA development and implementation, and thank you.

Next, I would like to introduce the next speaker, Andre Raw, to talk about and summarize KASA accomplishments today. Thank you.

FDA Presentation - Andre Raw

DR. RAW: Hello. I hope everybody can hear

me well. I want to thank the organizers of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting to discuss the accomplishments of KASA today, especially in the context of the ANDA program and as a prelude to its extension to both the NDA and BLA programs. But before I proceed, it is important to explain why we set out to develop the KASA system.

We did this because, historically, assessments have relied heavily upon freestyle narrative text consisting of unstructured information, summarization of application information, and copy and paste of data from the sponsor, and from our perspective, the system encumbered our ability to share and manage our knowledge within FDA's repertoire of approved drug products and facilities. It also hindered our decision-making capabilities, as assessors evaluated each application in relative isolation without fully assessing the wealth of information at FDA's disposal.

Due to these limitations of our traditional

narrative assessment, as early as 2016, a KASA type system was envisioned as a means of modernizing FDA's assessment, so we introduced this system that would utilize structure data as opposed to freestyle narrative and developed advanced analytics to enable knowledge management of our repertoire of drug products and facilities.

So over the course of six years, subject matter experts at various levels developed, tested, implemented, and refined various homegrown structured assessment prototypes as a prelude to our KASA system. Taking these learnings from these various prototypes and working with our colleagues in the Office of Business Informatics, the Office of Strategic Programs, and the Office of Information and Management Technology, all these elements culminated in the launch of KASA in the FDA's NEXUS IT platform system in the beginning of 2021.

Following this release, termed KASA 3.0 in our NEXUS IT platform in 2021, all incoming ANDAs for solid oral dosage forms were reviewed under

this modernized and structured review system, which we termed KASA.

What I would like to do is to go over the KASA platform and illustrate what we can achieve today. This slide shows the actual landing page of the KASA system that assessors utilize once they log on. As you can see, the KASA system is currently used by the three review disciplines that evaluate these ANDAs, including the drug product discipline that reviews the drug product design and its controls; the Office of Pharmaceutical Manufacturing Assessment that reviews the manufacturing process and associated facilities; and the biopharmaceutics discipline that reviews the dissolution as well as other aspects related to the biopharmaceutics performance.

Let me go more specifically into the drug product discipline to show how KASA works. One of the important facets of the drug product review is to capture or flag the inherent risk of the various drug product critical quality attributes such as dissolution, impurities, [indiscernible] assay

associated with a drug product, and also-- that's the first thing, not only to capture the initial risk, but also to capture how these risks are controlled or managed based upon the drug product design or testing control strategies.

As mentioned, one impetus of the KASA structured review is to ensure more consistency and objectivity among our staff, and this is achieved based upon objective risk ranking algorithms, which is the first thing, and structured descriptors for capturing risk control, which is the second thing I would like to discuss.

The first, the KASA has encoded algorithms in its software that capture inherent product risks associated with these various critical quality attributes present in the drug product, and these algorithms, using a failure mode effect and criticality analysis -- or FMECA for short -- system included in the KASA IT software, objectively rate these inherent or initial critical quality attribute risks as low, medium, or high. This prospectively flags to the assessor the area

of high risk that needs to be focused on and, conversely, the areas of lower risks that the assessor may not need to spend so much time on.

Secondly, and I think equally as important, KASA captures the risk mitigation on a control, based either upon formulation design or control measurement, control strategies, using a drop-down of descriptors of structured knowledge for formulation, design, and control strategy measurement that is typically used in pharmaceuticals.

For example, if the CQA flag is high for polymorphous transformation of an amorphous form, one of those fundamental strategies in our drop-down, if you select it, it would say, "the addition of a stabilizing excipient to avert crystallization of the amorphous form," amongst other drop-downs. That's one of many. In essence, these drop-downs, which are based upon our fundamental scientific understanding of pharmaceuticals, are descriptors of that structured knowledge for formulation design and control

strategy.

The importance of this is that it provides consistent scientific dialect in KASA assessments, which were previously lacking in our freestyle narratives. And by having these consistent descriptors and dialect, it not only ensures consistency of our assessments, but more importantly it enables knowledge management, as I will show later.

In addition, as I mentioned, our traditional assessments were long narratives with cut and paste from submissions, which as indicated, it covered our ability to share and manage our risk information and knowledge amongst the many applications that we have.

Here the slide depicts how the KASA would also, in addition, enable more compact assessment. Once the assessor selects the fundamental formulation strategy to mitigate the CQA risk, then they have the option to explain via a short narrative how that formulation strategy was specifically applied to the application.

For example, if they select a drop-down stating that an excipient in our drop-down menu is used to stabilize an amorphous form, they would write after that drop-down a short narrative explaining what that excipient is, the API, or active pharmaceutical ingredient, an excipient ratio, and how the sponsor systematically optimized those features of the formulation in their pharmaceutical development.

Rather than cutting and pasting large sections of the pharmaceutical development report, which we previously used to do, they would simply link to their corresponding page from the eCTD submission from the sponsor. And by adopting this strategy, this makes for a more compact assessment where all the information is really assessable in a highly structured format.

Let me just take a step and put this all together. One of the reasons we developed KASA was to enable knowledge management, and this is nicely illustrated here. Based upon adopting the same inherent risk algorithm and a drop-down of

structured descriptors for risk control, we enable drug product risk analytics and can now objectively compare risks across a drug product line, e.g., we can compare an application of various generics approved across the product line and the corresponding NDA or RLD as to how these risks are controlled among the different applicants, and different applicants will have different ways to control these risks.

For example, first we can see all these products have the same inherent risk for assay failure due to the instability based upon our algorithm, which is used similarly in our application. So we have the same inherent product risk, which is high.

Secondly, using this structure of risk control, we can now objectively see why one manufacturer mitigated this risk by a de minimis approach of relying solely on a stability testing program, which was captured in that drop-down, and others incorporated, to varying degrees, formulation design features, which were similarly

captured in those drop-downs that I alluded to previously, to mitigate this risk for over-and-above testing.

By having this structured review format in the KASA, we can now run risk analytic reports in KASA to compare these relative product risks among applicants, depending on the risk control selected on those drop-downs; and thus, in the drug product, whether in the supplements or in determining inspections at facilities, we can run these reports to allocate our resources to the products we believe are at high risk.

Can I ask a question? I can't see the document.

DR. MORRIS: I think we've lost the slides, Joanna.

(Pause.)

DR. RAW: Okay. I'm going to go to that slide. I don't know where you lost the slides, but I think I have an idea.

DR. MORRIS: Yes. I think 32 was the last slide.

DR. RAW: And the point that I really wanted to mention was by really having this structured review format, both within the initial risk and in the risk control strategies, we can now run risk analytic reports in KASA to compare these relative product risks among the various applicants, depending upon the risk controls that they select to do so.

Some will do better; some will do more than others. Thus, in the drug product lifecycle in the supplement or determining inspections at facilities, we can run these reports and use this information strategically to allocate our resources to the products we believe are at highest risk.

So similar to capturing risk control in a structured format, we can also capture the drug product control strategy such as specifications and a generalizable rationale for the control drop-downs, similar to what I showed you before for the risk.

By having these structured formats for the controls, similar to the risk analytics, we can

also run reports that compare these attributes across a product line; so we can easily determine if an incoming ANDA for a product line -- we can easily determine with these reports, that if the ANDA would have any of these attributes, we could determine whether the ANDA with these attributes was within the space of the approved products within that product line, and conversely, we could determine if the ANDA had attributes that were outside the appropriate space of that product line. As such, this can be used to inform the risk of the ANDA in question. So that's really the power of these analytics.

The next slide that I would like to go to is to illustrate, a little bit, the structured review in the manufacturing integrated assessment, just very briefly. As you can see, the manufacturing assessment is very similar conceptually to the drug product assessment, but rather than focus on drug product design, measurement, and control, it focuses on the risks of the various unit operations that may affect the various drug products' CQAs.

It similarly identifies the inherent risk of the unit operation via algorithms, as we did for the drug product, and then also in the corresponding risk control via drop-down, similarly like we did based upon the drug product. But in this case, the drop-downs for the risk control are based upon a combination of factors of both KASA's factors as well as facility factors.

I know this will be covered in more detail in the next presentation, but the bottom line I want to emphasize here is that similar to what we have shown you for the drug product, we can now run reports, based upon the structured data, to discern the site's capability to manufacture these various dosage forms based upon their history, and particularly their history with these unit operations, and such reports will review the risks of the sites they have demonstrated capability to run those unit operations, and with that degree of scrutiny required as we make the decision to inspect or not inspect these facilities.

Finally, let me briefly go over the

biopharmaceutics assessment in KASA. Biopharmaceutics are complex, and partly because of that, rather than invoking a paradigm of three risks levels -- low, medium, or high -- for each CQA, as we did for the manufacturer of drug product for inherent risks, biopharmaceutics invoke five risk levels, from very low, low, medium, high, and very high.

At one extreme of very low, a simple standardized dissolution test would be sufficient to mitigate the risk for that product, and at the other extreme of very high, in vivo studies to develop an IVIVC or IVIVR may be needed to support a patient-centric dissolution test. Rather than invoking risk algorithms to determine each of these risk levels, as we do for the product, the manufacturing, the biopharmaceutics assessments use predefined decision trees that are encoded within our KASA software to guide each assessor as to where the product falls within these various risk levels.

Similar to drug product integrated

manufacturing risk assessments, these structures not only provide for more objectivity of risk as we assess these products, but also enables KASA analytic reports related to various aspects of biopharmaceutics across a product line.

With all this effort toward development of KASA, I believe we have made significant strides. I can say with confidence that we are certainly realizing our vision of knowledge management, and this is evidenced by the fact that today, KASA has 17 analytic reports that provide assessors with critical information for making informed decisions based upon KASA's structured knowledge of drug products and facilities. These reports were not previously available in our unstructured narratives, so this is quite an important development.

Just as important, we have made significant steps towards solidifying the use of KASA amongst our assessors, and since the Go-Live in early 2021, over 1400 reviews across the three review disciplines have been finalized for ANDAs for solid

oral dosage forms.

In sum, with the KASA 3.0 launch, we have made a significant step toward realizing our vision of structured review to ensure objectivity in knowledge management, but this is just one step of many in our roadmap as we move this paradigm to drug substance, other dosage forms, INDs, NDAs, and BLAs, as will be discussed later by my colleagues.

I just want to mention that next in our journey -- and I think we're pretty close to it -- we are on track to fully deploying this KASA format to the drug substance evaluation early next year. The slide shows the KASA assessment card in the NEXUS platform that we intend to deploy in the first quarter of 2023, and with this future release, this will realize -- similar to what we have achieved for the drug product, manufacturing, and biopharmaceutics disciplines -- the concept of a structured review, and with that more objectivity and also knowledge management of drug product risk, based, for example, on the synthetic pathway.

What is really, I think, very exciting is

that this is not only applicable to drug substances, [indiscernible] ANDAs, or DMFs, but also extended to NDAs moving forward. This is the prelude to the extension of KASA's initial inception for ANDAs and BLAs, as will be discussed by Dr. Wu's and Dr. Welch's later presentations.

To conclude, the KASA system measures risk associated with how a product is designed and manufactured using established rules and algorithms. It establishes how the risk is mitigated and controlled through standardized drop-downs that capture product design features, as well as measurement features. It assesses the manufacturing controls and demonstrates the capability of facilities involved in a structured format. It uses all this information, and it really takes knowledge management to a whole new level to show that we can provide oversight through the product's lifecycle based upon the risk. Thank you very much.

FDA Presentation - Stelios Tsinontides

DR. TSINONTIDES: Good morning, everyone.

This is Stelios Tsinontides, office director of the Pharmaceutical Manufacturing Assessment of OPQ. I'm excited to be joined today also by Dr. Shah, who is our associate director of Science and Communication, and who has been leading our experts in collaborating across the various offices and disciplines to bring forward these exciting systems that we are presenting today.

My presentation today will cover the overview, again, of how the KASA tool integrates manufacturing assessment at the commercial scale, and provide you with a roadmap of what's coming next, and then Dr. Shah will describe the salient features of how we have built into KASA to enable our SMEs to evaluate systematically the risk of the proposed manufacturing at the commercial scale and facility.

As described by our recent speakers, KASA employs models that allow our integrated team to evaluate the drug product. It's also a dedicated model that incorporates manufacturing integrated assessment and also a biopharmaceutics assessment.

As noted earlier, this system allows us to intake the application data and capture the critical assessment information in a very structured format that can be easily viewed by all of our SMEs performing the assessment, share this information readily, and utilize it to determine what actions are necessary to be taken on the application.

As noted again, our KASA manufacturing assessment is utilized by our SMEs to measure the risk associated with the product design and manufacturing, using established rules and algorithms, and especially assess the manufacturing controls and the capability of the facility to manufacture the product over the lifecycle of the product beyond actually the approval point, and basically evaluate the risk, and mitigation, and the control throughout these manufacturing lifecycles, and bring the facility into our assessment, and basically take this knowledge management to a whole new higher level of the product lifecycle.

As noted earlier, our integrated quality

assessment is performed by a collection of disciplines and teams that are shown on this slide. The Office of Pharmaceutical Manufacturing Assessment is concentrating on assessing the application element related to microbiology, facility, and process, and also linked into any inspection information that we have around the facility, and especially in addition to also determining whether a facility requires a pre-approval inspection, and work together with our other offices to perform in these facilities, and obviously ensure that the information is captured into our KASA system.

Here is a broad overview of the KASA roadmap related to the manufacturing. As noted earlier, we already have implemented the manufacturing models for the generic solid and data analytics with the 3.0, as we launched the system in 2021. What we anticipate to expand KASA this coming fiscal year is to expand the model to include manufacturing and microbiological assessment models for the generic liquids and data analytics, and then continue to

expand KASA with the manufacturing models for the NDA solid, including established conditions and data analytics, and then follow up with the liquid formulations, and eventually expand KASA to include biologics micro and facility model.

At this point, I will welcome Dr. Shah to describe a little bit more detail of what entails inside KASA for manufacturing.

Dr. Shah, please take it from here.

FDA Presentation - Rakhi Shah

DR. SHAH: Thank you, Dr. Tsinontides.

Hi. This is Rakhi Shah, and I'm going to cover a little bit in detail what we do in OPMA and how we are utilizing this KASA currently, and what are our future plans. As previous speakers mentioned, we have launched our assessment in KASA for solid generic applications for all three disciplines, including product quality, manufacturing, and biopharm. Dr. Andre Raw explained drug product quality assessment in KASA, and this part of the slide presents manufacturing KASA.

We are utilizing smart templates to do our assessment, which is based on science and risk principles. We are utilizing those principles even outside of KASA, but I will show you how we are organizing this KASA and other assessments and structured format.

As Andre said, the structured assessment is very helpful when we want to call it out and when we are doing our future assessment. The assessment is organized starting with overview page, where some of the information is auto-filled from the data that we get from our 356h form, such ANDA number, drug substance, drug product, name, then list of facilities, function, addresses, et cetera. Of course, we verify that information -- our assessors do that -- and then the KASA template is activated.

First thing we perform is, of course, initial risk assessment or initial risk analysis. We start with facilities, then OPMA will maybe evaluate all commercial facilities, including drug substance, drug product, testing, and primary

packaging facilities. We have built in risk-based algorithms, which actually includes some of the factors such as prior facility experience with related dosage forms, related processes. Then if we have any quality concerns from that facility or compliance issues, all of that is included in our algorithm. Based on the information that is included in the application and what information we can find for the same facility from previous applications, we go through that systematic risk assessment.

For doing this, we currently have to go through forms, establishment, inspection reports, recalls, field alert reports, and compliance case reviews. A lot of this information is buried in our Word documents or PDFs, so it takes a lot of time, but that information is found, and then we try to use that. This is where KASA comes to our rescue, where information is systematically captured, and that I will show you in the next upcoming slide how we use that information.

So that is the facility, and then we

understand whether the facility has risk factors or outstanding risks. We will need to do a pre-approval inspection, or in cases where we have adequate information and adequate confidence that that facility can perform this product or processes without our presence at the facility, we could waive the inspection or we could utilize some other alternate tools that you might have come across. So that is what is done in this facility risk module.

Next is the manufacturing risk assessment module. Since OPA may be focused on drug product manufacturing processes, we perform our initial risk assessment. Again, we use risk-based algorithms. Andre Raw mentioned about failure mode effect analysis. We utilize the same principle, where we have our risk factors that are based upon the unit operations and based upon the facility. We incorporate all the factors, in addition to drug substance and excipient factors, as well as the drug product design factors.

We look at this holistically. We have

developed our algorithm based on that, and we take the application information and the facility information, and then that gives us the scoring of low, medium, and high, and we have a cutoff. Again, this FMEA [ph] was developed three years ago in OPMA, so we are still modifying and looking at how the risks scoring can be modified based on what information we get.

So it's a continuous improvement of the model, but we use that, and then that guides our assessor in doing the unit operation assessment, or the assessment of facility and unit operation, either in abbreviated fashion or in full fashion, depending on what risk score we get.

For example, if we get a low score for, say, unit operation, the assessor doesn't have to spend a whole lot of time in assessing that unit operation, but if the risk scoring is high, of course they will look into all the process development, product development, data, and all the other in-process controls and factors, as well as scale up information and assess that in the unit

operation module, which is the fourth module as shown in this slide.

If the scoring is low, the assessor doesn't have to do this in-depth assessment in the unit operation section. They can do abbreviated, and then the final risk assessment is done manually. So we won't have automatic algorithm for now. We still do qualitatively the final risk scoring, so any sub-risk scoring is quantitative, but our final risk scoring is qualitative in OPMA.

