FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY (ACPS-CP)

WEDNESDAY, SEPTEMBER 25, 2013

8:00 a.m. to 4:00 p.m.

Bethesda North Marriott Hotel and Conference Center

5701 Marinelli Road

Bethesda, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Yvette Waples, PharmD

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY MEMBERS (Voting)

Jessie L-S Au, PhD

Chief Scientific Officer

Optimum Therapeutics LLC

San Diego, California

Rose Marie Caballero, MSN, RN

(Consumer Representative)

Director Associate Degree Nursing Program

Career Point College

San Antonio, Texas

Fernando J. Muzzio, PhD
Director, NSF ERC on Structured Organic
Particulate Systems
Distinguished Professor of Chemical and
Biochemical Engineering
Rutgers University
Piscataway, New Jersey

James E. Polli, PhD
Professor
Department of Pharmaceutical Sciences
University of Maryland School of Pharmacy
Baltimore, Maryland

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

Jack A. Cook, PhD
(Industry Representative)
Clinical Pharmacology
Specialty Care Business Unit
Pfizer, Inc.
Groton, Connecticut

James J. Keirns, PhD

(Industry Representative)

Vice President

Chief Clinical Pharmacology Scientist

Global Clinical Pharmacology & Exploratory Development Astellas Pharma Global Development, Inc.

Northbrook, Illinois

TEMPORARY MEMBERS (Voting)

Jeffrey S. Barrett, PhD, FCP

(Acting Chairperson)

Research Professor, Pediatrics

Department of Pediatrics, Perelman School of Medicine

University of Pennsylvania

Director, Laboratory for Applied PK/PD

The Children's Hospital of Philadelphia

Philadelphia, Pennsylvania

Ruth S. Day, PhD
Director, Medical Cognition Laboratory
Duke University
Durham, North Carolina

David Flockhart, MD, PhD
Director
Indiana Institute for Personalized Medicine
Indiana University
Indianapolis, Indiana

John R. Horn, PharmD
Professor
University of Washington School of Pharmacy
Department of Pharmacy Practice
Seattle, Washington

Daniel Malone, RPh, PhD
Professor
University of Arizona College of Pharmacy
Tucson, Arizona

Michael J. Miller, RPh, DrPH, FAPhA
Associate Professor
Department of Pharmacy
Clinical and Administrative Sciences
The University of Oklahoma College of Pharmacy
Tulsa, Oklahoma

Marilyn E. Morris, PhD
Professor
Department of Pharmaceutical Sciences
University at Buffalo
Buffalo, New York

Kathleen A. Neville, MD, MS
Associate Professor of Pediatrics
University of Missouri
Children's Mercy Hospitals and Clinics
Kansas City, Missouri

Alice Pau, PharmD
Staff Scientist (Clinical)
Clinical Pharmacy Specialist
Division of Clinical Research
National Institute of Allergy & Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Jürgen Venitz, MD, PhD
Professor
Department of Pharmaceutics
School of Pharmacy
Medical College of Virginia Campus
Virginia Commonwealth University
Richmond, Virginia

GUEST SPEAKERS (Non-Voting)

David W. Bates, MD, MSc
Medical Director of Clinical and Quality Analysis,
Partners Healthcare
Chief Quality Officer, and
Chief, Division of General Medicine
Brigham and Women's Hospital
Boston, Massachusetts

David Juurlink, BPharm, MD, PhD
Associate Professor
Department of Medicine, University of Toronto
Attending Physician, Division of General
Internal Medicine
Sunnybrook Health Sciences Centre
Scientist, Institute for Clinical Evaluative
Sciences Toronto, Ontario

Karl Matuszewski, MS, PharmD
Vice President, Clinical Editorial
First Databank, Inc.
South San Francisco, California

SPEAKER (Non-Voting)

Tricia Lee Wilkins, PharmD, PhD
Project Officer, Beacon Community Program
Office of the National Coordinator for Health IT
Washington, District of Columbia

FDA PARTICIPANTS (Non-Voting)

Issam Zineh, PharmD, MPH
Director
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
CDER, FDA

Kellie Schoolar Reynolds, PharmD
Deputy Director
Division of Clinical Pharmacology IV
OCP, OTS, CDER, FDA

Lei Zhang, PhD
Special Assistant to the Office Director
OCP, OTS, CDER, FDA

Shiew-Mei Huang, PhD

Deputy Director

OCP, OTS, CDER, FDA

Darrell Abernethy, MD, PhD

Associate Director for Drug Safety

OCP, OTS, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:01 a.m.)

Call to Order

Introduction of Committee

DR. BARRETT: Good morning, everyone. If I could have everyone please take your seats, we're going to start the meeting, get started.

I'd like to remind everyone before we begin if you could shut off your BlackBerrys, all devices, all your cell phones. And if you already haven't done so, please, again, put everything away as best you can.

I'd also like to identify the FDA press contact for the meeting, Mr. Stephen King. If you're here and present, can you please identify yourself? Well, we'll get to that in a little bit, then.

My name is Jeffrey Barrett. I am the acting chairperson for the Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology. I will now call this meeting to order.

I will start by going around the table

and introducing ourselves. If you could state your name and your affiliation. Let's start here on the right. Jack. Jack, I'm sorry.

DR. COOK: Jack Cook with Pfizer.

DR. KEIRNS: Jim Keirns, Astellas.

DR. NEVILLE: Kathleen Neville, Children's Mercy Hospital.

DR. MORRIS: Marilyn Morris, pharmaceutical sciences, University of Buffalo.

DR. MILLER: Michael Miller, University of Oklahoma, College of Pharmacy.

DR. MALONE: Dan Malone, the University of Arizona.

DR. HORN: John Horn, University of Washington.

DR. FLOCKHART: Dave Flockhart from Indiana University.

DR. POLLI: Jim Polli, University of Maryland.

MS. CABALLERO: Rose Caballero, consumer member.

DR. WAPLES: Yvette Waples. I'm the

designated federal officer for this meeting.

DR. VENITZ: Jurgen Venitz, Virginia Commonwealth University.

DR. AU: Jessie Au, Optimum Therapeutics.

DR. PAU: Alice Pau from the NIH.

DR. DAY: Ruth Day, director of the Medical Cognition Lab at Duke University.

DR. ZHANG: Lei Zhang, Office of Clinical Pharmacology, FDA.

DR. ABERNETHY: Darrell Abernethy, Office of Clinical Pharmacology.

DR. REYNOLDS: Kellie Reynolds, Office of Clinical Pharmacology, FDA.

DR. HUANG: Shiew-Mei Huang, Office of Clinical Pharmacology, FDA.

DR. ZINEH: Issam Zineh, Office of Clinical Pharmacology, FDA.

DR. BARRETT: For such topics as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal here at today's meeting will be a fair and open forum for discussion for

these issues, and that individuals can express their views without interruption. As a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. So 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 in their conversations about the topic at hand. Because this is an open forum meeting, we are 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 these proceedings. FDA will refrain from discussing with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during the breaks or at lunch. Thank you.

Yvette will now read the conflict of interest.

Conflict of Interest Statement

DR. WAPLES: Good morning again. The Food

and Drug Administration, FDA, is convening today's meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 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 particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions at today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 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 discuss optimal strategies for the evaluation, interpretation, and communication of drug-drug interaction information. FDA will seek input on:

(1) Best practices in DDI communication through prescription drug labels, namely

a) appropriate format for presentation of DDI information; b) level of detail of DDI study results; and c) appropriate wording for clinical recommendations based on empirical data versus anticipated interactions;

(2) Appropriate criteria for determining whether or not to describe DDI information derived from the literature in product labels; and

(3) How package insert information on DDIs is used by various end users in decision-making and/or communication.

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 Dr. James Keirns and Dr. Jack Cook are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Drs. Keirns' and Cook's role at this meeting is to represent industry in general and not any particular company. Dr. Keirns is employed by Astellas Pharma Global Development, and Dr. Cook is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any products, firms, or other issues 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 with the firms that could be affected by the committee's discussion. Thank you.

DR. BARRETT: We will now proceed with the FDA opening remarks. At this time, I'd like to introduce Dr. Issam Zineh. I want to remind the observers at this meeting, the public observers, that while the meeting is open for the public observation, public attendees may not participate except at the specific request of the panel.

Dr. Zineh?

Presentation - Issam Zineh

DR. ZINEH: Good morning. I want to first start by welcoming the public to this meeting, as well as acknowledging in advance on behalf of the Office of Clinical Pharmacology the advisory committee members as well as the speakers, we are confident that we will gain valuable insights into very important aspects surrounding drug labeling. And so what I wanted to do is just provide a little bit of context to the motivation for this particular advisory committee meeting as well as what we expect the outputs to be.

We already heard a bit about the scope, so I won't describe that again. But I want to emphasize

that the best practices, outputs, lessons learned, et cetera, that we hope to gain from today's conversation, we expect those to be portable to other aspects of labeling. And so we think that this is very important, not just for drug interactions, but for other relevant information in drug labels.

In terms of relevance, this particular meeting, the output and discussion from this particular meeting are intended to inform a variety of improvement and policy exercises within the Office of Clinical Pharmacology as well as the Center for Drug Evaluation and Research.

These include but are not limited to revisions of guidances from our office, regulatory guidances from our office that have a prominent labeling component; development of standardized approaches to labeling of complex clinical pharmacology information beyond just drug interactions; as well as planning for key center-wide initiatives to improve labeling, such as the Prescription Drug Labeling, Improvement, and

Enhancement Initiative.

So it probably is worth pausing to describe why we're actually focusing on labeling to begin with, and that is simply because the label is ultimately the agency's primary communication tool for maximizing the likelihood that the drugs that are approved are used in a maximally effective and safe manner.

The label is also a legal document that serves as the basis for prescription drug promotion, and it could also have implications for liability. In essence, it's the major end product of a drug development program, as well as the regulatory evaluation of that new drug.

We feel the time is right to discuss labeling, specifically to build on some of the successes and momentum of our current programs in the agency with respect to labeling, such as the physician labeling rule and other labeling modernization initiatives.

Essentially, we have a renewed focus on the importance of labeling at the FDA, particularly in

the Center for Drugs. A labeling review is happening much, much earlier in the drug evaluation and drug regulation process. And industry and regulatory teams are gaining much more experience with these new requirements and formats in terms of organization of information for the public.

So there are also some efforts to take the labels of already-approved drugs and update them to be maximally informative. And so there's, I guess, an organizational context and a public health context to put this into.

That said, there are still some challenges, despite the enthusiasm and the momentum, to optimal labeling. These include these formatting requirements, which are fairly new and extremely detailed. In some situations, the regulations and the formatting actually drive the content.

So another complicating factor is that clinical pharmacology information is multidimensional, complex, can occur in any of a number of sections of the label, and so this really does necessitate development in labeling best

practices from a clinical pharmacology perspective.

So clinical pharmacology information is so diverse, why focus on drug-drug interactions? Well, drug interactions are probably amongst the most complex types of information to convey. Clearly there's a major issue of public health relevance here. It's very well documented that either lack of awareness or mismanagement or drug-drug interactions has a tremendous economic, clinical, and humanistic toll from a public health standpoint.

In addition, reductionist approaches to evaluation of drug-drug interactions in drug development always leave this question of generalizability of drug interaction information to the general public that will receive these medications in very complex clinical scenarios.

Additionally, data are constantly emerging in the public domain in terms of new information on drug interactions. And this raises some very challenging methodological and evidentiary issues for FDA. How do you assess these reports from the

literature? How do you do it in real time? How do you update the label in a timely fashion in a way that's appropriate?

Quite frankly, there are different philosophies on what to put into labels, how much to put into labels, and what is the most valuable way of presenting information stylistically and in terms of comprehension. And so I think we'll hear a lot about that today.

So with that, I just want to go over very briefly at a high level what the questions are to the panel. These are already in the packet, so everyone should have these.

So what we'd like to do is seek input on the format and presentation of drug-drug interaction information in the labeling, specifically with respect to level of detail, and the relative merits and disadvantages of presenting this information in a variety of visual and textual ways.

In addition, there is a lot of complexity around drug interactions, and we would like to have the committee weigh in on the level of information

to be provided in these complex drug interactions. We have some examples of what those complexities might be. But essentially, when you consider the multifactorial nature of patients and their responses to therapies, the drug interaction conversation gets very complex.

The other area of drug interactions that we'd like to get some feedback on is you cannot empirically test all possible scenarios of drug interactions, specifically in varying contexts of patient conditions. And so some of these scenarios can be predicted in silico or through other in vivo mechanisms or in silico analyses in the absence of dedicated drug interaction studies. So we'd like to hear about the appropriateness of inclusion of some of those types of information in the label and to what extent they should be called out.

Finally, the last two questions have to do with the meaningfulness of certain language in the label in terms of clinical actions as well as the issue of curation and interpretation of drug information from the literature. We propose a

general framework on how that should be done, and we appreciate feedback on that.

So again, I thank everyone, and our FDA speakers and other speakers I'm sure will provide much more context around these questions. And we look forward to the discussions. And with that, I will turn it back to Dr. Barrett. Thank you.

DR. BARRETT: Before we get started here, I just wanted to recognize that a short time ago we lost one of our members of the committee, Dr. Joseph Kosler. So if we could just take a moment of silence, recognizing his public service in the past and his efforts on behalf of this committee.

(Moment of silence.)

DR. BARRETT: We will now proceed with presentations from our guest speaker, Dr. David Juurlink. And then those will be followed by presentations from the FDA.

Again, a final time, I will remind the public observers at this meeting that while it is open for public observation, public attendees may

not participate except at the request of the panel. Thank you.

Presentation - David Juurlink

DR. JUURLINK: Good morning, and thank you for the opportunity to present to your committee. It's nice to see the FDA devoting attention to a topic that I think is mystifying to many clinicians. It's confusing to a good number of us.

