FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY (PSCP) ADVISORY COMMITTEE

Thursday, September 20, 2018

8:00 a.m. to 10:52 a.m.

Morning Session

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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Division of Advisory Committee and Consultant Management Office of Executive Programs, CDER, FDA

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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

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. AMIDON: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I'd like to also identify the FDA press contact, Jeremy Kahn. If you're present, please stand.

My name is Greg Amidon, and I'm the chair of the Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee, and I will now call this meeting to order. We'll start first by going around the table and introducing ourselves. So let's start down here on the far right, of my right.

DR. AWNI: I'm Walid Awni. I'm the vice president of clinical pharmacology and pharmacometrics at AbbVie.

DR. COOK: Jack Cook, industrial rep, clinical pharmacology, Pfizer.

DR. TENJARLA: Srini Tenjarla, Shire

Pharmaceuticals, head of pharmaceutical sciences and analytical development.

DR. DONOVAN: Maureen Donovan, University of Iowa, College of Pharmacy, professor of pharmaceutics.

DR. SUN: Duxin Sun, professor of pharmaceutical science, University of Michigan.

DR. LI: Tonglei Li, professor of pharmaceutical sciences, Purdue University.

DR. FINESTONE: I'm Sandra Finestone. I am the consumer representative.

DR. MAGER: Don Mager, professor of pharmaceutical sciences at the University of Buffalo.

DR. AMIDON: Greg Amidon, University of Michigan.

CDR SHEPHERD: Jennifer Shepherd, designated federal officer.

DR. CARRICO: Jeff Carrico. I'm the service chief for clinical pharmacy and investigation drug research at the NIH clinical center.

DR. TERZIC: Andre Terzic, director, Center for Regenerative Medicine at the Mayo Clinic and professor of medicine and pharmacology.

DR. SLATTUM: I'm Patty Slattum. I am professor of pharmacotherapy and outcome science at Virginia Commonwealth University.

DR. SMITH: I'm Paul Smith from the University of Maryland, where I'm the director of the statistics program and a member of the math department.

DR. ROSENCRANCE: And I'm Susan Rosencrance, director for the Office of Life Cycle Drug Products in OPQ or Office of Pharmaceutical Quality.

DR. YU: Good morning. Lawrence Yu, deputy director, Office of Pharmaceutical Quality, CDER, FDA.

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

DR. AMIDON: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are very strongly held. It's our goal that today's meeting be a fair and open forum for the 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 look forward to a very 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 the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the topics during breaks and lunch. Thank you.

I'll now pass this to Lieutenant Commander Jennifer shepherd, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

CDR SHEPHERD: Good morning. The Food and Drug Administration is convening today's meeting of the Pharmaceutical Science and Clinical Pharmacology

Advisor Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, 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 USC, 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 USC, 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 services outweighs his or her potential financial conflict 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 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 USC, Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAS, teaching, speaking, writing, patents and royalties, and primary employment.

Today, the committee will focus on two topics related to the Office of Pharmaceutical Quality's priority of promoting the availability of better medicine. For this morning's agenda, the committee will discuss the modernization of assessing drug applications through a knowledge-aided assessment and structured application initiative.

FDA will seek input on the potential

enhancement of a submission format consistent with Casa to improve the efficiency and consistency of regulatory quality assessment. This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, 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 that they have made concerning the topic at issue. With respect to FDA's invited industry representatives, we would like to disclose that Drs Walid Awni, Jack Cook, Srini Tenjarla are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company.

Dr. Awni is employed by AbbVie, Dr. Cook is employed by Pfizer, and Dr. Tenjarla is employed by Shire Pharmaceuticals. We would like to remind members

and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have regarding the topic that can be affected by the committee's discussions. Thank you.

DR. AMIDON: Thank you. We'll now proceed with Dr. Kopcha's introductory comments.

FDA Introductory Remarks - Michael Kopcha

DR. KOPCHA: Good morning, everyone, and welcome. In order to kick off this meeting, what I wanted to do is I wanted to give you a little bit of background and understanding in terms of the Office of Pharmaceutical Quality is actually hosting this meeting, if you will, and give you a good understanding in terms of what we do, our strategic priorities, the two topics we're going to be discussing during this advisory committee meeting, and just to make some

conclusions as well.

In terms of the Office of Pharmaceutical Quality, pharmaceutical quality is a shared goal, and as you see in the slide, that is italics because it is a shared goal. It's not only FDA's responsibility, it's not only the patient's responsibility, or industry's responsibility; it's our shared responsibility. And it's a shared responsibility of assuring consistently safe and effective drugs are available to patients and consumers, so not only focused on patients but consumers as well because we do also get involved with OTC or over-the-counter products.

Pharmaceutical quality, or at least the way I like to define it, or one of the ways I like to define it, is what gives patients and consumers confidence in their next dose. Confidence in what? It's confidence in safety and efficacy. So it's one of the ways I define quality. It's the safety and efficacy of the next dose.

Our mission is to assure that quality medicines are available to the American public. The

mission is that simple, but unfortunately it's not that simple to execute. The vision is for OPQ to be a global benchmark for regulation of pharmaceutical quality. So I don't want individuals to misunderstand that. It is not an arrogant statement on our part, but it is a statement in terms of our vision that we do want to be the global benchmark. So it's aspirational for us and what we strive to do going forward.

In terms of the office itself, the things that we're involved in or the areas we're involved in as it pertains to quality is that obviously we set policy in terms of how quality is regulated within the industry. We do assessments or reviews of the applications that we receive. We also do inspections, inspections of the process of facilities that are going to be making the drugs and products that we regulate.

We also do surveillance of the marketplace of the industry to find out what the quality trends are and if these trends can be mitigated if they are adversely affecting the products that are either being developed or that will subsequently end up on the market.

We also do research, but the research we do is not necessarily academic research. It's research to help us guide our policy and to help us with the assessments that we do of the applications that are submitted to us.

If you take a look at the left of the slide, we are involved in new drugs. Those are the NDAs. We're involved in biologics, which are BLAs, as well as generic drug products, which are ANDAs. So we cover the quality for all the applications that come in to the FDA.

We also deal with compounded drugs, over-the-counter drugs as I mentioned previously, as well as biosimilars. So all this comes together, and this is what we work on from a quality standpoint. We typically work on the CMC or the chemistry manufacturing and control sections of the applications that come in.

We get involved in the early development of these products. We also take a look at the premarket, and we get involved in the premarketing part of these products. And that typically involves the applications

that come in, so as we do the assessments for those applications, it's premarketing. But once those products get on the market, we are responsible then for doing any postmarket changes that involve those products as well. So you can see the scope or the breadth and depth of the work that we do is rather extensive.

In terms of the office itself, you can see on this slide how we are organized. We have the immediate office, which is really more or less where the administrative part of the work is done. However, we also do have a science research staff, the SRS group as we call it. In government, we love acronyms, so I apologize for some of that. I will try to stay away from as much of that as I can as I go through the presentation.

We then have below that the Office of Programs and Regulatory Operations, so this is our operational group. Of course, like any other organization, we need to know how we're going to operate and function. There are SOPs or standard operating procedures about how we do our business.

We also have the Office of Policy for Pharmaceutical Quality. It's the office that obviously helps us set up the policy around quality. The next line down is our review offices, so we have the Office of Biotech Products. As you can imagine, those are where the biotech products are reviewed. Office of New Drug Products is where the NDAs are handled.

We have the Office of Lifecycle Drug Products, which is where the ANDAs are reviewed. And then we have the Office of Process and Facilities, and as that name implies, we look at the processes used to make the drugs and the facilities in which those drugs will be manufactured.

Below that, we have the Office of Surveillance. The Office of Surveillance, as I mentioned, helps us to surveil the industry and be able to see what the industry is doing in terms of trends in quality. We also have the Office of Testing and Research, and that's where we do quite a bit of our analytical testing as well as some other advanced testing to be able to characterize the products that we're asked to review.

In terms of our strategic priorities, there are four of them. The first one is to collaborate, as you could imagine. We want to strengthen OPQ's collaborative organization, so this includes collaboration both internal as well as external to our organization, as well as to CDER and the FDA.

We innovate. We promote availability of better medicine. When I talk about innovate, what we mean here is to minimize the barriers to encourage innovation within the FDA and in the manufacturing sector through sensible oversight. Again, it's sensible oversight. We don't want to over-regulate, but we do need to have some sensible oversight over the industry and the products that we are responsible for.

We do research, risk-based decision-making, and continuous process improvements. So as in the industry, we're always looking to continuously improve the way in how we do things and is one of the reasons why we're here today with this advisory committee.

The third one is to communicate. We want to elevate awareness and commitment to the importance of pharmaceutical quality, which is important to us. So

we need to effectively communicate the importance of quality and that the American public can trust their drugs that are on the market and that they take.

The fourth one is to engage. We want to strengthen partnerships and engage with our stakeholders. We want to really build productive relationships. This way, what I look for is to have an exchange with our partners or with our stakeholders both within and outside of our group and within and outside of the FDA.

In terms of the advisory committee meeting, this meeting touches all of the OPQ priorities that I showed previously. We collaborated in the sense that we organized with effort and input across OPQ offices to put this advisory together. We also collaborated outside of our own organization.

We innovate and focus on decision-making tools and resources that enable effective risk-based decisions. We're going to talk about two of those things today, which is the nexus of this meeting.

Communicate, we want to have a public meeting, which is what we're here doing today, to encourage all

stakeholders to join FDA in its commitment to quality. Then the fourth part is to engage, and we foster effective engagement with external stakeholders to meet the needs of the American public. So ultimately, what we're all here to do is to make sure that we bring quality products to our patients, to the consumers.

The first topic that we're going to be focusing on is what we call KASA; again, another acronym that we like. But it stands for computer [sic] aided assessment and structured application. So my house is your house. As the expression goes, "mi casa, su casa," for those who know that expression more specifically in Spanish.

KASA is a system that captures and manages information, so we want to capture and manage that information about intrinsic risk and mitigate approaches for product design.

So again, this is a science-based/risk-based approach that we need to take, not only around product design but manufacturing and facilities. We want to do that in a structured way and in a structured template so that we have consistency in terms of how we review

those applications and what the industry or what the sponsor that put that application forward can expect.

You can see here we start out, and this is the actual house that we have. So we bring in a structured application that is brought into this house, if you will, or into KASA. You can see the three pillars. We start out with a knowledge base, which is the product manufacturing and facility of that product, and then we take a look at the assessment of the risk to quality.

We then go into risk mitigation by assessing the product design and understanding and putting that against our quality standards. Then risk mitigation by assessing manufacturing and facilities. Then all of that then rolls up or folds up into the knowledge-aided assessment that we're going to be talking today.

So I really don't want to go into too much detail there. We'll have a chance to go into that a bit later through this presentation.