Under other considerations -- I'm just skipping microbial assessment for the time being, but other considerations, we evaluate the batch record, executed and master batch records, any yield, reconciliation data, as well as hold time and comparability protocol. Now, with ICH Q12, we have PACMP, which also will be evaluated when we have NDAs in the module, and process validation if the data is submitted. All this is assessed in the other considerations section.

Microbial assessment, in OPMA we perform microbial assessment also since we have our

microbiology colleagues in our office, and we try to do that in an integrated fashion. Right now, since we only have solid generics, we are doing non-sterile microbial assessments for drug product control, and then assessment summary, which is the last module in our manufacturing KASA. And here we have the discipline summary for manufacturing, the discipline summary, as well as the updated risk table. That is present in our assessment summary.

Since we already have our solid generics experience, now we have started developing our liquid generics since that will be coming up next in KASA, hopefully. This internal development has been going on for a year or so. We are starting to use our solid modules as a backbone so that we can use that as a leverage and develop our generic solid modules.

With liquids, we also include solids. There are some salient features. We have unique unit operations that we need to cover, so we will have the unit operation module expanded. And then we have combination products, which comes with liquid

products, so we have a combination product module. For example, we will need to incorporate a device facility in our facility assessment, which is not currently present in our solid module.

With these modifications, we would be able to achieve other ANDA drug product liquid modules. With liquid, we will have to have the sterile modules also, so microbiology modules for aseptically and terminally sterilized products will be developed, which, again, the Division of Microbiology Assessment colleagues have been helping us develop this module.

For manufacturing, we also take a look at extractable/leachables from manufacturing assessment to [indiscernible], et cetera, so we will need to develop that module. We already have our risk-based algorithm for extractable/leachable, but again, that is being refined and finalized. When we have that, we will incorporate those algorithms into the liquid module. Our hope is to enhance the current solid module to incorporate liquid modules with considering all this in mind.

Next, as Dr. Tsinontides mentioned, we are developing new drugs. KASA, again, OPMA made it responsible for developing manufacturing, which includes facilities, so we have already started. This effort is based on -- again, we will take other drug product generic modules into consideration, however, when it comes to NDAs, there are some unique considerations that we need to do.

For example, I was heavily involved in Project ORBIS for oncology product reviews, which utilizes the collaborative global approach of assessment with other regulatory agencies across the world. We utilize product quality assessment aid for that program, so that is kept in mind when we start developing our manufacturing modules from NDAs, as well as real-time oncology release because that needs the consideration.

Now we have an expedited assessment program, so all that should be kept in mind. We do keep in mind that in OPMA, we assess not only ANDAs; we also assess NDAs already for manufacturing, so we

have quite a lot of experience of how we can build the KASA modules, keeping the flexibility that will be needed for NDAs in mind.

While we develop NDAs, we will need to develop non-sterile liquid modules for microbiology, which is not present currently in our drug product models since, of course, it is non-sterile solids, and non-sterile liquids will have a little bit of differences when it comes to microbiology.

Yesterday, I hope you guys were present. We heard about ICH Q12 established conditions. We have seen that during our pilot program that we got NDAs or supplements containing established conditions, so we are going to build that capability along when the NDA gets into KASA, so that will also cover the post-approval change management protocol.

As I alluded to earlier, underneath other considerations, comparably to the protocol currently, we will enhance those to cover PACMP into that. And when the NDA comes in, we also are

trying to incorporate some of the complex dosage forms, which are not present currently in the generic platform; for example, transdermal and some of our dry product inhalers, and topicals, which we do not currently have in solid generics, so that we can enhance our NDA modules to include those.

Next is biologics. Again, Dr. Joel Welch will cover in detail what they are covering in terms of drug substance and drug product, and as Dr. Tsinontides has mentioned, OPMA may be focused on facilities and micro assessment for biologics. Those modules would be a little bit easier for OPMA to develop since we also have an NDA in planning for the micro and facilities module. We are thinking that with modification, we can utilize this similar concept for biologics.

Of course, a lot of things will be looked at when we develop the biologics module because there are some unique considerations which need to be considered. We will have established conditions and PACMP incorporated, and we are working extremely closely with our Office of Biotechnology

Products when we are developing this KASA module for biologics.

In OPMA, we lead the facilities inspection for biologics as opposed to small molecules. That is led by ORA, so those also need to be considered. But again, we are in the very, very preliminary stage for biologics KASA, so I don't have a lot of details. This is under construction, as you can see on this slide.

This slide, up to now, I showed you what we have done and what we are doing, but the main power lies in the analytics that we get, the analytics package from KASA. Dr. Andre Raw showed this same slide, so I'm not going to go into too much detail about this slide.

But again, as I mentioned earlier, so far, our assessments and inspection reports have been in PDF format, and it is very cumbersome to get information if we want to gather information. It takes some time; not only hours but sometimes days to gather the data that we can utilize in a meaningful way to make our informed decisions.

With KASA, we are able to gather, actually, the data. The analytics package is formulated in a way that we can utilize that to make an informed decision.

As Andre mentioned here, we can look at the dissolution as a CQA, different unit operations, and what process and facility factors and risk mitigation strategies the facility is using or the applicant is using. This is comparing the same CQA across different unit operations, however, we can utilize different applications and RLD information in a very structured way, and very quickly so that we can make informed decisions.

Another main thing that I wanted to show you is how we are utilizing these data analytics to conduct our manufacturing facilities assessment. Here, it's a little difficult to see, but consider that I got an application, which is listed as XXX. Again, this is all mock data. That came into my queue today, and I have this facility, which is Y facility, and then I have a profile code. These profile codes are in the IOM, operation manual, for

the other ORA colleagues. And here there is a slight error. It should be listed as TTR.

So consider that I have an extended-release application today that came, and I need to now see at this facility what kind of information I can gather. I'm particularly interested in functional coding, whether the facility has done any functional coding prior to this application and whether I can gather the data quickly. Before KASA, if I want to look at it, I have to look through the inspection report; sometimes I may or may not find. I have to call my ORA colleague if they remember they covered this. They might have seen this, but they might not have put it in the EIR report because they did not find any concerns.

It took a lot of time to gather that data, but with KASA, this output table is generated automatically, based on the information that we have included in other applications in KASA. For example, there are four or five other applications which utilizes the same facility, YYY. That application information is presented here, so I can

look at not only what drug products were covered, but also I can look at what were the unit operations covered in those applications or in those at that facility.

Since we are linking every unit operation with facility in KASA while we are building other reviews, that information can be easily accessed. Now, I can see whether the facility of interest was present in other applications and whether they utilized any types of coding unit operation. Depending on more information I can find, I can say, oh, the facility has prior experience, and maybe it's very related to the product that I am doing; utilizes similar drug load; utilizes similar unit operation; and I may be able to waive that inspection, or I can even utilize some of the alternate tools if I have some residual risk or, again, we can indicate whether pre-approval inspection is needed.

All these decisions are made in OPMA, whether the facility will need pre-approval inspection or use of alternate tools. So,

actually, data analytics is extremely powerful. This gives us that kind of visibility and helps us make informed decisions. Then these decisions are sent to ORA, and we work very closely with ORA in conducting inspections, finalizing inspections, et cetera. This is the most important slide that I really wanted to show but, again, there is a slight typo. TTR should be listed in the profile code in the input table.

This again was covered by Dr. Andre Raw, how we are utilizing, and I can now gather information on the site, which was present in some other application. I can look at sites' capability to manufacture related dosage forms. I can even look at the compliance history and any approved control strategies. I showed you one example of unit operation, but we are able to capture control strategy also for those unit operations.

I can compare with the pending application, and if the capability is there, if the control strategy is present, I may be able to lower the risk. I don't have to really dive down into the

review or dive down into the facility review; however, if I can't find any information or the proposed site has not demonstrated that capability, then maybe I will be able to spend more time. So we can utilize our time wisely. We can do these reviews quite efficiently.

To summarize, KASA is live for generic solids. We hope to utilize the modules and modify the modules to make them amenable to NDA and biologics in the future. This will actually improve efficiency and consistency. We can have what we have been talking about, a lifecycle approach. KASA makes that possible.

I hope I gave you a good talk of what we do in OPMA and how we are utilizing KASA. Next, Larisa will present KASA development efforts for new drugs.

Larisa, it's all yours. Thank you.

FDA Presentation - Larisa Wu

DR. WU: Thank you, Rakhi.

Good morning, everyone. My name is Larisa Wu, and I'm the associate director for Science and

Communication in the Office of New Drug Products in OPQ. As mentioned today, I will talk about application of KASA to new drugs.

So far, you heard from my colleagues about the successes that we just registered when using KASA for quality assessment of generic applications. But moving forward, OPQ also plans to build on these successes and apply all the lessons learned from KASA for generics in order to expand the KASA program to new drug assessment.

One such lesson learned and, really, the key to success that we applied over and over -- with each KASA release, we applied involvement of the user of the KASA system, which is the assessor, in every stage of the project, starting with development and testing; continuing with implementation; refinement of the prototypes; and finally ending with communication of the requirements to the IT group, and completing also a user testing ahead of each KASA full IT release.

For development and implementation of KASA for new drugs, we're taking a sequential approach.

First, as mentioned, we will implement KASA for drug substance, which is applicable to assessment of drug substance information, submitted in drug master files, generic applications, and I guess more importantly new drug applications. This release will happen at the beginning of 2023 in the CDER IT platform as part of KASA 4.0.

It is worth mentioning here that the KASA for drug substance prototype actually has been used in Office of New Drug Products since April 2021, and dozens of assessments have been completed using this prototype. Second, we are also developing KASA for IND, and we're doing this through development and testing of a smart prototype for review of commercial and non-commercial INDs.

Third, as mentioned, we plan to adopt existent biopharmaceutics and manufacturing interfaces that have been developed for review of generic applications to new drug assessment needs. And not lastly, we are also working on developing KASA for assessment of drug product information that is being submitted in NDAs.

Rakhi and Stelios already told you about efforts that are being done in the manufacturing arena, so in my presentation I will focus on our plans for development and implementation of KASA interfaces for drug substance, INDs, and new drug products.

I'm going to start with KASA for drug substance, and, really, the next six slides that you're going to see include the highlights of two and a half years of work that we put into developing and implementing KASA for drug substance.

So first, let's see what determined us to develop this interface. I've listed here on the slide a few reasons. There may be more, but the thing that I want to highlight here is reason number one, which is to quickly identify problems with the drug substance synthetic pathways that can potentially generate high-risk impurities.

I think you are all aware of the recent situation that we faced related to nitrosamine impurities in a pharmaceutical product. Rakhi

already mentioned in order for us to gather data, we spent countless hours researching information that is needed to mitigate these risks. In the future, using KASA, we hope that we can quickly respond to these situations by quickly retrieving information from KASA in a matter of seconds.

Not least important, through developing KASA for drug substance, we wanted to make sure that consistent assessment standards are applied for drug substance information that is being submitted in new drug applications, generic applications, and drug master files, as I said, and we wanted to facilitate the assessment, and through the use of KASA analytics inform our decision making and eventually increase our efficiency.

Not lastly, we wanted to achieve a milestone regarding KASA implementation in the CDER IT platform, and once KASA for drug substance will be released, have a complete integrated quality assessment, what we call an IQA review, for solid oral products, and it is done in the CDER IT platform.

We started this project back in December 2019, as I mentioned, with the goal to create and implement KASA for drug substance interface that would be applicable for assessment of drug substance submitted in NDAs, ANDAs, and DMFs. We spent a little over a year to develop requirements for a standardized and structured drug substance assessment, and then we programmed a complete KASA prototype that we tested with 20 super users.

In the next step, we trained all assessors of drug substance information in ONDP, and on April 1, 2021, we implemented this prototype internally in the Office of New Drug Products. Since then, as I said, dozens of drug substance assessments were completed using KASA, and we continue to collect feedback and refine the prototype as per the suggestions received.

We are now in phase 2 of the project and, we're currently working to move this prototype to the CDER IT platform. The interface is currently being tested, and it will be released in two stages. In February 2023, so in a few months, we

will release the KASA for drug substance modules, and about a year later, once the KASA drug substance database is robust enough, we will release the KASA for drug substance analytic capabilities.

The KASA for drug substance interface really was designed as a one-stop shop for assessors to review the drug substance information, and similar to other KASA interfaces that you have seen so far, the structure of the drug substance KASA does not follow necessarily the organization of the information that is being submitted in an application, but rather follows the assessor's thought process when performing an evaluation.

Just shortly, I could give you an idea about the structure. We have an overview page; a standardized risk assessment. We have a manufacturing page, characterization, drug substance control, and drug substance stability section. In terms of the KASA drug substance functionalities, our interface shares functions with other KASA interfaces, and I refer here to

linking to submissions that you heard from Andre, following deficiencies across iterations, as well as enhanced communication between primary and secondary assessors.

Moreover, we have developed features that are specific to our interface. These features are the drug substance risk assessment algorithm and the analytic for structured drug substance synthetic pathway that include chemical registration, as well as capturing the synthetic steps in a structured format, which would be performed in the global substance registration system, GSRS, and integrated with KASA as part of the KASA 4.0 release starting next year.

In addition, as part of the KASA 4.2 release, most probably in 2024, we will have analytics that will allow to search, to visualize, and to analyze the drug substance synthetic pathways, and I'm going to talk a little bit more about this next.

One of the features that really sets KASA for drug substance apart and makes it complex,

comparing to other interfaces that we have developed so far, is the structure of drug substance manufacturing module. When we designed this module, we thought in terms of our needs for knowledge management, and we structured the information accordingly.

We are capturing in a structured format the flow of the action steps, the synthetic inputs and outputs for each step, as well as critical process controls, impurities, solvents, and reagents. And depending on the criticality of each step, the assessor has the option to perform a full or a simplified assessment of that step.

As you can see on this slide, in a full assessment format, the assessor is prompted to input all synthetic inputs, outputs, as well as control approaches employed, whereas in a simplified format, only synthetic inputs and outputs can be captured, and we do this through integration with the GSRS library for chemical structures.

In addition to this information, we also

have separate subsections in the interface for control of study materials, intermediates, impurities, and reagents. We realize that capturing all this information will need some upfront effort, especially when it comes to registering new molecular entities, but we believe that the payoffs in terms of knowledge management and facilitated decision making are substantial, so worthwhile.

This slide gives you a snapshot on how we can capture chemical structures in a structured format through integration, with GSRS. We can register a new critical compound such as starting materials, intermediates, the final drug substance, and impurities by recording its chemical name, the structure, the role of the compound, and the synthesis. By doing so, we would receive an associated identifier such as unit number in GSRS that we can later use to retrieve this compound.

We are currently working with GSRS staff, so when the KASA for drug substance will be placed in the CDER IT platform, chemical structures will be

easily accessible in the system, and once the structure has been registered into GSRS, it can be used by the next assessor for the next review without any duplication of work. And even better, I think we're already taking one step further, and we intend to minimize the manual work that the assessors are doing in order to draw and register structures by using the so-called SD or structured data files.

SD files are text files that tell the computer how a chemical structure looks, and SD files are submitted by the applicant. Our original intent for SD files was to support QSAR review, but we can also use these files to facilitate the registration of new chemical structures via GSRS into KASA. At the FDA, we have been accepting SD files since August last year, and we are currently asking drug master file holders, as well as applicants, to voluntarily submit SD files.

Based on capturing the synthetic pathway in a structured format, we want to develop drug substance analytics that would allow us to display,

search, and analyze drug substance synthetic pathways so we can easily mine information and, like I said, inform the decision-making process. We have developed a rudimentary tool in the prototype, as shown here on this slide, which allows diagram-like displays of the drug substance synthesis flow, synthetic inputs and outputs, and function of each synthetic step.

Going into the CDER IT platform, we plan to enhance this tool to include reagents, solvents, impurities, and once we do that, we believe we will be able to mine the structured information and search and identify reactions and combinations of reagents, starting materials, or intermediates that can potentially generate high-risk impurities.

So now that you've heard about our plans for drug substance, I want to spend a few minutes to talk about KASA for investigational new drugs or INDs. We initiated this effort a few months ago, and I'm happy to report that we already have developed the first version of the KASA for IND prototype, which is applicable to small molecules.

And in the months to come, we plan to test and refine this prototype, and hopefully sometime next year, we can implement this prototype internally in ONDP.

All these steps we believe will prepare us better to finalize our requirements and communicate these requirements to the IT group when the time comes to transfer this prototype to the CDER IT platform, which we hope it will happen sometime in the 2024-2025 time frame.

A few of the highlights of KASA for the IND interface are listed on the slide. KASA for IND streamlines the assessment documentation for future IND assessment. It contains a built-in decision tree for selection of the IND assessment template, giving assessor the option to use either a full template or an abbreviated one. Moreover, KASA for IND contains built-in risk assessment considerations to facilitate a consistent review approach across assessors. And not lastly, it is expected to enhance assessment efficiency and to pave the way for future knowledge management

integration, which really spans the product's lifecycle from the initial IND phase.

So as I mentioned, in parallel with KASA for IND development, we are also actively working internally on the development of modules for KASA for drug product, for new drug product prototype interfaces. We initiated this effort in spring of this year, and we are steadily making progress. We plan to spend, really, the next year discussing the requirements for a standardized and structured new drug product assessment, and possibly, also, we can code prototypes that are reflective of the requirements that we come up with.

As for other KASA interfaces, we will test these prototypes and collect feedback from assessors in order to make refinements as needed, and then we plan to implement the prototypes internally. Starting with 2025, we hope to be able to transfer these prototypes from the desktop application to the CDER IT platform in order to really take advantage of full knowledge management in KASA.