Importantly, as was alluded to in the opening comments, it causes a great deal of harm. In fact, I don't think we really have a good sense of how much harm befalls our patients as a result of what is often well-intentioned prescribing.

I'll speak for about 20 or maybe 25 minutes, and none of what I have to say is particularly complicated. But I want to cover three things.

I want to briefly discuss the perception of frontline clinicians, and by that I generally mean pharmacists and physicians, of drug interactions. I'll talk a bit about the labels and how they are used or how they are not used, and what some of the problems with the labels are, as I see it, anyway,

and offer you some suggestions for how the labels might be improved.

So I gave rounds at my hospital last week to a group of senior pharmacists, many of them specialized pharmacists, and a small group of physicians. And the topic wasn't drug interactions, it was something else. But I asked them to indulge me for a minute and repeat the first word that comes to mind when I said the phrase "drug interactions." And here are the responses I got. There were a few other ones that I couldn't put up here.

But I think these responses -- and you can read them as well as I can -- are a testament to how much consternation this topic brings to clinicians. And keep in mind, this is not a group of clinicians who work in isolation in a practice in rural Ontario. This is a group of very smart academic pharmacists and physicians in a tertiary center.

So I think it's important to realize that there are some interactions that most physicians

appreciate. I think if you asked a hundred doctors or a hundred pharmacists to list some, here are a few that they would list.

Opioids and benzodiazepines and alcohol or other CNS depressants, this is not rocket science. Most docs know that 1 plus 1 plus 1 isn't 3, it's 5 or it's 10 when it comes to these drugs. And not a week goes by on my clinical service when I don't admit somebody who's on aspirin and an oral anticoagulant; more often than not, they should not be.

There are a few that are ingrained. Right? So whether it's MAO inhibitors and meperidine, or MAO inhibitors and SSRIs, most people know that this is not something you're supposed to do. But by and large, clinicians are other overwhelmed by this topic. And they're overwhelmed for a couple of reasons. The first is the sheer number of drug interactions that exist, and importantly, the complexity that was alluded to earlier of their mechanisms and their terminologies.

This is an important point. So the language

that we use and the phrases that roll off our tongues easily, that we don't have to think to understand, befuddle many front-line physicians. Even terms like pharmacokinetic or pharmacodynamic, or even synergism and antagonism, things that we don't think twice about, they have to engage their brains and figure exactly what those mean, let alone terms like area under the curve or Cmax.

Most physicians and pharmacists know that P450 is a thing, but they don't know -- and I think even a diligent clinician might not be expected to know -- the difference between 2B6 and 2D6 and 2C19 and so on. And that says nothing about transporters, P-gp and OATP1B1 and so on.

So this is a complicated business for us, and it's an overwhelming business for docs and pharmacists on the front line. And frankly, most of them are too busy and not inclined to catch up or keep up with something that is, even at baseline, overwhelming.

So how do clinicians use the labels? And I think it's important to make the point that

physicians generally don't. They sometimes do, but it's very physician-dependent. I think most physicians rely on pharmacists and the resources at their disposal.

The pharmacists have a variety of tools, and I know this because I was a pharmacist for five years. The most important of those tools is their brain. But the brain is a soft and porous organ, and it's essential to make clinical decisions, but it's simply not adequate. And even the most diligent clinician can't be expected to keep on top of this topic on their own.

There are a variety of drug interaction specific resources, whether it's textbooks, or more often nowadays, electronic, the Web and whatnot, and Google, and PubMed, and review articles. I'll come to a few of these in the course of my presentation.

Here's one reason why physicians don't use labels, and this is an example from Bristol-Myers-Squibb, a monograph retrieved in about 10 seconds from the Internet. And I think it's

worth looking at this.

This is the introductory comment of the drug interaction section of that label. And the first paragraph here makes the point that it's good practice to monitor the patient's response after they leave hospital or after you add drugs or take drugs away, and that states what I think is obvious to most clinicians, and it's probably a good motherhood and apple pie statement. But physicians who are going to the label already know that. They already know. This is why they are looking in the document in the first place.

The second paragraph contains some of the phrases that I alluded to earlier, that most physicians and pharmacists don't intuitively understand pharmacodynamic, pharmacokinetic, and so on.

There's a phrase in here regarding the pharmacodynamic interactions involving a physiologic control loop for vitamin K. I don't even know what that means. I know a lot about warfarin; I don't know what that phrase means, and

it shouldn't be in here.

So I think for most frontline docs and pharmacists, this inundates them with words they don't understand, and it sedates them and causes them to just turn the page.

This is the next section of that monograph, and it gives examples of classes of drugs with potential interactions with warfarin. These aren't drugs, these are classes of drugs, and so collectively I would say that this represents about 80 percent of the drugs I might prescribe on my internal medicine service.

This is where it gets specific. So this is where specific drugs, specific drugs reported to interact with warfarin, are listed. And I don't think I need to tell you what's wrong with this. Okay? But this is what the meeting is about, so let's go through what's wrong with this.

It's exactly what someone who has gone to the trouble of going to the label does not want to see. There's no structure here. There's no sense of directionality. Does this drug on this list

increase the risk of hemorrhage or decrease the effectiveness of the drug? It's not clear. There's far too much information.

Some of the information is wrong. A good number of the drugs on that list have no plausible interaction with warfarin. There are drugs that I've never heard of, drugs that I think aren't even in existence any more. There's no conveyance of the magnitude of risk. Is this a big deal? Is it a small deal? It's not clear. And there's no guidance on what to do.

So how might we make these labels better? This is where I'll spend most of my time. I have five simple suggestions. I think it would help if the labels were simplified. And it would help if they were decluttered. And the imposition of some structure would be helpful. It would be helpful if they were updated periodically, and I think for those who have the inclination and the time, a link to more information, should they choose to go there.

So the first is to simplify. And I think

again this is important, and it depends on who the target audience should be. All right? If this discussion pertains primarily to the internist or family physician or psychiatrist in his office, I think we want to minimize the use of terms like pharmacokinetic and pharmacodynamic and AUC and Cmax, and a lot of detailed mechanistic information about why an interaction might happen. And we certainly want to eliminate meaningless phrases, like the one I alluded to earlier.

I think there's a lot of white noise in these monographs sometimes, and warfarin's a good example. All right? There are archaic drugs in that list. I know what two of those drugs are. There are other coumarins. Right? It should come as no surprise that if a physician elects to give a patient two coumarin anticoagulants, that the patient might be at increased risk of bleeding.

But you don't expect to see that in the monograph any more than you expect to see atenolol listed as an interacting drug with metoprolol in the metoprolol monograph. It doesn't make any

sense to be there. And warfarin overdose is not an interaction. It's an overdose, and it doesn't belong in the monograph.

I think maybe "reported" shouldn't be the bar here. Right? The fact that something is reported shouldn't suffice to get it on the list because reports are reports for a reason, and that's especially the case, I think, when there's no drug-drug interaction mechanism apparent.

I'm not sure if this suggestion is at odds with the liability issue that was mentioned in the introduction. I don't know. But simply the fact that it was reported somewhere I don't think is sufficient to put it on that list. And this is a major means by which decluttering could be accomplished.

So in terms of structure, here's just a suggestion of how a monograph for warfarin and drug interactions might look. And this is not meant to be inclusive; it's just meant to show what I mean.

Physicians who are going to add a drug to a patient who's already on warfarin are concerned

about one of two things. They're concerned that the patient might bleed, or they're concerned that the drug's effectiveness will be reduced. That's all they are concerned about.

On part A of that equation, drugs that might increase the risk of hemorrhage, there are only a few mechanisms by which that can actually take place. And I've suggested that perhaps drugs that impair platelet function could be grouped together, drugs that reduce warfarin's metabolism might be grouped together, and drugs that in some patients might actually have a direct effect at the pharmacodynamic level in terms of augmenting warfarin's response could be listed here.

Conversely again, drugs that might reduce warfarin's effectiveness could be treated in exactly the same way. I've listed a few of them here. Now, I'm not saying that this is the ideal solution. This list could get very long, especially the drugs that inhibit warfarin's metabolism.

But I showed this to my wife, who's an

internist and a very capable one at that, although she's got no special interest in pharmacology per se. I showed her first the warfarin monograph that I showed you, and then I showed her this, and she gave a very strong endorsement to this suggestion. And I don't think it's just because she was my wife.

The updating thing, I think, is a big deal. All right? So this is a paper published this month in Clinical Pharmacology and Therapeutics that addresses this exact topic and uses as one example imatinib, which still contains an emphasis on CYP3A4 when in fact we know more and more that CYP2C8 is actually an important determinant of this drug's metabolism, and drugs that modulate 2C8 might influence and might be expected to influence imatinib, especially at low doses.

Here's another interaction that I think probably happens less often nowadays than it used to. This is the ECG of a patient who came under my care as a resident about 16 years ago, and she was on digoxin. She had atrial fibrillation, and she

had a history of an allergy to penicillins.

So when she developed a cellulitis, her physician said, well, I can't give you cloxacillin and I can't give you cephalexin. Here's a prescription for clarithromycin, and away you go.

So she came to our hospital about a week later with a heart rate of 28 and a digoxin level several times higher than the upper limit of normal. And she got some Digibind, and she went home and was fine. But she could easily have died in the ambulance on the way to the hospital, or she could have died in her sleep.

So when I first saw this patient, I recognized that there was a drug interaction at play, but I had been misinformed about the mechanism even though it had been elucidated a couple of years earlier. But here is the monograph.

This is the Lanoxin pediatric monograph from a few years ago that touches on drug interactions. And again, this is the issue about updating. It talks about this mechanism, having something to do

with a gut bacteria that is inexplicably interfered with only by some macrolides and tetracycline, and yet impervious to the other antibiotics we use. This is not true. This is wrong information. It's been known to be wrong for at least 15 years now and has no place in the monograph.

We know that this is a simple interaction. Right? This is a P-gp-mediated interaction, and clarithromycin causes you to absorb more digoxin and excrete less in the biliary system and eliminate more at the level of the nephron. It's not complicated, and it happens to most people who get these drugs in combination.

We've studied this interaction ourselves. We've actually studied it twice. The first was in 2003, and this is from a few years ago that highlights that the translation of this is that if you've got an older person in front of you on digoxin and you elected to prescribe them clarithromycin, the approximate relative risk of them coming to hospital in the next two weeks for digoxin toxicity specifically is about 15.

If you instead chose erythromycin or azithromycin, it's about 4. And if instead you chose cefuroxime -- which might or might not be appropriate, depending on the patient; cefuroxime doesn't inhibit P-gp -- there is no incremental risk here. So this is a good example of something that I think physicians might appreciate knowing or having a sense of the magnitude of this interaction.

I want to contrast the monograph, and you can maybe use the warfarin one as an example. This is from Dr. Horn, who's sitting in front of me here, his textbook on Drug Interactions, Analysis, and Management from a few years ago.

I think that this is exactly what a frontline doc wants to know. It talks about this interaction in particular. It summarizes it. It makes it very clear. It's a single sentence. It talks about the mechanism. It doesn't use the word pharmacokinetics anywhere. In fact, it does mention P-gp, but it mentions it in a very simple way. This is exactly what a doc wants to know and

nothing more.

It has a sensible interpretation of what the literature looks like. It gives clinicians some sense of how big a deal this is. Notwithstanding the fact that different texts might disagree on this -- as Dr. Malone has shown, the person to Dr. Horn's left. Again, this gives a sense of how big a deal this is if you're going to elect to give these drugs together, and gives you some management options because really, this is what people want. They want to know, can I do this safely? And if I can't, what else might I do to avoid causing my patient harm?

I think the link in the electronic age -- it was different 20 years ago when you had to go to the library and pull a reference text. But nowadays, I can go to Dr. Flockhart's drug page and I can click on one of his interactions and be transported to PubMed for the original citation.

This is, I think, the way of the future. This is a program that I use a lot, UpToDate. I use it at home. I use it in the hospital. And

when I open it up to look up anything, whether it's acute myocardial infarction or bacterial meningitis or some disease I've never heard of before, this is the opening screen.

The opening screen has my search options here. But below, front and center, is this link to drug interactions. And they use Lexi-Comp. And here I've entered the clarithromycin/digoxin example that I just gave you, and it gives a somewhat more detailed description or discussion of this interaction. It goes on and on past this. But for people who want a little bit more in the way of detail, this is exactly, I think, what they need.

So this doesn't need to be in the monograph, but it would be nice, especially for electronic monographs, if a physician or clinician could click a hyperlink and be transported to what exactly -- they've never heard of P-gp; they can click on it, a brief review of what it does.

So that largely concludes my talk. I think, from a clinician's perspective, the ideal drug-drug

interaction label is easy to access and easy to navigate; has minimal jargon -- it's going to have to have some, but the more jargon you have, the less intelligible it will be to most clinicians.

Some degree of structure, I think, is actually helpful; some sense of the severity of risk, even though that's sometimes a very patient-specific decision, and there are drug combinations that are absolutely indicated in patient A and absolutely contraindicated in patient B. This would be helpful. It should not include archaic drugs or drugs that don't interact or drugs that are simply reported yet lack a plausible mechanism of interactions.

It would be nice if we could link, especially in the electronic age, to more information -- link to case reports, link to reviews, link to PubMed, link to something that gives you a sense of the magnitude of risk if in fact that's available; and importantly, some management suggestions.

With this digi-clarithro, use a different

antibiotic. Monitor the patient. Maybe empirically reduce the dose of digoxin, which those are all reasonable things to do, but many docs won't appreciate that as they're sitting in their office trying to figure out what to do.

So I'm not sure if that's what you wanted, but that's what you got. And thanks very much for inviting me to talk to you today.

DR. BARRETT: Thank you so much, Dr. Juurlink. I think you really framed the setting for our future discussions very well.

We're going to move on to the FDA presentations next, and then we'll have time for clarifying questions afterwards. With that, I'd like to introduce Dr. Kellie Schoolar Reynolds from the FDA.