The question that we're posing or that we want to discuss is relating to the KASA initiative, should the FDA considered the enhancement of submission format? This is the format in which the submissions

come in to improve the efficiency and consistency of regulatory quality assessment. So again, we're looking at the quality piece, the CMC piece of it. We're not talking about the clinical assessment.

The second question is in vitro and in vivo relationships, IVIVR. We want to take a look at extended-release solid oral drug products. There is a critical need to develop predictive dissolution tests to be used as effective surrogates to establishing the clinically relevant quality standards.

We've struggled with this for a long time. I remember when I was in pharmacy school and then when I went through graduate school, this issue still lingers. And it's something that we really do want to start discussing today and start getting some feedback in that area as well. The question is, should FDA established patient-focused dissolution standards for extended release solid oral products?

In conclusion, we do have a shared responsibility as I mentioned in the beginning, and this is with a focus on patients so that together we can provide them confidence in their next dose. And

again, it's confidence in the safety and efficacy of those products that are out on the market.

I thank you for the opportunity to introduce our PQ and the topics for today's discussion. I'll turn it back over to Dr. Amidon.

DR. AMIDON: Thank you. We will now proceed with the FDA presentations beginning with Dr. Rosencrance.

FDA Presentation - Susan Rosencrance

DR. ROSENCRANCE: Good morning, everyone. It's my pleasure to have this opportunity to speak with you about the KASA Initiative or knowledge-aided assessment and structured application. I'm going to give introduction, some background information, and talk about KASA at a high level. Then Andre Raw, who I'm going to credit as being a major driver and strong force behind KASA, is going to talk about product risk assessment and mitigation as it's connected with KASA.

Christina Capacci-Daniel will talk about manufacturing risk assessment and mitigation under the KASA Initiative. And then Larisa Wu will conclude by talking about the structured application and wrap up on

some of the overall benefits of KASA.

The beginning introduction, you already saw the OPQ mission and vision statement from Dr. Kopcha. This slide is just to emphasize that quality is our focus. How can you assure a patient that their drug is safe and effective if you can't assure that quality is the underpinning behind it?

In OPQ, we do what we call a quality assessment. It's like in CMC review, but it also includes microbiology, biopharmaceutics, as well as information about facilities. This quality assessment determines whether a drug's formulation, the manufacturing processes, and the facilities will deliver a safe and effective medication for patients.

In OPQ, our quality assessment is done with a group of experts, and we do it that way so we can have better decision-making. All the different experts come together, different disciplines. You can see in the blue box here all the different disciplines that work together to generate what we call an integrated quality assessment, which is based on risk, knowledge, and the impact to the consumer.

Also in OPQ, we strive to maintain a life-cycle focus on quality covers pre- to postmarketing. We want to ensure that all the programs that we support -- NDAs, ANDAs, BLAs, all meet the same quality standards. We hold them to the same standards. And in order for us to do this effectively, it really requires good knowledge sharing.

Now, we have a number of external challenges as well as internal challenges. Let me start with the external challenges. We in OPQ are getting an ever-increasing volume of new applications. Just on the generic side alone, we see approximately a thousand applications a year.

We also have increased user-fee program expectations. For example, in GDUFA II for the generic program, some of our ANDAs are receiving tighter timelines, from 10 months to 8 months for review. There are always expectations from the commissioner, Congress, the pharmaceutical industry, and the public. And of course there are technology advancements going on, lots of tools available in the 21st century.

Internal challenges, the biggest one that I

see is that our quality assessment right now is a freestyle narrative, meaning that it is unstructured text. It's essentially a summarization of the application that the firm submits. It also includes a lot of copy and paste data tables.

Essentially, the reviewers or the assessors are just capturing the story of the application. They're also assessing and making judgments, but they're telling a narrative. We see this is as a roadblock because it's encumbering breast practices for knowledge sharing, something that's very critical for OPQ; for managing quality across the product lifecycle, also part of our objective; and it's hindering overall modernization.

To give you an example of how our quality assessment works today, there's a template for the quality assessment. The template contains multiple sections, and in each section there are subsections. These subsections contain questions or points for the assessor to focus on.

What I've done here is just extracted two sections from our quality assessment template. P.2 for

the pharmaceutical development, this is what that section would look like when the reviewer picks it up. You can see it's broken down into three subsections, one about formulation development; one about container closure; and another about compatibility. Then there are points under that for the assessor to address. Another example here is P.5, control drug product, again, broken down into three different sections with points for the assessor to evaluate.

So our quality assessment template actually includes 7 sections for the drug substance and 8 sections for the drug product. All these have subsections under them. There's a section for regional information in case the firm provides a comparability protocol or something like that. Then there's also a section where labeling information is captured.

You can see you have 15-plus sections here with subsections under each. The template alone is very, very long.

Right here what I've done is just pooled out an example of the template filled out for the P.2 pharmaceutical development section. You can see here

the reviewer is just capturing information about the drug substance. Perhaps that table there was something they copied and pasted from the application.

But if you look at this, it's just really a freestyle narrative in unstructured text. I counted the pages in this particular example. P.2 in this review, or this quality assessment turned out to be 9 pages long. So you can see if you have 15-plus and if each section is that long, you easily end up with a document that's 100-plus pages.

The challenges with this current state where we are now, a narrative-based quality assessment means that the risk assessment we do initially when we pick up an application and the evaluation of the applicant's mitigation approaches gets really lost in this lengthy 100-plus page document.

It's dispersed throughout, and there's no real easy way to capture it, then knowledge management becomes very cumbersome for us, and the assessor's ability to objectively compare relative quality and risk across drug products and facilities becomes hindered. Then you get a quality assessment that tends

on the side of being subjective because the reviewer is just focusing on what they have at hand and their expertise.

It can also lead to inconsistent application of quality standards, something we don't want to see. And probably most critical of all, it can lead to late intervention and preventing or addressing a drug shortage or quality failure of a marketed product. It makes OPQ reactive instead of proactive.

So we see a real need for change. We recognize we have to modernize. We're assessing doing an assessment using 20th-century techniques and tools. There are lots of new better tools available to us that are 21st century. We need to move in that direction and take advantage of it.

So we've been actively working on creating and developing this system called KASA, knowledge-aided assessment and structured application. You saw the pictorial diagram that Mike showed. It's loosely based on a Greek temple, but I'll explain that a little bit more in a couple of more slides here.

I first want to tell you what the KASA system

is being designed to do. It's being designed to capture and manage knowledge for OPQ, the agency. For example, knowledge like established conditions, a concept that's captured in ICH Q12. It's also being designed to establish rules and algorithms to facilitate risk identification, mitigation, and communication for the drug product as well as manufacturing process, and for the facilities.

It's being designed to perform computer-aided analyses of applications so a reviewer can compare the standards and compare the quality risk across all the approved drug products and facilities in our repository. And it's being designed to give a structured assessment, and that way we can radically reduce that text-based narrative approach and the tend [ph] or the need to summarize information from the application.

So let me explain this diagram a little bit more because it really sets the stage for the next three speakers. We created this to capture the overall understanding so we could explain it for people to more easily understand.

If you look at the bottom of the house or this Greek temple, the idea here is that when an application comes in, we review it or assess it in the context of the knowledge base that is available to us in the agency, the vast repository of information we have about approved products, manufacturing, and facilities out there.

The three pillars represent the major components of KASA. Pillar 1 addresses the assessment of risk to quality by establishing rules and algorithms. Remember I mentioned that KASA is being designed to do. Pillar 2 gets to the drug product assessment and the quality standards, and looking at the risk mitigation approaches being employed by the firm. Pillar 3 gets at the assessment of manufacturing, facility, and the link with performing preapproval inspections.

Andre Raw is going to talk more now about Pillar 1 and Pillar 2, and Christina will talk about Pillar 3. This house or KASA system will work like this. We'll be able to achieve that goal of having a structured quality assessment, and we'll be able to

have knowledge management to look at the repository of information available to us.

Larisa Wu is going to talk to you about the idea of a structured application from the industry. This would be an application that could connect with the KASA system, that could talk to it, that could feed it information. And this would really take the whole initiative to the next level. Think about the enhancement this would provide to KASA.

So with that thought, I'm going to turn it over to Andre Raw, who is now going to talk a little bit more about Pillars 1 and 2.

DR. YU: Excuse me. Could I have a question here? Before we move to the next topic, I don't know if the committee has any clarifying questions they want Susan to answer. Thank you.

DR. AMIDON: I think what we'll do is hold our questions until the end if that's okay. Let us know, and we'll recognize you, and you can direct your questions at that time.

DR. YU: Thank you.

DR. AMIDON: Yes. Thank you.

FDA Presentation - Andre Raw

DR. RAW: I'm going to talk first about the Pillar 1, which is the assessment of risk, the initial assessment of inherent risk using established rules and algorithms, and what we have done within this framework.

The first question is why do we even do a risk assessment? We all know that drug products have failure modes, and based upon their design and manufacturing, that could result in a substandard product. So we obviously need to assess those failures modes to ensure that they're appropriately mitigated.

But we can't look at everything with extreme detail because it's the question of limited resources. We have an ever-increasing number of applications. We had a lot of generic applications, but we also have a lot of new drug applications. And with those applications, we have very tight GDUFA and PDUFA timelines that we need to meet. So it's a question of limited resources. We don't have infinite resources. We can't look at these applications forever, so we have to make these decisions.

With that, we have to develop risk approaches so we can focus on those failure modes of the product that really have the greatest chance that could result in product failure or potential harm to the patient. That's why we essentially do the risk assessment.

Before I talk about the risk assessment, I want to make sure that we're talking the same vocabulary so we don't lose each other in this discussion. What I want to talk about is something called the critical quality attribute.

A critical quality attribute is a physical, chemical, or biological property, or characteristic of the drug product that needs to be within an appropriate range or limit in order to ensure product quality. Examples of critical quality attributes are like assay or content uniformity, purity limits, or dissolution.

That's actually a very important concept that I want to lay out because when we developed our risk assessment models -- there are many approaches to do it, but we decided not to say that this product is high risk or this drug product is low risk because that's very hard to do because a product has many critical

quality attributes.

One product could have one critical quality attribute that's very high risk and all the other ones are very low risk. So when we developed the algorithms, we didn't focus on developing the algorithms to determine the overall product risk. We developed an algorithm that would focus on the CQA risk.

Basically, when we developed these algorithms, we would first determine what are the CQAs associated with that product. And once those CQAs were determined, we would rank the CQAs as high, medium, or low risk. And of course with the high risk CQAs that have an inherently high risk, there's the expectation that our assessment should pay very careful scrutiny to the formulation design, the process design, and the sampling control strategy to insure that risk is mitigated to an acceptable level before approval.

Of course, if the initial risk assessment indicates that it's very low risk, probably there will be a more abbreviated -- less scrutiny on the mitigation strategies. So that's basically the concept

of risk-based review and how we're using it in terms of the CQAs.

We were looking at a lot of tools that we could use. And the two that we decided to use was the failure modes, effects, and criticality analysis tool, which I'm going to call FMECA for short in the next part of the talk.