For development of KASA for new drug products, in addition to our lesson learned from KASA for generics, as Dr. Shah already mentioned, we also rely on our experience with ORBIS, which is a project that allows collaborative assessment of critical oncology drugs between FDA and other regulatory agencies.

For this particular project, in order to increase efficiency of assessment for applications that are participating in ORBIS, FDA developed a unified template, or what we call Product Quality Assessment Aid, PQAA, that allows a systematic capturing of quality data by the applicant, as well as systematic capturing of commentary and analysis by the FDA assessor.

The advantage of this template is that while allowing this structured assessment, also at the same time it focuses the assessment on the critical analysis and also minimizes the copy and paste. We want to build on this experience for developing KASA for new drug products, and in this regard, some preliminary work has already been done in

order to reconcile the PQAA ORBIS template with KASA for manufacturing, KASA for drug substance, and for biopharm interfaces.

As I mentioned, when developing KASA for new drug products, we will leverage the already existent KASA interfaces for generic drug products, as well as KASA for drug substance. However, we do realize that comparing to generics, KASA for new drug products interface will need some increased flexibility of assessment in order to accommodate new modalities or new technologies.

In addition to flexibility, our interface will be customized to various drug product dosage forms, and in the first stage, we already started with developing the interface for new drug solid oral products, and later on we will continue with the development of new drug liquid products, as well as other complex products.

Based on some preliminary discussions that happened in ONDP, we also plan to have similar interfaces for new molecular entities and 505(b)(2) applications. This interface, as I mentioned, will

allow increased flexibility, but possibly the analytics report that we'll get for these different types of applications will be different, depending on the needs of the assessment. At this time, we are also considering creating a separate KASA module for labeling chemistry manufacturing control assessment.

So I hope that in the last 20 minutes or so, I was able to provide you with a good overview of our plans to expand KASA for new drugs. The take-home message here is that KASA for new drug products presents opportunities for knowledge management, consistency in decision making, and improved assessment efficiency. And like I said, we are building the modules for KASA for new drug products, using a similar approach as KASA for generics, but we are mindful in order to include unique elements, increased flexibility, and analytics tools based on the needs of the new drug product assessment.

As was mentioned before, all of these projects really will not be possible without the

hard work and dedication of many people in OPQ, OBI, GSRS staff, as well as IT contractors, so I would like to thank them all for their contribution. And with that, I will hand it to Dr. Joel Welch, who will talk about the application of KASA for biologics. Thank you.

FDA Presentation - Joel Welch

DR. WELCH: Alright. Thank you for the opportunity and the privilege of being here. I'm excited to tell you today about what I think is an incredible next chapter in our KASA journey, which is the possible extension of this program to biological products in CDER.

I think we all acknowledge the uniqueness of biological products, so I'm going to spend some time today telling you how we're going to capture and manage that uniqueness; how biological products kind of fit within the overall KASA development program; and then talk about why these differences offer some opportunities as well; and from there, moving to explaining our development to date in terms of prototype and building KASA environments;

and then finally to sharing some screen captures at the end because I think it's important to see what an actual system can and does look like.

We spent a lot of time already talking about the key objectives and the why on KASA, but I think it's critical to highlight what these objectives are and how they apply to biological products. First, we need a KASA system that's able to capture and manage knowledge rather than just information during the course of a product lifecycle.

Secondly, we need to build expertise, and as assessors to use that understanding to establish rules and algorithms, and to use that in a way that facilitates the identification of risk, as well as how to mitigate it, and even communicate it as well.

Thirdly, we want to leverage the power of informatics and search across the portfolio of products, and finally to do it all in a way that radically eliminates text-based narratives, and with it offers tremendous opportunities to improve efficiency.

While you've heard these goals already, and some really good presentations this morning, what is critical to highlight here is that these opportunities and these objectives apply equally to biological products, and they offer really the same potential, and it's why we're excited about the chance for KASA to be extended to biological products in CDER.

Obviously, biological products are unique, and they're unique in a variety of different ways. Whatever KASA system we build, it will need to consider some specific nuances. Biological products are complex, and that complexity is not just size, but it's also a number of CQAs, critical quality attributes, relative to small molecule products. So any system we build, we'll need to consider the complexity in these molecules and how to capture this variety of critical quality attributes.

Secondly, biological products often have not just product-related impurities, but also product-related substances. Those substances may

retain atypical activity, and that drives a need for not just understanding those attributes, but also how we think about characterizing molecules, and from there how we control that molecule.

As we think about a control strategy, our KASA system will need to reflect that some of our understanding is not derived from just commercial processing scale data, but frequently scaled-down models, which are needed to evaluate some aspects that we can't perform at scale, such as viral clearance. So understanding how a model is qualified and how it relates to a commercial manufacturing process will be a key consideration.

As we think about attributes and what we monitor, we need to acknowledge that not all attributes are fully resolved by a particular method. You see in the bottom-right of my slide a charge variant profile, one of our most sensitive assays, but one that does not necessarily resolve all critical quality attributes. So our KASA system will need to understand the totality of how we monitor attributes and how the control strategy

reflects that.

Finally, you see in the bottom of my slide that molecules may have indication-specific critical quality attributes, not just molecule-specific quality attributes, depicted here as a monoclonal antibody, which in one case demonstrates binding, and in another case demonstrates antibody-dependent cellular cytotoxicity, but perhaps only in a subset of indications. So for this reason, our KASA system will need to reflect not just an understanding of process, not just an understanding of a molecule, but also an understanding of a molecule's mechanism and its context.

Nevertheless, despite the challenges, biological products really do offer some unique opportunities, and I've chosen to highlight some examples of those on this slide. First, in the top-left, you see biosimilars, and they are certainly unique in their development approach. You see a very common schematic picture that reflects the traditional development paradigm for a

biosimilar, which shows how analytics are truly the foundation on which the entire development program resides. This deep analytical characterization, and in some cases dozens and dozens of assays, plays a key role in the development, and with it offers tremendous opportunities, and managing knowledge and information can be leveraged.

Secondly, a renaissance in biotech manufacturing is underway, and in particular we see tremendous development of platforms, company-specific manufacturing processes, and in some cases plug-and-play unit operations such as modular manufacturing that allows us to see both the opportunity to capture and understand critical prior knowledge, as well as its uses and its limits. All these are opportunities for a KASA system.

Thirdly, submission elements that are unique to biologics such as completed prospective process validation are particularly suitable to KASA. You could envision, for example, the power of an assessor looking side by side at characterization,

validation, and proposed operating conditions all at once. Indeed, the power of looking in a structured way at all this data would be incredibly exciting for any assessor.

Finally, key questions you could imagine an assessor's asking for biological products, such as understanding whether a particular pathway or target has been studied previously could be asked as well.

In this slide, I have tried to show our development program to date for KASA, for biological products. Certainly, we have seen the value of KASA in the small molecule space, and we've asked ourselves how can we do the same?

First, you've got to start certainly with an idea of where you want to focus your attention. We started with our initial energies on drug substance and viral clearance. Drug substance makes a lot of sense at this place where a majority of complexity in biologic manufacturing resides. Viral clearance is an important companion piece to that manufacturing, and I've mentioned previously it's a

place where small-scale models might be used and where they need to align with how we understand commercial manufacturing conditions. Viral clearance also has some pretty well understood calculations that make it pretty suitable to KASA informatics as well.

From there, we began identifying an approach to creating individual modules and developing them. Obviously, this strategy included discussions with assessors on what to capture, how to layout particular elements of the system and other considerations, and elements they'd like to see built in. Soon after, we moved to creating testable prototypes, and from there, beginning to evaluate and study them.

In an exciting new development, we've moved to a new phase where we're really beginning to evaluate some of these modules under real-world pilot conditions. And finally, all this is going to set the stage for us to really move towards integrating these modules into a live environment, and I'm going to show you some screen captures of

some of these modules in just a moment to give you a better sense of what they look like.

Here, I'm going to talk to you about the modules we've built to date. Like any pilot system, you need to start with a small meaningful piece and build a prototype out from there. Our first prototype was built for a subset of our products, which are fed-batch monoclonal antibodies. This prototype was designed to apply to new BLAs, so I think you can envision how such a framework could be adaptable to lifecycle changes at some point in the future as well.

We selected this group of fed-batch monoclonal antibodies because of our robust familiarity, but also that they represent a majority of our submissions right now. From there, some specific modules were created, the drug substance manufacturing piece and the viral clearance and adventitious agents.

First, the drug substance manufacturing piece, it is designed to capture a description of the manufacturing steps and evaluation of the

process parameters, including their ranges, and highlight the key descriptive elements that are not characterized but need to be captured as part of any assessment. You could envision, for example, a descriptive element being a volume or scales of a production bioreactor. This viral clearance/adventitious agent molecule is designed to capture all aspects of adventitious agent testing and viral clearance evaluation that are needed as a part of an assessment application.

I'd like to highlight now some greater details about what these systems actually do, describe some of their key features and usability, and try to explain why it could be a particular value for assessment staff. First, critically the system is designed to reflect not just the role in scientific understanding, but also that data and understanding of an applicant drive assessment decisions. This includes risk ranking and understanding ranges of a particular proposed manufacturing step and process. Critically, this ensures that an applicant's data and scientific

understanding drive the final ranking.

For both modules, our prototype attempts to capture information requests, revisions, assessor comments, and are designed to be consistent with ICH Q12 concepts. As Dr. Shah already mentioned, at this stage, microbiological and facility considerations are not yet included, but will be needed in the future system.

As we move into a piloting stage, we intend to test our system in a variety of ways. This includes hopefully new and existing applications. This is hopefully to ensure that we will evaluate a broad portfolio of submissions and ensure that we capture critical information from our assessment staff on any needed augmentations.

We hope this identifies gaps, areas of improvement, and more holistically, if we've been successful to maintaining the vision of KASA, right-sizing the information we capture, and have built in the strengths and opportunities for KASA we see to that biological product portfolio. Hopefully, if we do this right, it sets the stage

for the continued development of new modules.

I'd like to now show you a few screen captures. There's a cliche that a picture is worth a thousand words. I think in this case, it might be worth even a few more than that, so I've tried to show you a few examples of what this system does look like.

Obviously, any screen captures you see here are not final and certainly would reflect hypothetical data that are mocked for presentation purposes, but here is just the starting page where you reflect unit operations to describe a potential manufacturing process.

Gone are the days of copying and pasting pictures from submissions, and cropping tools, and right-sizing them into a Word document. Instead, you click on unit operations from a prespecified list. You pull them, and you drag and drop them, and rearrange them into an order based on an actual manufacturing process. This allows an assessor to quickly move into an assessment process, and critically this allows for a system that can

rapidly be expanded to other unit operations and new manufacturing modalities, things like continuous manufacturing as processes and science continues to develop. It's readily expandable and why we think we see such value within this type of system.

I've chosen to show you here a second set of screen captures. Again, this is a hypothetical example of a fictionalized application, but you see here viral clearance data, and this is the final summary page for the viral clearance module. It would reflect what an assessor does after each individual unit operation has been evaluated and a final summary of the safety factor for viral clearance validation is assessed.

You see first it captures critical key information such as log reduction values at the top of the screen, and then it performs in an automated way a calculation we've been performing manually for 25 years, since the finalization of ICH Q5A back in 1998; only here you see rather than a manual process, automation and a final assessment

against the known expectation that can aid and automate something that assessors do already, and why we think that even for this simple example there is so much opportunity within the KASA development program.

As we move forward, this piloting is going to set the stage into a final push for integration of KASA into a real, live final program, and really the success is taking these pilot systems and incorporating it into a live environment, and not just using it for a handful of assessment topics but, really, the entire dossier.

Critical to us being able to do this will be continuing to build in key learnings from our pilot development to date, and those learnings will be about usability features we might identify, and learnings from the small molecule world about things we can leverage such as facility and microbiological concerns. All this will set the stage for a phased implementation where we can group like topics and begin to integrate them into a final assessment module.

In conclusion, I'd like to just pause and say, we're really excited about the opportunity KASA offers in the biological products area, and we feel like it presents, really, breathtaking opportunities for knowledge management, consistency in decision making, and assessment efficiency. For biological products, KASA will build on the same philosophy of small molecules, but I hope I've convinced you today that we are going to be able to reflect the needs and nuances of biological products within our system.

As mentioned previously, we're going to need to build in not just complexity of manufacturers but complexity of critical quality attributes and some unique considerations, and we're going to do all that as we continue to learn from other organizations on their KASA journey as well.

With that, I'm excited to tell you we've entered a final stage, which is exciting, which is piloting a real system that will allow feedback and utilization of the system in a real environment, so that's an exciting final development today. So

with that, I'm going to pause, and thank you for your attention, and now invite Dr. Lawrence Yu to the virtual podium to talk about cloud-based assessment. Thank you.

FDA Presentation - Lawrence Yu

DR. YU: Well, thank you, Dr. Welch, for your introduction.

Good morning, everyone. Good morning, chair and members of the FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. I'm Lawrence Yu, rapporteur of the Office of New Drugs Products and director of ICH M4Q Expert Working Group.

Dr. Lee discussed the vision and roadmap of KASA, Dr. Stelios Tsinontides and Dr. Shah discussed the application of KASA for facility and manufacturing, and Dr. Wu, Dr. Raw, and Dr. Welch discussed the application for KASA for generic products, new drug products, and biologic products. My task today is I will cover cloud-based regulatory assessment and submission. I will describe the vision of the cloud-based assessment

and structured application. I will cover ICH M4Q(R2) common technical document and the revisions. I will discuss very briefly the pharmaceutical quality, data standards.

KASA stands for knowledge-aided assessment and the structured application. As you can see from this slide, it consists of the KA and SA. KA stands for knowledge-aided assessment. It's pretty much FDA's internal delivery, as you heard this morning from Dr. Lee, Dr. Wu, Dr. Stelios, Dr. Shah, and then Dr. Welch, all the talks related to facility and manufacturing and related to the generic drugs, new drugs and biologics.

Certainly, we want to talk about SA as well, specifically related to the content information of submission, which we call M4Q revision, and the PQ-CMC or what we call electronic data standards. In fact, our efforts related to the application specifically responded to your recommendation, which I want to thank you, in 2018 at the advisory committee meeting leading to recommendation. Specifically, you voted, related to the KASA

initiative, should the FDA consider the enhancement of submission format to improve the efficiency and consistency of regulatory quality assessment? You voted all yes, 10, with that in 2018.

Specifically, the committee unanimously agreed that related to the KASA initiative, the FDA should consider the enhancement of submission format to improve the efficiency and consistency of regulatory assessment on the KASA initiative. Several members stated that that would increase communication while making submissions from industry easier and more transparent. In fact, both brand and generic industry represented on the committee agreed that KASA will be good for both industry, of course, and for the FDA as well.

So our effort this morning, we're hoping to come back to report our progress in the submission format, our effort in this area, but first I want to share with you the vision of the future regulatory submission and assessment.

First, I want to discuss current regulatory submission and assessment. When I joined FDA

23 years ago, new drug applications or generic drug applications were submitted using track off of full binders with paper documents. In fact, to be the first generic application to file, the company physically stood in the line at the door of the office building.

With the issuing of the ICH M4Q(R1) in 2002, across the region of the world, industry and regulatory agency started a submission based on a common technical document. Later, it would become an electronic format, or eCTD as we call it. Typically, this is achieved through an electronic gateway. For example, you submit the application to the FDA; it goes through an FDA gateway. Of course, if you want to submit an application to Japan or Europe, you have to go through the Japan or Europe gateway. But there's no question, this system is much more improved compared to paper copies 23 years ago.

Therefore, today the regulatory submission and review is absolutely an advanced version in the eyes of 23 years ago. But in today's environment,

in the world of the digital age, this regulatory submission and review, to a certain extent, is outdated. The lengthy, unstructured textual narrative, as mentioned by previous speakers, with dispersed information and lack of efficient information exchange in knowledge management data and analytics made our system not only inefficient but also not effective. In fact, the industry had a very open voice. When need of consistent regulatory assessment is open, we'll review, but will not know what has been done by another reviewer for the same or similar regulatory application. Therefore, it's much needed for us to move into the new world, which is IT friendly, user friendly IT world, which is a facility with information exchanging data analytics and knowledge management.

So as we can see, the FDA looked at this issue and the need for modernizing regulatory review, and we need to move from the 20th century to 21st century technology. Specifically, we need to move away from narrative unstructured data to

structured data in order to best capture and manage knowledge so it can be easily used for assessment of future submissions.

Structured data is highly organized and formatted, so it's easily searchable in relational database. The good news is FDA has gone through a six-year effort, that we now are sitting -- especially in generic solids -- in a high secure cloud environment. There's no question, because the environment demands availability of the computer system, which offers many, many benefits that otherwise would not be offered.

One of the fundamental issues we're still facing is despite regulatory agencies such as FDA, for generic drugs, moving into the cloud-based system and digitalization is realized, they're still receiving lengthy submissions with unstructured text narratives and lack of efficient information exchange. This I want to say is the current status of a current environment.

Now, one comment I would mention, and you

would probably ask from the previous speakers' information, why does it takes so long. I have to tell you, this year, we got tremendous support from leadership and the staff. We're working very hard. It's simply because there's a lot of effort that needs to be made. Thus, moving from the current cloud-based digitalization system is not just moving, but the current review goes through a system to get there. In fact, it requires three stages, as you heard from previous speakers.

First, we have to change our review template because our template is not fit for the needs of digitalization. Second, before we are putting our system in a cloud-based environment, we have to test out. We want to make sure all of the issues are resolved before we move to there, so we call it a prototype, as you heard from Dr. Wu's presentation.