FDA Presentation - Kellie Schoolar Reynolds

DR. REYNOLDS: Good morning. So now we get to see how close the FDA labels are to the ideal that we just heard about.

Just a little bit about the goals of the information for drug interaction information and

labeling. I'm sure any of you who have looked at the drug interaction labeling, you see that there's a lot of information there, and it is sometimes quite detailed. But ultimately, the goal of the information is to inform the healthcare provider. We recognize there may be multiple audiences who read the label, but in the end, we want to inform the healthcare provider.

The source of information for the information in the labeling about drug interactions, there may be in vitro or in vivo studies that are conducted and submitted to FDA that reviewers review. There may be predictions and extrapolations -- we can't study every single possible drug interaction -- and sometimes literature, which you'll hear about in the next presentation. And the information, before it goes into the drug label, is reviewed by FDA reviewers.

I'm going to quickly go through the different sections of the label that may include drug interaction information. It is spread throughout the label because it is for multiple

audiences.

The first place that you will see drug interaction information is in the highlights section of the label, and the highlights section is about a half page on the first page of the label, and it's supposed to highlight the information that is considered essential for the healthcare provider.

So if the healthcare provider only reads one part of the label, hopefully it is the highlights section, and if there's more details you need to see, there should be a reference to that section of the label.

So as far as drug interactions, the highlights should -- typical information are contraindications -- it will indicate if there are contraindications -- dose adjustments, and potential for serious drug interactions. And there may be a short statement about the mechanism of drug interaction, but there shouldn't be a lot of details.

The dosage and administration section will

include dose adjustments for the specific drug that the label is for. It does not include the dose adjustments for the other direction. And contraindications lists drugs that should not be given with the drug.

Warnings and Precautions, if there are serious or clinically significant outcomes due to drug interactions, it may be listed in that section. Usually not a lot of details, just indicating that there is a concern.

The drug interactions section is one section off the label dedicated just to drug interactions. And in that section, it should include practical instructions for managing the drug interactions.

Then the clinical pharmacology section, that's often where you find the most details because that's where the results of the studies show up, and also information about the mechanism.

So there's a lot we could talk as far as drug interactions and labeling, and we don't have time to talk about all of it today. But just to let you know what the intent of the discussion

today is, we want to talk about the content of the information, the specific wording that we use to describe drug interactions, and the level of detail.

So we'll talk about this for the mechanism information in the labeling, the study results, the predictions that are made, and the management instructions, and then also some discussion about drug interaction information from the published literature.

Topics that we are not going to focus on today very much -- one is the appropriate section for the information. It may come up during conversation because it's kind of hard to avoid during the discussion. But we really don't want to talk that much about where to put the information. We just want to talk about how it's worded and the level of detail.

We're not going to talk about technical details about the analysis of drug interaction study results. We could have an entirely different advisory committee to talk about that. And we're

not going to talk about technical aspects about appropriate study design.

So next I'm going to go through some examples of drug interaction information in labels. I hope some of it is similar to the ideal we've already heard about, and we know that some of it will not be similar to the ideal that we just heard about.

There is drug interaction mechanism information in the label. And this is scientific, and it probably does include some lingo. The content usually has -- it talks about the enzymes and transporters that are responsible for the ADME of the drug, enzymes and transporters that are affected by the drug, and genetic variation of relevant transporters and enzymes.

This is really just background information for the drug interaction information, and it puts any study results into context, allows you to make predictions, and it may also rule out the potential for interactions with some drugs.

So I just have one example here from the

darunavir label. And in this label, it's divided into two different sections for the mechanism information. It talks about the mechanism for darunavir to affect other drugs, so it's an inhibitor of 3A and 2D6, and what may happen because of that. It may result in increased concentrations of other drugs.

In the other direction of the interaction, darunavir is metabolized by CYP3A, so that's the mechanism. And based on that, there's a certain mechanism that concentrations may increase or decrease. So this is the typical information that might show up as far as mechanisms of drug interactions.

I'm going to give probably six or seven slides showing how we present study results for drug interaction studies. The content of this information is the results of drug interaction studies, and it may also include some study design information just to put the results into context.

The reason that this information is included, we recognize that the physician may not

be interested in this, but it does support the drug interaction management information that is useful to clinicians. And if the clinician is being assisted by a clinical pharmacologist or clinical pharmacist, this information may be important to those individuals.

I'm going to show some tables. That's one format that we use for drug interaction study results. And then after that, I'm going to show several forest plots.

First I'm going to start with the posaconazole label, which has its drug interaction information in tables. And the specific table that I'm going to show is the effect of co-administered drugs on posaconazole, and there is another table that shows the opposite direction.

So the information that shows up is the co-administered drug, the dose and schedule for both of the drugs, and the percent mean change in Cmax and AUC. So you don't have to read this; I am going to focus in on just one column. But just to show you how much information may show up, and this

is probably not the biggest table you're going to see today.

Just to focus in on one row, it shows the co-administered drug with voriconazole was efavirenz. It shows the potential mechanism for the interaction, of that's of interest. It shows the dose and schedule for both of the drugs. And then it shows what the effect is. So there's a 45 percent decrease in mean Cmax, and it also includes the information for AUC, and it shows the variability. So there's a 90 percent confidence interval.

You'll see for all of the examples that I show, it's usually a 90 percent confidence interval for the variability. So one question that may come up is how do we capture outliers? And you'll see that all the examples that I show today, they don't really capture outliers. So if that's something that's important, we need to understand the best way to include that information in the label.

The next example in the table is for the darunavir label. And again, it shows the

co-administered drug, the postulated mechanism for the interaction, dose and schedule for both of the drugs, and you'll see that there was more than one regimen evaluated for some of the drugs.

It has a little bit more information than the previous example you saw. It does show the sample size for the study, and there's an arrow that just summarizes the result, whether it's an increase or a decrease, and then again, the ratio of darunavir exposure with and without the other drug.

So this table is a little bit bigger. We may want to also talk about how many drugs we include the results for, but I'm not even sure if this is the entire table. Or I think there are two tables, so there's twice as much information in the darunavir label as you're seeing here.

Just to focus in on one of the results, this is the darunavir in combination with lopinavir/ritonavir, and you'll see that there were two different regimens that were evaluated. So it shows the results for both regimens that were

evaluated. It shows the sample size of 14 or 15. And then there's a down arrow, just to let you quickly see that there's a decrease in concentrations, and then again, as presented as a point estimate.

So the Cmax, 0.79, you have to be able to do the math in your head and figure out how much of a decrease that is. It's presented a little differently. And it shows it for all three parameters, Cmax, AUC, and Cmin.

Next I'm going to show the results as a forest plot. And in this case you'll see the co-administered drug, so in addition to apixaban, what was the other drug that was studied. The plot shows the fold change, largely what we saw in the table, the 90 percent confidence interval for Cmax and AUC. And this specific example shows vertical lines for the no-effect boundary, so what change would be significant or of concern. And there's also a recommendation.

This is what the entire plot looks like. It's not quite as big as the table. There were

less studies conducted for this drug. And just to focus in on one, you'll see that the interacting drug that was evaluated was ketoconazole, and you can see the dose was 400 milligrams; the potential mechanism, -strong 3A and P-gp inhibitor; and you can see the fold change and 90 percent confidence interval. And then the dotted vertical lines are the no-effect boundary. So because the results are outside of the no-effect boundary, there is a recommendation for a dose adjustment.

The next example shows the opposite direction of a drug interaction, so its effect of mirabegron on the exposure of the co-administered drugs. And so it shows pretty much the same information that we saw in the previous example, but one difference this time is that there's no vertical dotted line showing the no-effect boundary.

Because we're talking about the effect of this drug on other drugs, it's really impossible to show the dotted vertical lines because the exposure-response may be different for all of the

drugs.

So an important thing to remember when you're looking at this type of forest plot is just because one change is bigger than another, you may interpret it differently, depending on what the co-administered drug is.

This just focuses on one of the examples. And in this case it was one where there was very little drug interaction, so the results are included. But there's no recommendation because there wasn't a significant drug interaction.

In some cases, there are complex scenarios that are evaluated, and we haven't quite figured out how to fit them into a table or a forest plot. And these are scenarios where it really would be nice to come up with a simple way to include the important information, but also make it understandable.

The type of scenarios include interactions that differ between poor metabolizers and extensive metabolizers; interactions that change over time; interactions that may differ with concomitant organ

impairment, so if it's a drug interaction plus kidney impairment, drug interaction plus liver impairment; or interactions of patients who take three or more drugs, but all of the drug interaction studies were done in pairs. And we don't have examples for all of these. These are just the scenarios we thought of. And I'll show a few examples.

So the first example is fesoterodine. It's a substrate for CYP3A4 and CYP2D6. And the effect of a strong 3A inhibitor on Cmax and AUC was evaluated, and 2D6 extensive metabolizers and 2D6 poor metabolizers. And this is information that's included in the results section of the label, and it's included in a paragraph so I just pulled out the relevant information.

When ketoconazole is co-administered to extensive metabolizers, it has the result there of a doubling of Cmax and AUC, a similar result in poor metabolizers. However, it also points out that in poor metabolizers versus extensive metabolizers, not in the context of a drug

interaction, the concentrations are higher, which we would expect.

Then it links all of that information together in case that's important, 2D6 poor metabolizers receiving ketoconazole compared to extensive metabolizers not receiving ketoconazole, it's a 4.5-fold increase.

So there's a lot of information there. We would need to determine which information really is most important for the clinician, and how do we provide it in an understandable way.

The next example is for bosentan. It's metabolized by CYP3A4. There was a study of ritonavir -- or it was a combination that included ritonavir -- on bosentan, and it changes over time. This is important to include in the label because clinically, it's two populations that may exist together. There are HIV patients with pulmonary arterial hypertension, so it's important that we understand how to co-administer these drugs.

The following paragraph is from the approved labeling for bosentan, and it indicates that a drug

interaction study was done. It was a multiple-dose study. And the results differ depending on which day you looked at the interaction.

So on day 4, there was a 48-fold increase in the bosentan concentrations, but by day 10, it was only a 5-fold increase. And I'll come back to this example when I talk about dosage and administration instructions.

Next I'm going to talk about drug interaction predictions. It's not possible to study every single possible drug interaction, so sometimes we make predictions based on other studies.

The first example I'm going to give, the tamsulosin hydrochloride example, it's a substrate for CYP3A4 and CYP2D6, and two of the studies that were conducted, there was a study with a strong 3A4 inhibitor, and you can see the results there, Cmax and AUC, a little bit more than a doubling.

Then there was a study with a strong 2D6 inhibitor; Cmax increased 30 percent and AUC increased 60 percent. However, what was not

studied was 2D6 poor metabolizers with a 3A4 inhibitor. And because we typically don't determine who is a poor metabolizer and that may be of concern, there is a recommendation not to use strong 3A4 inhibitors, where really the concern is only in the poor metabolizers, not in the extensive metabolizers.

Then also the effect of co-administering a 3A4 and 2D6 inhibitor together was not evaluated. So there is a potential for a larger interaction there. And although it doesn't say don't co-administer together, there is a recommendation to use caution in that case.

The next example is rivaroxaban. Rivaroxaban is a CYP3A4 substrate, a P-gp substrate, and it's eliminated by the kidney. So there are multiple potential mechanisms for drug interactions here, and then you combine the different mechanisms also.

A physiologic-based pharmacokinetic simulation was conducted, and some drug interaction information that's in the label is based on the

simulation.

Here's the specific wording from the labeling. It does come right out and say that it was based on simulated pharmacokinetic data. It doesn't come out and say PBPK; I guess that probably would not be understandable. But it does say it was simulated.

Based on the simulation, patients with renal impairment, then combined with P-GP and weak or moderate 3A4 inhibitors, may have increases at exposure. So that was not studied, but the prediction is included in the label.

Next I want to talk about drug interaction management instructions, and many may view this as the most important part of the label regarding drug interactions. The information for clinicians may indicate that based on a drug interaction, that therapy needs to be adjusted, either dose-adjust or don't co-administer. And there may be specific monitoring instructions, and in some cases nonspecific monitoring instruction.

These instructions are based on the study

results or predictions, so they're quantitative results. But then we also consider exposure-response, both for efficacy and for safety.

I'm going to give a couple examples from the highlights section first. As I mentioned before, the typical information in the highlights section for drug interactions is dosage administration or contraindications.

So for the lurasidone label, there is dosage administration information, and it doesn't include all the potential drugs. It just talks about the mechanism, and then you may need to go to the full part of the prescribing in order to get the specific instructions.

But if it's administered with a moderate 3A4 inhibitor, the dose needs to be reduced. So that specific reduction is included, although it doesn't list all the moderate inhibitors. And if it's used with a moderate 3A4 inducer, you may need to increase the dose, but there's not a specific dose increase listed.

Then also it indicates that there are

contraindications, and it mentions the mechanism but not every potential drug that would be contraindicated; so strong 3A4 inhibitors and strong 3A4 inducers, but it doesn't list all of the drugs.

Another example is the darunavir label. In this case, for contraindications it does list all of the drugs that are considered contraindicated. There's a little bit more information in the full prescribing information, but all the drugs are listed here.

However, for drug interactions, you saw the results table for the darunavir label. That was the one that was two columns long. And you couldn't include all that information here, so the drug interaction part here just indicates there are drug interactions; you need to go to the full prescribing information for more information.

As far as the dosage administration section, this is where specific dose adjustments for the drug that is the subject of the label is adjusted in the face of drug interactions. So that

information would go here.

This is the example that I talked about before, where the drug interaction differs depending on which day you look at it, whether day 4 or day 10. So if you are starting bosentan in patients who have already been taking ritonavir, then you have a specific dose adjustment. And this is because ritonavir inhibition has also been combined with induction over time, so you can do the dose adjustment.