Basically, it's an algorithm that is used to capture the initial inherit risk of the CQA, and it basically allocates the risk of the CQA based upon a risk priority number. This risk priority number is calculated by three factors. It's calculated based upon the probability of occurrence, the detectability, detecting that failure, and the severity of harm potentially to the patient.

I'm going to give you an example of content uniformity. That's probably the easiest one to illustrate that concept. If you have a very low dose, which we have micrograms of the drug, a 1-gram tablet, the inherent probability of a content uniformity failure would be on the higher scale using our algorithm. It would probably be using a 3 to 5 scale

because without any knowledge of risk mitigation, that's the inherent risk of the product. But conversely, if it was a high-dose drug and what's mostly active is the tablet, of course the probability of content uniformity failure would be on the low end.

For detectability of failure, we have a low-dose drug, and we use the traditional USP 905 content uniformity sampling in which we sample 10 tablets or 30 tablets out of a million tablets. The detectability of detecting a failure is actually pretty low, so the detectability would have a high score here. But if we're doing stratified sampling and we're looking at lots of tablets, obviously detectability of potentially a substandard product would be increased, so the score potentially would be on the lower scale.

The severity relates to the -- it's something that we can't control in terms of quality, but it's an inherent aspect of the active ingredient. If the active ingredient is an NTI drug, then variations in content uniformity could definitely have a very significant impact on the patient. However, if it's a drug with a wide therapeutic window, the variations in

content uniformity would have a much lesser impact on the other patient. So we would make the score according to that scale, 5 obviously for the NTI and a much lower score for the ones that have a wide therapeutic window. That's basically the idea of the algorithm that we use.

There is also another reason we chose FMECA. The idea is that when people were doing reviews -- in our paradigm, we have lots of experts, but people have different trainees, have different biases, and have different perceptions of risk. While one reviewer may look at one application and make one perception of initial risk, another reviewer may have another system and may have a different perception of risk. So there were a lot of inconsistencies in these risk assessments.

The reason we like FMECA is because of its objectivity and scoring. As I told you, there's a 1 to 5 scale, so we can assign scores of 1 to 5 based upon certain attributes of the product, which I already talked to you, using that example of the content uniformity. We can assign those things. What that

means is that an assessor, regardless of their background, they can use that scoring system and come up with the same score regardless of the assessor. So that really provides for consistency in our risk assessment.

Then the other thing that we also did, which really gives me a lot of confidence in this FMECA system, is we took about 30 or 40 products, and we did an informal risk assessment. It's more subjective, but there's no scoring system. Then we compared the results with our FMECA ecosystem, and we could see that there is very good correspondence through these wide variety of products.

So that sort of validates the scoring model we used in the FMECA for ascertaining these initial risks for the CQA with its cross-validation study. And of course the algorithm is continuously going to be approved based upon additional information and gathered as we're proceeding along in this journey.

Risk management is now really part of our review. This is something that we adopted a few years ago. The initiative was adopted for the generic

program because we had lots of applications. But similarly, it was a very successful model, and even the new drug program adopts this model. So in every single application, we use the FMECA scoring paradigm to ascertain the initial risk for these CQAs. I just want you to all know this background.

That's the first part, which has been very successful and we have been implementing over the past few years. Pillar 2 talks about structured mitigation and quality standards. Basically, what's the idea of risk mitigation? When we do the FMECA, we only focus on the inherent product risk without any consideration of how the product was designed or the sampling strategy.

You take an example of the content uniformity, a very low dose, micrograms, gram tablets, and it's an NTI drug. The inherent risk is going to be calculated as high using our FMECA. But that doesn't take into consideration the sponsor's process of understanding in relation to averting this potential failure mode based upon formulation design or process design.

You could have something inherently high risk

by FMECA, but following this mitigation, it can be mitigated to a very, very low level. So what we do is have our reviewers evaluate that mitigation strategy, particularly for the higher risk CQAs. We obviously want them -- severity we can't change. Severity is inherent to the API, but we obviously want sponsors to decrease the probability of occurrence based upon robust formulation design and process understanding.

If they have the wide operating space, those types of things decrease the probability of the occurrence of that potential failure, or alternatively, or it could be a combination, the other is to increase the probability detection of a failure so we could have an enhanced sampling detection strategy. So those are the ways by which we expect people to mitigate risk before we improve the product.

When we initially implemented this, we implemented with structured initial risk assessment but unstructured risk mitigation. So basically we use this algorithm. It provides the review staff with a starting point to look at the CQAs that are very high risk, and then we would have the reviewers talk about

the risk mitigation.

I really want to stress what Susan had previously mentioned, is that when we did that analysis, the risk mitigation, we found that there was a high dependency on reviewer opinion and expertise, is how it was mitigated. The other thing is that that risk mitigation was interspersed into narrative text. So it was very hard to retrospectively analyze.

Actually, that was somewhat of a problem for us because one of our missions is to have an understanding of the final product risk, final risk mitigation of our drug product repertoire across the product line, and to compare products, and to see which products are higher risk. So they would need more surveillance scrutiny or more scrutiny throughout their life cycle. But it was very hard to do with this unstructured approach.

What we decided to do was develop something called structured risk mitigation. This is a very important theme of this KASA concept, which will be discussed also later. But the thing is you have CQA distribution impurities. You have the initial FMECA

algorithm determining whether it's low, medium, or high risk. Then when we talk about the risk control or the risk mitigation, what we decide is instead of moving from unstructured text, which is very hard to use for comparing products, we decided to have almost like structured information. So we'd have a drop-down.

So basically, if you have high risk of dissolution, there are not a number of ways by which people can mitigate dissolution. We felt we could capture all the orthogonal conceptual ways that people can mitigate dissolution through these drop-down menus. So when our assessors would look at the application, everyone would be on the same page, and they would select the appropriate drop-down menu associated with that risk mitigation strategy.

We did this actually for all the CQAs. This puts everyone on the same page and provides consistency of our evaluation of risk mitigation, which is very important for various reasons.

Basically, the idea is basically using these descriptors of structured knowledge, of formulation design, and control strategy using these drop-down

descriptors. This is very, very important. In line with that, the way that would work would be you would have the CQA and the risk. They would select the drop-down, which would be the fundamental approach. And then they would explain how that fundamental approach was specifically applied to the NDA or ANDA in question. And instead of cutting and pasting, they would provide the supporting information link to the page and the electronic submission.

To give you an example, CQA dissolution, it's an NTI drug, amorphous dispersion, BCS class 2, clearly high risk from our algorithm. So the FMECA would say it's high risk. Then you have a drop-down menu. One drop-down menu could be did they optimize the API polymer ratio to stabilize the amorphous dispersion. That's a conceptual approach. They would select that from the drop-down menu, and then the reviewer would explain which carrier was used, which ratio was used, and how it was optimized.

There would be some discussion about that, but it would be very brief. And all this reporting information would be linked to the application with a

link to the direct page of the application. As a matter of fact, we already have a prototype of the software that can really do this, and we're currently even piloting this within our review framework right now.

So that's how it works. This is a very powerful tool. Not only does it promote consistency, but more importantly, I would say it also promotes knowledge management because, remember, we could have a generic product and a brand name product. They all have a CQA, and let's say the CQA is assay. It's very prone to degradation, and it's an NTI drug.

The algorithm, would flag it as high risk, but then we want to know a question repertoire of products following the risk mitigation, which products are higher risk and which ones are lower risk. Right now it's very hard to do, but using this tool, we'll be able to do that. The reason we'll be able to do that is because now we would have that information in highly structured form.

For example, let's say we compare an NDA and two generics of the same product line. We would see

that, in this case -- this is just for illustration purposes only. In this case, the NDA, you can see that they invoked three fundamental strategies in product design to mitigate that approach, and of course they used the traditional product-release testing; whereas at the other extreme, we could have a generic -- I mean, this is just for illustration purposes.

They could have just a traditional release strategy, and of course detectability of that is not very high. So you can see that in this case there is a significant amount of risk mitigation designed to the product and confirmed by testing, whereas in this one there's minimalistic.

Basically, what we can do is that when we want a retrospective look at these products, we would know which products need the appropriate regulatory oversight by our surveillance officer or throughout the drug product life cycle. This really provides a basis for our knowledge management to allocate risk in our repertoire of drug products and allocated resources based upon risk in our drug product repertoire.

When we were developing the software, which

we're currently piloting, we also thought maybe we can also do this for drug product standards because I think it's an awesome match. When we make some decisions about drug product standards, there are also some inconsistencies. When people make decisions about acceptance criteria, and we would expect this to be structured information -- I think Larisa will allude to this later on -- for example, when we make a decision about impurity limit, when people would make a decision about impurity limit, again, it would be narrative text, unstructured information, and it's prone to inconsistencies. But with this, we can have the drop-down menu of fundamental approaches by which people make those decisions. And of course they would provide how that applies to the application and the NDA or ANDA of interest and supporting information.

Especially with the structured accepted criteria, this provides, really, the beginning of something, which is called cause informatics. Basically, the idea is that once we have those structured acceptance criteria with the rationale, we would have a database of the approved tolerances across

ANDAs and NDAs for that particular attribute; let's say an impurity limit.

Actually, that's a very powerful tool because when there is a pending generic or another, we can compare it to that database of tolerances for that particular acceptance criteria. And if it falls within the tolerances, it should be considered generally low risk. The reviewer doesn't need to be very worried about it as much. But if it falls outside the tolerances, it doesn't mean it can't be approved but definitely requires more scrutiny in the product. It's sort of akin to the Turbo Tax. It provides you an additional computer-aided means by using a broader database for more rational decision-making for the assessor staff.

With that, Christina is going to talk about the same concept but used for manufacturing and facility with mitigation.

FDA **Presentation - Christina Capacci-Daniel**

DR. CAPACCI-DANIEL: Great. Thank you very much, everyone. It's a pleasure to be with you today as well. I wanted to first return back to our house

model just to summarize where we've gotten to this point, discussing inherent assessment of product risk through our Pillar 1; Pillar 2 looking at drug product design, mitigation approaches; and now moving on to Pillar 3 where we're looking at manufacturing risk and mitigation approaches specifically for manufacturing.

As Andre brought up in the previous presentation, there are both design and manufacturing elements in pharmaceutical risk. We can mitigate some of these through product design, but we also need to focus on what sort of strategies are used to mitigate manufacturing risk.

Conceptually, as we've seen already, once a high-risk CQA is identified, an assessor could select from standardized control approaches or mitigation approaches, and thereby a demonstration risk has been mitigated through that mechanism and is now low residual risk in this example.

Manufacturing risk has several components I want to provide a little more detail on. What is manufacturing risk mitigation? A manufacturing process is generally considered well understood and controlled

when all critical sources of common cause variability are identified explained; variability is managed by the process at all scales through successful implementation of the control strategy; and process performance and product quality attributes can be adequately and reliably monitored and controlled.