Next, of course, is we go through the IT system and put into the cloud so that all the information and communication can be freely exchanged, and the information can be searchable.

In fact, because of the availability of information, or data, at the facility, the next big wave will be artificial intelligence, or deep learning, or the machine learning process comes into play, which certainly the KASA system is facilitating the deep learning, which facilitated artificial intelligence for our analysis to get where we want to be.

We envision that future regulatory submission and review will be that both submission and review will be accomplished in the cloud platform. In the future, if all the data could reside in the cloud, it would be more readily exchanged between companies and regulators, among regulators, or even among companies if you have permission to access.

Companies simply would inform FDA when a product's dossier is ready to review. FDA would then assess the data information from the structured cloud environment. The use of a cloud-based solution for regulatory submissions would enable a dynamic more fluid exchange of

information between regulators and our model industries, and the end result is a speedy response to public health needs.

To enhance efficient industry regulation, we all need to come together to align our approach to a cloud-based data system, which could support large data set submissions and facilitate a coordinated global regulatory review that proceeded simultaneously instead of country by country, as you can see right now, or region by region.

We believe this system will promote faster, more streamlined interactions between companies and regulators, and empower regulators to perform more sophisticated analysis across the spirit [ph] of these studies, applications, and review. So there's absolutely no question that the future regulatory system, which is called a cloud-based platform, will offer many, many advantages compared to our current system, which we are in.

So we know the question is how do we get there? What things do we need to do? First, of course we need to have a regulatory assessment

transformation. It's not just a change; it's a transformation. So therefore, we believe that FDA's knowledge-aided assessment system, we call the KASA, is certainly good for us to get there. Besides the internal changes or transformational changes within FDA's internal, or regulators, or the like, we also need to change the regulatory submission for transformation, which includes the revision M4Q's CTD format, along with the electronic data standards so that all the information could be freely shared between industry and regulators, and among the regulators.

Therefore, I want to say a few words that are related to our effort in M4Q opportunities for the modernization of regulatory submission. As mentioned early on, there's no question that clearly the CTD format is much more improved than what we had 20 years ago, and much more important than what we had where the paper was tracked, the paper version. But this still has a significant opportunity in the age of digitalization.

Specifically, we perceive there are

significantly some issues with the current CTD format, including, number 1, several ICH regions have not fully implemented M4Q(R1). Modernization will support and clarify global understanding of the future -- CTD means common technical document -- enabling great regulatory coverage [sic - convergence] and harmonization, and decrease redundancy.

Number 2, the new guidelines will align with the modern quality guidelines Q8 through Q14 and other relevant ICH guidelines that have been developed and given greater focus since the issuing of M4Q(R2), which was developed 20 years ago, exactly in 2002.

Number 3, the M4Q(R2) guideline will provide guidance on the location of the information and support multicomponent or complex products, which was not available 20 years ago, such as antibody drug conjugates, vaccines, and so on and so forth; and 20 years ago continuous manufacturers were never heard of, but today it's become a reality.

Also, the M4Q(R2) guideline will facilitate

leveraging advances in digital tools, data management, and standards, and analytics to enhance efficiency, effectiveness of regulatory submission, and assessments.

What are the specific issues we want to resolve? What do we want to achieve over there with ICH M4Q? First, we want to expand the scope of M4Q(R1) to include all pharmaceutical drug substances or drug products, both chemical and biologics.

We want to establish the role of M4Q(R2) as the main source of structure and location for regulatory quality information. We want to organize the product and manufacturing in a suitable format for easy access, analysis, and knowledge management. We want to incorporate concepts and data expectations presented in ICH quality guidelines, aligned with the current recognized international standards and guidance, and better capture pharmaceutical development and the proposed overall control strategy, which should be the backbone of the revised M4Q structure. And

last but not least, enhance the quality Module 2 to facilitate efficient effectiveness of regulatory assessment in submissions.

Specifically, we have 6Es in mind when we talk about objectives here with M4Q revision or M4Q(R2) objectives. One, encourage global coverage of science and risk-based regulatory approaches in the preparation of dossiers or application. We want to explain and define the organization and the positioning of the information for Module 2 and Module 3.

We want enriched communication between regulators and applicants and an enhanced lifecycle and knowledge management. We want to embrace product and process innovation, enabling efficient use of digital tools for submission assessment, preparing for the closely linked upcoming ICH guideline on structured product quality information, which is the next project, and elucidate regulatory expectations and support efficient assessments, decision making, and actions.

With these changes, we believe they will benefit, with first and foremost importance, patients and consumers, and M4Q(R2) guideline will speed up patients' and consumer' access to pharmaceuticals. It will help provide a benefit to industry as well, and include clarifying regulatory expectations; facilitate and apply enhanced ICH quality strategy and revisions; streamline regulatory application preparations; improve quality submissions, data standards, and so on.

Not only will M4Q(R2) benefit the patients, consumers, and industry, it certainly will benefit regulators as well, such as FDA; enhance benefit-risk considerations; increase access to quality standards; streamline regulatory assessment; and facilitate decision making and communication.

So where are we today? From 2018, the recommendation of the committee, and in 2019, FDA drafted the proposal, it goes through FDA's chain of command, and is submitted to ICH. ICH endorsed the FDA proposal in May of 2020, and in 2021, ICH

approved the outline of the concept paper, which was developed by FDA.

Last year, ICH formed informal working groups, and eventually we began to develop and endorse the concept paper and business plan last year. Now we are in the progress of developing a high-level structure of thinking for M4Q(R2) and details of the structure. We will have a meeting next week and will continue to develop new revisions of M4Q(R1).

Here is a specific review of the work plan, as ICH is pretty much a long process. We're envisioning, hopefully, to release step 4 in 2025, which is called the finalization of document for adoption around 2024 and 2025.

With that, I discussed with you our effort related to our vision for cloud-based regulatory submission and assessment. Also, I want to very briefly talk about data standards because in order to realize cloud-based assessment and submissions, we have to not only change the concept and submission format, but we also need a set of

regulatory data standards, which is an ongoing effort.

As you can see, and which was discussed quite often by myself here, and with also previous speakers, the current format is certainly an advantage compared to 20 years ago, but it's certainly outdated because the cut and paste of PDFs not searchable really creates a significant burden for industry and also a significant burden for regulators. We're hoping to move to an electronic data format in the ICH, what we call the structured product quality system, and also within FDA we call it the PQ-CMC, but it's basically a set of regulatory quality standards to facilitate visualization and facilitate submission.

So at the end of the day, we want to achieve cloud-based regulatory submission and assessment, and with our effort with KASA, someday we'll be there. I'm very excited about the future. Certainly we need to work together -- industry and regulatory -- all together, to get our future vision of a cloud-based regulatory submission and

assessment; facility decision making; facility submission; facility assessment; and eventually benefit to the consumers and patients.

With that, I conclude my presentation. Thank you very much.

(Pause.)

DR. YU: Hello?

DR. L. LEE: We hear you, Lawrence.

DR. YU: Okay. Thank you.

MS. BHATT: Thank you, Doctor.

We'll take a 10-minute break now. Panel members, please remember there will be no chatting or discussion of the meeting topics with other panel members during the break. We will reconvene at 11:28 Eastern time.

DR. YU: Thank you.

(Whereupon, at 11:18 a.m., a recess was taken.)

Clarifying Questions to the Presenters

DR. MORRIS: Hello, everybody. We'll reconvene.

First, thanks very much to the FDA speakers

for excellent presentations, and 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 have asked your question.

When acknowledged, please remember to state your name for the record before you speak, and direct your question to a specific presenter, if you can. If you wish a specific slide to be displayed, please let us know the slide number, if possible. And finally, it would be helpful to acknowledge the end of your question with a thank you and end of any follow-up question with, "That's all for my presentation" or "all of my questions," so we can move on to the next panel member.

I'll start with a general question for either Dr. Lee or Dr. Yu, and then go down the line as hands are raised.

The question that I had, or the clarification I have, is really not to diminish the Herculean effort it took to get all of this in

place, but as far as the sponsors go, irrespective of revisions to the ICH guidelines, the information that's being required of them is no different, as I understand it, from what's required now, the B2 or B3 modules, as we said.

Is that correct, and could one of you please comment?

DR. L. LEE: Yes --

(Crosstalk.)

DR. YU: Larry, you want to take off?

DR. L. LEE: Lawrence, would you want to go first?

DR. YU: Okay.

Dr. Morris, yes, this is correct. Clearly, as you can see, we implement for solid oral dosage forms, and the sponsor probably will feel no difference. In fact, one other thing I want to say, as informed by Dr. Larisa Wu's talk, is we implement KASA for drug substance, including new drug substance as well, certainly within the prototype information. But certainly, with the NDA sponsor, you will not notice any difference about

the FDA's response.

So therefore, Dr. Ken Morris, it is correct, that at this moment, we implement internally, and no impact whatsoever on the sponsor side in terms of format application, whether ANDA, NDA, or BLAs.

Larry, please?

DR. L. LEE: Yes, I agree with Lawrence. That's one of the things I emphasized during my presentation, is we apply the same standard. The knowledge is that you're solving a math equation where you can either use the calculator or the paper. But the way you solve the addition or subtraction is the same thing. I'll just leave it there, I guess. So there's no change.

DR. MORRIS: Thank you both for clarification. So I'll go on.

Dr. Carrico, I believe is next.

DR. CARRICO: Hi. Thank you. This is Jeff Carrico with the Dana-Farber Cancer Institute. I believe this question would be for Dr. Lee or Dr. Raw, but if anyone else feels suited to answer it, I'm fine with that.

I want to start out and say that this is kind of a question about the functionality of the system, and I certainly accept all the positive attributes and results that have been presented for us, and saying as well that I certainly support harmonization and standardization anywhere that we can. But I'm wondering, in the recent experience, how often did data or information not fit into the pre-approved categories or the selections that a sponsor can make in order to classify it?

I guess I'm wondering -- I know I saw that there was the option for free text on certain items, but could you just speak to was it most of the time that the pre-approved categories worked, or were there times when free text still had to be used? And if that was the case more often than not, what are the plans to address those issues? Thank you.

DR. L. LEE: Andre, can you take that?

DR. RAW: Yes. This is Andre Raw. I just want clarity of the question.

Just to be very clear, this KASA that we

implemented is for the assessor staff. The sponsor didn't have to make those selections. We make the selections, the assessor. So the sponsor did not have to change anything in their submission. I want to be very clear of that.

DR. CARRICO: Okay. Can I jump back in, then?

DR. RAW: Sure.

DR. MORRIS: Yes, please do.

DR. CARRICO: Again, this is Jeff Carrico.

Okay. I see what you're saying, but I guess my question would still be, the pre-built options, did they suit the needs of the assessor, then, most of the time, or were there times when free text still had to be used?

DR. RAW: Yes. In terms of those drop-downs that you mentioned -- that I mentioned, too -- we spent a lot of time developing those drop-downs, so I would say that in the vast majority of cases, they would be sufficient. People would not have to select additional drop-downs based upon what we have seen so far. However, we do understand that

sponsors do develop new technologies, and as new things come out in manufacturing of pharmaceuticals, we may have to update some of these drop-downs.

DR. L. LEE: Andre, I can definitely talk a little bit to that, and then I also welcome Lawrence to also add a little bit to your question.

So yes, based on what Andre said, we have enough info experience to really design the interface such that we'll cover most of the assessment we do using the drop-down menu. But certainly, we also understand that sometimes there's a possibility that it will be needed to allow assessor to raise some questions, which may be more like application-specific. We do have that flexibility to build into the KASA, but the drop-down menu, at least at this moment, will cover most of the questions.

Then on top of this, as part of continuous improvement, we will continue to monitor the KASA development to make sure that if there's some area we can improve in terms of a drop-down menu or

building additional flexibility in the field, we will do so as well. So we definitely incorporate the continuous improvement to continue to improve the system.

Lawrence, do you have anything to add to --

DR. YU: No, Larry. You said it very well.

I want to emphasize, Dr. Jeffery Carrico, the KASA system is a dynamic system. Initially, certainly algorithm building will not be perfect; we recognize that, so we'll continue to improve the process. When new information comes and new cases come, we'll continue building up our system and building up our rules [ph] algorithm as well.

We recognize, for example, with the solid oral dosage form, immediately this may be simpler, but in some cases very complex dosage forms may be coming. So we want to make sure KASA does not just apply for a certain percentage of applications; we want to make sure KASA applies for all applications. So therefore, we'll leave the door open and continue to have manual input of some information. But with time, I'm confident the

system will become stronger and much better, and in today's system, solid dosage form is probably much, much better already than what we had five or six years ago.

I'm hoping this answers your question. Thank you.

DR. CARRICO: Yes, that did answer my question. Thank you very much.

DR. YU: Thank you.

DR. MORRIS: Thanks, guys.

Next, I think Dr. Kraft is ready for a question -- ready with a question, I should say.

DR. KRAFT: This is Walter Kraft from Thomas Jefferson University. It's a question for Dr. Larisa Wu, and it's specifically about INDs for academic users and the KASA interface, specifically about investigator-initiated INDs and expanded access INDs, so neither of these are leading to NDAs.

What are the plans for stakeholder input and outreach as these would be expanded to those IND activities in KASA? Thank you.

DR. WU: Yes. Thank you for the question. This is Larisa Wu. In terms of INDs, again, the effort that we are developing right now is internal, so we are working on developing and testing smart templates that will help us evaluate IND submissions.

We plan to continue with stakeholder engagement as we did in the past. Nothing will change in that regard. The only thing that will change is the way we will perform internally our assessments. I hope this answers the question.

DR. KRAFT: If I can maybe just follow up and ask, is this going to be staged? So specifically for investigator initiated IND, and probably more for expanded access, would this follow the timeline on your slides or would this be subsequent to those timelines?

DR. WU: I'm sorry. Can you specifically tell me which slide are you referring to?

DR. KRAFT: I guess there is a timeline that you had for the rollout --

DR. WU: Right. So like I said --

DR. KRAFT: -- 3-2.

DR. WU: -- right now, we are working internally to develop a prototype and, really, the focus is on commercial INDs --

DR. KRAFT: Yes.

DR. WU: -- but in the future, yes, sometime after 2025 we'll probably roll out to non-commercial INDs as well. But at this point, I don't see any impact on the external stakeholders.

DR. KRAFT: Okay. Great. Thank you.

DR. WU: Um-hmm. Thanks.

DR. MORRIS: Thank you.

Next, I believe Dr. Slud you're ready with a question.

DR. SLUD: Yes. thank you. This is Eric Slud. My question is from the point of view of statistics and data handling to enable the analytics, and it's especially related to the KASA 3.0 that's already been implemented and that you have some data experience with. It's related also to Dr. Carrico's question.

As far as we understand, most of the data

entry will be done currently by assessors from what may be text-based submissions. There's an issue of reliability, repeatability, and completeness of the categorical data fill-ins that these assessors do into what is necessarily a uniform data format for the purpose of doing analytics afterwards.

So my question relates to ensuring the correctness. It's a level of error, the correctness, the uniform repeatability of the data entry from the assessors. Thank you.

DR. YU: Andre, can you help out?

DR. L. LEE: Yes. Who would like to address that?

DR. RAW: I can help out.

There are two parts of it. This first part is the review part. In the review part, they have to make those assessments, and the risk of them making an error is the same risk that is linked -- an error to reviewer or not. I'm a little bit confused about that question. And also, we do have --

DR. MORRIS: Can you please make sure to

identify yourself when you're answering.

Thanks, Andre.

DR. RAW: Okay.

DR. MORRIS: Go ahead.

DR. RAW: This is Andre Raw speaking. So to be very clear, there is going to be --

(Pause.)

DR. L. LEE: Andre, do you want me to help you?

DR. RAW: Yes. Why don't you [indiscernible - audio gaps], Larry.

DR. L. LEE: Yes. This is Larry. Let me make sure if I understand the question correctly.

Are you asking about the accuracy and also the precision about our data analysis using our current review process?

DR. SLUD: Thank you. This is Eric Slud again. Yes. To clarify the question, I'm interested in what amounts to data entry for purposes of having a uniform product to analyze in your risk analytics.

The issue is whether entries are being made,

for example, from text input to what amounts to categorical data levels, whether these are correct and repeatable, and in some cases there may also be missing data. So it's those data handling aspects that I'm asking about. Thank you.

DR. L. LEE: Oh. Yes. Thank you. This is very clear. In terms of the missing data, we will not be concerned about this one because we do have the ability to ask for data from the sponsors. Then with our current process, as I mentioned before, we have an integrated quality assessment team, so each discipline will have someone very expert in that particular area to do the data analysis to ensure the data entry.

On top of this, because we also make sure that the data entry is correct, we also have a secondary level of review to look at the assessment, including those data analyses to make sure that that is not going to impact our final decision.

So as you can see, we internally, from the process perspective as well as using a different

discipline, allow for a checkpoint to make sure all these data are correct and precise for the purpose of the regulatory decision. That's one of the reasons why -- but I have to say it's going to -- based on what we have right now, it takes a lot of time, so that's one of the reasons why we actually moved to the 21st century to utilize more structured data, as well as IT to help us to streamline this process.

Lawrence, would you like to make a little bit more comment? At least, right now I'm pretty confident that what we have is correct, but it just takes much more time and takes more manpower to do so.

DR. YU: Larry, you answered it very, very well.

The first question is with our FDA internal review process, we typically have a two layers review. We call it the primary review and secondary review. One of the functionalities of the secondary review is to make sure what the primary reviewer did is correct. Certainly, we've

touched on this right now manually, but in the future, this application is structured format information. Not only certainly the secondary continues to verify, but all the application data could be verified by computer automatically as well.