However, the second example, this is where you would have the 48-fold increase in concentrations, which is of more concern. So in order to avoid that, you need to discontinue the bosentan before you start the ritonavir so that there's not as much bosentan on board when you start the ritonavir. Then you give the ritonavir time to have the induction, and then you can start it back with the dose adjustment.

So this is the dose administration section for the guanfacine label, and it has several different scenarios. So the best way to organize

the information was to put it into a table. You do have to stop and read through the table to understand what all of the scenarios are.

They're looking at the co-medications that they're concerned with or strong 3A inhibitors, or strong 3A inducers because the drug is a 3A substrate. And there's several different scenarios that are important.

One is when you're starting the guanfacine when the other medications are already on board. So there's a specific dose adjustment in that case. Or if you've already started the guanfacine, you could continue it and add another drug; that's a different scenario, that's outlined here. Or if you're going to stop the guanfacine, take it away -- or you can stop the co-medication but continue the guanfacine.

So there are three different scenarios, and you do have to stop and really understand which scenario you're dealing with in order to understand what the dose adjustment is.

This is the contraindications information

in the darunavir full prescribing section, contraindications section. And there are nine different rows; I've only highlighted two of them here, but all of them include similar information.

In the highlights section, it just listed all the drugs. In this case, it also includes a clinical comment about the reason that the drugs are contraindicated, so just a little bit more information. And some drug labels do include clinical comments about contraindications, and others just list the drugs and indicate there may be something serious that occurs, but it doesn't include the details.

Now I'm going to talk about a few other sections of the label that include management information. And I think I'll get ready to show you the biggest table that I'm going to show for my entire presentation. So this will be even bigger than the one you saw before.

This again is for the darunavir, and it's an HIV drug, so we expect to see a lot of drug interactions. This table shows expected and other

potentially significant interactions, so it's interactions that were studied and also some that are predicted. You'll see the co-administered drug, the effect on the concentration of either drug, and then the clinical comment. This is actually two columns, so it's twice as long as it looks up here.

Just to focus on one of the interactions, you can see the type of information that's included. In this case it's darunavir combined with lopinavir/ ritonavir, and you can see that in this case darunavir concentrations decrease and lopinavir concentrations do not. But it's not possible to give a specific dose adjustment, so in this case the clinical comment is just the fact that we don't know what the appropriate dose adjustment is.

I'll go through a few of the other comments from this same label. One, with antimalarial drugs, there's the potential for QT prolongation. So that's just highlighted without a specific dose adjustment. With warfarin -- this may be one of

the cases where it's something that we already know -- but when you give darunavir with warfarin, you need to continue to monitor the INR.

This is a comment that has a little bit more specific information. When you give darunavir with the statins, it indicates that you need to titrate atorvastatin, pravastatin, or rosuvastatin dose carefully, and you should start with the lowest necessary dose, which may or may not always be the case. But particularly when you're giving with darunavir, you should do that. And it has a specific recommendation for atorvastatin to not exceed 20 milligrams per day.

This is the last example that I'm going to show, voriconazole. And this is clinical comments for when you give -- the effect of other drugs on voriconazole pharmacokinetics. And the information that's included are the drug and drug class for the concomitant medication, the mechanism of interaction, the effect on the voriconazole plasma exposure, and the recommendation for the voriconazole dose adjustments. So still it's not

as big as the darunavir label, but it's a lot of information.

Just to focus on one of the interactions, when you give voriconazole with HIV protease inhibitors -- so this is covering the entire class of HIV protease inhibitors -- it highlights that, and the potential interaction is because of CYP3A inhibition. And there's in vivo information for indinavir, so that's mentioned here. "In vivo studies showed no significant effect on indinavir on voriconazole." So in that case, we know that a dose adjustment is not needed.

However, the other HIV protease inhibitors were not studied at the time this example was created. And in vitro studies demonstrate a potential for inhibition of voriconazole. So in this case we're not certain that the other drugs don't have a significant interaction, so frequent monitoring for adverse events is important here because there may be an interaction that has not been detected.

So those are all the examples based on

information that is submitted from studies that drug companies have conducted that we review. Next Lei Zhang is going to talk about inclusion of literature-based drug interaction information in the label.

DR. BARRETT: Lei?

FDA Presentation - Lei Zhang

DR. ZHANG: So as Kellie mentioned earlier, there's various sources of drug interaction information that FDA may review and include in the label. Here are just some examples. They could be either from dedicated drug interaction studies or case reports that maybe happened during clinical practice.

In terms of dedicated drug interaction studies, they can be either conducted by the sponsor during drug development or postmarketing, or sometimes they came also from literature data. Most of them, they are conducted by investigators.

In some cases, full study reports may or may not be available. And a lot of times, these studies are conducted postmarketing when the drug

is on the market. So today's discussion is going to be focused on the middle category, which is the literature data that are mainly initiated by the investigators.

So according to the CFR 201.56(a)(2), the labeling will need to be updated when new information becomes available that cause the labeling to become either inaccurate, false, or misleading.

So historically, those literature drug interaction information are being incorporated into the label, especially if they have a clinical impact, to guide the safe and effective use of therapeutic drugs.

But we also see drug interaction reported in the literature may not be included in the drug labeling. There could be various reasons. Two major reasons could be there may be a time lag when the study was reported and when the study was being thoroughly reviewed by the FDA to put in the label; and also, we observe the quality of the data from the literature can vary based on either study

design, or how they conduct the study, or how they interpret data and analyze the data.

So the quality may not meet FDA standards for us to feel it's warranted to put them into the drug label. So that could be the factors that need to be considered.

Why I want to bring this topic to today's discussion, because we do observe there are possible differences that exist in the criteria that may be used in terms of how FDA include those literature data into the label, versus how a scientific journal decide to publish that particular drug interaction study, versus we know there's various curators of various drug-drug interaction databases; they also monitor a lot of literature data and decide to input into the database for clinical decision support.

So potential differences could exist, and those heterogeneity in the labels or in the sources of information could create a challenge to the clinicians, who may attempt to integrate or get dose information to guide their therapy.

So we think it may be worthwhile to come up with a criteria that a community can accept, that FDA can adopt in that can ensure consistency, including the important drug interaction information, into the label.

So the purpose of today's discussion is mainly to discuss the criteria or factors to be considered in determining whether and how to incorporate literature-reported drug interaction information into the label, and hopefully the similar criteria may be set up for evaluation of drug interaction literature data for various projects to aid clinical decision support.

Internally at FDA, we had set up a working group in 2011 -- actually, we have representatives from various review divisions -- to come up with some criteria we can use that can ensure consistency, at least among the reviewers, when they review the literature-reported drug interaction data in the NDA submission.

We also see the potential of such criteria may also be helpful on some other initiatives, such

as the one which we just saw mentioned about physician labeling rule initiative, which we are in the middle of converting many old drug labels into the new drug format. The goal is to assist the physician to how to best in fact use the label, and warfarin was one example was presented by David earlier.

Actually, the example he showed is the old format of the label. Recently, in 2011, we did convert warfarin label into the PLR format, which we will manage to use that process to declutter a lot of the drug interaction information. It may not be the perfect way, but we think it's one step forward.

The other things we see the utility could be a lot of herbal drug interaction may not be particularly studied by the sponsor, but they can be reported in the literature. It could be very important during the practice because the herbal medication can be also used by various drugs. So we think this criteria may also help us in assisting to get those drug interaction information

into the label.

So there are many factors. If you talk to different people, they may have different criteria that can be used. So we try to distill down to major questions for consideration during this process.

The first one is -- the big question is, under what circumstances should DDI results from the literature be included in the labeling? So mainly from a clinical perspective.

The second consideration is, what factors should be considered to determine, if we decide yes, we should include them in the label. Then the next question is how we incorporate them into the label based on the literature data, whether they should be included qualitatively, meaning general description of the drug interaction, or quantitatively.

This is a higher level of the incorporation. It means we will put those quantitative information in the label to guide the dose adjustment. I'm going to show you two hypothetical just examples to

illustrate what qualitatively versus quantitatively.

So example of qualitative description of drug interaction in the labeling, which means that we will not put the quantitative PK results -- for example, how many percentage increase/decrease -- in the label, but we will talk about the trend and also make a recommendation in general for dose adjustment.

For example, co-administration of drug A and drug B may decrease exposure of drug B. In this case, drug B is getting affected by drug A, and a dose increase in drug B may be needed when co-administered with drug A. And therapeutic drug monitoring of drug B may be indicated, particularly during dosage adjustment. So this is a qualitative description of the DDI results.

Next we move to the example of quantitative description of drug interaction results in the labeling. So quantitative means we are going to describe what's the exact PK change, along with the relevant dose recommendation.

So example here, same example. If we put it quantitatively, we may say, co-administration of drug A and drug B was associated with reduction in exposure of drug B, and 50 percent reduction in drug B has been reported.

Used with caution, a dose increase -- for example, double of the drug B -- may be needed when co-administered with drug A, and therapeutic drug monitoring for the pharmacodynamic effect may be indicated, particularly during dosage adjustment. So to keep that in mind, I'm going to go through the decision framework that we are going to put today for discussion.

So here's the proposed decision framework to include the literature-reported drug interaction information in the label. As I mentioned earlier, that's the first key question we want to ask, is should literature-reported drug interaction data be considered to be included in the labeling.

So there are two aspects of this question. First question we will ask, are those drug interaction results being reported likely to have

a clinical impact? By saying clinical impact, that would be decided whether there's a potential efficacy or safety concern due to this drug interaction. And this will depend on the previously documented exposure-response relationship and therapeutic range of the affected drug.

The second question is going to be, yes, this study was reported. Whether we think the study design was adequate to understand this particular drug interaction. If the answer to either of these two questions is no, then we will think the DDI results probably need to be further investigated, and we will not review to be included in the label at that time point if we did not believe that either the drug has a clinical impact or the study is adequate.

If the answer to both of these 1A and 1B questions are yes, then the next step we will see whether the full study report, which including full analytical report as well as the raw PK data set available for review because this is -- mainly we

deal with a lot of sponsors. That means that we have all these information available for us to have an overall evaluation of the study.

So now we move to the next. If the answer, the second box, we will move to that question 2A. Then we move to our second key consideration, is if we decide that yes, we want to include that drug interaction into the label, the next question is what factors we need to consider either to include the results qualitatively or quantitatively.

So our question is whether the full study report is available for review. If the answer is yes, then this will default to our standard review process that we will treat as other study reports we receive. But if the answer is no -- because a lot of times we know if it's literature-reported, we may not have the full study report from the investigators -- then the next question we will ask are the essential details of the study, which could include some summary of the analytical report or PK summary available to review. At least we have some information to determine what's the quality of the

study.

If the answer is no, then if we still decide that drug interaction is important or clinically relevant, we might describe the results qualitatively in this case in the label upon the review.

The next step is also if we think the results are so important that we need a clear understanding of the DDI, we may ask the sponsor or applicant to replicate the study if we think the quantitative information is important.

So if the essential detail of the study is available for review, the answer is yes, then we move to another question, 2C, is are the DDI study results consistent with other public literature, or anticipated based on what is known about each drug?

If the answer to this question is yes, we will have more stronger belief of the study results maybe reflect what's the true DDI and its clinical relevance. So we may consider to include quantitative DDI information in the label along with the relevant recommendation, as appropriate,

upon review.

But if the answer to that is no, which means the study may not be what we expected but yet may be clinically important, then we will describe the DDI results qualitatively in the label, if appropriate upon review. And we may even consider to ask the applicant to replicate a study if the quantitative recommendation is important and has clinical safety implications.

I just described to you the proposed decision framework that FDA reviewers may use to follow to ensure consistency when we review the literature data to be included in the label. This is just in a nutshell about this decision tree when I put them all together. It is also in the background brief package, so we will have more discussion later today.

So before I leave, I would like to acknowledge our office. We have a planning committee to put all these topics together, distill down the key questions for the advisory committee to comment on. We also would like to thank CDER

Division of Advisory Committee and the consultant management staff; without their support, we cannot put this meeting here together.

In addition, as I mentioned earlier, we also had a working group two years ago who put this preliminary decision framework to include literature DDI results in the label. It has been evolving since then, but today that's what we present to you.

We also would like to thank our team leaders and review staff in our office, who gave us many suggestions and case examples that help us to put today's presentation together. So thank you so much.

Clarifying Questions

DR. BARRETT: Let's take some time for clarifying questions now. So if I could ask the committee members, if you have a clarifying question, identify yourself. And then when you are speaking, please announce your name.

Before we go to that, though, I do want to recognize to Dr. Muzzio if you could please just

state your name for the record and your affiliation.

DR. MUZZIO: My name is Fernando Muzzio. I am a professor at Rutgers University, and I am a member of this committee.

DR. BARRETT: Thank you.

Clarifying questions?

(No response.)

DR. BARRETT: Okay. I'll start.

Dr. Juurlink -- I know you're still here -- I had a question regarding when you were giving us some background in terms of other sources, and you, I think, articulated very nicely in terms of perhaps the desire from prescribers to have more consistent and more clear material. But I wondered if you could comment on some of the, let's say, Internet-based tools. Are you reluctant at all to consider the information behind the scenes? This is not really necessarily vetted against any other kind of information. What's your perception about the quality of the information that's in some of those other tools that you

pointed out?

DR. JUURLINK: I think that the answer depends on where you go. It's easy to find websites that contain misinformation. It's also easy to find websites that are actually quite authoritative.

So I think it would be important, if there is ever to be some sort of link between a basic monograph and more detailed information, that people who opt to go that route are directed towards more authoritative sources.

So the Web is full of information that is wrong, and I've given you a few examples of that, things posing as monographs that contain information that is simply not correct. So I think the answer to your question is simply, it depends where you go, and so I think we agree that the Web is a dangerous place.

DR. BARRETT: Dr. Venitz?