We think more critically about how this is operationalized, particularly the last example; the ability to monitor and control the process includes design of the control strategy, process parameters, testing strategy, as well as the implementation of those elements-added facility, which will be conducting the actual unit operations, monitoring the process, and manufacturing the product on a day-to-day basis throughout its life cycle.

So with that in mind, we can see manufacturing risk actually breaks down into two different components. One would be the process, including process understanding and development, the design and control strategy, and the second would be the facility. This is the implementation of that control strategy and implementation of other broader control strategy

elements, part of their GMP controls at a facility.

Including these into our assessment approach allows us to document all the different risk mitigation approaches that can be selected to mitigate a high CQA risk.

We've discussed so far risk in the context of critical quality attributes. The manufacturing process physically is material transformation through multiple, sequential unit operations. Each of these unit operations may impact one or more critical quality attributes. So when we discuss about mitigating manufacturing risk, we look then at the unit operation and how those risks are mitigated through the design and implementation of that unit operation and that residual impact to critical quality attributes.

Conceptually, returning to this layout again of how an assessor may think about a manufacturing process and mitigating that risk, beginning with the critical quality attribute here, content uniformity, there's going to be an initial assessment of risk. There's a connection then to what unit operations impact that critical quality attribute. And then from

unit operation, you can break down into both process and facility elements and those respective mitigation approaches.

Whereas for process risk mitigation, this may return to process understanding development, design of the control strategy, and established conditions, the specific parameters that will be used for that process, if we look at the facility elements, this may include the implementation, equipment, procedures, and other larger GMP elements of the control strategy that are used to mitigate that CQA risk for that unit operation.

Thinking about an assessor's thought process as they approach this type of KASA initiative, they're determining whether a process as described in a submission and for a proposed facility can reliably manufacturer quality material. One of the considerations here are understanding potential failure modes with these unit operations and intrinsic risks in manufacturing that product.

Some of the potential drop downs, these structured risk mitigation approaches that KASA would capture relate to process elements such as

understanding obtained through development and the extent of the development studies submitted in a application; also looking at the design of the control strategy; what process parameters have been selected and the rationale for that; as well as in-process tests.

Some of the facility elements then would be looking at procedures, equipment, sampling plans, other material controls and elements that will be implemented as part of a broader GMP systems-based approach at the manufacturing facility. And I'll go on to provide some more detail on this.

In summation, thinking about the advantages of taking this approach, this allows the recognition and the capturing of risk mitigation approaches. You can see taking the standardized approach allows for a tool that enables really consistent risk determination across a variety of product types and a variety of facilities.

The risk determination can then be compared and risk mitigation approaches can be compared across applications for consistent and standard regulatory

decisions. This also impacts the identification of deficiencies and IRs so that standard criteria are applied across all applications.

Looking at residual risks as it relates to manufacturing processes, this also helps identify preapproval inspections, an opportunity to evaluate a process and a facility at the site of manufacture to understand the implementation of those risk mitigation strategies.

As I mentioned again, a broader comparison between products within a facility and comparison of products between different facilities is enabled by having this type of structured assessment. And then with that understanding of broader residual risk across products, you can then use that as a prioritization factor and identify surveillance resources that will most benefit and address risk to patients.

I want to walk graphically through a schematic example of how this might look within the assessment process. As an example, we have three conceptual applications, which are each high risk for content uniformity, which can be attributed back to control of

the blending unit operation, so we'll just be looking at blending.

An assessor has an opportunity then to think about what sort of process mitigation approaches have been selected and what sort of facility mitigation approaches have been selected for each of these applications.

From a preset set of descriptors, the assessor is able to select what approach. They're color coded here just to indicate the effectiveness or the extent to which those mitigation approaches are used to reduce risk. But you can see that comparison can be made between the applications very easily. For instance, you could understand how the control strategy was designed and selected for similar products.

With an automated capture of process parameters and with additional computer elements to support the KASA, an assessor would be able to drill down into these mitigation approaches and easily compare what mitigation approach has been selected for the three different applications. So we have established conditions captured and readily available

for broader regulatory knowledge management.

Likewise, we can compare facility risk mitigation approaches. I'm going to go into a little more detail about this since the understanding of facility risk considers elements that may not necessarily be submitted in an application. This will also include knowledge about a facility's history and capabilities.

A facility risk mitigation is going to consider the ability of the manufacturer to support and control the continued performance of these proposed operations. This can include, fundamentally, if the site has any knowledge of these operations, any history, and any experience, and we'll be using that to influence and select the appropriate mitigation factors.

Additionally, we're considering inspectional evidence with similar products, experience with that unit operation, including both cases where there may have been deficiencies controlling these operations and how corrective actions may have been implemented.

Another element would be quality oversight and

the site's adherence to current good manufacturing practices, which encompasses the larger quality system and how the site itself operates. Then lastly, we would also consider lifecycle management and these quality signals related to similar marketed products. This can include field alert reports, recalls, or other regulatory actions.

In considering the process mitigation approaches, the facility mitigation approaches, there's an identification of the updated risk associated with that unit operation for that application. There will be cases where the identified mitigation approaches are not sufficient. There are still residual risk, and those will be used to flag cases where preapproval inspections would be necessary.

Preapproval inspection is recommended in these cases to resolve any of these remaining process and facility risks. Because the KASA is so structured and we're using these predefined criteria, we can also use KASA flags and algorithms to identify the risk-based preapproval based on multiple factors, complexities, and using really standardized risk thresholds. This

allows for consistent comparison across a variety of product types and a variety of facilities.

Following the preapproval inspection, the facility and process risk are reexamined and updated if there's any additional information that mitigates the initial high risk. You can see here the updated scores. At the end, the final residual risk is recalculated based on that new information, and the assessment is near completion at this point.

I want to flag, though, there will be cases where the manufacturing risk, that implementation is used to largely mitigate risks, so it's relying heavily on those on-site implementation elements. There are also going to be cases with some residual risks. Those two scenarios are then flagged for lifecycle knowledge management.

With this final understanding of unit operation as it relates to CQA risk, we can now feed that into a regulatory lifecycle risk management program. The KASA now allows us to standardize and capture this residual risk and feed that forward into our surveillance activities.

As I mentioned, we can see products where risk is largely mitigated at the facility itself. We can also see higher residual risk products by comparison, and this allows us to have more robust surveillance inspections that focus on those products with residual risk were onsite controls are most needed to ensure product quality and adherence to CQAs. In this sense, we're getting very efficient regulatory oversight and focusing on the highest residual risk products.

Just as a graphical representation of this, you can compare within the red there three similar products to understand their residual risk. But we now place them in the context of their manufacturing facility and understand how they rank relative to other products at that facility and how facilities compare to each other based on their remaining products and those remaining risks associated with the products that they commercially manufacturer.

I hope I've been able to provide a general summary of how we're approaching manufacturing risk, how we would apply risk mitigation approaches, and it's part of our assessment process.

With that, I'd like to invite up Larisa Wu to talk about the structured application as well as additional benefits to what I've already addressed. Thank you.

FDA Presentation - Larisa Wu

DR. WU: Thank you, Christina.

Good morning, everybody. It is my pleasure this morning to talk to you about the structure application and conclude the KASA presentations today with some recap of the benefits of KASA.

As Susan already mentioned, the KASA as a system can function on its own, as it is. However, looking into the future, the KASA system would greatly benefit if applicants would submit a structured application with a more organized layout and standardize the data that would integrate with the KASA system and would enhance the knowledge-aided assessment. So I will spend the rest of my presentation talking a little bit about our vision for a structured application and how a structured application will enhance the knowledge-aided assessment of KASA.

We see structured application as being, if you want, an evolution, not a revolution. The current submission at FDA, the current drug application submission at FDA uses the so-called eCTD format, electronic common technical document format. I will talk a little bit more about the background of this format.

Although the eCTD has its benefits, it also has its challenges. We currently explore new ways of having an application submitted to FDA. And of course a structured application is one way. We believe such an application, like I said, would enhance the current system that we have with KASA.

We're also looking into leveraging some of the efforts that FDA has undertaken, one of which being pharmaceutical quality, chemistry, manufacturing, and control, the so-called PQ/CMC project, that is looking into standardizing data and how that would be able to be submitted in a structured application. So I will talk a little bit about this project in the later slides.

I mentioned the electronic common technical

document as being the current format for the submissions at FDA. The eCTD was developed by ICH, to streamline variability of submission requirements among Japan, European Union, and USA. It is, like I said, the preferred way of submitting applications at CDER since 2008.

An application in an eCTD format collects quality, safety, and efficacy information into a common format that has been adopted by ICH regulatory authorities. An eCTD application has a modular structure comprised of 5 modules as shown in the figure. For the purpose of today's presentation, we will focus of course on the information that is being submitted in module 3, the quality data. This information relates to process and product understanding, and it constitutes, as Susan mentioned, the so-called CMC submission.

I mentioned despite the benefits -- and of course the most obvious benefit of an eCTD application is that it comes in an electronic format. However, these type of applications also have their own challenges. From the point of view of an applicant,

the eCTD application does not follow the development flow of the drug product. It also varies in levels of granularity with information being fragmented across multiple sections in the application.

From the point of view of the assessors, of an OPQ assessor if you want, the format of an eCTD application is challenging because it contains multiple PDF files, text-based PDF file with unstructured data that are not easily mined or searched. That of course leads to various challenges in life-cycle management because it is difficult to link data across a product line or a product life cycle.

Of course it was mentioned earlier today by Susan that these type of lengthy PDF files often times lead to lengthy assessments done at the FDA as well as redundancy between different assessments.

The current KASA system would greatly benefit if the applicants, as I mentioned, would submit a structured application. What we do currently is we're using, of course, the submissions, but the OPQ assessor is basically taking the unstructured data as extracted from the eCTD submission and is manually entering that

data into the KASA platform.

That model, of course, is not ideal because it leads to possible errors from transcribing data from the PDF files into the KASA platform, as well as it is very inefficient. Imagine the time that the assessor is spending actually copying, pasting that data or typing that data into the platform. It is basically part of the time that the assessor is given to assess that application and could be better used to look at the high-risk areas in the application instead of basically performing some sort of administrative tasks.

So we're hoping that this current model can be changed through the introduction of the structured application. We're already seeing the first steps being made. We started to use KASA. And KASA was actually highlighted in one of the latest FDA blogs written by the commissioner.

In June 2018, the commissioner recognized the importance of modernizing the drug review from a text-based to a database assessment. As he says, "Having a structured template that completely replaces the current largely narrative based review will allow

for more consistent and predictable entry and analysis of data. Current assessments require manual review of the entire application. However, KASA will enable automated analysis of some portions of the application, which will save time and ensure consistency."

As I mentioned, the current KASA is striving to do so, however, the knowledge assessment that we have in house today could be greatly enhanced if we would have a structured application in place. Our vision for the desired KASA system would be one that uses a structured application that communicates with the KASA interface, and that would of course serve as an automated enhancement to the system.