So therefore, the KASA system will increase the effectiveness of the whole assessment, and that's why we say it facilitates our decision-making process.

Dr. Eric, I hope this answers your question.

DR. SLUD: Yes. Thank you very much. It's very encouraging that you not only have these uniform formats, but that you plan to continually audit the process of data entry. But I'm asking this partly from the point of view of enabling the automatic data analytics and risk assessments because things must be fairly complete, not too much missing, and presenting some of the data experience you have of that sort would be very useful to, for example, statistical reviewers of your system. Thank you.

DR. YU: Absolutely. Yes. One example we have right now is a lot of stability data. At this moment, we look at the stability data, we look at computer and company analysis, and primarily we make an assessment in terms of solid condition and the shelf life, and sometimes some data is missing when you test the long-time data. But in the future, if all data coming was electronically, if FDA has the internal data analysis function in place, a lot of things which we manually do right now will become automatic.

You can hear from my voice I'm so excited about the future. There's no question that the computer will help make our analysis and regulatory assessment a lot easier. Thank you.

DR. SLUD: And thank you.

DR. MORRIS: Thank you, guys.

Next is Dr. Amidon. Greg?

DR. AMIDON: Yes. This is Greg Amidon, University of Michigan. I think you've already touched a little bit on the question I have, but I'll ask maybe for some additional insight. I

think this probably goes, first anyways, to Dr. Raw.

Your slide that comes to mind is slide 32. The questions I have are specifically, I guess, related to that assessment of, I'll say, initial risk that you've identified. Who and how is that initial risk determined? Is that done by FDA? Is it done by the the company?

The second part of that question I guess relates to that risk control strategy, and you've already talked about how flexible it is in terms of input and the strategies that might be used. Obviously, some strategies are well known, but there may be innovative novel approaches, and it's good to hear that that's an option.

The third part of the question, really, I guess is related to that residual risk. I understand that's at least, in part, analytics, but I guess I was still looking for maybe some clarification. Is there FDA input in that residual risk assessment as well? Maybe a little bit more detail on how that will work could be helpful.

Thank you.

DR. YU: We need to go to slide 32.

(Crosstalk.)

DR. RAW: I need to go to slide 32.

DR. MORRIS: We're getting the slide.

DR. RAW: Let me see if I can actually answer the question. The first one is about the initial risk assessment. Just be advised that when we made this initial risk assessment, this was actually discussed. We did a very -- this is done not by the company. It's done by what we're doing in FDA, based upon the knowledge we have.

Okay? So that's the first thing. Does that answer the first question? We actually spent a lot of time developing this model. Some of this was discussed in the previous advisory committee meeting that was done several years ago.

DR. MORRIS: Dr. Amidon, does that --

DR. AMIDON: Yes, I think that addresses the initial risk part.

I guess the third part of that question was really related to that residual risk, and I'm

wondering if you can just provide a little more insight into how that's determined. Analytics is part of it. Is it all of it or what's the view there?

DR. RAW: Oh, the residual risk. Okay. When we talk about the analytics, what we really generally compare are the risks, the initial risk and the risk control strategy, amongst other applicants. We'll know what applicant did one risk control strategy versus an applicant that did four or five risk control strategies. The residual risk, we have to admit, we don't have an algorithm for the residual risk from the initial risk to the risk control strategy.

So I guess what I'm trying to say here -- maybe I can be a little bit clearer -- is essentially they all have the same initial inherent risks because it's sort of the same product. But then the question is, we want to know which applicant -- by knowing which applicant did just one risk control strategy versus that one that did an abundance of risk control strategies, we'll be

able to capture that in the analytics. So we'll be able to rate which applicant has a more robust control strategy versus our other ones, and we can allocate our risk.

Does that answer your question?

DR. AMIDON: Yes. I think it gets to it. I was, I guess, wondering if there's an FDA input there, say, sort of a manual input, or if it's just driven solely by analytics at this point.

DR. L. LEE: Can I also make a comment? This is Larry. I also may want to ask Lawrence to chime in a little bit.

Just to add to Andre's clarification question, this is an excellent question. I want to emphasize that the risk assessment and the risk algorithm we are doing is really based on a lot of input from our assessor. The experience they see in the product, remember, we have a process with the facility assessor.

So basically we build upon this, and it's no different from what they are doing right now, the type of risk, the concept, and the mechanism, and

the risk assessment mechanism is pretty much similar to what we are doing now. But because of the KASA, we can really formalize these type of risk assessment frameworks, where it becomes more consistent.

Usually, we will eliminate the human-to-human variation in terms of the reassessment. Of course, internally, FDA provides a lot of training of how to do the risk assessment, but this risk assessment framework is really built upon what we have and what we've learned from different applications and different facilities.

So what we are doing now in KASA is no different from we are doing now but, really, the purpose is to reduce the variance of our risk analysis of this assessment here. So hopefully this addresses your first part of the question.

Then the second part of the question is about the residual risk. What I want to actually mention here is anything we can talk about residual risk, it's really uncertainty. It's basically how much uncertainty you are willing to accept and

where you are willing to go with it. In terms of our risk framework, what we really are looking at is to make sure that as long as they have a control strategy in place, based on our framework, we are going to be able to -- because of the control strategy in place, the residual risk becomes low level, which we will be happy to do so on the medium or low level. It depends on the criticality of the specific quality attribute.

Then on top of this, remember we still have a quality assessor there. They will also make a judgment there to make sure all this overall risk, including the consideration of the residual risk, will be comfortable to move forward with the regulatory recommendation. So I think, hopefully, this will give you a little bit more clarity in terms of our risk analysis.

Lawrence, do you have any other things to add?

DR. YU: No. Thank you, Larry. You said it very well.

Dr. Greg Amidon, the residual risk is pretty

much. When we approve a product or not, it depends on the residual risk, but certainly we will also talk about the benefit of this specific product. So therefore, we will consider the benefit of the product and also the risk of the consideration, and FDA will make a determination whether this application will be approved or not. If this product is very critical to the patients' unmet medical needs, we're probably going to tolerate a little high residual risk than low risk. Also, with residual risk, at the end it's determining how much FDA is going to pay attention after post-approval.

So therefore, yesterday we talked about quality managing the system; in other words, when quality and maturity comes into play, in the big-picture thinking, residual risk will impact our continuous monitoring after approval. Of course, low risk certainly will be appropriate. High risk, especially unmet medical needs, we may still approve a product, but certainly FDA will ensure that future quality is maintained, even after

approval.

I'm hoping I answered your question, Dr. Amidon.

DR. AMIDON: Yes. Thank you. That's all for me. Thank you.

DR. YU: Thank you.

DR. MORRIS: Thank you.

Next, Dr. Venkateshwaran is ready, I believe. T.G.?

DR. VENKATESHWARAN: Hi. This is T.G. Venkateshwaran. I have a couple of questions that are kind of related and one is a clarity question.

Through the presentation, one of the things that I gleaned is that the inputs for KASA may come to various other initiatives such as QSD, ICH M4Q, PQ/CMC, and IQA. My understanding, based on it, is that we will be working on ICH M4Q to make sure that the inputs for KASA are consistent, and this in turn will minimize what the sponsors of companies have to provide the FDA. That means they'll be providing similar information based on this, and there will be no other information.

Is my understanding accurate? That's the first one.

The second one was, in terms of new products, you see a number of different types of products: accelerated products, standard review products, and breakthrough products. The amount of information that you will get on these products vary, and some of these may not have enough data to calculate things like Cpk.

How will KASA distinguish this in terms of review, and what will be the challenges? This is the question that I had.

DR. YU: Thank you, T.G. This is Lawrence Yu. I'm going to answer your question.

We recognize that KASA is not like a one-stop shop; we flip switch, we get there. We recognize a step-wise approach. So therefore, when we design KASA, you probably noticed that actually even then we called it knowledge-aided assessment and structured application. Therefore, in a way, knowledge-aided assessment, which is FDA, internal-driven, we apply to generic drugs, new

drugs, and biologic products. The company continues to submit, as of right now, in PDF format, except FDA's internal process is moving into digitalization to facilitate data analysis and knowledge management.

As I said in my presentation, right now for new drug substance, for all the NDA new drug substance, for small molecules, we already implemented KASA, and you probably will not notice any difference on the FDA site. So that's number one.

Number two, certainly M4Q, there are two changes. Along with the PQ/CMC, the future structured application will greatly facilitate and will help because, right now, as you can see, our assessor has to manually input a lot of information. In the future, it's all automatic. I guess if you'd look, today is good, and tomorrow is better, and the day after tomorrow is great. So it's a kind of a perfect situation we're in right now.

So at this part, we're talking about a

step-wise gradual process. And, T.G., I'm hoping I answered your first question.

DR. VENKATESHWARAN: Thank you, Dr. Yu. That does.

DR. YU: Thank you.

Regarding your second question --

DR. MORRIS: Thank you.

DR. YU: -- about the complexity of the application type, complexity of the technology, we want to make sure that KASA is not a rigid system. This is why it comes to risk-based approach. We want to make sure that KASA is flexible enough and able to deal with advances in technology and advances in dosage form, especially when we talk about gene therapy or cell therapy. Those are not even available.

So we want to make a system to be flexible enough to handle this. That's part of the reason why it takes so long for us to develop it because it cannot be one size fits all. And that's part of the reason that we cannot simply move, for example, from generic space and new drug space without

changes. We'll have to make a lot of changes.

For certain small molecules to large molecules, it's even more significant change, as you can hear from talks from Dr. Wu and also Dr. Joel Welch. I'm hoping this answers your second question.

DR. AMIDON: Thank you, Dr. Yu. It does. Evolution is what I hear, so thank you.

DR. YU: Yes, absolutely. Absolutely. And I can assure you we'll be risk based here.

DR. AMIDON: Thank you again.

DR. MORRIS: Thanks.

Next up is Dr. Lee, Dr. Kelvin Lee.

DR. K. LEE: Thank you. This is Kelvin Lee. I think this question can be for Dr. Welch, but I certainly open and welcome anyone else from the agency to help clarify. I do very much appreciate the presentations, and a lot of work has been done to date, and I can certainly understand the arguments and the benefits of having such a system to understand the risks, particularly known risks.

I wonder about your perspective on how the

system, as its envisioned, might, or might not, be used to address unknown risks, given that the system and the thinking here is that it's based on our latest scientific understanding, which is of course always advancing. So I'm thinking this might be more relevant in thinking about biopharmaceuticals, which is what you presented about, where this could be more of an issue, and maybe that's why it's being proposed as later in the kind of rollout development plan for KASA.

I think my specific drilling into that is, are unknown risks things that are envisioned to also be addressed through the KASA platform, perhaps through future advances in machine-learning, big data approaches; or is the going-in assumption that unknown or unanticipated risks are not to be addressed with KASA, and would be addressed through other mechanisms? Thank you very much.

DR. WELCH: This is Joel Welch, and let me kind of get started, I think, with the response.

I think one of the hallmarks of what you've

heard this morning is really the flexibility of the system, and from that perspective, we're trying to understand evolution of science and building in those considerations as we go along, and that's why back to this idea of continuous improvements. We're going to be building in refinements as we learn things and go along.

I think to the question of how do we handle uncertainty in kind of a bigger way, our system is designed to be flexible, to have have those types of flexibilities already defined within the system, and for new types of molecules, having not a fixed list of all situations but having the ability to have additional CQAs, for example, captured by an assessor as a different type of molecule is captured, as we think about new types of manufacturing technology.

Certainly, we see what the future is coming, and in some cases, hopefully ETT, the emerging technology program, can help foresee some of those needs. But I think we will be building in flexibility to capture additional parts of

manufacturing controls, additional testing strategies, additional process parameters, and whatever that need is, the system isn't going to be rigid; it's going to be flexible, and we're going to accommodate that type of need, I think, in the flexibilities we design up front.

I would say as a general philosophy, KASA is a tool, and it's a tool to help assessors. But ultimately, the judgment around a process, a product, a control strategy -- and this kind of goes back to the last question of what about when there's less data -- the system is going to help us identify risk and understand it, and then build links to understanding how we think about managing that risk. So my strong opinion is we're going to build that flexibility up in front as we learn how the system can accommodate changes that we need as we identify the need to make them.

Does that answer your question, Dr. Lee.

DR. K. LEE: I think it does. This is Kelvin Lee again.

If I just drill into a little bit, a risk

that could come up that would be, let's say, not based on our current scientific understanding, but could emerge in the future, could be perhaps an unknown issue related to a raw material, for example, where perhaps the current state is one where there was no particular concern that had been identified, but the future state is one where the regulated industry realizes, hey, maybe there's something we need to pay attention to here.

Would KASA as a tool help facilitate early identification of those kinds of concerns and drill into, in that hypothetical example, what the raw material issue might be, or is that not sort of part of the intended use of KASA?

DR. MORRIS: This is Ken Morris. If I can just interject, and maybe this helps and maybe not, and if it doesn't, please ignore.

Are you saying, essentially, if there's some sort of data mining in a sense that says that we've seen correlations that might suggest this ahead of time? Is that what you're thinking at all, Kelvin?

DR. K. LEE: Yes. I think that's a fair way

to put that. Thank you very much. That's a much simpler way of putting it than what I just tried to express.

DR. MORRIS: Good.

Sorry, Dr. Welch.

(Pause.)

DR. WELCH: Hello?

DR. YU: Joel, are you there? We kind of lost you.

MALE VOICE: Yes, we lost you, there.

DR. L. LEE: We lost you, Joel.

(No response.)

DR. YU: So maybe I can help.

DR. L. LEE: Lawrence, why don't you go first?

DR. YU: Okay.

DR. MORRIS: Please.

DR. L. LEE: Yes, go ahead.

DR. YU: One of the purposes for building KASA certainly is flexibility and also as a tool to facilitate the talk about the knowledge management and also the digitalization, but certainly the

consequence of all this data is to allow us to do an analysis. So the reasoning is once we have all the data in the electronic data format, we'll study and use artificial intelligence, or machine learning or deep learning will come into play.

All of these analysis tools could help us identify issues which we do not know at this moment right now and in the future. So I really feel very grateful we went to a system such as this kind of system, and building up we're able to detect issues which maybe the human eye is not able to detect it.

But I want to emphasize that those are tools, and the final decision making is still our human beings. We are the reviewers to make a decision, and those tools help us to identify issues to help our decision making, but it will not make a final decision. Thank you.

I'm hoping, Dr. Kelvin, this answers your question. Thank you.

DR. L. LEE: Kelvin, this is --

DR. K. LEE: Yes. Thank you --

DR. L. LEE: -- Larry. I just want to just

emphasize that KASA will be learning, so anything -- if we feel like something is important, the KASA is built upon flexibility. We can incorporate those risks into the system as well.

Then on top of this, remember, the assessment, if we talk broadly, it's not just the application and assessment in KASA. In the biological area, it's a holistic approach which will also have the inspection component as well. So whatever we learn, we can actually go back to update or modify the KASA. And just like Lawrence said, at the same time we can also use the data analytics to see whether there's any specific trend which we are not aware of to be able to detect some of the new high-risk areas, as you mentioned.

Also, I want to emphasize that everything is relative. I think we probably need to really compare to what we are doing today versus what we can do in the future. With this type of system in place, we do believe that we can do better in the future.

DR. K. LEE: Thank you very much.

DR. MORRIS: Thank you. That's very interesting.

Dr. Zamboni is next.

DR. ZAMBONI: Yes. Hi. This is Bill Zamboni from the University of North Carolina. My question is specifically for Drs. Raw and Shah, but others could clearly join in.

The two of you, and many others, have clearly shown the advantages of KASA. My question is, if you could currently expand on what has been identified as the limitations of KASA through some of the pilot programs and things that you've run; and then also, what are other theoretical limitations that still may occur? Thank you.

DR. MORRIS: Thanks. Maybe we could start with either you, Dr. Lee or Dr. Yu.

DR. YU: I think that's for Andre --

DR. SHAH: This is Dr. Rakhi Shah. I can start, and then, Andre, you can chime in.

I think there are limitations, but we have launched quite a lot of these from other solid generic KASAs, and we see some of the gaps that we

consider opportunities for advancement when we build our next module.

For example, when we are going into liquid products, we understand that we do not have a combination product module and that we can have an opportunity to build. Then I just heard about some of the unknown issues, unknown problems. When we get into the next modules of KASA, we are trying to incorporate, modify, and update our models, not only the risk assessment model, but also some of the things that are missing from current KASA.

I would say the limitations, Dr. Andre Raw showed that about 500-plus assessments are completed within KASA, so every day we learn that, yes, there are -- regarding a new IT system, it may be a little bit challenging in the beginning. People have to get used to a new system, but those are all being mitigated and being discussed with our IT folks. They are on board with us, so we discuss with them, and then we eventually come up with a better product with every release.

So it's a continuous improvement project.

We understand that it's not perfect when it was launched back in February, but we have made significant improvements. One improvement that I can say, for example, is when we built our solid generic modules, when we are comparing with our data across applications, we realize that since NDAs were not done in KASA, it will be difficult to compare, so we went ahead and built a module so that we can have data manually done for our NDA information upon which the generics rely so that we can have a clear comparison, as you can see in this slide that is displayed.

These opportunities are found, and they are being rectified as soon as they're found. That is what I wanted to mention but, Andre, please go ahead and chime in if you have any additional thoughts.

DR. RAW: Yes. This is Andre Raw speaking. I want to make some comments.