DR. VENITZ: Yes. Let me ask you a follow-up question to one of your slides, where you talked about how clinicians perceive drug-drug

interactions. Let me tell you how I perceive how clinicians perceive DDIs. And that's based on their training. They know a lot about pharmacology, so all the interactions that you've listed as top interactions are all based on pharmacology or pharmacodynamics.

On the other hand, you also pointed out to us that lingo such as kinetics, area under the curve, isoenzymes, transporters, are things that are typically not taught at a sufficient level, shall we say, in medical school. Is my perception correct?

DR. JUURLINK: I think your perception's correct. I think the extent to which clinicians come to their practices armed with the basic pharmacologic understanding to allow them to interpret drug interaction data is highly variable.

A lot of physicians really don't know anything. And I don't mean that in a critical way. I just mean there's so much to know in medicine, and this is -- even to somebody who thinks about drug interactions with some regularity, to me this

is a daunting topic. So to the family physician in Omaha, they just simply can't be expected to come to their practice with a great deal of information.

I think the question you've raised is an important one, and I think, as this discussion unfolds, I think it's important to remember that we do things for patients, not to patients. We do things for patients.

In general, when we prescribe a drug, we do it for one of two reasons. We do it to make people feel better or to make them live longer. And in the interest of doing that, whatever physicians get when they go to a monograph needs to be usable.

So I think we've seen a couple of examples where sometimes there are -- usability is inversely related to the amount of information that is present. And so I think that that's just another -- I wanted to reiterate that point.

DR. VENITZ: Thank you.

DR. PAU: I do have a question. This is Alice Pau from NIH. I use the label a lot for many different reasons, including putting together drug

interaction tables for our treatment guidelines.

One question I do have for the FDA with regards to the use of data from the literature rather than from the sponsor, what do you anticipate as far as who should be the one to initiate the process of identifying information that should be or considered to be put into the label?

Should it be the investigators themselves coming to the FDA and share with you the information and think that this is important for the label? Or should it come from the FDA looking into the literature, evaluating all the literature out there, and someone within the division decides this particular interaction is important? Or should it come from the sponsor?

So what is the mechanism you anticipate this type of information to be initiated to go into the process and review?

DR. ZHANG: I think it's all of the above because there should be -- because it's the responsibility for both the sponsor and FDA, and

also the investigator. If you think that a drug interaction is very important for the safe use of the drug, yes, I think all of the above.

DR. PAU: The reason I'm asking is that I don't think all investigators are aware of that, and they don't even know how to go about doing that. So I think if we are going to be talking about trying to include the literature information on the drug interaction in the label, then there might be some way to communicating to investigators would be an important thing to do as well.

DR. BARRETT: Any other comments from FDA?

DR. ZINEH: Yes. I would agree with that. I think it would be very helpful to identify mechanisms to make sure that investigators are able to submit this information to us, but with specific criteria, perhaps of quality control, et cetera, built in because there is a question of bandwidth here.

DR. BARRETT: Dr. Flockhart?

DR. FLOCKHART: Yes. I guess my concern here hinges around the uneducatability of the

clinicians we're talking about, having done this for many, many years -- I don't mean me doing it, I mean everybody doing it.

So I'd be very interested in your perspective, Dr. Juurlink, about the value of patient education because nobody's more motivated, usually, than the patients themselves. But I'm not aware of good evidence that we can demonstrate that's really helping.

That kind of segues to a question for the FDA, which is, I think the -- and I'll just say this -- I think the way in which evidence and data about drug-drug interactions are presented in the label influences not only, obviously, what clinicians get, but in the sense that it provides a huge amount of data that might not well be prioritized. It limits the ability of anybody who might want to take the FDA's mission a little bit further and communicate that to patients.

So first to Dr. Juurlink, whether he thinks there is actually something important here; and then whether the FDA has thought about this at all.

DR. JUURLINK: Yes. So as to whether or not the patient engagement is important, I think the answer is an easy yes. All right? A well-informed patient is a useful safety mechanism.

I don't know of evidence that it makes a difference when it comes to drug interactions; perhaps there's some out there that I don't know of. But if I've had a patient on cyclosporin or a patient on warfarin -- these are drugs where I fear both the consequences of too much or too little -- when I send them out into the world at hospital discharge, I don't know what's going to happen to them. I don't know which other physicians or pharmacists they're going to encounter, and I don't know what they might take off the shelf without asking anyone.

So I think it only makes sense to say to a patient on a drug like that, that before you take anything else, please check with a pharmacist. Check with a physician. Better yet, check with a pharmacist.

Just to add one more layer to the Swiss

cheese model that Dr. Bates may talk about a little later on, to me, the patient and their engagement in their own health is one more layer that can hopefully avoid harm reaching the patient.

DR. FLOCKHART: Are there resources you have in Canada for patients that we might not have?

DR. JUURLINK: I don't think there's anything in Canada we have that you don't have here except more ice.

(Laughter.)

DR. FLOCKHART: Well, except the beer, yes.

DR. JUURLINK: No, I don't think so. I think that one resource that comes to mind -- and I don't know the extent to which it's available in the States as opposed to Canada, but in some jurisdictions in Canada, there are province-wide realtime access to prescription drug data.

So in British Columbia, for example, if a patient goes to Victoria and gets a prescription for clarithromycin and they've been in Vancouver getting digoxin for the last five years, the pharmacist in Victoria doesn't -- this information

is readily available to them.

So I don't know the extent to which realtime access to prescription data reduces the likelihood of harm befalling a patient, but it certainly can't hurt. But I think, in general, there probably are no other resources that we've got that you don't, certainly none that I'm aware of.

DR. BARRETT: Dr. Polli and then Dr. Au.

DR. POLLI: I have a question for Dr. Juurlink. I enjoyed your presentation. Dr. Reynolds indicated there's a highlights section of the package insert for sort of summarizing the most important information.

So in the context of what we're talking about here, package inserts, if that highlights section were made supremely excellent, do you think that would have any effect on your observation that physicians in general don't read package inserts?

DR. JUURLINK: I think it probably would. Supremely excellent sounds like an excellent objective. It sounds supremely excellent.

(Laughter.)

DR. JUURLINK: But I think that -- and I was commenting to Dr. Bates after my talk that I think there is merit in the idea of a highlights section and a digging down deeper section because most physicians and pharmacists, when they go to a monograph, don't want to know what the change in AUC is or the change in Cmax is when you mix drug A and drug B. Some of them do. But most of them just want to make a therapeutic decision. They want some guidance.

Probably the single best example of that isn't from a monograph. It's Dr. Horn's book with the digi/clarithro example I showed you. A physician who doesn't know the first thing about P-gp can go to that page and in 60 seconds know exactly what this is all about. And if they want to spend 10 minutes reading more, they can.

So to me that's like a highlights section. And so I think the direct answer to your question is yes, a highlights section that is relatively simple and intended to help make therapeutic decisions would probably do exactly what you've

alluded to.

DR. AU: Actually, the question I want to ask is to someone who's not here, and that's the practicing pharmacist, because when I see my physician, I know I'm allocated 10 minutes or 15 minutes, and I'm out the door very fast. This is reality that we're dealing with in the situation we're in.

So the next person that really should educate me on drug-drug interaction is the practicing pharmacist. And then I reflect on my own experience that when I finished my PharmD degree 41 years ago and started my first career as a hospital pharmacist, and I look at what you presented to me today, and I thought, "Oh, gosh. I'm glad I'm not a practicing pharmacist any more because I don't think I can handle it."

Actually, I'm a science junkie. That's why I spent the last 30 years doing academic science, and I continue to do so. And I love reading this stuff. The problem is, who are we talking to with this label, the whole thing? The pharmacist is the

one. And being the mother of three children, I dealt with pharmacists a lot of times. They never really spent time to tell me what to do.

How many minutes do they have if they're working in a retail setting like in a Walgreens or a Ralph supermarket? They don't have time to tell me. And when I read this label -- when I was coming in, I read this 27 pages of background material you sent me, and I go, "My God. I can't keep up with this." Most of the drugs on the list I never used when I was a pharmacist.

So I think here's the problem. I think we're really not communicating to the consumer. I think that's your best bet, is communicate to the consumer, not the physician, not even the pharmacist, because they don't have time.

So this is a question I really want to ask, is how much time is a pharmacist allowed to spend on educating the patient? And if they're not allowed the time, then should FDA take on this task? And as the first speaker said, put some links up there, but now have it powered by FDA

rather than by Wikipedia, someone that you know has the patient's well-being in mind, and have it done that way.

But also another thing for a patient, I've done a number of clinical trials in my academic work, and I learned a lot from patients. For example, one trial I'd done is to limit patients' water intake for 8 hours so we can reduce urine output.

But one patient taught me -- we said, no liquid. No drinking, we said. No drinking. So he came in and he said, "I did not drink. I only ate milk with my cereal." So I know now I have to change my protocol to say no liquid whatsoever.

So my point is, you don't know what level of people you're dealing with in terms of knowledge, and you have to prepare for that. And a lot of those patients get this huge long list of names that I cannot tell what they are.

It may be more useful to say them, "If you are taking medicine for treating an ailment -" say, hypertension -- "you most likely will be taking

this drug that may have an interaction with this particular drug."

DR. BARRETT: These are wonderful comments, but I would remind everyone we're focused on clarifying questions now for the morning speakers.

So I'll go back to FDA, and actually, Lei, I think this is for you. But my question when you were reviewing the literature data and what's the intention there, most of it seemed to be focused on the classic drug interaction studies done by another investigator outside of the sponsor's venue.

But could you comment on the utility in terms of that same process for pharmacoepidemiologic data, more perhaps surveillance data that doesn't necessarily fall into the same category? But in terms of the value of that information and the rigor the agency brings to moving that information down the decision tree, is that well thought out in your mind? Do you feel that the intention is to accommodate that source of information as well?

DR. ZHANG: Yes. I think it is out of scope of today's discussion. But that's also part of the -- because that's the totality of the data. We cannot ignore that information. Also, we didn't cover the case reports because they do have value, but how we evaluate them, that's going to be a different consideration.

DR. DAY: As a follow-up, for deciding whether to review and then include literature-based studies, perhaps you mentioned this and I didn't catch it. But is there some sense of allowing for the test of time before moving to include something in the label?

So a study may come out and create a lot of interest. But over time, it may turn out that some of its methods were special, and so no one else has replicated it, and so on and so forth.

So there would be no strict amount of time or number of papers. But how does the amount of time that's elapsed and standing the test of time work into your decision framework?

DR. ZHANG: It is a very good question. We

have that kind of discussion all the time because how soon and -- like what type of the evidence we need. So I'd like to hear from the other advisors what their input may be because there's a balance about too much information versus the information you want delivered on time. So it is not one-size-fit-all criteria, I would think. Probably we have to deal with it on a case-by-case basis.

DR. MILLER: Thank you. I'll start by saying it's an honor to be here, and your efforts are quite noble.

I approach this from a perspective of health literacy for the end user or the consumer. And I'll tell a little story about what we teach. We teach clinicians to assume universal precautions, that everyone doesn't know. And we start with simple information: What is your main problem? What do you need to do? And why is it important for you to do this? Those three things.

Can we not take that approach -- and so, stepping back a moment, we don't bludgeon them with a ton of information up front. If they want to

know more after we begin that initial dialogue of the main problem, what you need to do, and why it's important, then they can dig in deeper and learn more.

I think this speaks to the whole issue of having that excellent highlights section because you don't take the framework in that health literacy context for the clinician to that level and say, what is it you need to know? Why do you need to know? What do you need to do? And why is it important to do it?

Because what I see here, as someone that did practice pharmacy many moon ago, I used to think that -- and I was in the Air Force, and I could force information down everybody that came to the pharmacy's throat. I had the ability to do that. They had to stand there and listen to me.

But I realized they weren't listening to me. And what I see is we create these enormous documents, and nobody's listening to that information. That's what I keep hearing. We need to simplify that and have -- we have the technology

to then, if you want to know more, to link to that and go to that and learn and dig deeper if you need that information.

I sat here and I wondered, well, how is some of this information translated into clinical practice, as I listened to the presentations earlier. So I ask that you maybe think about that in terms of a framework, the simplification. Take that health literacy perspective for the clinician. And it's not just for the consumer, but for the clinician. Thank you.

DR. BARRETT: Shiew-Mei?

DR. HUANG: I want to address some of the earlier comments on when do we put information in the FDA labeling. And I want to mention that later on we're going to hear about clinical decision system, which we believe the FDA labeling will be a very important part.

As far as how we update the labeling, it's very important that we keep our labeling updated. But we only have so much resources available, so we have to prioritize them. And I can tell you there

are a lot of instances where, when there's a submission of a drug that's already on the market, either because of new indication, new labeling changes, or others, then this is a good opportunity for labeling update.

Sometimes the sponsor will do a thorough job in updating their labeling, and we can review as usual. At times our reviewers will have to take the initiative to review all the to-do data. And all information-specific study or epi study, as Jeff mentioned, they will all be reviewed in coming up a best labeling language.

Then depending on whether it's a brand-name drug, generic, there will be some discussion with the sponsor, and we come up with the best labeling language. So they're always trying to include either literature or sponsor-submitted. Sponsor could submit literature data as well.

In addition, we also receive many either emails or official letters not exactly in the citizen petition form about why FDA did not update certain labels, sometimes from the investigator,

sometimes from other scientific researchers.

Then we would review. At times we'll invite the individuals coming to the FDA. And we see if that information is very critical; then we will update the labeling. And obviously, you have to go through the labeling process, the modification process.

So timing from its publication until its label, it may not be immediate because there will be a lot of processes in between. Thanks.

DR. BARRETT: So Shiew-Mei -- and this is really for all of the FDA speakers -- as you talk about the labeling process, and in recognizing that this is really a dialogue with the sponsor and reviewing that information and putting that in the appropriate places, but several of you pointed to the fact the recognition that there's multiple audiences for the labeling.