A structured application would have standardized data that would integrate with the knowledge-aided assessment of KASA. As I mentioned, our intention is to leverage some of the efforts that are currently undertaken by FDA at project PQ-CMC, and we consider this project as a stepping stone towards achieving that structured submission goal.

I mentioned PQ-CMC. I want to give you a little bit of background into what PQ-CMC is. The

pharmaceutical quality, chemistry, manufacturing, and controls, or PQ-CMC, project is an initiative undertaken by FDA to identify and prioritize eCTD quality sections amenable to a structured approach. Its goal is to provide a recommendation for the standardization to facilitate application review and quality data management.

Now that I talked about the project, one may ask what is the relationship between the PQ-CMC and KASA? We see PQ-CMC as a project that mainly deals with data management with a focus on structured data and submissions, whereas KASA has a slightly broader scope. It deals with knowledge management with a focus on structured content assessment and enabling comparisons, as I mentioned, across product lines, product life cycles, and of course facilities, as Christina talked earlier.

One can establish a direct relationship between PQ-CMC and KASA through the use of automated tools. Automated tools can be used to extract standardized data from an application that is submitted as per the PQ-CMC requirements and use those data to

autopopulate certain sections in the KASA platform, therefore increasing efficiency of the assessment as well as consistency.

For example, if you look at the information that would be submitted in a P.5 section of the application, so dealing with the control of drug product and similarly the structure of that section in the KASA platform, information such as drug product specification and acceptance criteria can be, as I said, extracted using automated tools from structured submission containing standardized data and autopopulated in the KASA platform, whereas other sections in the KASA platform such as justification could be selected from a drop-down, supporting information if needed, that could be linked directly to the submission. Of course the assessment would be typed in the KASA platform directly by the assessor.

Now that I gave you a high-level overview about our vision for structured application, I would like to spend a few minutes remaining in this presentation to talk about the overall benefits offered by KASA. I want to emphasize that KASA is the system

that moves the narrative-based assessment into a data-driven assessment. That can be done, as I mentioned, using structured data, standardized data, using a common language, as well as a uniform output. That of course will eventually improve the consistency, the transparency, communication, and objectivity of the regulatory actions.

Again, through standardized data, KASA enables assessors to automatically retrieve the historical data and facility information, which in turn contributes to better informing the regulatory evaluation and decision-making progress.

It was mentioned before by Andre that KASA is using tools and algorithms, therefore it facilitates assessment of risk and reduces subjectivity of documentation and the time that is spent on assessing risk. Also, Andre mentioned about having KASA informatics that can be potentially used to run applications and compare those applications against a broader KASA database, which would allow detection of outliers and control strategies and risk attributes that would significantly improve quality and efficiency

of assessments.

Not lastly, through capturing risk mitigation strategies and risks, KASA also conveys residual product manufacturing and facility risk for each regulatory submission. It will eventually become instrumental in capturing established conditions. Also, it helps the assessment of post-approval changes and the life-cycle management of drug products. At the agency level, KASA is important because it helps focus resources for the post-approval and surveillance inspection on high-risk products.

That concludes the presentation on KASA today. Thank you for your attention.

Clarifying Questions

DR. AMIDON: Thank you.

Are there any clarifying questions for the FDA speakers? If there are, and we hope to have a dynamic discussion, just raise your hand, and we will recognize you in order. Please remember to state your name for the record when you speak, and if you can please direct your questions to a specific speaker.

Dr. Mager, first.

DR. MAGER: Thank you. Don Mager. It really isn't directed to any one person, but I was wondering, within the system, to what extent can the data be exported to external analysis tools, or to what extent can external analysis tools be integrated into the KASA system? In thinking about informatics, that would seem to be highly desirable, or was this meant to be more of a stand-alone, self-contained platform?

DR. YU: Can I clarify? So when you talk about externally the, you talk about outside the FDA or within FDA?

DR. MAGER: Within the FDA, but analysis tools -- you stayed KASA informatics. But I'm wondering, there may be analysis tools that should be accessible to an assessor outside of that system or would it become part of that system?

I'm just wondering to what extent is this flexible in linking out to other analysis programs? Having the data available addresses the assessibility part, but then having that to be readily used in analysis programs I think would also be incredibly important. And I'm just wondering to what extent this

is going to be flexible in that regard.

DR. RAW: Well, I can tell you we ready built a prototype, but now we're working with our IT folks to build this. But presumably, I don't see any reason why it can't be flexible. We're going to get all the data, and then we can -- I don't see that to be an issue.

We're going to get all this data, but then we want to mine this data. So whatever tool that we need to use to mine the data, we're going to try to incorporate into the framework. But we're not there yet. We're building the tool right now. But eventually, once we have all that structured information, I don't see that to be an issue at all.

DR. ROSENCRANCE: I'll just add to that my. My understanding in talking with the IT people is they can pretty much connect it up with any other kind of tool. We're just not there yet. We're still trying to develop KASA. But I think it's certainly feasible in the future to be able to connect it up so we can really analyze things and make the most use of it.

DR. YU: In the agenda presentation is a [indiscernible]. Right now in the current stage, the

company submitted all the information and data in PDF format. I know in the clinical side, they have data extraction automatically sharing. In the CMC site, pretty much all the information is encoded in PDF file, in the PDF file where the section relates to characterization of drug product, characterization of product development, manufacturing information, [indiscernible] information, stability information, and packaging information, and so on and so forth.

So an assessor within FDA evaluates those data, submit paper, and make an evaluation whether the data is sufficient to be able to allow the company to produce medicine which is high quality. As Christina pointed out in her presentation, if we find a significant risk related to quality, for certain, we will conduct inspection.

So there's a clinical stage -- when I joined FDA many years ago, I was thinking FDA would have all the data be available allowed to develop those modeling databases. Of course they are still available, except they're all in the basement. So you have the go there and dig out by hand. But today we're much better.

They do electronic storage, so we're not able to dig out data except in PDF file, which is difficult to search and difficult to construct.

The grand version of the KASA in the future as we move forward is essentially is information sharing and information processing. So we're hoping that the company as a sponsor shares all this information electronically with us without extracting, without retyping, without cutting and pasting. And when all this information within FDA is on the IT platform, we will do the analysis.

For example, pharmacokinetic analysis could be a process, and the PKPD model, and obviously the quality side. All of this information will be searchable. So as in Andre's talk and Christina's talk, when we what's a specific model application, what is a pure specification, for example, and what is the dissolution going on, we're all interchanging within the facility and within FDA.

So to answer your question, we're hoping that we'll have a labasta [ph] ?? [indiscernible] system that will allow information sharing and information

processing eventually to make a scientific regulatory decision for any application, which at the end of the day will ensure high quality of a product. So in a simple way to answer your question, the answer is yes. Thank you.

DR. SCHMUFF: This is Norman Schmuff from FDA. In the context of the PQ-CMC project, one of the goals is to structure the data in such a way so that it's databasable [ph]. One of the goals would be to pre-process and pre-analyze the data, and for example, present the reviewer with tables that look the same every time. For example, we could pull out what's the maximum amount of stability data in the proposed container closure system.

We could create such a table like that by pre-processing the data and showing that to the reviewer every time, which we think would facilitate the review process. So that's very much one of the goals of structured submissions.

DR. KOPCHA: If I could just add to that as well, one of the things we want to do -- we do need to have this in a database. It does need to be searchable

because as we start taking a look at generics, you need to go back to the reference listed drug, which is typically your NDA or the innovator product.

So in order to be able to do that, you've got to be able to search. But what we really want to do is to be able then to search for where the risks are so that we can evaluate the generic products similarly to the innovator product, so you have that standard in consistency in terms of quality review for both the innovator and the generic products that come along.

DR. YU: Greg, just for the record, the person who just spoke is Norman Schmuff, associate director for science and communication within office process and facility within office products and pharmaceutical quality, just for the record.

DR. AMIDON: Good. Thank you.

Dr. Tenjarla, next please.

DR. TENJARLA: Thank you. Very good presentation and very well presented. Thank you for that. My question is not specific to any one speaker, so anybody can respond to it. I was wondering what is the timeline for implementing the structured

submission, and when would be an opportunity given to comment on the proposal? I can see the value of it. I would also like to see if it can be improved even further by people who have experience on it and have an opportunity to comment. Thank you.

DR. ROSENCRANCE: I will say that we're not at the point of even having a timeline for the structured submission. We're still in a development phase of the KASA itself. But for that, we do have planned a soft rollout in a phased approach. In that soft rollout, we're targeting for 2019.

So we'll see how that goes, and then we'll get to the point where we would definitely communicate with industry regarding structured submission and definitely get their input into what would work best for everybody.

DR. SCHMUFF: Let me just mention, as far as PQ-CMC structured submissions, we intend to make that a 745(a) binding guidance, so it will be required to submit in that format. But as described in 745(a), there will first be a draft guidance, and then there would be a final guidance, and the requirement would

come and place two years after the final guidance. And we haven't even done a draft guidance yet, so you can sort of calculate in your own mind what the time frame would be.

DR. KOPCHA: And just to add to what Susan had said, when she's talking about a soft rollout, she's talking about internally a soft rollout so that the reviewers or assessors can start using the system, troubleshooting it, ironing out the bugs there before this does actually go out to having structured submissions coming in. I just wanted to clarify.

DR. TENJARLA: Thank you very much.

DR. AMIDON: Thank you. Dr. Donovan?

DR. DONOVAN: Thank you. Maureen Donovan, and I don't really know who to direct this to either because it's more forward-looking in the transparency of some of the evaluations that the FDA makes about a particular product and its activities and life-cycle management.

How much of that information are you planning on communicating to the applicant themselves so that they both know how to improve potentially as they go

through changes in their product and reevaluation, or how will that be implemented and communicated regarding further inspection strategies from the FDA?

DR. ROSENCRANCE: Well, it's a good question. It's a very good question. I don't know that we have an answer for it yet because we're just not to that stage. But we always believe in communicating with applicants in an effort to increase the quality of submissions. So I imagine we will at some point. I don't know exactly how much, though, at this stage because we're still trying to develop the system itself.

DR. AMIDON: Dr. Cook?

DR. COOK: Jack Cook, Pfizer, industrial representative. I'll direct this one towards Michael. It's another comment on an improvement because I think we're beyond clarifying questions.

Mi casa, su casa is a wonderful thing. I'm actually excited about this because I think we have an opportunity to give something back to the applicants. Imagine a system where it gives the algorithm back to the applicants saying, these are the things that we've

identified that we think ought to be mitigated. And then we as the applicant, as we think about them, put in what we think our mitigation strategy is.

So that whole half of the initial assessment is done. And for somebody who uses FMECA to look at protocols, always include another because there will be things -- and I'm sure you will.

DR. KOPCHA: For sure.