First of all, when the KASA 3.0 was launched last year in 2021, first of all, it's not like we were just a static system and that we didn't make

any updates. We realized there were some problems, and we did work to update the system for two reasons. One is to better capture inside aspects of the assessment, and also to make it easier to use for the assessors. So we are continually improving the system.

I also want to talk about this concept of unknown risks or risks that we didn't know. I think that's a very important concept. I just want to be very clear that when we develop these algorithms and these risk mitigations, it's based upon the risks that we know. But again, if there are some risks or some mitigations that we didn't know, or some mitigations that were unknown, we'll definitely update the system.

But one thing I do think that is very nice about the KASA is the assessor. If there is a risk that is not in the KASA right now and the assessor wants to flag it, they have the capability to flag it. And also, if there is a risk control strategy that's not within our drop-down, the assessor can flag it. One of the really nice things about that

is that we can mine all this. So basically, if there are new risks that are identified or new approaches to control are identified -- the assessor can do that -- we can mine those things, and we can use that information to improve upon the KASA.

Previously, when we did text-base narrative, we didn't have that capability because it was all text-based; we couldn't mine it. But now that we have this ability and we have this structured data, we can start mining unknown risks and new strategies, and incorporate them into our model. So I'm going to end there.

DR. MORRIS: Thank you. Is that sufficient, Dr. Zamboni?

We'll take one more question and break, and we should have time after the open public hearing to continue clarifying questions.

The final before lunch would be Dr. Tonglei Li.

DR. LI: Thanks, Ken. This is Tonglei Li from Purdue University. First of all, kudos to the

FDA team for making KASA a reality, and thanks for your presentations this morning.

I just have a general question. I'm very interested in knowing more about the methodology and the algorithms that are used in the computer-aided risk assessment. My question is whether FDA has plans to publish this methodology and algorithm; for example, slide 40.

DR. MORRIS: I think we've lost you, Tonglei.

DR. LI: Yes. I have just a general question. Does FDA have plans to publish the methodology and the algorithms that are used in the computer-aided risk assessment?

DR. TSINONTIDES: Joel, do you want to --

DR. WELCH: Alright. Can you hear me?

DR. YU: Yes, we can year you.

DR. WELCH: Thank you for the question.

DR. MORRIS: Yes, now we can.

DR. WELCH: Speaking about text-based, the published answer is no. And I think the reason is that so many of the conversations that inform risk

are conversations that happen outside of KASA; questions around, for example, how you validate a continuous biotech process. Those conversations are happening in the annexes of Q13; where are the unit operations and what are their critical features for viral clearance? Those conversations are happening in Q5A.

So KASA, to me, isn't the horse; it's the cart on this, and what informs science and risk is really something that happens outside of KASA, and that I think translates to other topics as well, down to how we organize dossiers with M4Q. So I think there's a place for a conversation of how risk is determined, but I think that's a scientific consideration that happens outside of the KASA system and other places instead. And I'd invite my other FDA colleagues to weigh in on that as well.

DR. MORRIS: Can I just weigh in for a second? This is Ken Morris. When you say they're outside of the KASA formalism, like from Q5A, you're going to be using algorithms that are already existing outside of KASA or are you

developing new ones? I think Dr. Li may be thinking about that in terms of publishing.

DR. WELCH: I'm talking about an understanding of the scientific model of what risk is. Again, I'd invite my other FDA colleagues to weigh in on this topic as well.

DR. TSINONTIDES: Joel, this is Stelios. Maybe I can add to what you know, is that KASA is the tool that we utilize to, obviously, enter information, and then alleviate -- and the program to provide us with a suggested level of risk and some results. Once we see the results that come out of these tools, the team as a whole discusses that. So it is not taken and then run with that, necessarily, without further consideration.

I believe that's what Joel mentioned, that the decision eventually about the level of risk happens outside the tool and allows our assessors to have a complete picture of what the result is being shown or is being calculated, and discuss it. Then a decision is made how to treat that, an informed decision. Thank you.

DR. MORRIS: Thank you, Stelios.

Dr. Li, is that --

DR. LI: Yes. I guess that decision risk assessment decision actually is joint made by assessors, in addition to the computer provided suggestions?

DR. YU: Dr. Li, when we talk about computer-aided assessment, we, frankly, in a way use common scientific knowledge in textbook. For example, in the, let's say, small molecule, we look into the physical stability of the molecule or physical chemical properties. We're looking into the chemical stability of the molecule. We're looking for the biological property of the molecule. Then we can inform like an initial informed decision.

Then from there, we're looking into the dosage form design like formulation approaches, for example, amorphous material or manufacturing process with the continuous manufacturing as a risk over there. Then we'll look at the facility -- the manufacturing facility is also very critical -- and

look at the impact overall.

So we look at the product risk. We look at manufacturing risk. We look at facility risk to make a holistic decision about overall risk collateral. Many of them could be yes or no and some of them qualitative. So it's not just a simple answer like 1 plus 1 equals 2; this kind of equation is going to use it, but it's a very holistic overall process looking into the overall risk.

That's part of it, and it's kind of very difficult to communicate outside of the FDA, and also information could be evolution because once we're published, and people say this is what FDA reviews as final, then tomorrow we could change the result. It evolves because, I said -- Larry and the many others who have been talking -- KASA is an evolution process, and includes all the tools which utilize whole-risk assessment; risk mitigation; risk intention; also all the analytical functions was also involved in the evolution process.

So we'll continue to improve upon right now.

If we share with the public, it could potentially impact our ability and also impact the public as well because, frankly, common knowledge is in the textbook or scientific research, so it's probably not much difference overall when we give a scientific presentation here. That's part of it, because it's so difficult to present it externally because we want to make sure, when we present it, especially from the FDA site, it's correct.

So therefore, it's an overall analysis of the execution, both quantitative and qualitative, from product risk, from drug substance risk, from an manufacturing risk, and from a facility risk, and make the overall assessment of that probability application. Thank you.

DR. L. LEE: Thank you.

DR. K. LEE: Thanks, Lawrence. That's all I have.

Thank you, Ken.

DR. MORRIS: Thank you.

Great. In response, the feedback to the sponsor would always be implicitly controlled or

contained, these decisions.

With that, we'll break for lunch until 1:20 Eastern Standard Time, and we should have some time after the open public hearing to entertain a few further clarifying questions. There are still a fair number pending. So with that, we'll now break for lunch and reconvene at 1:20 Eastern Standard Time.

Panel members, please remember that no chatting or discussions of the meeting topics with other members during the lunch break should occur. Additionally, you should plan to join about 10 minutes early to ensure you're connected before we convene at 1:20. So with that, thank you, and have a good lunch.

(Whereupon, at 12:26 p.m., a lunch recess was taken.)

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

(1:20 p.m.)

DR. MORRIS: Hello, everyone. Just before we start the open public hearing session, I'd like to turn it over to Rhea for an announcement.

Rhea?

MS. BHATT: Thanks, Dr. Morris.

Just before we resume and begin the open public hearing session, I would like to make a brief announcement. One of the industry representatives, T.G. Venkateshwaran, informed us that he will not be able to join for the remainder of the meeting.

Back to you, Dr. Morris.

Open Public Hearing

DR. MORRIS: Okay. Thank you.

Thank you, Rhea.

We'll now begin the open public hearing 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 an individual's presentation.

For this reason, FDA encourages you, the open public hearing speakers, at the end 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 relationship. 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 always 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, and 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.

If we can have the connection for speaker number 1?

Your audio is connected, so will speaker number 1 please begin and introduce yourself, and also please state your name and any organization you are representing for the record. Thank you.

MR. ABERNATHY: And can I just confirm that you can effectively hear me?

DR. MORRIS: Yes, I hear you fine.

MR. ABERNATHY: Perfect. Thank you.

I represent Amgen. I have no financial ties

directly to the KASA initiative. First, I would like to thank FDA and CDER for the opportunity to speak today. My name is Mike Abernathy, and I come to you not solely as an Amgen staff member, or a representative for Accumulus, but as an advocate for our industry, and most importantly, as an advocate for patients, of which I am one.

Though the health science industry, and specifically the biopharmaceutical industry, is a late arriver to the 21st century technologies, when compared to other industry peers such as the airline and banking industry, FDA's KASA initiative supports our transition from antiquated to modern technology, and thus, Amgen agrees with FDA that technological advancements through the processes by which regulatory submissions are prepared, submitted, and reviewed have the potential to transform the speed and efficiency of these processes with potential benefits to patients and driving faster and more efficient regulatory decision making.

As a founding member of the Accumulus

initiative, we are committed to developing tools that will deliver on this promise that recognize the essential leadership role that regulators have and will continue to play in this change. Amgen strongly supports the general direction of FDA's use of technology to advance regulatory modernization. Nevertheless, we encourage FDA to acknowledge that KASA is a US-centric tool that could inadvertently create further divergences in regulatory requirements across regions.

In addition, divergence would have substantial economic impact by requiring sponsors to submit applications in multiple formats to satisfy U.S. PQ/CMC KASA initiatives and other international efforts. It would also hinder efficiency through potentially extending submission timelines and delaying overall regulatory processes on a global scale.

FDA should further clarify the relationship between KASA and other related initiatives, such as FDA's HL7 PQ/CMC initiative, including the scope of PQ/CMC and the extent of its coverage across

Modules 2 and 3, as well as ICH's emerging structured product quality submissions guideline. Accordingly, we strongly recommend that the agency consider a comprehensive CMC solution that factors in the evolving international regulatory landscape to ensure optimal implementation and use of KASA and PQ/CMC to drive efficiency and cost effectiveness.

Such collaboration need not result in a delay to the introduction of this highly promising and potentially transformative technology. To the contrary, we believe that it will ensure the most rapid adoption. And though, due to socioeconomic and geopolitical constraints, we will likely never achieve a single global regulatory submission to a universal global health authority, we can leverage technology, automation, artificial intelligence, and a cloud-based ecosystem to build structured and standardized regulatory filings that can be submitted to and reviewed by many health authorities concurrently. FDA's KASA initiative helps our industry take a positive step towards the

future vision.

I'd like to thank you for your time today, and I'd like to thank you for your service on behalf of patients. Thank you.

DR. MORRIS: Thank you, Mike.

We, I believe, have a second open public hearing speaker.

Is that correct, Rhea?

MS. BHATT: Yes, that's correct.

DR. MORRIS: Okay.

Speaker number 2, your audio is connected now. Will you begin and introduce yourself, please? And state your name and any organization you are representing for the record. Thank you.

Speaker 2?

DR. PANNALA: Good afternoon. My name is Raghuran Pannala. Am I audible?

DR. MORRIS: Yes, I hear you fine. Thank you.

DR. PANNALA: Thank you. Thanks for the confirmation.

My name is Raghuran Pannala. I'm working at

ScienGen Pharmaceuticals as a senior vice president of regulatory affairs, pharmacovigilance, and corporate quality compliance. I'm involved in PDA and other pharmacopeia companies, briefly or for a more period of time. I don't have any financial commitments to disclose.

To start with, I'm involved in regulatory filing compilations of DMFs or the APIs, and the ANDAs for generic drugs from 1994, and I have seen, therefore, hybrid and electronic filings for various regulatory agencies. I thank FDA and CDER for providing me an opportunity to speak in the advisory committee meeting on KASA, known as knowledge-aided assessment and structured application.

I appreciate the FDA and KASA, NCA [ph], too, and I could see the benefits outlined as easy access for research, and in terms of structured data, accelerated data analysis, and eliminating the text on the [indiscernible], text-based narratives, and eliminating those things. Sorry.

I will start with a positive note on the

navigation, benefits, and quick turnaround times with CDER NextGen, and the endorsement [indiscernible] we have seen, I really appreciate it, in terms of CDER NextGen portals.

I would like to make a few comments and suggestions for the agency review. It seems FDA is aiming at moderately aggressive timelines for this. I'm having some concerns with all the forms and if we'll be able to match the timeline in terms of resources updating and in terms of technical financials. In the presentations, it was told that this will be implemented for API and drug product as well.

I hope the FDA will be able to provide the basic data structures and any associated open-source software for this and associated validating tools, as it involves financials. If an application is being rejected for any of the technicalities, the filer would lose a lot of money for it in the user fee program.

It may be early or FDA may be already working on it. I heard, Dr. Lawrence, you speaking

on the stability data statistical analysis. I hope FDA will make it clear what are the calculations followed. I know it should be as pricey [ph] as Q1E or not any other associated guidance in the same way for other data analysis. FDA may have to disclose the rationale or calculations. I can understand creating the residual risk calculations are part of the agency's internal protocol and need not be disclosed.

Coming to the unicode data or unstructured data to be loaded in the drop-down menus, this may be forcing all the firms to embrace an entirely new structure for additional data generation. How is it so? If you take stability data as an example, as of now, forms scanning the stable data sheets are attaching electronic data PDF sheets. If KASA is implemented, the dossier compilation may be additional work or [indiscernible] work, and this may sometimes lead to typo errors. I'm agreeing that in the future, new solutions may come in place to avoid this.

I think the KASA implementation in oral

solid generics, CDER also takes into consideration that the data extraction from the machine readable [indiscernible], uploaded by the filers or the NDA sponsors. And of a related subject, the data integrated part, which manufacturers need to take care, basic protocols and expectations need to be met to answer internal QA, as well as the inspectors from FDA. Forms cannot avoid the raw data recording and subsequent report preparation; maybe lack of stability or analytical method violations, or process violations, under the registration associated data. These KASA related protocols, their generation may be additional work to the firms.

I hope ICH will also align with the FDA timelines and expectations for the recipients. As rightly told by my previous commenter, it involves membership representation from other regulatory and geographical regions in addition to FDA, and geographical region USA.

FDA may help clarify data, which has to be scanned and uploaded from programs or any other

machine-related data. Also sometimes, we see CDER reviewers are issuing few [indiscernible] integrity, or on data batch records, the [indiscernible] data, or any analytical raw data electron programs presented in the filings. I hope this human intelligence or intuition part will not be marked down by machine intelligence.

Stating all the above, I feel positive to an implementation. Maybe I would like to quote an associated example like recent advancements or changes in the health data management. Updates in the pharmacies or doctor's office have been successful despite the educational and employee attrition [indiscernible] rate at those institutions.

I'll personally leave you with concern on the data stored in the cloud and the associated risk versus benefit analysis, but as it was rightly stated in the presentations and the data presented on the website, we learn new things as we move forward. On the whole, the data presented today was a little bit overwhelming, but I understand it

is the future, and I wish FDA will drive this change by helping all the stakeholders understand the requirements of KASA. Thank you again for providing me an opportunity to speak.

Clarifying Questions to the Presenters (continued)

DR. MORRIS: Thank you.

I believe that's the final speaker.

The open public hearing portion of this meeting has 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, the careful consideration of the data before the committee, as well as the public comments.

Since we have time left in the open public hearing segment, as we said before the break, we'll take more clarifying questions that started before. And again, as we take the clarifying questions, please use the raise-hand icon to indicate you have a question, and remember to put your hand down after you ask your question. And please remember to state your name for the record before you speak and direct your question to a specific presenter,

if possible.

If you want a specific slide to be displayed, it would help if you have the slide number; and a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you, and end of any follow-up with, "That's all for my questions," so we can move on.

From before the break, we have some folks who are already listed. We'll start with that. The first question is from the Dr. Richmond.

Frances?

DR. RICHMOND: Thank you. My question is a little bit different than some of the others that have been asked up to this point. You talked about the stakeholders being largely isolated from the process, and I understand that. But there is one stakeholder, and I think that is the regulators in emerging economies who are using the judgments of stringent authorities as the basis for their reliance [indiscernible] activities.

I'm wondering, are they going to in the future be dealing with the submissions that are

made primarily by the sponsors in the open-text type format or are you thinking that you may be able to share these documents for their education? Thank you.

DR. MORRIS: I'm not sure --

DR. YU: I'll respond.

DR. MORRIS: -- yes, please, go ahead.

DR. YU: Maybe I'll keep it a little short, and maybe Larry or others can chime in.

Certainly, we recognize that each country, each region, is developed in a different space, like a different evolution of development. As you can see from the adoption of M4Q(R1), some regions FDA adopted 20-plus years ago, and some regions are just actually beginning adoption of M4Q.

So the reliance [indiscernible] approval has come into play, and I think we want to achieve regulatory convergence at first. Then we're helping that -- that's why our goal with M4Q(R2) is that each region we'll adopt as soon as possible, including the developing countries. Also, whether we're going to share CMC information or not, we'll

have to design some kind of agreement among the regulators themselves. For example, we may have shared with the EMA, but not necessarily other countries. In other words, we'll have a bilateral relationship. Especially when we share the sponsor information, we need permission from the sponsor to allow us to share.

So many factors come into play, but I do believe that in KASA, our whole effort in facilitating the communication will facilitate the reliance space and the regulatory action.

One good example we had with the FDA, where we had plenty of experience, is ORBIS. When ORBIS was in [indiscernible] a couple years ago, we had a relationship, for example, in the UK, and also [indiscernible], and Health Canada. So to me, those approvals are much bigger and they're much less time consuming.

So therefore, I guess to answer your question, the KASA, M4Q, and PQ/CMC will facilitate, but certainly to what extent we'll have to rely on not only the scientific and technical

approaches, we'll have to rely on some kind of relationship among the regulators. I'm hoping this answers your question, Frances Richmond. Thank you.

DR. RICHMOND: Thank you.

DR. MORRIS: Thank you.

Our next question I think comes from you, Maureen, Dr. Donovan.

DR. DONOVAN: Thank you. This is Maureen Donovan from the University of Iowa. My question is more related to the pilot studies that have been going on, on the generic solid side. Were there any metrics associated with those pilots? Have you tracked reviewer time commitment? Have you tracked communications to the the sponsors and whether those have increased or changed in the time frame of review?