Could you comment? Is there any vetting, though, against the audiences? Do you get feedback from the various target audiences you're trying to achieve? Is that part of the process, or is that

the intention at some point?

DR. HUANG: I'll let Kellie comment on it.

DR. REYNOLDS: During the review for a specific drug, that's usually not part of the process. We do have this forum here. There have been other scientific meetings where we have asked specific populations to comment on that.

I did that for HIV drug labels. Kim Struble and I did that probably six years ago now, where we had clinicians comment on what they thought of the drug interaction labeling. And we are starting to engage specific patient populations also. FDA has started initiating conversations with different patient populations.

We had already done that with the HIV community. So we had received specific comments about labeling from them. Usually they ask for more, to tell you the truth, but it depends on the patient population. So that may be one reason that you see different levels of detail in different labels.

DR. ZINEH: Just to add to that, it's

probably important to provide some insights onto internally how labels are updated. So it's not like Shiew-Mei can pick her favorite drug interaction and put it in a label. This has to go through a multi-disciplinary review process, which includes clinical pharmacologists. It could include physicians, pharmacists, biostatisticians. It really depends on what the issue is.

For drug interactions, it's mostly our crowd as well as our counterparts in the medical side of the house. But there's a multi-disciplinary staff that has to look at these label changes that are assigned to specific drugs and teams. So again, it just depends on what the label change is.

That's a very heterogeneous community. And what you see as the end result of a label is a series of internal negotiations of what these multiple parties think is important to communicate from a public health standpoint.

Then you have to negotiate with the holder of that drug, the drug company, to say, this is what we think your label should look like, and

there's a negotiation on what that language should be. Of course, we have mechanisms -- if we firmly believe that a label should look a certain way, then we have mechanisms to make sure it looks a certain way in terms of the information and what goes into it.

So I think this hopefully provides insight onto two issues. One is the multi-disciplinary nature of the label change; and two, any lag time that might occur; and thirdly, why some labels don't even get updated.

Because there might be something very compelling in the literature, but when it goes through this multi-review process, it doesn't necessarily pass criteria where everybody believes, one, that it's true, and two, that it's clinically meaningful or useful information to the public.

DR. BARRETT: Dr. Au, and then Dr. Cook.

DR. AU: In the flowchart you presented, it gave very clear decision points that you make, especially with the level of evidence that you have to deal with. So there's one aspect where you talk

about very conflicting data; you will go back to the sponsor, maybe, and ask them to do extra study or clarify.

What if you do not have the ability to convince the sponsor -- say it's a generic drug -- to do this clarifying experiment? Does FDA have a mechanism -- do you have a mechanism that you can go to, issue an RFP, ask the field to clarify or to confirm two conflicting data that are obviously important enough to look further into?

DR. ZINEH: I invite my colleagues to respond as well because I think they're involved in multiple mechanisms that could facilitate that.

To your first point, depending on what the drug interaction is, if we're going to keep it in the drug interaction realm, companies can be compelled to do those, especially if there's a safety concern there. So there's the FDA Amendments Act that allows us to actually say, for safety reasons, we really want to see this. That raises to a specific showstopper bar. Right?

Additionally, there's internal capacity to

do some research, specifically teasing out -- usually teasing out mechanisms of metabolism, mechanisms of drug interaction, but not necessarily per se -- and I'm talking about internal FDA labs and experimental capacity -- not necessarily to do drug-drug interaction studies, although we do have, through other mechanisms like what's called the CERSI mechanism, Centers for Excellence in Regulatory Science, collaborations with other institutions that have that ability.

If it I think rises to a drug-drug interaction issue of major public health importance, I don't see any reasons why we couldn't reach out to the community to do those studies. It just becomes then a capacity issue of whether or not investigators have the resources to do those for us.

DR. ABERNETHY: Jeff, I think you raised an important question, and that is how to think about observational data in comparison to prospectively and randomized sorts of data.

I think that it would be very interesting to

hear some discussion from the group about that because I think this is not the only sphere that we're trying to understand how to make use of observational data.

DR. BARRETT: Jack?

DR. COOK: So I'd like to respond to a question that actually Dr. Zhang asked. And again, thanks for your presentation. I thought it was very well laid out. And that comes at one of the end steps, where the sponsor will be eventually asked -- or somebody will be asked to do a study to confirm it quantitatively.

In the case where it was an unusual one, it all has to do with this time that people are wondering about to establish a drug interaction. I think that there is also an incumbency on those involved to figure out the why. If you had that, it would be much -- you wouldn't have to depend on time. Right? You would get both the quantitative answer, and you would understand why the drug interaction occurred.

Now, eventually, to my question. Since

there are usually two drugs and usually two sponsors, which one do you ask?

(Laughter.)

DR. COOK: The reason I ask that is -- I know I'm going to turn it back and speak as a particular sponsor -- I'd like to know, and I'd like to be involved in that. Because there's at least a 50/50 chance that I don't know something about my drug, and I think that's important. And please don't use the usual, "That will be a review issue."

DR. ZINEH: I think, if I understand the question right, it's how do we ensure cross-label consistency? You have a victim drug and you have an offending drug, and how do you -- am I understanding?

DR. COOK: Well, I'm not so concerned about -- well, cross-labeling consistency is what we need to strive for. But how do you decide who's the owner? I actually think you have two owners because one of the two entities -- in this case, there's something we didn't -- if it's true, the

interaction is true, and that's why you do the repeat study, you don't understand why. And I think both should be involved because somebody needs to learn something.

DR. HUANG: If this is something new that this drug has been recognized as an inhibitor of certain enzyme or transporter, which we don't know, if the reported study, the substrate we already know, a substrate of certain drug, a certain enzyme or transporter, then we wouldn't ask the sponsor for that victim or substrate drug.

We would ask the sponsor for that very important inhibitor because we're going to extrapolate, and we will modify the labeling of that first. Kellie can comment on cross-labeling. But it's very important that one of the drugs has that information, or at least if we confirm that's the case.

Then later on, once you have any other drug that's affected by the pathway that's affected by this drug, then you will be able to know because we're going to hopefully indicate that this drug is

a strong inhibitor.

But if there's a new pathway -- for example, a new molecular entity -- now all of a sudden we say it's a 2C19 drug, but in the past we always thought it's 3A, then it's very important to talk about the sponsor of this victim drug; especially maybe it has certain adverse events or efficacy that will be affected by the other -- what is that name of that? Precipitant -- perpetrator drug. Then we will ask the sponsor.

DR. COOK: I just had the pleasure of reviewing a paper about two old drugs, and there was probably something that needed to be learned about each drug that the authors did some very nice work on. So that's a case where I would encourage it would probably be a good idea to talk to both sponsors rather than just one.

DR. ZINEH: Yes. And that's done. But you do raise a good point about the challenges of updating very old labels. Sometimes you can't even find the original NDA holder for drugs that have been around for decades. So it's a fair point.

DR. BARRETT: So after your no-fault insurance policy on the interaction part -- I think that's what Jack's calling for -- let's go to Dr. Pau and Dr. Muzzio, and then we'll take a break.

DR. PAU: I just want to -- I know that Kellie knows that I want to reemphasize the importance of cross-label referencing. I have made many mistakes when I only go to one label and didn't find an interaction.

I know that there are lag time between, and there have been occasions where, when I asked the antiviral group, they didn't realize that another label had changed that involves the antiviral drug.

Oftentimes clinicians will only go to -- let's say they're starting a new drug. They go to that particular label to make sure that the list of the drugs the patient is on, there is no interaction. They might not go to every single label of the 10 drugs that the patient is on to see whether there are changes in those labels.

So I think it's extremely important for the

consumers, for the clinicians, that whenever there's an important interaction, I know that when a new drug comes out they have done interaction with, let's say, 20 drugs that you put into a new label.

The sponsor may not go to those 20 companies and let them know that we found this significant interaction, and then the 20 drugs will be changed in their label. But the best, if the FDA can, the most significant interactions, to reach out to the other sponsor and make them aware of that to make sure that that is in the other label, it will really do a major benefit and major impact on the consumers.

DR. REYNOLDS: We do have an internal process where we try to maintain consistency, and the process is for -- within clinical pharmacology, the clinical pharmacology team leaders are supposed to communicate with each other. And it is only for the most significant interactions, and I guess where things may fall through the crack is how do you define the significant interactions?

The way we define it is if it's a contraindication, a warning, a dosage adjustment. We definitely inform the other clinical pharmacology team leader. Then they go through the clinical division that they work with.

So there is a lag time, of course; it does take time. And I guess the other place, there are some labels that are more detailed than others. So we have to make sure that all the clinical divisions agree on the type of drug interaction information that should go in the label. But we definitely agree that that's important.

DR. MUZZIO: I missed some of the presentation, but in looking at the meeting materials, I have a two-part comment.

It seems that a lot of the discussion is in terms of two-way interactions or pairwise interactions. Right? Drug A and drug B. And in some cases, you even mentioned some foods. But in many of those pairwise interactions, some of the same mechanisms are repeated over and over for different interactions.

So that suggests that, to a significant degree, this could be a network problem where things interact in higher orders, too, three-way, four-way interactions.

I know that the two-way interactions are complicated enough. I'm not trying to make it harder. But there are tools that come from other areas in science when people use network models to try to organize this information so that they begin to see some of these three-way, four-way mechanistic interactions.

You were talking about how to make this information available to the public or to physicians. That's something that conceivably could even be a tool that is in a computer that could be immediately invoked to see, what if A interacts with B in the presence of C? Over time you build it up, and then you know, well, D is going to be affected, too. But somewhere you have to have a framework to put all that information together.

Has there been any thought to building

something like that?

DR. ZHANG: Yes. I think we -- right now, our drug interaction guidance, we kind of address that because if we can understand mechanism, that's one way to connect the drug. That's one way of doing it.

Also, we talk about how we classify drug as strong, moderate, mild CYP inhibitor so we can translate that information without another DDI study to other drug that fit into those categories. So other things Kellie has mentioned is maybe the modeling, PBPK modeling, which we can connect multi-factor together without a study.

So these are multiple ways of doing it. So I just wanted to comment.

DR. ZINEH: Yes. I would add that the closest thing we have to multi-dimensional assessment is things like PBPK, physiologically-based pharmacokinetic modeling.

But that doesn't really answer your question, which is how you have a live -- do you have a live realtime data set where you can add

inputs and understand over time, I think, what the clinical condition is, what the pathways are, and how those things interact?

It's a major problem about how do you get dynamic information into a static system, which is the drug label. And this is the thing that we struggle with all the time. So I'd like to piggyback a question onto that after you're done elaborating.

DR. MUZZIO: So maybe to clarify, I'm looking at this thing as a multi-dimensional data set. But what you end up seeing is a projection of that multi-dimensional data set onto a 2D space because you're looking at two-way interactions. You might not even know the dimensionality of the data set. But there are methods that come from physics that have looked at that question.

I have a very complex set of data. It looks like there is a hundred factors. There might be eight that matter. How do I actually extract that information to start with? How many factors do really matter, and how many are just covariants and

things like that? And this problem seems intuitively a good problem to be approached that way.

DR. BARRETT: Shiew-Mei, please.

DR. HUANG: I think it will be very helpful if the committee can provide some suggestion how to display this type of information in the labeling. Kellie already has shown some example on, I think, fesoterodine when you have 3A and 2D6. So she's essentially using 3A inhibitors and 2D6 genotype to see the interplay.

When you have one factor with this, you're taking inhibitors, you poor metabolize it, what happens? When you're taking a strong inhibitor or a moderate inhibitor -- so PBPK has been used to predict the outcome. But the way it's in the labeling, it's in text. So what is the best way to display that kind of information?

In addition, a patient has other concomitant disease or organ impairment. She uses rivaroxaban, as an example, renal impairment plus 3A. But if you have a drug, 3A, 2D6 renal impairment, or

others, how do we put that information?

Are we considering something like a warfarin dosing? But that's outside the FDA labeling, where you actually have a website. You can enter information, the genotype 2C9, genotype VKORC1. What other concomitant medication the patient's taking? Is it female? The age? The INR range? Et cetera.

But that I believe is outside the FDA's labeling unless we are endorsing a certain dosing regimen in the labeling. But I would like to hear your comments on how best to present in the FDA labeling because the labeling is what we're discussing today. Thanks.

DR. BARRETT: Okay. This is a good comment to end our morning discussion on. So we're going to take a 15-minute break now. So if everyone could come back in 15 minutes.

(Whereupon, a brief recess was taken.)

DR. BARRETT: We're going to hear from Dr. Tricia Lee Wilkins next, begin the rest of the morning session.

Presentation - Tricia Wilkins

DR. WILKINS: Good morning, everyone. My name is Tricia Lee Wilkins. I am with the Office of the National Coordinator for Health Information Technology, the Chief Medical Office.

I was told that I have 10 minutes, so I'm going to talk very fast and try to get through all of this, not too much, but have a listening ear, and I'll talk a little bit at the end about some implications about what we're doing. I was also informed that not everyone here understands what ONC is and what we do, and so I'll talk a little bit about that as well.

The Office of the National Coordinator, we have two main functions: adoption of electronic medical records. We also focus a lot on standards and certification of electronic health records. That's that second bullet there. And we also are involved in promoting Nationwide Health Information Exchange -- that's two different grant programs -- on the state and local level.

The Chief Medical Office, we are primarily

charged with taking care of health IT safety, usability. We also do clinical quality as related to electronic quality measures. And we are certainly the voice of clinicians relating to the use of health IT products.

What is a meaningful use program? We work in conjunction with the Centers for Medicaid and Medicare. This is an incentive program whereby there are certain criteria that constitute meaningful use, and providers can receive incentive payments for using their certified EHR technology in a meaningful way.

There are stages to the Meaningful Use Program, and the big red just highlights what the point is. Stage 1 meaningful use was a 2011 addition. It just focuses on adopting these tools, so getting providers from a paper-based system to an electronic-based system.