DR. COOK: For all of those things, there's always another round, and that's the innovation that comes.

DR. KOPCHA: Sure. I mean, typically, Maureen, to answer your question as well, we always give back, through our communications with the sponsor, where the issues are and how they're going to take a look at mitigating that. And the feedback we get is, look, you have different investigators that focus in different areas. And we understand that and we know that. It's inherent in individuals having different levels of expertise and focus in terms of what they do and their own personal biases; let's be honest.

So we do want to feed that back so that the industry can get better because when we send out our information requests, our IR letters, industry has come back and said these are great teaching tools for us as well because then we can continue to increase our standards of quality as we go along.

Also, what we would like to do is to be able to take that information and with our surveillance group be able to determine where are the recurring issues around quality so that we can go back to the industry and say, look, these are the areas that we keep seeing problems with. Let's work together to be able to figure out how to resolve that. We do that now, but this will give us a more thorough review because it will be done electronically as opposed to some of it we do now is manual because of the free text, not structured texts.

DR. COOK: And the idea of making that available, for me, is actually before you ever get the application, if somehow the algorithm of the tool is out there, you'll actually have the sponsor of the application thinking about it, filling it in, and

having it done closer to right rather than having them proceed and then need to go back and rework.

DR. KOPCHA: Right. And Norman may chime in here as well. But typically, through our draft guidances, we put that information out there so that individuals know the areas we're focusing on and how to address those areas. But I have to be honest with you. Not everybody reads them. Not everybody actually follows them. So we still get a lot of the same problems and issues that are recurring.

DR. COOK: Absolutely. But here's something you flagged. The guidances don't always have the algorithms in there or even thinking here's the way that you can pass your learnings off even faster than it takes to get a guidance out. I know you're really fast about that. He smiled.

DR. KOPCHA: All of this has to go through internal review in terms of how much information we could actually share and the extent of that. A lot of people had interest in our site surveillance model and how we do that. That was just recently published on. So we try to share what we can when we can, and

hopefully that will enhance the quality of the submissions and the products that get on the market. And that's the ultimate goal of everything we do.

DR. AMIDON: Good. Thank you. Dr. Carrico next.

DR. CARRICO: Jeff Carrico, NIH. Another general question, unfortunately. But I think anytime that we standardize things that we have to think about the potential for outliers. And you may have answered this partially with the idea that links can be provided to additional information, but I guess, one, would you agree that there is a chance that things might not fit nicely and perfectly into the drop-down options? And if they don't, how will that be addressed?

In other words, will outliers be locked into those categories or will there be a way to actually recognize that some things don't fit perfectly?

DR. RAW: Actually, we did discuss this with the IT informatics group. Basically, we think drop-downs capture most of the issues. But you're right. There could be something that's novel. And when it's novel and it's really orthogonal,

conceptually different from the different ones, yes, we can add it. We talked to the IT folks, and we'll have some super user capability that we can add if it's applicable.

DR. KOPCHA: Just to add to that as well, one of the things we're trying to minimize is that we don't want our reviewers to use that part of it, the free text piece, all the time because we're trying to get away from that. So we try to standardize as much as we can and minimize the amount. We realize there are going to be outliers, and that's great. We can figure out a way to do that.

By the same token, we just want to make sure that the reviewers are not continually writing things because then we're going to be back to the same issue we're trying to correct by using the system to begin with. So it's going to require some training, oversight, and follow-up and follow-on in terms of the quality of those reviews, which we do now to make sure that people can standardize things as much as possible and that they follow the guidances, the SOPs, and all that that we've put in for ourselves for our own

internal work.

DR. CARRICO: Thank you.

DR. AMIDON: Dr. Terzic?

DR. TERZIC: Andre Terzic, Mayo Clinic. I think the presentations were indeed, as mentioned before, outstanding, very timely, very clear. The comment generically you are receiving, and I will underscore it a little bit more, is that the value of this approach may go clearly beyond the regulatory process and the regulatory authorities. So as you're still having time developing these algorithms, keep in mind how to emphasize the proximal piece, which may be first to industry, may be first to increasing the academic institutions and also the knowledge cycle beyond the regulatory process. I think in formulating the value of this overall initiative, that will be important.

A very minor, specific question maybe to Andre, the examples you mentioned were in the NDA and ANDA space. Will this apply also to the BLA space, and will it be a specific algorithm or generic algorithm?

DR. RAW: Right now, we develop the structured

drop-downs for ANDAs and NDAs. A lot of it is small-molecule pharmaceuticals. We think we can capture all that structured information. With BLAs, you have a little bit more complex active ingredients. The question is if we can use those drop-downs and actually capture that information, I would say for certain classes of BLAs -- I mean, I would have to refer it to Steve. But when we're at the point that we can capture that information and people are comfortable, yes, it could be applied to the other.

DR. YU: So as any initiative within FDA, I'm sure this happens to any organization, we will have a steering committee and monitor its progress, design the vision, and design the future and the project management. Of course, the working groups get a development IT platform, the inside activation, and all these rules [indiscernible]. So make sure to make all the decisions, which we talk about drop-down menus.

In the steering committee, we do have representation of course, obviously from generic drug site, we have a new drug site, as a biotechnology site. So I can envision down the road with the success with a

generic, we will most likely move into the BRS [ph]. It likely will depend on the maturity of the knowledge of a specific application and when we feel comfortable with the information. But whether we can develop a drop-down menu or not, knowledge sharing, knowledge analysis or information sharing or information analysis will all be there.

We actually corrected that. If all the information within FDA will be available for the impurity level, just the full context and the format, that information will be anonymous, and FDA intends to analyze them and share with the public so that industry knows what's going on and FDA knows what's going on. And eventually, it will be convenient for you and it could be convenient for the regulator. The eventual benefit is for the patient and consumer [indiscernible].

DR. SCHMUFF: Just to address this use of data outside the regulatory environment, we are currently involved in a number of things that impact the electronic health records and electronic prescribing, including the ISO effort in identification and

medicinal products. We currently have been working with EMA and with the ISO organization to be sure that the terms and definitions that we use are consistent with the 5 ISO standards on identification of medicinal products.

So we are cognizant of the uses outside the regulatory area, and we're collaborating on that.

DR. TERZIC: Thank you very much.

DR. AMIDON: Thank you. Dr. Sun?

DR. SUN: Yes. Duxin Sun, University of Michigan. I have a quick clarification question, a comment, and also another question to ask for Andre. The clarification would be, assuming once you develop, the version you guys are using internally will be the same version that industry uses so that you can guide them to submission. That's the quick clarification, assuming it's yes.

I have a comment and a question. You will not have a different version for you to use internally and external use to use as a submission.

DR. SCHMUFF: In the longer term, yes. In terms of the drop-downs for risk mitigation,

potentially I think in the longer term, it would be very similar. I would say so.

DR. SUN: I have a question for you also. The problem that I have is I clearly see the benefits from a regulatory science point of view. You guys did a really terrific job presenting the benefits internally. From a sponsor perspective, it is also very helpful.

So one help will be, the sponsor is a very different level. Big firm, they know what to; medium or small firm, they don't know how to do. They don't know what to submit. It's a mystery to them for an FDA submission. If it's released, it's very structured and they help everybody. That's number one.

The number two benefit I see is that regardless of the company, there's a glitch during the development. Sometimes you have to move further along. You finish a clinical trial. Then with the clinical trial already done, if I was the sponsor, I would try to make a justification with I don't want to make change. I want to make a justification and discuss with you, and it makes it very difficult to evaluate. I may downplay some of the things, some of the red

flags for you not to say. So if it is structured, you really help them to avoid that situation.

So the question I have is, for the risk number, the high and a low, are you envisioned to also give industry that capability? We have hands-on data to assess the risk number, 5 or 1. You have internal data more to risk, 1 to 5. Do you envision you give them that capability to also give a numeric number for the risk?

DR. KOPCHA: Let me just clarify. The question you had asked previously or I guess the clarifying question is, are we going to use KASA to give it to industry for them to put their submissions in? The KASA that you saw that was presented today is for our internal review, so that system is not what's going to be given to industry to make their submissions.

Industry now uses an electronic common technical document. They use the eCTD date. So there is a way to structure the information that they send into us. But our KASA is to be able to take the information that comes into us from the industry and do

the quality assessment.

The system that we use is not what we're going to give to the industry to make their submissions. We do want to, though, put together a structured template that the industry can use that would be compatible with our KASA system such that when the application is submitted, it pre-populates all of that information into the KASA template for our then assessors to make that assessment.

So to answer your second question, we're not going to be looking for the industry to make their assessment in terms of assigning a risk to the areas in their submissions per se. When they make their submissions, it is incumbent upon the industry to identify where the risk is and how they're addressing that risk.

Now, we may or may not agree that the areas that they've identified are the areas of risk, to answer your question; because you said they may downplay certain areas. Yes, you're right, but that's where we need to go in there and review or assess what they've provided to us.

So our intent as assessors is not to tell people what to -- I want to make sure I state this correctly. We want to assess what they provide to us, the information they give to us because they know the process the best. They're the ones that have developed it. They've gone through all of that work. They should really be -- we want to see what they're telling us, and then we will assess the information that they've given us and decide whether or not we agree with it, or we need additional clarification, or if we need to do pre-approval inspections to get some of those additional answers or clarifications that we may need.

So hopefully that structures it a bit differently. But I did want to just kind of clarify what is we're doing. So again, what we presented today is strictly for our internal assessments.

DR. SUN: Thank you.

DR. AMIDON: Dr. Tenjarla, please?

DR. TENJARLA: Thank you. Srini Tenjarla, Shire Pharmaceuticals. Again, this question is to any

of the speakers. As I said earlier, this is an excellent initiative from the FDA. My question specifically is that during global submissions, you get to be evaluated by different standards on the vendor application under review. I was just wondering if the FDA socializes with any of the other agencies like EMA or PMDA, or is it too early to do that right now but you plan to do it down the road?

DR. ROSENCRANCE: Yes. I would say it's too early right now. We're trying to socialize this internally, actually. It's certainly a good point. And when we get to that stage, I think we would certainly consider it.

DR. TENJARLA: Specifically, the reason I was asking was, for example, if you go into a zone for a country, there may be a migration of the drug from the drug polymer complex because of the high storage conditions and things like that. So they may have a slightly different point of view to take into consideration.

DR. YU: Can you clarify or maybe come close to the microphone.

DR. TENJARLA: Sorry. I was saying that there may be examples in other countries like zone 4 countries, where there may be a migration of the drug from the tablet, between the tablet from the polymer complex for various different reasons. So those factors are also taken into consideration when we do an evaluation of the drug product at a process or a facility. That would be very helpful.

DR. ROSENCRANCE: Yes, I definitely agree.

DR. SCHMUFF: I would mention that the EMA is aware of our structured submission efforts. We hosted the manager of the EMA spore initiative about a year ago, and we talked about IDMP specifically, and we did talk about structured submissions. So they at least are aware of that. And we did get a number of Federal Register notice comments suggesting that maybe this should be taken to ICH.