Really, what I'm getting at is, as these data or portions of the applications are able to be looked at more consistently, post the time frame to input that data, is that shortening the review period, and are problems being identified earlier

in the process where additional data might be needed, and that communication can go back to the sponsor?

DR. YU: To answer your questions, yes, we have not kept track in what is really going on, I guess, with our constraints, but we know what's happening has truly helped quite a lot.

Just to give you a very simple analysis, which myself had experienced, I was the acting director, and now Stelios Tsinontides is joining as the director. We actually for our review had a very simple analogy. We needed to enter the company's address into our assessment template. Before, you had to manually enter it, where, on average, each application would have six facilities, so you basically entered six addresses.

Now, entering six addresses of the facility takes us some time. It probably takes a half hour, and many of you made a mistake, especially a lot of the sites that are foreign, the very strange addresses, and stuff like that. But with KASA, with the automation, it's very simple. It's not

necessarily the KASA with automation, [indiscernible] becomes automatic. Just this alone saves probably at least 30 minutes.

The benefits are obvious, and we know it includes consistency. We know the effectiveness, but in a way to truly track, we'll probably have to develop our matrix to see how we're doing at this moment.

I don't know. Andrew Raw, do you have any additional comments, or Larisa? Feel free to chime in.

DR. WU: Yes. This is Larisa Wu. As Lawrence mentioned, the feedback that we received from our colleagues so far is informal and, in general, is a positive feedback. But we have not looked at KPIs yet. I know we have colleagues that are working on a survey as we speak, and hopefully in the near future, we'll be able to provide some statistics in terms of reviewers' time commitment or communication with sponsors, and whether we improved on that or not.

DR. YU: Thank you, Larisa. I think the one

point I want to make is the development of KASA is the evolution, and KASA, certainly the interface will be user friendly, and that's why it's so widely accepted by all the reviewers.

But another point I want to make is in order to be fully functional, you have to have a database. Now database building takes time and takes effort. We'll continue evaluation, and our data will be much more robust, and certainly the functionality will continue to be increased or enhanced.

So therefore, if you judge today's phenomena versus tomorrow or the day before yesterday, the evolution process makes the judgment certainly a little bit more challenging. But we will keep tracking, and hopefully some day will come where we report back to what are we doing. But we know, based on informal conversation with all the reviewers, with assessment, and the implementation, as Larisa pointed out, it is very positive.

I want to share one of the stories of why we're doing this. One of the things that actually

we're doing is way back in 2014 or 2016, when we got the iPhone, we recognized the iPhone was able to search all the public information about all the medicines, drugs, and dosage forms, but within FDA, we're not able to search. So eventually, we wanted to build in a search function. Of course, we wanted more than that. We wanted to build not only a search function of the older data, but we also did all the data analysis that was going as well.

I think there's no question -- for example, today if I ask you not to use an iPhone, it's almost impossible. The same thing is true to all of you as well. So it just gives you some kind of analogy of how KASA is powerful, and informative, and user friendly to all assessments. Thank you.

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

DR. DONOVAN: Thanks to the FDA speakers for those additional follow-ups.

With the permission of the chair, could I ask a second question?

DR. MORRIS: Please do.

DR. DONOVAN: My second question is perhaps somewhat related to a couple of the public comments, in that are there already discussions regarding how the FDA is planning on using results that they internally find from their deeper dive into the data, as the databases get built out, regarding communication of thoughts, changes, things learned via guidances or other documents so that applicants are able to, in real-time, provide the information that the FDA is going to be looking for?

DR. YU: Well, maybe I can give a shot on the second question. Clearly, when we have data, we will do an analysis. When you do an analysis, you have knowledge. And we would love to share all the knowledge with the public because we believe at the end of the day, those will all serve the other regulators, industry, academia, and also eventually serve the public, the public health.

Yes, absolutely. Once we learn internally all the data, we'll be happy to -- we will love to share with the public about our learning.

Absolutely.

Larry, do you have any additional comments?

DR. L. LEE: No. I think I just want to clarify that -- I just want to let you know the concept and what we do, actually, for KASA. It's really, basically, using an IT concept, and all this stuff. Actually, we do it in the past as in human, using our brain manually.

The things that really make KASA different is that we will be able to do it automatically. Really, from my perspective at least, I don't feel like there is a guidance where we need it because we are not going to do anything different. We still apply the standard. For example, we agree on the ICH, and the quality standards in the ICH, and we apply those.

So I think that, definitely, it doesn't seem to me -- I just want to make it very clear, is that we are not doing anything different, but to build KASA is just to help us; no impact on the industry, but it's really just help us to do our job efficiently by using the same principle also.

DR. TSINONTIDES: Larry, this is Stelios. If I may also comment here in trying to answer, again, the question.

As we explained, KASA is an internal tool that allows us to collect all of the relevant information around a particular application or a process, and allow our assessors to utilize that information in determining the next step in determining its adequacy.

As a result of that, as we collect information from other relevant applications that are related, if we see something, we will definitely reach out to those impacted applications or sponsors, and let them know what we find as a result of doing these analyses, and as a result of having these data available at our fingertips. Thank you.

DR. MORRIS: Thank you all. Good discussion.

I'm sorry. Was there more? Please go ahead.

DR DONOVAN: No. I was just going to thank

the speakers once again for the additional information.

DR. MORRIS: Oh, thanks, Maureen. Thank you.

Dr. Slud, I think you're next up with a question.

DR. SLUD: Thank you. This is Eric Slud. It occurs to me that you've been speaking about the KASA functionality in two different ways. One is just as a general way of aggregating information more conveniently for the assessors or for the FDA evaluators, but you're also proposing something that isn't just a continuation of past methods, which is to do automatic risk scoring in a way that might economize on human effort. And to the extent that you rely on that risk scoring, it's a matter of concern, of interest, that you might want to publicize just how effective and correct that risk scoring is.

Correct means that you will be fitting the models on the basis of which all of this artificial intelligence is done with data, with data on

adjudicated risk, adjudicated meaning evaluated by human experts. And presumably, the quality of the risk scoring and the quality of the AI will have to do with the accuracy of the AI systems in reproducing something like what human evaluators in a time-consuming way would have arrived at.

So I acknowledge that this will always be a moving target, but even if you didn't want to publicize the direct algorithms that FDA uses, you could publicize, in a way that would make it susceptible to external peer review, the overall accuracy you're achieving in mimicking and in reproducing human adjudications of risk through artificial intelligence. Thank you.

DR. RAW: Hello. This is Andre Raw, and I'll take a start at answering your question. One thing that we do -- I think your concern is, we have these algorithms, and are they in line with human adjudication, and should we evolve with that.

Well, first of all, when we develop these algorithms, previously we did validate with human adjudication, so we thought we had a good start.

But then one thing I just wanted to also mention, and I think it needs to be very clear, is that when we had the low, medium, high for the initial risk assessment, if human beings determine there's a big flaw with that, and they say like, for example, it's overestimating the risk, or it's underestimating the risk, what we do is we have something in the KASA system to say it's high. The KASA will say it's high, but the human will say, I think it's wrong, it's overestimating, and I'm going to override it, and I'm going to say it's low or vice versa. KASA could say it's low, and the reviewer would say I think it's underestimated and want to say it's high.

The really nice thing about KASA that we have is we know exactly what those interventions are, so we can use that information to optimize the risk algorithms. So we'll know that if there's another disagreement between the human expert and the algorithms, we'll know those things, and we can mine that data, and then update the algorithms as needed. I hope that answered the question.

DR. SLUD: Well, thank you. It does partially answer the question, but it seems to me, in the nature of AI systems and machine learning, that, of course, you're going to keep on updating the system to mirror what the humans would have evaluated as time goes on. But the question is, overall, what effectiveness are you achieving?

People will want to know that you're using tools that really benefit the organization and that AI is panning out in terms of giving accurate assessments, and that's something that you might certainly publicize within the organization, but maybe even publicly so that it can be evaluated as a tool overall.

(No response.)

DR. MORRIS: Is there any follow-up from FDA? I actually have the follow-on question that might require some attention to. So is there any follow-up before I weigh in?

DR. SHAH: Yes, I just wanted to -- go ahead, Lawrence.

DR. YU: Go ahead, Rakhi.

DR. SHAH: Yes. Hi. This is Dr. Rakhi Shah again. I just wanted to follow up on what Andre commented and what the question is.

So when we are developing our risk-based algorithms, we are utilizing prior knowledge into building those risk algorithms, but we do have a validation set or test set that we evaluate against. We kind of know its accuracy, and we keep modifying it. Now, it gives us initial risk scoring. It gives us how much time we need to spend on one versus another, where there is a risk ranking from low, medium, and high, however, assessors can always modify that.

So when we take a deeper dive into an application, when we take, for example, a deeper dive into facilities, there are more risk factors that we might not have accounted for in the beginning, so we can modify, we do our assessment, and we then ask clarifying questions to industry; so that goes on.

So we are not really utilizing artificial intelligence, if you are going in that direction.

So far, we are using assessors in doing our assessment. I think we just want to differentiate. Of course, there are risk-based algorithms, and we are trying to develop, and we are trying to improve that, and as the time passes, we have more information and more knowledge. But KASA is helping us to learn what type of data we already have. We put it in our reviews, and that into knowledge that we can utilize, and we can make informed decisions. KASA doesn't do decision making for us.

I just wanted to clarify that. I hope that answers your question, Dr. Slud.

DR. MORRIS: If I can weigh in also, and voting or non-voting members are more than welcome to comment, of course.

This is Ken Morris. If I can backtrack a little bit, reviewers have always used their historical knowledge to assess risk at some level, subjective maybe to some degree, but it's based on experience with other filings. The way I was interpreting what we were talking about earlier

during your presentations, and particularly Dr. Lee, is that one of the advantages of KASA is that you have that historical knowledge of the visual reviewer, but now you have it across products and you have it across other reviewers if KASA works as you intend it to, I believe.

The question part of this is what we were talking about a little earlier with Dr. Slud, is that at some point, instead of just mining the data and looking at the data across products and across investigators, are there also going to be algorithms? I heard prior knowledge, or is this like Bayesian algorithms or is this going to be just the accruing of the information and drawing conclusions?

I hope that makes sense. I'm way out over my skis when it comes to Bayesian analysis.

DR. L. LEE: Yes. This is Larry. If it's ok, I'll make some comments as well.

DR. MORRIS: Please. Please do. In fact, I'll throw this to you.

DR. L. LEE: Just to clarify, yes, I think a

lot of people are very interested in how we actually do the risk analysis and also how do we actually get the information. From my perspective, I think we do have no issue to really point out some of the high-risk areas in our algorithm to make sure people can understand which area they need to pay attention. So I think those definitely can be -- we plan to consider sharing that information.

Lawrence. I think you have some comment as well?

DR. YU: Yes. Thank you. Thanks, Larry.

Absolutely. KASA, it's not just that we develop, but it's also digitalization efficiency, and not just to add benefit to FDA. We certainly want to eventually benefit our stakeholders and benefit the public as well. So therefore, as much as we can, when time matures, we will be happy to share key risk factors we consider, so industry should be aware.

For example, we have published a number of papers called The Common Deficiency, where the

common deficiency is related to the generic drug application or common deficiency related to drug substance application, so the industry can learn what factors we pay attention to and rank the high-risk factors.

We will do the same, again, to all the committee members in the future when time is appropriate and we feel confident with our own analysis of data. So we'll share with the public so the stakeholders and industry can learn whether our thinking eventually benefits the public at the end.

So absolutely, I want to assure you we're certainly happy to share. Especially Larry, our deputy director, has already promised, yes, we'll share. It's not because we don't want to share any publishing. We want to publish as many papers as we possibly can, but sometimes you're experimenting in the middle. You are in the middle experiment, you have not reached a conclusion yet. If you want to publish data, it seems very high risk unless you want to get a tenure.

I'm sorry. I'm not saying you'll get a tenure through this, but certainly I want to make sure that our knowledge about risk, as it becomes mature, we'll be happy to share in the public; so thank you.

DR. MORRIS: Thank you, Lawrence. Actually, I think everybody at the committee, the consensus is they understand not being able to share specifics. I thought between Dr. Slud and Dr. Lee, that the question was whether or not there's at least the consideration or the potential for using these models internally; not so much whether or not they were shared immediately, although, God knows, academics hate to publish. You know how that is; yes.

DR. YU: I apologize. I'll take some comments back, ok?

(Laughter.)

DR. MORRIS: Thank you.

I think that clarifies it. I think I'll do a summary after we get closer.

DR. YU: Thank you.

DR. MORRIS: Thank you.

I believe that was the end of discussions for clarification, and with that, I think, if I'm not mistaken, Rhea, we're ready to go on to question 1?

MS. BHATT: Yes, we can move on to question 1.

Questions to the Committee and Discussion

DR. MORRIS: Okay. So if you could go ahead with the instructions. This is a voting question, and Rhea Bhatt will provide the instructions for the vote.

MS. BHATT: Thank you, Dr. Morris.

Voting question 1 is a voting question. There are two questions today. 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 to 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, 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 round 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 numbers 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, then 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, if you wish to.

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: Thank you, Rhea.

The voting question number 1 is, do you support the long-term strategy for developing and implementing KASA at FDA and expanding the system from generic drugs to new drugs and biologics assessments?

At this point, if there are any issues or questions about the wording of the question, please raise your hand, and we'll acknowledge you.

(Pause.)

DR. MORRIS: I'm just giving people a minute to decide. I see hands up.

Dr. Lee, Kelvin, is your hand up for this or is that residual?

DR. K. LEE: No, it's up for this.

DR. MORRIS: Okay. Good. Thank you.

Dr. Lee?

DR. K. LEE: Thanks. This is Kelvin Lee. I

have a question to help me understand the phrase, "long-term strategy." I wonder if there is a more simple description that can be shared of what is included from the agency's perspective on long-term strategy.

The reason I ask, in case this context helps, I think we've heard and discussed a number of important reasons for why the agency is interested in KASA. They include data collection issues. They include helping to make agency staff work more efficient. There's of course the assessment and understanding of risk, and then on the longer term, there's not only the development and pushing for pilots, but also a globally harmonized cloud-based system as an endgame.

So I'm not clear what part of that long-term strategy we're thinking about and whether that also just refers to the expansion of the system from generics to new drugs and biologics, or is long-term strategy one part of the question, and the "and expanding the system" is kind of a part B of that question. Thank you very much.

DR. WELCH: This is Joel Welch. I'll start, and certainly invite others to chime in. I would say it's really an intent to continue to develop the system, and for that development to reflect using this approach across the entire portfolio of products, generics, new drugs, biologics, as well as doing it across the lifecycle of the product, INDs, original application assessments, as well as supplements.

DR. WU: This is Larisa Wu. I can chime in. Certainly, as you could see, we have been working on KASA for a few years already, and we have made tremendous progress, but we're not yet where we want to be. With implementation, in every IT system, as I mentioned in my presentation and you saw in my colleagues' presentations, there are certain stages that we have to go through for development, testing, and implementation of KASA into the CDER IT platform, and that takes time.

I think Andre Raw in his slides showed the roadmap for KASA IT productions. We are now in 2022, but this effort really will continue to 2027,

and probably beyond, in order to be able to have all the disciplines and all application types that we want in the KASA system.

I hope this answered the question, but I'm welcoming others to chime in.

DR. L. LEE: Thank you, Larisa.

This is Larry. Kelvin, this is a good question. I think it's just a very simple way to expand what we learned from the generic side to apply the similar concept to the new drugs, as well as biologics. The workload we have in all the different spaces is quite tremendous, so this system will be critical for us to make sure that we continue to meet our increasing workload, but at the same time maintain the quality of our assessment to make the best science and risk-based decision. Thank you.

DR. MORRIS: Thank you.

Are you fine, Dr. Lee?

DR. K. LEE: Yes. Thank you. This is Kelvin Lee again. I think I understand it. I think what I'm hearing is a slightly different

wording. We're going to vote on the words on the page, of course, but one of the things that I was hearing is, it's also about supporting the continued development and implementation of KASA, and expanding is another way to think about the phrasing. So if that's way off base, I hope somebody will clarify for me; otherwise, I think I'm good.

DR. L. LEE: No. I think that's correct, Kelvin. This is Larry. Thank you.

DR. K. LEE: Thanks.

DR. MORRIS: Good. Thank you.

Dr. Slud, you have a wording question?

DR. SLUD: Yes, thank you. I would like to ask a little bit -- this is about the long-term strategy part. Certainly, the development of a unified system for collecting data, this is something that's been extensively argued, and persuasively argued, and will help the FDA's mission.

I'm concerned about the possibility, though, that agencies do sometimes develop legacy software

that then has a life of its own. I didn't hear, as part of the long-term strategy for example, an evaluation of whether in addition to the unification of the database, whether the software tools -- for example, the automatic risk scores -- could conceivably turn out to be a little bit counterproductive if they weren't quite accurate in mirroring what humans would have evaluated as appropriate risk scores, and that's something that will be an empirical outcome and require evaluation.

So it seems to me that as part of this long-term strategy, there are these two aspects, the development of the unified database but also the development of the unified data analytics, and I wonder if those need to be distinguished. Thank you.

DR. YU: Dr. Slud, could you please clarify your question again? I did not catch your last question about the one with the comments.

DR. SLUD: The question is whether there's an evaluative part that certain elements,

especially the risk analytics part of the strategy, would then become an ongoing tool that risk assessors would use, and whether this is going to be evaluated for effectiveness.