The 2014 edition, which is stage 2, which will roll out in 2014, we are focusing on exchange. We're also looking at closing care gaps, referral loops, having more access of information to

patients. And stage 3, which is forthcoming, will focus a lot on improvement.

What's the scope of the EHR incentive program, meaningful use program? This shows you an idea of how many providers and hospitals are involved or enrolled in this program. So this is the reach that our program has. If you think about a provider who has an electronic medical system, they are most likely enrolled in our EHR incentive program. Most likely they're using a certified meaningful use product.

I want to talk a little bit about what this means as far as the impact on e-prescribing, and then we'll shift gears into what this means for drug-drug interaction alerting.

So prior to, in 2008, and after the advent of the stage 1 meaningful use, we can see it's a huge jump. We went from about 7 percent to 57 percent. And many things can contribute to that, but obviously, I think the Meaningful Use Program has had impact in that as well.

So there's increasing opportunity for

drug-drug interaction alerts through the work that we're doing in certifying these products and enabling clinicians to have access to CPOE and those kind of functionalities.

If we look specifically at what's been happening in the outpatient ambulatory care setting, outpatient physicians, here you can see there's also an increase in their use of computerized order entry, e-prescribing, drug-drug interactions right here. That also can be attributed to the EHR incentive program. You see the same increase with that as well for the hospital side here.

Specifically, what are we really doing? We certify EHR vendor products. And so if you are a vendor who makes an electronic medical record product, we certify standards and criteria that you have to meet, and functionalities, and based on that, providers and hospitals know that you are a certified product that they can then purchase and use.

Then for providers and hospitals, we also

have criteria that must be met in order for payments to be received. So using a certified EHR product, they then have to meet a sample of core -- well, they have to meet the core objectives and then also some menu options.

I want to focus in on some sample core objectives, in particular the clinical decision support item. In the 2014 edition, here is where drug-drug interaction alerting resides. So in the 2011 edition, drug-drug interaction alerting had its own separate objective. Here it's rolled up into clinical decision support.

This is a big slide on that particular criteria. It's right here at the bottom, and we'll zoom in for that. So what are we asking or requiring of providers to do?

They have to have a drug-drug and drug allergy interaction alert that is displayed or delivered to the provider in electronic and automatic fashion. So this does not require the provider to have to prompt to receive this information. It should be automatically displayed

to you based on the patient's medication list and based on a patient's allergy profile.

We have also added these features here, and these are adjustments. We are allowing the severity rating of these interactions to be adjusted. We're requiring, though, that that is limited to only specific individuals given that authority.

So this is not any provider who can just say, I want to turn on -- well, we're not turning on or off anything. This is not the ability for a provider to change a severity rating based on their own preference, but this is only given to some administrator in that setting to be able to do this.

I want to touch on some ONC-sponsored work. This here is work that was sponsored and done with RAND. This is a high priority drug-drug interaction list that was worked on. And so the idea here is, can we create a minimum or a floor for drug-drug interaction alerts? We know that there's inconsistency between different knowledge-

based vendors and how this information then comes to providers and how that's received.

So this work was done, and it convened a variety of stakeholders, a variety of experts, whether they're from industry, from academia, from actual clinical practice, to review a list of medications deemed to be a high/high severity rating, and then to go through and to distill those down into drug-drug, drug-class, and class-class interactions.

The final result was a list of 16 high priority lists. I'm going to not talk much about the study itself. I want to get to the implications. And I will move on to the next set of sponsored work that I think is worth noting.

So we had work that sponsored creation of the high priority list. This next set of work, again sponsored by our office through RAND, identifies a list of drug interactions that should be non-interruptive. This does not mean that information should not be presented to a clinician; it means that the presentation of that information

does not interrupt the clinician's work flow.

The idea there is also that this reduces alert fatigue and increases likelihood that these alerts are actually taken seriously, are not overridden, and that we're not now going into the realm of not being safe or having effective alerts.

So this work was also done using a group of experts who reviewed alerts at one medical center. They took a group of alerts that were overridden about 90 percent of the time and then distilled those down again to the same as well. And this was the resulting list here.

Again, I won't focus in on the methods here. We can talk about that at length or ad nauseam if you'd like to, but I want to focus in on what the policy considerations are.

So we have these two lists that we sponsored their creation. Obviously, this is the beginning of understanding what some of these lists could look like. But there are several things to understand, at least from our perspective.

We are not clear, and we're not sure, how

these lists are being adopted or used, or what the desire is for them to be adopted or to be used. And that's something that we need to set up some type of feedback mechanism where we can understand how knowledge vendors, how academic medical centers or folks that have their own custom systems might be utilizing these.

Obviously, there's implications around the membership of drug classes. So there's differences in how knowledge bases assign membership and assign severity ratings, and that's something that hinders us setting the floor across electronic medical record systems when there's differences in how the knowledge bases themselves have these drugs assigned.

The third bullet here about certification, so ONC, we certify EHR vendor products, and we create standards for meeting full use. Presently we do not certify knowledge-based products or knowledge-based content.

So there's a big distinction there in these lists and how the work that we're interested here

can be used and uptaken by the industry and by the market as a whole because we don't do that. Knowledge-based vendors operate outside the realm of ONC certification, and reasonably so, because there's certain criteria they have to follow that aren't beholden to our policy-making.

Stewardship and maintenance. I think these lists are important for us to understand. But who owns this. Right? Who owns this? Who has the resources or the bandwidth to update these lists? If you think about the timeline for the meaningful use program, incentives are paid out on a yearly basis.

What does that mean when we have updates and changes and new pharmacologic agents being added to the market? And what does that mean then for what we might want to do in a particular stage of a meaningful use program?

I want to talk a little bit about usability and safety considerations. Alert fatigue has huge implications for safety. If providers are overriding information, then that's a problem. I

heard a lot in the panel discussion on the label itself. But obviously, for all intents and purposes, these EHR systems are the label for a clinician. These are the electronic version of that information displayed to a provider at the point of care they have to make decisions. And so I think it's important that we realize that the labeling information ends up being delivered to clinicians through this fashion.

We are not at a point consistently where we have specificity and sensitivity. These drug interaction alerts, are they sensitive enough to be tailored based on a clinical metric or patient information or current lab value? No.

Are they specific enough to identify or exclude certain drugs within classes, or do they just lump everything into one category and then the clinician is now forced to take time to figure out whether or not their drug is actually going to be an offender or not?

We are particularly interested in applied human factors and the display of these EHR systems

and tools. And again, usability is important. The clinicians, depending on how these alerts are displayed to them, may or may not be received the way we intend.

So although we've certified a certain functionality in standards, we do not certify to certain designs. And I think this is an appeal for those of you who work in these areas to help inform us. We are very much interested in getting to a place where we can say definitely that certain designs, layouts, appearances, and displays are better suited for uptake and responsiveness to these alerts.

Huge implications for legality of turning on or off DDI alerts in an EHR system. Again, for the 2014 edition, we are not allowing -- well, we have not certified for folks to do that, but we are allowing the capability for the severity ratings to be adjusted.

I also want to say a little bit about federal alignment. I think that we have to make sure that we're not being duplicative in our work.

I wanted to highlight that AHRQ, another federal partner, who is working on the same area and evidence, content usability, we talked a lot about the evidence.

I heard Dr. Zhang talk about criteria for including studies and literature to support a drug-drug interaction, so I would just encourage -- I see Dr. Malone here -- that we make sure that we are working together for the same agenda when there are other agencies who are also working in this realm.

I heard also in the panel discussion a lot about how do we deliver this information to the end user, that being the customer or the consumer or the patient? I want to say that we are working hard to have access to patient information for patients. A lot of that is playing out in the realm of patient portals.

So I'd be interested in hearing more discussion about how we can allow patients to view this information on drug interaction or drug information, whether it's through an info button

or some other link out through these patient portals.

I think the take-away from this presentation, and I hope I'm staying under my 10 minutes, is that again we are talking a lot about labeling here. And again, these electronic medical records and systems and tools, for all intents and purposes, these are e-labels, if you would, for providers.

This is how this information is being used at the point of care. And I think that it's -- we want to work with you all to understand how we can work with the vendors, EHR vendors, to make sure this information is displayed appropriately, at the right time, and in a way that's not going to create a safety hazard in becoming over-burdensome or creating alert fatigue, which would then be counterproductive to what we're all here seeking to do.

So I think I'm done now. And if there's any more questions on what we're doing, certainly you can just email me or we can I think take follow-up

questions. I think I'm at my time now. Thanks.

DR. BARRETT: Thank you.

We're going to hear from Dr. Bates next.

Presentation - David Bates

DR. BATES: Thanks so much to the committee for the opportunity to present to you. And I'll note that the FDA's mission is to protect the public with respect to food and drugs, and I believe to do that effectively, it's going to be essential for it to think very carefully about this new electronic world because things have really very dramatically changed in the last five years, as Dr. Wilkins just underscored. And I think this may require some paradigm shifts in the ways that we think about labeling going forward.

From the electronic health record perspective, I want to note that drug-drug interactions have had a highly disproportionate effect on the ability to get people to use electronic health records and decision support in particular, and sometimes far too many drug-drug interactions have been displayed, resulting in

providers being unwilling to use systems altogether.

Within electronic health records, I think the two most important things are when to interrupt providers, and you heard some about that just now, and then what messages providers see. And it will be important to think about how the label interacts with what providers see so that the management instructions are really especially important, as was underscored earlier.

I also would like to suggest that the electronic health record is going to be the way that providers will be able to navigate the future in which they're thinking about how fast somebody is metabolizing this one drug and how they're doing things with another drug. Without that, I think as Dr. Juurlink pointed out, providers really have no hope. It's just too complicated to negotiate the world.

So what I'm going to talk about, I'm going to start with clinical decision support in general. Then I'll talk about drug-drug interactions in

particular. I'll talk about the current state of warnings around drug-drug interactions.

I'll talk about how they're actually implemented; give you a few recommendations about drug-drug interactions, both in terms of content or which drug-drug interactions should be displayed, but also about management, how they should be delivered because that turns out to be a very important thing as well. And then I'll wrap up.

We published a paper a number of years ago called, Ten Commandments for Effective Clinical Decision Support. And it turns out that if you want to make a difference in convincing providers to behave differently, you have to follow a number of these tenets or you just won't get to where you want to go.

The first is that speed is everything. Providers are really in a hurry. If you are trying to take them through some big monograph, they just will not go.

Second, you want to anticipate people's needs and deliver in real time. And with this,

with drugs, it should be possible to know what medications somebody's prescribing and bring the information that a provider might want right to them. That goes together with fitting into the user's work flow.

It turns out that little things, like where you set the default, keep the prescription or cancel the prescription, have a very big impact on what providers do. Physicians resist stopping, so if you tell them to stop, even if they're doing something that's really a bad idea, they often won't do it.

On the other hand, if you say, well, instead of stopping, "We'd like you to, say, prescribe a little different dose of this medication," they're much more willing to do that. That's human nature, but it's important to consider that.

Simple interventions work best. You can ask providers to provide additional information on occasion, but if you do that too much, things won't work.

It's absolutely critical to monitor what the

impact of the decision support is. In many of the health records today, the tools to do that had not previously been built in to enable that. And because of meaningful use, that is a required thing going forward. It will be essential for organizations to look and see how providers are responding to warnings and then for us to make iterative changes.

Finally, these knowledge-based systems have to be managed and maintained, as has been noted repeatedly. The state of the art here is constantly changing, and if we don't keep up with that, we won't get to where we want to go.

Now, how do things work in the real world with respect to drug-drug interactions broadly? Well, most institutions get their knowledge, the databases, from one of several vendors. And you'll be hearing from Karl next, which is really terrific.

It's not practical for most organizations to maintain these databases because they're very complex. However, the fundamental problem so far

has been that for drug-drug interactions in particular, far too many warnings have been given. And in addition, the way that the alerts have been delivered is often suboptimal.

Over-alerting has really perverse effects. It can make systems very hard for providers to use them, and organizations may even turn off decision support altogether, which is undesirable because a lot of the benefits from electronic health records do come from decision support. So finally, both content and management have considerable room for improvement.

Now, it is clear that drug-drug interactions do cause harm, and much of the data for that comes from Dr. Juurlink. So one example is glyburide and clotrimazole, resulting in hypoglycemia, again a very big odds ratio. And you heard before about the clarithromycin example.

I think that that evidence is some of the best evidence about how harmful these interactions can be. However, if you look at the flip side of things, drug-drug interactions are responsible for

a relatively low proportion of adverse drug events overall. It's about 5 percent in most studies. And yet in many systems, they're responsible for a lot of the alerts.

So I feel like this is a place where there's big opportunity for improvement. They clearly cause harm. Particularly if we could start to take into account more factors, I think we could do a lot better. But right now we have this scattergun approach.

It is possible to do better with medication-related rules. We went through in our system, which is a big integrated delivery system, and identified a highly selected set of drug alerts for the outpatient setting.

One thing that we did was to make most of those alerts non-interruptive. When a non-interruptive alert appears, mostly the provider can look at it, but they don't have to do anything different. Only 29 percent in this study were interruptive, and of the interruptive alerts, 67 percent were accepted. The industry standard

around this is around 5 percent. So this is considerably different than has been reported in many other studies.

In addition, it's quite clear that tiering is valuable. We did a study in which we took advantage of a natural experiment to look at this. We studied two academic medical centers, which were using exactly the same knowledge base, which was nice.

Site A used three tiers. So in tier 1, you basically could not give the interacting drugs together. Tier 2 strongly suggested that you do something different; that might include, for example, monitoring more carefully. And tier 3 was non-interruptive. Site B had all the alerts as interruptive, which is the way that things are done in many electronic health records today.