DR. TENJARLA: Thank you.

DR. FINESTONE: I have a question, and it's certainly not going to be as technical as the ones you've heard. My assumption is that you're going to base the criteria for high, low, medium, 1 to 5, based

on past experience, as the data that you currently have, that I understand is in a PDF format, is rather narrative as opposed to numbers structured. So the criteria has to be developed within that confine.

Is there going to be some flexibility to take into consideration the expertise of the assessor? Eliminate the bias as much as possible. But you'd take that into consideration, or is the criteria going to be so stringent that this is what fits in number 3 and this is what fits in number 1? Is there going to be some availability for that personal assessor's input?

DR. YU: Those criteria originally is developed by experts within FDA. We have a number of people expert in different areas that get together and develop them. Reviewers always have the opportunity to make their own scientific judgment, and the original criteria simply provides a basis for them to move forward as in the new situation, because in FDA, we're facing multiple challenges, for example, the drug shortage situation, unmet medical needs.

So we evaluate them not based on absolute number, for example, medium, high, we consider the

patient's needs, the consumer and the patient's needs. As Dr. Kopcha [indiscernible], we cannot emphasize more about significant, well [indiscernible] patients. So therefore, we emphasize much more in our consideration. Certainly, the criteria provides a basis for us to move forward. Thank you.

DR. FINESTONE: Thank you.

DR. AMIDON: Thank you, Dr. Finestone, for that question. I have a question. This is Greg Amidon.

You've talked about using KASA in the submission process. And I was wondering if you could just add a little bit more about how you might see this being used throughout the entire development process and dialogue and discussion with industry.

DR. YU: Our goals are much more structured and increase certainty and decrease uncertainty. I think some of the advisors are talking about the sharing of knowledge, the sharing of an algorithm. When all of this information is shared, FDA will extract from different applications and will share with industry so that industry can facilitate not on their

regulatory development, but more significantly also their development process as well. And we will come together to ensure high quality in the marketing place.

In simple way to answer your question, I do envision this initiative not only to just benefit the format, but mainly
KASA will focus on the context of the submission.

DR. AMIDON: Good. Thank you.

Dr. Smith, first.

DR. SMITH: What I haven't heard is the availability of the knowledge base, which is the foundation for the temple. Could you talk some more about that, please?

DR. ROSENCRANCE: When I was showing this schematic -- I'm not sure I quite fully understand your question. But what I was trying to say is that we have a huge knowledge base in the agency with the applications we've approved and the facilities we've looked at.

The point I was trying to make was that when an application comes in, whether it's structured or not, we would do the quality assessment. With a good

knowledge management system like KASA, we could do the assessment while using this knowledge base in the context of this knowledge base.

Is that what you're -- I'm not sure where we didn't discuss it. I thought the emphasis was that we will definitely be tapping into this knowledge base and using it whenever an application comes in.

DR. SMITH: My question had to do with the availability of the knowledge base in a forum that it could be rapidly absorbed into the KASA system say to help to evaluate a new drug. Can one immediately put the availability of related knowledge into the system? Because if the available knowledge base is not well structured -- and I take it from your comments that it's not 100 percent -- then that's going to essentially delay the whole process. And it seems to me if the FDA is serious about KASA, which I think is a very good idea, it needs to simultaneously develop the knowledge base in an immediately interpretable form by KASA, and I haven't heard about that.

DR. ROSENCRANCE: A knowledge base for internal use, right, not for -- yes.

DR. SMITH: For internal structure.

DR. ROSENCRANCE: Well, we've got to start somewhere. There are applications years ago that's not readily -- but we'll have to start somewhere. I think Andre alluded to it that as the -- maybe, Andre, you can clarify more. But as a reviewer, we have to build the knowledge base. And then as a reviewer assesses the applications, it can be flagged as to whether it's within those limits. But it's going to take time definitely to get that knowledge base fully developed, but we do have to start somewhere. And that's the whole idea of KASA, is it captures it all in one unified place.

DR. YU: In that way, KASA will facilitate the decision-making process to think about. And clearly we have knowledge with each individual subject matter experts. When the [indiscernible] specific patient evaluates, they make a decision what information they need and to ask industry to probably provide additional information in order for them to make a decision in many cases.

So now, the knowledge will be captured in the

rule-based approach, that we call the drop-down menu. Those will be available, number one.

Number two, in some cases, it may not be captured completely. With the full KASA system, the reviewer will be able to search in other applications with similar -- for example, the same product. We will see what the regulatory action has been taken for applications instead of relying on [indiscernible] memory. That will facilitate the information availability and eventually facilitate the decision-making process.

So we clearly envision that the KASA system will increase our efficiency and facilitate the decision-making process, and eventually increase the speed of availability of medicine to our consumers and to our patients. I hope this answers your question

DR. SMITH: So you're saying that you're developing the knowledge base at the same time that you're developing the software?

DR. YU: Well, I want to say that KASA is not a one-time thing. For example, we develop it by -- let's say December of 2019, we'll stop

developing. No. KASA continues the evaluation process evaluation because in 2020, we will receive additional information, which you have not experienced and may have the knowledge. We will continue to build in our rules [indiscernible] so that additional information and additional knowledge will continue to build into our KASA system. So it is an evaluation process. Thank you.

I'm sorry. For the record, I should have said -- it's not evaluation. It should be evolution process.

DR. AMIDON: Dr. Slattum?

DR. SLATTUM: This is Patty Slattum from Virginia Commonwealth University. And my question was related to Dr. Smith's question, actually. I want to make sure I understand the framework.

The idea is that this processes is adaptive, and it will be adaptive over time. And what's adapting is these decision rules or the risk rules, and what mitigation strategies work is going to be evolving over time. And I'm curious as to how we see the communication around that happening so that the

knowledge that's being gained is shared.

Also, how what you already know goes past what individuals know and into this process of building that algorithm; how is it then built so far?

DR. RAW: The way that it's been built so far is when we develop those drop-downs, we sat with all the experts in other fields. We had experts from biopharmaceutics, experts in process, process engineers, and we had formulators. That's where all those drop-downs came from.

DR. SLATTUM: You accumulated knowledge of the people involved so far. Got it. But the idea is that this is going to turn into some kind of a machine-learning, adaptive, as data comes in, we can refine our algorithms because we see what works in them and what doesn't?

DR. KOPCHA: And that's exactly right because what we want to do is, years ago there were expert systems. And the expert system was to grow and be developed by experts, because as those experts leave an organization, that information would typically get lost. But now we want to be able to capture that

knowledge. So actually, instead of calling it an expert system, which indeed is what it is, we call it knowledge management.

Just to go back to Dr. Smith's earlier question, we do have a lot of this knowledge internally, but we have to sift through it manually. As time goes by, and as we start receiving applications now and doing that as reviews, we can put that information into our knowledge management system. But at some point, and it depends on products because we don't have unlimited resources or money, depending upon what we view as being a critical work that was done previously, we may want to go back and start putting that information into this knowledge management system manually; go back, get it manually, and then started entering that in while we're adding to it as we do application reviews.

I mean, let's face it. The FDA has been around for a long time. There's a ton of information. Some of it's hard to find, some of it is easier to find. But to Susan's point, we've got to start somewhere. So the new applications that come in will

be electronically downloaded into that knowledge management system, and then maybe some of the earlier ones that were done, again, depending upon the product and the criticality to patients, we may have to go back and do some of that manually. So we have to pick and choose because, again, we just don't have unlimited resources to be able to do all that.

DR. AMIDON: Okay. Thank you. Dr. Tenjarla next.

DR. TENJARLA: Srini Tenjarla, Shire Pharmaceuticals. I think my question probably has just been answered. But my position was to -- one of the speakers said that the review either -- it's a challenging job for a reviewer to transpose the data from a PDF file into the KASA system, and I completely agree with that.

I'm just wondering if FDA can take advantage of the fact that you have a lot of historical information on failures from previous products, and rather than enter all the data from the past, you can maybe enter the hundred failures or whatever the number is. You're making your database stronger up front

rather than collecting the information from the time you introduce the KASA to the public.

DR. KOPCHA: Yes. We have to set priorities and figure out where we're going to do our work because we still have our day jobs to do, which is in terms of reviewing the applications and getting drugs to the market as quickly as possible. We've got a lot of that information, and our surveillance group has been key in doing that, and hence, the reason why we have a surveillance organization within the Office of Pharmaceutical Quality.

They're looking at ways to be able to garner the information, not only what's been done internally, but also what's out there in the public domain because there's information that comes out in the public domain that's not necessarily submitted to the FDA.

So our surveillance group is working on that. You've got to realize that group's only been in place for a little over three years. We're looking at technologies to be able to do that, and we've got some promising ways of being able to pull that information, because ultimately we want to be able to, within our

site selection model, be able to determine where the high-risk facilities are, because again, we don't have unlimited resources to do inspections of every single company. So all this kind of plays together to solve a lot of the needs that we've seen over the years.

DR. TENJARLA: I agree. Thank you.

DR. AMIDON: Dr. Awni next.

DR. AWNI: The question I was going to ask is already covered, so I'm going to pass.

DR. AMIDON: Good. Thank you.

Dr. Sun, next.

DR. SUN: Dr. Kopcha already answered my question, but I will comment anyway. As an outsider, when I come out a research question, I think to myself. I said, "FDA has this data already. I'm sure they have the answer," whether the answer is in the basement of somewhere. So ideally, I have access to dig that out, and I can use, but I cannot access.

So I think in terms of knowledge, the knowledge is there. The FDA has a lot of research knowledge, rich knowledge, in the basement. The problem is, it's not accessible to you and, of course,

not to the outsider.

So my understanding is, really, [indiscernible] you start to capture all of those and make the future much easier, then I do agree to the question. If there is an effort to put those basement papers into electronic data that's searchable, that has to be very, very rich. Nobody else has that data, and a lot of answers are already there. We do not need to do research anymore. It's already there.

DR. KOPCHA: Right, and we realized that. There is a lot of information there. Even some of the IT systems, they're so old that they don't communicate with each other any longer, and we've run into that problem as well. So even though we've electronically captured that information or that knowledge, we have issues with trying to allow that to communicate with some of the more modern systems as well.

So it is a tough piece, but it's just the reality that we've got to deal with.

DR. AMIDON: Thank you. Dr. Li?

DR. LI: Tonglei Li from Purdue University. I definitely commend FDA on developing the system. I

believe informatics is mentioned in the discussion. I'm just curious about what initiated efforts will go ahead in terms of data mining. Centered around identifying hidden risk, that may be a field to be identified in early assessment.

Because I teach students about solid-state chemistry, one example we have is ritonavir. That's in NIDES [ph]. A new form was identified in the early process. So I'm just thinking that what if in the future there's a similar product with hidden risk. Can that be identified by processing the database, by data mining the database? I definitely would like to hear more about those efforts.