It's less clear to me that that will go on forever than this unified database will be of use forever.

DR. YU: Stelios, do you want to make a comment here?

DR. TSINONTIDES: Thank you, Lawrence.

I want to assure Dr. Slud that this is part of our continuous effort of enhancing the system, and always evaluating its accuracy and performance is part of an ongoing process. I would say yes, of course, it will be part of that strategy to continually test how well it performs and continue to improve it. Thank you.

DR. SLUD: So that does augment the wording of the question in a helpful way. Thank you.

DR. MORRIS: Good. Thank you.

I do not see any more hands up for clarifying questions.

Am I correct, Rhea?

MS. BHATT: Yes. I don't see any additional hands raised, so we can have move on to voting now.

DR. MORRIS: Okay.

If there are no more -- sorry. Go ahead.

MS. BHATT: Go ahead, Dr. Morris.

DR. MORRIS: If there are no questions or comments concerning the wording anymore, then we'll begin voting on question number 1. Rhea Bhatt will now take us into the voting section.

MS. BHATT: Thank you.

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

(Voting.)

MS. BHATT: Voting has closed and is now complete. Once the vote 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. Dr. Morris will go down the list and each voting

member will state their name and their vote into the record. You may also state the reason why you voted as you did, if you wish to.

There are 13 yeses, zero noes, and zero abstentions.

Over to you, Dr. Morris.

DR. MORRIS: Thank you.

So, we'll go down the list and have everyone who voted state their name and vote into the record, and you can provide justification of your vote, if you wish to.

We'll start with Dr. Slud.

DR. SLUD: I voted yes.

DR. MORRIS: Thank you.

Dr. Richmond?

DR. RICHMOND: I also voted yes.

DR. MORRIS: Dr. Amidon?

DR. AMIDON: Yes. This is Greg Amidon. I voted yes.

DR. MORRIS: Thank you.

Dr. Carrico?

DR. CARRICO: This is Jeff Carrico. I voted

yes.

DR. MORRIS: Dr. Kelvin Lee?

DR. K. LEE: This is Kelvin Lee. I voted yes with the understanding that this is a continued rollout of a pilot that has shown value and opportunity, and where expansion seems reasonable. At the same time, I think it's going to be important to take into account the need for regulatory convergence instead of divergence, which would otherwise undermine some of the benefits.

So I look forward to the agency continuing to work with other agencies, as well as the regulated industry, to ensure that the gains that the agency receives in doing this, which I think promise to be many, are also considered in the context of efficiency gains from other agencies, as well as the regulated industry itself. Thank you very much.

DR. MORRIS: Thank you.

This is Kenneth Morris. I voted yes.

Dr. Kagan?

DR. KAGAN: This is Leonid Kagan. I voted

yes.

DR. MORRIS: Thank you.

Dr. Donovan?

DR. DONOVAN: This is Maureen Donovan. I voted yes.

DR. MORRIS: Thank you.

Dr. Finestone?

DR. FINESTONE: Sandra Finestone. I voted yes with the caveat that the analysis will be part of the process.

DR. MORRIS: Thank you.

Dr. Tonglei Li?

DR. LI: This is Tonglei Li. I voted yes.

DR. MORRIS: Thank you.

Dr. Kraft?

DR. KRAFT: This is Walter Kraft. I voted yes, and I would like to encourage the FDA to publish and share any pre-competitive findings that arise from KASA in publications and presentations; and secondly, that the interest of non-commercial stakeholders be kept in mind during the development process. Thank you.

DR. MORRIS: And thank you. Good point.

Dr. Zamboni?

DR. ZAMBONI: I voted yes, as there is a clear benefit to the technology and that the tools will evolve over time. Thank you.

DR. MORRIS: Thank you.

I believe I summarize before I go on to the non-voting question.

Is that correct, Rhea?

DR. HANCOCK: Can I jump in for William Hancock?

DR. MORRIS: I'm sorry?

DR. HANCOCK: Hello. I just want to say William Hancock. I also voted yes.

DR. MORRIS: Oh, did I miss you?

I apologize, Dr. Hancock.

DR. HANCOCK: Not at all. I just wanted to say I believe this initiative is very important, particularly with the advent of new biological therapies, so I look forward to the databases getting more and more enriched.

DR. MORRIS: Thank you. Apology again. I've been up since quarter to 5 this morning in Arizona, so it's my excuse.

DR. HANCOCK: I understand the problem in California, too.

DR. MORRIS: Oh, yes.

I believe I can summarize some at this point, and then we'll summarize after the non-voting question, too.

Is that correct, Rhea?

MS. BHATT: Yes, Dr. Morris. That's correct. If you could please summarize before we move to the discussion question 2.

DR. MORRIS: Yes.

The summary, I think it's very clear that everybody is in agreement that the potential for KASA is very significant. The questions are always in the details, of course, which makes sense, and those include, in broad categories, ensuring the veracity of the techniques that are used for the risk assessment and also not losing the experiential part of reviewers' jobs, which are

very valuable, so making sure that translates into the more structured filings.

Also, the continued flexibility to handle different product complexity levels, and certainly as you get more into biologics, there are concerns, both from the committee and other stakeholders, that the quality attributes be more fully defined as time goes on, which is part of the plan, of course.

Sharing the techniques that are used, I think, will become more important as they build, and I think the inclusion of stakeholders, that are not necessarily the pharma companies or the pharmaceutical companies, becomes important to the committee.

As far as the potential for limitations, I think the continued development part of that was well enough explained, and the committee has understood that, as well as the wording of the question to be inclusive of the fact that this is ongoing development and ultimately will lead to not only benefits for the assessors, but there's the

cautionary tale of making sure that that's also a benefit that's real, as by the companies, and ultimately the public.

That was my summary of it, and I think that bears out summarizing the topics.

That being completed, we'll move on to question 2, which is a discussion question. I'll read the question. In the age of digitalization, what additional actions should the FDA take to realize cloud-based assessment?

As with the last question, if there are any questions or issues with the wording, please raise your hand, and we can go through them as we did in the last one.

(No response.)

DR. MORRIS: I'm not seeing any hands.

Am I missing anyone, Rhea?

MS. BHATT: I don't see any hands raised for the wording.

Oh, Dr. Finestone may have a question.

DR. MORRIS: Oh, I'm sorry. I missed that.

Dr. Finestone, please?

DR. FINESTONE: No, you didn't miss it. I just raised my hand.

I'm a little bit distressed that analysis and evaluation wasn't discussed in the previous question. It seems to me that the emphasis is on efficiency, and not as much as perhaps I would like on outcome.

Is there any consideration, or has the FDA considered utilizing this application with projects or processes that have already been approved through the old method to see how they match up with each other? I don't know if that's possible, or if it's even a consideration, or would be of any value. But again, I think -- and some of the others -- that I'm concerned about evaluation not being a high priority.

DR. MORRIS: If I can interject, you're actually talking about the vote that was already taken, though. You're not talking about discussion question 2?

DR. FINESTONE: Well, yes and no.

DR. MORRIS: Okay.

DR. FINESTONE: Yes. What additional actions should the FDA take? And mine would be a more robust evaluation.

DR. MORRIS: I see. Thank you.

I don't know if it's ok to diverge from that, Rhea, but I think there was in the presentations some use, in the past studies, of going through already approved products, but if it's allowed, Rhea, can FDA comment?

DR. YU: Ken, this is Lawrence. Absolutely. This questions is basically an open-ended question. We're seeking advice from members.

Sandra Finestone, Dr. Finestone, these certainly are good comments. We certainly will take back any advice we receive from this committee, and to think about this, and to see what we need to do. Certainly, the reassessment of the robustness of our current system should be a good option for us to take on. Certainly, we think of whether we develop a system or evaluate the older system, so we have to keep a balanced decision here.

Ken, hopefully I answered this question.

DR. FINESTONE: Yes, I'm [indiscernible].

DR. YU: Absolutely.

DR. MORRIS: Yes. There were no questions on the wording, so we're opening it up to general questions. That the only distinction I was making, Dr. Finestone.

Are there any other questions, not necessarily on the wording, but any other questions before we move on?

(No response.)

DR. MORRIS: Alright. I don't see any other questions unless I've missed something, but I've gone down the list.

MS. BHATT: Dr. Kraft may have a question as well.

DR. MORRIS: I'm sorry. Who?

DR. KRAFT: This is Walter Kraft. So are you now opening it up for discussion on the discussion point or are you soliciting questions about the clarity of the discussion point?

DR. MORRIS: I think the clarity of the

discussion point was the wording, yes.

I was going to summarize, but there's not a lot to summarize on discussion question 2. We didn't really hit on it specifically during the clarifying questions. Indirectly, though, again, because it's the cloud, there was mention of security in the cloud and the tools that are available in the cloud.

One of the things that came out during the overall discussion was the idea of using data analysis tools, and, in particular, in the presentations there was talk of data visualization tools. And I think it was pretty well agreed that the cloud tool, the arsenal has grown incredibly quickly, and there are a lot of tools that already available out there that FDA could take advantage of, not necessarily for risk assessment, although perhaps. But I was thinking from our discussions, that could be more for us to [indiscernible], both to the sponsor, as well as how it's used internally by FDA.

I think we're approaching adjournment unless

I'm missing something.

Rhea, is that correct?

MS. BHATT: Dr. Morris, I just want to confirm, if there are no more questions about the wording of the discussion question, then we can move into discussion for discussion question 2.

DR. MORRIS: Oh, we can? Oh, okay. I didn't know it was open. That was, I guess, your point, Dr. Kraft, yes.

So now we're open for general discussion for the question. I've already gave my opinion that the idea of data visualization really needs to be explored in order to take full advantage of the cloud resources.

Now, if there are others who have discussion on the question, please raise your hand and be recognized.

Dr. Kraft, if you want, please, weigh in.

DR. KRAFT: This is Walter Kraft. I would just encourage, as this is being built, to think through the potential for third-party access to the data. Patient-level data, HPI, is pretty mature in

terms of privacy and the availability of third parties to access large health system data. And I would just encourage that, obviously, there are competitive imperatives, but that, again, at the time of creation or formation, having the foresight to think about the ability to share to third parties deidentified data would allow, I think, a great resource for all parties. Thank you.

DR. MORRIS: Thank you. Good point.

I don't know if FDA has any comments, but for the rest of us on the panel as well, any advice to FDA I'm sure gladly would be welcomed.

DR. YU: Ken, do you want us to comment, or maybe we just summarize all the recommendations from this committee?

DR. MORRIS: Yes, please.

DR. YU: I think the purpose of this question is we collect all the recommendations and comments from the committee, then within FDA, we can look at other recommendations and prioritize on which action we're going to take. So maybe it's probably a little bit of a challenge for us to make

a comment, yes or no, at this moment here.

DR. MORRIS: Oh, right, right.

DR. YU: Thank you.

DR. MORRIS: So is there advice --

MS. BHATT: Dr. Morris, I believe --

DR. MORRIS: -- yes, go ahead.

MS. BHATT: -- Dr. Slud has his hand raised as well.

DR. MORRIS: Oh, okay. I don't see that, but thank you.

Dr. Slud?

DR. SLUD: Yes. This is Eric Slud. I'm responding partly to this suggestion about data visualization and other tools. I'm primarily a statistician, so, of course, all data analytic and machine learning tools should be in scope. But I'd like to make the comment that in this kind of environment, the usefulness of those tools is, to a large extent, based on the response data of what it is you want those predictive tools to be able to imitate and predict.

So in this environment, the true responses

that you're trying to get at are what humans would have evaluated as high and low risks and which variables contribute to them. So in that sense, the FDA would possibly want to consider additional human assessments to add to this cloud-based database that could be used in the mining, and model fitting, and machine learning associated with letting the analytic tools do that work.

Of course, the regulatory decisions will be data that are routinely collected and presumably made part of the cloud database, but there could be other interim risk decisions that could, in a separate data collection from human experts, be of use in making these analytic tools more productive. Thank you.

DR. MORRIS: Yes. Thank you .

I believe now, actually I can see the hands now.

Dr. Amidon?

DR. AMIDON: Yes. This is Greg Amidon, University of Michigan. The comments I think that you made, Dr. Morris, regarding security I think is

certainly important. I appreciated the comments also related to third-party access. That can certainly facilitate the further advancement of KASA.

In terms of cloud-based assessment, my thought is that that could easily facilitate perhaps global registrations and speed the development and approval process; so maybe think globally in terms of constructing this system. I guess related to that is the multidirectional communication that this could allow between companies, between FDA, or between other regulatory agencies, and could all be perhaps integrated into this cloud-based assessment. Thank you.

DR. MORRIS: Thank you, Greg.

DR. YU: Dr. Morris, this is Lawrence. I want to make one comment --

DR. MORRIS: Yes, please.

DR. YU: -- if you don't mind.

DR. MORRIS: No, no. Please.

DR. YU: I want to make one comment related to security. I want let everybody know, certainly

the CMC information, there's a lot of proprietary information, for example, drug product formulation, so on and so forth. So when we discuss the development of this KASA, in fact, our security is the highest security possible, equivalent to military, to let the public know. Our CMC KASA system is sitting on a much higher security. This program is much secure than possibly the other disciplines of the FDA. So it's pretty much as secure as the military, just so everybody knows.

Frankly, because of the high security, the delivery of KASA has been delayed for several months because of the requirement. So I just let the members and the public know that KASA is sitting on a very -- we call it the FISMA -- high security, high like a military operation; so thank you.

DR. MORRIS: Thank you.

Is it as high as Facebook, though?

DR. YU: No comments here.

(Laughter.)

DR. MORRIS: Thank you.

Dr. Tonglei Li?

DR. LI: Thank you, Ken. This is Tonglei Li from Purdue University.

I think one of the things Lawrence mentioned in his talk is deep learning and AI. We have been working on deep learning over a few years. One of the things we think is very important is data, the quality of data. Manual data can really affect the quality of the deep learning model. So I'm really glad, actually, about the question about data sharing, and maybe that will open the data; not all the data, but some data that can allow the public to maybe validate or develop a similar deep learning method.

So again, I just want to support a previous question by Dr. Kraft.

DR. MORRIS: Thank you.

Dr. Slud, is your hand up for a question?

DR. SLUD: Yes. I would like also to weigh in on this issue of privacy. From my perspective, it involves Census Bureau work. We found that it's surprising, the extent to which large databases of

apparently deidentified data can be reidentified. So the problem of making databases that contain proprietary information really secure, from the point of view of reidentification of the parties and the information involved, is not trivial at all. It is not obvious that you will be able to share very widely without extensive additional consent by the submitters, by the sponsors.

DR. MORRIS: That's very interesting and valuable, yes.

Dr. Li, Tonglei Li, do you have your hand up again? No, it's down. Okay. I was just checking.

So let me re-summarize a little bit for FDA. There's a double-edge recommendation that cloud data be made available outside to raise all boats, if you will, in terms of access to these for modeling and other activities. On the other hand, as we just heard, it's pretty difficult to deidentify data reliably, so I'm sure that within the agency, that precaution is already being discussed, if not observed.

Also, the idea that multidirectional

communication is very important between the FDA and stakeholders, I would say the stakeholders, particularly given what we've been talking about the last two days, become even more important as we talk about the whole meeting discussion.

Then with respect to the tools that are used, the cloud-based tools, both in the agency and outside the agency, visualization tools to rapidly get a feel for the way things are handled is really a growing area and really a very kernel area for discussion and development.

Let me just go back to the script. I had missed a page.

At this point, now am I right, Rhea, that we're looking at wrapping up?

MS. BHATT: Yes.

DR. MORRIS: Good.

MS. BHATT: We can take comments from the FDA.

DR. MORRIS: Yes. I was going to say.

So FDA, any comments before you guys go push on to mine?

DR. YU: This is Lawrence. I want to thank you, Ken, and thank you for providing leadership, but also thank you for your time and effort. I want to thank all the members for your time and effort to join us for two days, especially today. I also want to thank all the FDA speakers, the panelists who provided comments, certain information, voting, and information that's truly valuable to us and FDA. We will take back your recommendations and certainly prioritize some actions.

We assure you that the time you spent is worthwhile not only to the public, but to the FDA, and to industry as well. So I want to take this opportunity to thank all of you for your time, effort, and thank you to the chair, Dr. Ken Morris, for your leadership. Thank you.

DR. MORRIS: Thank you, Lawrence.

I just want to echo that I thought the presentations were amazing. These last two days have been very exciting. The amount of change that this could bring to the whole process is, as I

said, pretty amazing; yet, it's being done in such a way that hopefully everybody not only sees the value but will have a smoother transition than they probably think they will as they go to this.

I think the idea with KASA, in particular being the logical evolution of the way the agency, and the agencies, internationally are trying to evolve the safety, and efficacy, and quality of drug products, is pretty impressive; and the panel for a lively discussion both days, is amazing. I don't think anybody has any extra time, but we certainly appreciate all of the effort that goes into prepping and participating in these events.

I want a special thanks to Yvette Waples and her team, especially Rhea Bhatt and Joanna Malsch, and the other FDA staff, for organizing a very successful couple of days. I've been doing this for about 20 years now, and the level to which we depend upon the FDA staff is also pretty amazing.

So without any other comments from the agency or Rhea, we can adjourn the meeting now, I believe.

Is that correct, Rhea?

MS. BHATT: Yes. Thank you so much, Dr. Morris.

Adjournment

DR. MORRIS: No, thank you. I don't do anything without her ok.

Thank you very much, and we'll now adjourn the meeting. And for those of us on the west coast, good afternoon, and everybody else, have a nice evening.

MS. BHATT: Thank you.

(Whereupon, at 2:45 p.m., the meeting was adjourned.)