DR. YU: In the case of ritonavir, as we share with the public a new polymorphic form, you can come back and look at the FDA's evolution of our regulatory assessment. In the '90s, we had little information related to the polymorphic form. In 2000, we began to have a policy for polymorphic form, so it's information sharing.

In the HIV inhibitors area, once we learned about the case, ritonavir, all the incoming future

applications are now being set up of additional regulatory expectations. This [indiscernible] in the pharmacometrics or mathematical term is adaptive.

As a perfect example, as we're learning from new experience and new knowledge, we'll bring additional rule and the criteria. So it's a risk to form a new polymorphic [indiscernible] form impact, and reviewer performance will be minimized.

In the future, this is an isolated case because the company discovered, FDA learned. And in the future if all this database is available, informatics, yes, it will all be significant to play. For example, there are so many formulations out there. There are so many excipients used in different formulations with a lot of stability predictions going on, as well as informatics in pharmacometrics area and clinical [indiscernible] -- will do a lot of the mathematical modeling and simulation, and will help us to establish our criteria and also makes the agency more current and adaptive to ensure quality medicine.

DR. ROSENCRANCE: And maybe to understand one quick point, I just want to emphasize that KASA isn't

meant to replace the role of the assessor. It's to aid the assessor and make more informed, objective decisions. I just want to make sure people don't misunderstand, the assessor's role is still very, very important to find these hidden risks.

DR. AMIDON: Very good. Are there any last clarifying questions?

(No response.)

DR. AMIDON: Okay. Good. We'll now take, I'll say approximately, a 15-minute break. Let's come back at 10:30 to resume the meeting. Please remember as panel members, there should be no discussion of the meeting topic during the break amongst yourself or with any members of the audience. Also, as a reminder, there's another meeting going on next door, so please keep your conversations out in the hallway or elsewhere, at an appropriate volume level I guess.

Anything else?

(No response.)

DR. AMIDON: Okay. We'll adjourn until 10:30. Thank you.

(Whereupon, at 10:12 a.m., a recess was

taken.)

Questions to the Committee and Discussion

DR. AMIDON: There are no statements from the public, so we will proceed to the question to the committee for discussion. I'd like to remind any public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

At this point, I'm going to read to you the question that we will be voting on and ask you first if there are any questions you have regarding the wording, and then we will open the floor for discussion by the committee.

The question, as you can see on the screen, is relating to the KASA initiative, should the FDA consider the enhancement of submission format to improve the efficiency and consistency of regulatory quality assessment? That's the question to us for this morning.

Are there any questions or thoughts specifically about the wording of this that, as I said,

we will be voting on?

(No response.)

DR. AMIDON: Okay. So if there are no questions or comments concerning that, we'll now move on to open that question to discussion. After the discussion, we will then proceed to voting.

Should I go through the voting process at this point? Okay. Following the discussion that we'll have, we will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing on your screen here and will continue to flash even after you vote. When you vote, please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may by simply pressing the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in, and then the vote will be displayed on the screen. The DFO will then read the vote from the screen into the record. Next, we'll go around the room following the vote and give each individual who voted an opportunity to speak. So we'll

ask you to state your name and your vote into the record. You can also state the reason for why you voted the way you did if you want to.

We just have one question to deal with this this morning. So with that, hopefully that voting process is clear enough. I think we can be open for discussion at this point. So please, as we did before, just raise your hand and let us know if you have comments that you want to make before we vote, and we'll recognize you in order. So let me open it for further comments or discussion on this.

Dr. Sun?

DR. SUN: Maybe more like a clarification for the question is, based on early discussion we had, it seems internally you will have a lot of effort going on to develop this system, which is wonderful. But these questions seem to refer for the submission from the sponsor. Do you require to submit and use this format?

That's the question. It really seems to where it's industry sponsor.

DR. YU: Chair, do you want me to answer?

DR. AMIDON: Do you have an answer?

(Laughter.)

DR. YU: I guess so. One of the slides in [indiscernible] will have a phased approach. It's related to internally the risk assessment, related to the product, and also related to the manufacturing process. It's all an internal phase, phase 1, phase 2, and phase 3. But this is for external. Yes, we do the input from the committee, from you, as to whether the FDA should consider enhancement of submission format, including the context to improve the efficiency and consistency of the regulatory assessment.

Without the structure submission, FDA can continue to move forward with this initiative and with the structured information, and it will increase our efficiency. So it's an enhancement. It's a desirable goal, but it's not [indiscernible] the KASA initiative. I just want to make sure. With or without this submission format, internally we'll move forward because, as you can see from the committee, the knowledge of sharing and the knowledge of process informatics is incredible and powerful. It not only helps with the regulatory assessment, but eventually

I'm hoping contributes to the evolution of the pharmaceutical science as well. Thank you.

DR. AMIDON: Thank you, Dr. Sun. Any other questions or clarifications that might be needed at this point?

Dr. Smith?

DR. SMITH: I think it would be interesting to hear what the industry reps have to say since we're sort of moving towards putting in a different requirement on them to submit data over information in structured form. I'd like to hear what they have to say about it.

DR. AMIDON: Yes?

DR. TENJARLA: So I think it's actually a good thing because it's very helpful to know up front what exactly is expected, and anything that contributes to the overall quality of the product is something that definitely would be of value to the industry.

DR. AMIDON: Dr. Tenjarla, thank you.

Other comments? Dr. Awni?

DR. AWNI: Actually, it's a very good thing. We're used to it in the clinical setting. Doctor, you

mentioned -- I mean, when we submit PK data, phase 3, we submit it in a certain format that the FDA could actually read it and process it very fast. So I don't see it any differently in this case.

DR. AMIDON: Okay. Good. Thank you. Anything else?

Dr. Cook?

DR. COOK: Jack Cook, Pfizer industrial representative, only to go on record that I too agree anything to facilitate your work and facilitating our review is fantastic. I didn't ask the question what's the burden do you think in industry and how many new people you think we're going to retire, I have to hire, but I don't look to that to be a problem, nor do I think you have any of those answers yet.

DR. AMIDON: This is Greg Amidon. Just a comment on my part, I think this is a very interesting direction to go. I just think it's important that it really be as transparent a process as possible between FDA and companies in particular as they're moving through this process.

Anything else before we move on to a vote?

Just as a reminder, after you vote, we'll go around the room, and you'll have an opportunity to indicate why you voted if you choose to do so.

Is there anything else or shall we move on to a vote?

(No response.)

DR. AMIDON: It looks like we're ready to vote. Please, on your microphone, you'll see the lights blinking. Press the button on your microphone for the vote that corresponds to your vote on this issue. You'll have approximately 20 seconds to vote, so please press the button firmly. After you've made your selection, again, as a reminder, the light may continue to flash. And if you're unsure, you can press the corresponding button again until the vote is closed.

So I think we are ready to vote at this point. Please enter yes or no or abstain.

(Voting.)

CDR SHEPHERD: For the record, the vote is 10 yes; zero no; and zero abstain.

DR. AMIDON: As a reminder, I think everyone

understands the industry representatives are not voters, voting on this. So we have a vote of 10 yes and zero no, with no abstaining. So that's the final vote I think.

At this point, I think we go around the room, so I'll make sure I start at the right point, I think with Dr. Donovan first. So your vote and any comments you wish to make?

DR. DONOVAN: Maureen Donovan. My vote was yes, and I'm in support of this initiative from the FDA. I like the word "consider" as part of the action that we voted on because I think that there's still some things in the system that need to be worked out, but it's time to be able to sort of bridge between internal and then external, helping internal in the future. So I am supportive of the initiative.

DR. SUN: Duxin Sun. My vote is yes. As I said earlier, not only can this help FDA internally, but also externally help industry to know what and how to submit. Actually another [indiscernible] may be helpful. Really, this process helps the industry to have a smooth process. And also, you can actually put

FDA and industry on the same page in terms of risk assessment.

DR. LI: Tonglei Li. My vote is yes, and I support the FDA initiative. I think the effort is really a scientific approach to handle the submission process. Also, I would appreciate in future opportunities for the university, faculty, and students getting involved in the development of the process. Thank you.

DR. FINESTONE: Sandra Finestone. My vote is yes. I appreciate the effort to bring you into the 21st century.

DR. MAGER: Don Mager. My vote was yes. I think this is a fantastic initiative, and I think it really is mission critical. I think there are so many cases of inaction or delayed reactions or responses not due to the lack of data, but more to the inaccessibility of data as we've talked about today. So I think the initiative is spot on.

As to the direct question itself, I think companies would want to embrace this to avoid any sort of issues in transposing data of any kind, so then they

know it's going to be directly implemented, as we've heard from the representatives today as well. And then just going forward, I would really encourage the flexible designs that we talked about early on such that the data are not only searchable, but could be easily transposed into formats that could be used for other analyses. That type of flexibility I think is important.

You mentioned the pharmacometrics example earlier. One of the biggest bottlenecks there is actually getting the data set in the right format to do that analysis. So it would be wonderful that, yes, the data are electronic; yes, they're searchable; but then also can be readily exported to other types of analyses.

DR. AMIDON: Greg Amidon, and I voted yes. I can see this, as well, as being a great benefit to the Food and Drug Administration, but to industry as well. I can see it facilitating the communication between government and industry.

As I had mentioned earlier, I think the more transparent this process can be, communication's going

to be better. And I'd like to comment as well that it's I think a more scientific approach to this and makes a lot of sense.

DR. CARRICO: My name is Jeff Carrico, and I voted yes. There have been some wonderful positive comments, and I concur.

DR. TERZIC: Andre Terzic. I also voted yes. This is a very timely initiative. It underscores the mission and vision of the FDA and also prepares not just the industry, but in general, the healthcare space to be even more scientifically oriented in the submission of new applications.

DR. SLATTUM: This is Patty Slattum, and I voted yes. I applaud the efforts for clarity and transparency, and I do see great opportunity for patients actually in quality of products when we can better use the information we have. So thank you for doing that.

DR. SMITH: I'm Paul Smith. I also voted yes. I think the work that's been done so far is excellent. Obviously, there's more to go. And it will involve changing the way information is presented, but I

believe that this is a win-win situation for everybody.

Adjournment

DR. AMIDON: Thank you very much. We're going to adjourn now. Lunch will not be available until 11:30, I understand, but as we're finishing early, we'll get a little bit earlier start on the afternoon session. We will adjourn for session 2 at 12:30. For those that are on the committee, there is a room behind us that's available for lunch. And as a reminder, again, no discussion of the topics amongst the committee or any others during that time.

Let me check and see if there is anything else. I got a thumbs up I think we're good, so back at 1230. The lunches for the committee are delivered back here.

Jack?

DR. COOK: Do we have a committee member who's not here, who's coming for the afternoon, and do they know about the 12:30 start-up time?

DR. AMIDON: Yes.

(Whereupon, at 10:52 a.m., the morning session was adjourned.)