What we found was that 100 percent of the most severe warnings were accepted at site A versus 34 percent at the non-tiered site. So what that means is that 66 percent of the time at the non-tiered site, people were running stop signs and

giving even drugs that can result in cardiac arrest together, for example. So not what you want to see. And furthermore, the overall alert acceptance was much higher at the tiered site, 29 percent versus 10 percent.

We've done some work to try and look at human factors and alarms, and worked with some groups that have a lot of experience around alarms and warnings from other industries, like nuclear power. And these results were published in JAMIA in 2011.

There are a few principles. One is that you need uniform alerting mechanisms and then standardized alarm responses. Second, alarm philosophies should minimize the number of false alerts that occur.

Third, the placement of alerts has a big effect on the likelihood that users will actually see the alerts. Visibility is critical. The font size has to be big enough so that things are readily legible. And the visual alerts need to be prioritized. In addition, color should be used to

help cue the user about the level of a specific alert, and the number of colors that you use should be minimized. Often systems today don't do that.

In addition, to make visual alerts more distinct, it's important to minimize the number of visual features that are shared between alerts. Again, in many systems today, all the alerts look exactly alike and you have to look at the textual information to know what the message is. And finally, the text-based information should be succinct.

We then took these principles and then superimposed them on actual electronic records, and looked to see what happened. And in this study we looked at 51,000 drug-drug interaction alerts. Providers accepted only 1.4 percent of the non-interruptive alerts.

For the interruptive alerts, user acceptance correlated positively with how often the alerts appeared; what the quality of the display was -- the odds ratio there is 4.75, so pretty large; the alert level. In addition, alert

acceptance was higher in inpatients, who tend to be a little sicker, and also for drugs with dose-dependent toxicity.

The textual information did influence the reaction, so providers were more likely to modify their prescription if the message contained detailed advice on how to manage the DDI. And again, that has obvious implications with respect to labeling.

Here is just an example of a drug-drug interaction, level 2. The patient here is getting trimethoprim/sulfamethoxazole. There's a very succinct message, and the provider has to then make a choice about what to do.

So how are organizations actually doing? Well, we worked with a group led by Jane Metzger to study a number of hospitals around the country and to see what they actually had in place with respect to drug-drug interactions, among other things.

The way that this worked is we developed basically a computer-entry flight simulator. People were given simulated patients, and then they

put in some orders that were errant orders, and we looked to see how often they were actually caught. For drug-drug interactions, they were caught 52 percent of the time. So about half the time, even important interactions just went right by.

In this study overall, there were 62 hospitals that voluntarily participated. Simulation overall detected only 53 percent of the orders that would have been fatal, not a very good performance. And they detected only between 10 and 82 percent of orders, which would have caused serious adverse drug events.

Notably, there was almost no relationship with vendor. So this slide shows the relationship with vendor, and you can see that every vendor had sites with very good performance; every vendor had sites with poor performance. This, from my perspective, argues for doing some post-implementation testing because it's really what the organizations put in place and not just what vendor system they use.

In terms of which alerts, we made some

suggestions about how to move forward. Those were, interrupt with only the most important warnings, and then tier. The jury is still out regarding whether it's even useful to display the non-interruptive warnings. Valuable to have regular review.

It's essential to track how providers are responding. As practices change, new information becomes available. Sometimes you begin using drugs together that were not okay to use together previously. And sharing regarding this would help.

We argued in this particular paper that this would be a common good. Reference to the RAND work, which Dr. Wilkins mentioned before, as a good start. This is the sort of thing that could actually be international because the issues are not really any different in other countries, and every country is struggling with this.

In terms of how to deliver, the key recommendations are to follow the human factors principles. So you should tier. You should have uniform display. Where you display suggestions is

important. Different levels of warning should appear different. You should use color wisely. And the textual information should be succinct.

I'm going to go through this very quickly because again, Dr. Wilkins talked about this. We did the work that she described earlier. But we basically, together with RAND, did this work in which we identified 15 drug-drug interactions, which should not be given together. Here are a few examples.

Some of the things that we did not include as interactions were things like abatacept and tumor necrosis factor inhibitors, which were felt to be more therapeutic duplication than drug-drug interactions. And many of the people in this room, I'll note, participated in that work, and we're really grateful to them.

At the end of the day, as was mentioned, we ended up with 15 drug class pairs, which should never be co-prescribed. We think they're candidates for hard stop alerts. We're not sure that this is a complete list, but this represented,

we believe, the best available consensus.

I want to note that the less significant drug-drug interactions are still very significant. They're much more prevalent. They probably cause much more harm. Most of the warfarin interactions fall into that category. But many of those tend to depend on patient characteristics and drug dosages and timing and concomitant conditions like hypokalemia, and our ability to deal with all of that so far has been limited.

We recommended that to improve the sensitivity and specificity of these, we need more investment and evidence review and generation, and then methods to make drug-drug interactions conditional on other patient data, which typically has not been done in most systems. But I'm sure the panel will discuss that more later today.

With low priority drug-drug interactions, I think that's also a helpful list, and I won't spend more time on this. I do believe that a consortium to maintain this list will be helpful, and I think this list is likely to be useful to organizations.

We're doing some work now to see how much uptake this actually gets.

Another set of work which I wanted to describe briefly relates to adherence to black box warnings, and this is some work that we published in the Archives of Internal Medicine in 2006.

We identified all patients who had a 2002 black box warning. We found that when we did this, 55 of the 95 warnings required clarification to be computable. So another message to the FDA is it'll be really helpful going forward is the black box warnings are made computable from the beginning.

We studied 324,000 patients who were prescribed a medication. Of that, 10.4 percent got a drug with a black box warning, so that's not uncommon. Of the 1,107 who got a drug with a drug-drug interaction warning, 36 percent also got a contraindicated drug. So that comes up really not infrequently.

Overall, we found that the black box warnings were often imprecise, and more precision would be valuable in making these things

computable. The violations appeared frequently, and it would help a lot to have better assessment of the actual level of risk in individual situations. Sometimes these were clinically reasonable; other times they were probably not.

We also did a study more recently in which we looked at the marginal benefit of adding black box warnings that we did not already include in our clinical decision support system, and added all the ones that were there that we had not included previously. And we actually saw slightly higher nonadherence after doing this than before, 5.1 percent after, 4.8 percent before.

The violations did decrease, though, for a couple of very important categories, notably for drug-drug interactions, and then also for drug pregnancy checks. So overall, adding more of the information that's in the black box warnings did not improve adherence at all, but it did for a couple of the really important subcategories.

So to wrap up, I believe that checking for drug-drug interactions can be highly beneficial,

but I believe that there's a lot of work to do both around which alerts to display. I think that having this consensus work is going to help greatly.

The RAND work is a good start. It doesn't take us through all the things that we want to do. And Dan Malone, for example, is leading a group to try and take us through some of the next steps around that.

We need best practices regarding both which alerts, and sorting out how to share those would be highly beneficial. We also need best practices regarding how to display them. Today drug-drug interactions are a big problem in the clinical systems which don't follow best practices, and that's many of the systems that are out there.

In addition, we need to leverage our systems to build the underlying evidence base, and that has to be much more robust. I do personally think we can use lots of the observational data. The data, for example, from Canada have been very compelling for me, and I think there'll be other opportunities

to do that.

As we get broad electronic health record adoption, we should be able to have much bigger data sets than we've had in the past, and it'll be possible, for example, to link that with claims and to see in much more detail what actually happens.

So a few specific suggestions for the FDA around this area. First, I would endorse the recommendations that Dr. Juurlink made before about labeling. And I believe that it would be helpful to include in the label both some very simple messages, but then also some more detailed, because people want both things. But if you want to make a difference, it's really important to get the simple messages correct.

Regarding format and how to display this information, there aren't a lot of good data that I could identify regarding which approaches are best. But one of the nice things about information technology is you can have your cake and eat it, too, and it might be possible, for example, to both have some forest plots and some tables and

narrative and let people pick what they want to look at.

I'll note that data suggests that users only consult referential material about 2 percent of the time. So it's an important role for the FDA to get that right, I believe. On the other hand, to make a difference, the short messages are important.

Finally, there are lots of complex situations which have come up today like multiple drugs, interactions changing over time, and labeling clearly will need to evolve to address that. That's a really tricky and complex matter. Thank you.

DR. BARRETT: We're going to hear from Dr. Matuszewski next.

Presentation - Karl Matuszewski

DR. MATUSZEWSKI: First of all, I want to thank the FDA for inviting me to present at this committee meeting. I'm from First Databank. First Databank is a drug knowledge database vendor, which there are about five of those in the United States. Three of them probably are responsible for about

80 to 90 percent of the use in current clinical practice.

First Databank has been in existence for about 40 years. We have the bank in our name; that was early on. We started the company with pricing information, but it's nothing that Ben Bernanke should get excited about. A subsidiary of Hearst Corporation.

Really, what First Databank does is it provides the granularity for drug knowledge. So we take a label, we take clinical evidence, and we put it in relational tables, and that is then consumed and used by EMR systems. It's used by pharmacy back benefit managers. It's used by insurance companies. It's used in the ambulatory setting, in the inpatient setting. So it's really providing what would be the knowledge that we hope drives decision-making.

You see what our goals are. Again, it's to influence medication safety. So one of the vision statements of First Databank, or FDB, is really to have zero medication adverse events. That's our

vision.

Now, we do that. We recently started sponsoring some research in the area of clinical decision support; recently published an article on sulfa antibiotic/non-antibiotic cross-reactivity. So it's one of these things, even though the knowledge has been out there for a long time, we still get calls to say, "Put back in those cross-allergies," even though there's no evidence base to support them. A number of our staff belong to a variety of national/international pharmacy organizations that look at drug safety, and we very much participate in those activities.

So this is what I hope to cover today, a quick overview of the complexity of clinical decision support and evidence review; talk about a three-pronged approach we have in terms of reducing alert fatigue; and finally, just touch upon some patient parameters that would ideally increase the specificity/sensitivity of the drug-drug interaction alerts that are provided.

So surveillance of evidence. When you look

at evidence, what we have is really the sources of evidence. So I would say the manufacturer labeling, the package insert, is very important. A new drug comes out; often that's your only source of information.

We have biomedical literature as it's constantly involving. We have clinical reviews. We had MedWatches from the FDA. We have guidelines that are created by guideline specialty organizations. Within all that evidence we have the factors, other factors, that impact how that works its way into clinical decision support. It could be the simple constraints of an organization for time to take and implement some of the knowledge. It's how it fits into the work flow. It could be what the local practice patterns are.

We also have prescriber constraints, so how long has a prescriber been out in practice? So I like to think that my highest knowledge level was probably the day I took my pharmacy boards, and it's just been a steady decrement since then.

(Laughter.)

DR. MATUSZEWSKI: I think I heard that confirmed from one panel member. But it's probably the same for physicians.

We also have patient information. So the more specific information that we can have about a patient, the more likely we can provide the alert that is appropriate for the prescriber at that point in time.

This is my evidence is in the eye of the beholder. We have here a prosecutor. We have here a defense attorney. I suspect if they looked at the same pile of evidence, they would both equally make strong cases for guilty or not guilty.

We are faced, in the knowledge database vendors space, with basically having to decide, is the evidence sufficient for us to include in the database, or is it inadequate in terms of it's not quite ready for prime time? And we have to make these decisions.

So here you see -- this is not my staff. It's not nine people. But I can tell you that often the decisions are not unanimous and they're

after great and lengthy deliberations. And at least our references, I think, are all still available by Web link, so we don't make our sources of judgment disappear after a while.

This is the part of maintaining and the data curation of a drug knowledge database. For the drug-drug interaction space, we have three dedicated pharmacists who pretty much have devoted their careers and their lives in the pursuit of maintaining this database.

It is something that we -- in terms of the trigger events. So it's MedWatches. It's journal publications. These are all part of our information capture system. And we have it all computerized hen a label revision -- so we have, I think, daily, probably about 10 label revisions come in from CDER. Those are tracked, those are dissected, and they go to the appropriate unit.

Besides drug-drug interactions, we also have dosing modules. We have side effects, indications modules, and allergy modules.

Then again, we have strict editorial

policies, timely review. So if a new drug came out today, that information would be incorporated in our database tomorrow. So we have a weekly clinical data push to all the customers of FDB.

Some of our sources of information I also mentioned, besides the biomedical literature, which I think is really important, so if there's one take-home message, the literature, if it can be incorporated into the label, that's great because that often is what defines current best clinical practice. We also are looking at some academic metabolism and drug transport databases to get some greater specificity in terms of some of the enzymatic pathways to improve our data.

Now, in terms of drug-drug interactions, FDB has been doing this since 1984 in a more referential monograph type of information. This is just the sleeve jacket from a hard copy of what we have, 2,000 pages, 18 chapters based on major therapeutic areas. And of course, we consult 14 external advisory board members, often from leading academic medical centers. And you can see some of

the sections and the information that's contained.

So I like what I'm hearing in terms of the greater granularity of information if somebody wants to dig into it; that info button and being able to click into it. Dr. Bates mentioned 2 percent. I suspect that maybe in an academic teaching hospital, it's 2 percent, but that in other venues it's probably much, much lower in terms of having the time to go and read these monographs and greater information. But it's available to individuals who use the knowledge databases.

So what exactly are we talking about in terms of the severity levels? FDB has four severity levels, and the number 9 is the miscellaneous, not really clinically significant. So the first three are of importance.

So severity level 1, that is the contraindicated drug pairs. And as the arrow points, it's about 24 percent of the drug-drug interaction contraindications in our knowledge base are what are contraindicated, don't use. And this

again comes from labeling, from literature.

The majority are level 2s. Level 2s are the severe, or as I'm now leaning towards, the series drug-drug interactions. These are the things that you should avoid if you can, but often there is no other therapeutic alternative, so these are the ones you should use with great care.

Often these are filtered and the prescribing physician may not see these. And it's the pharmacist who then deliberates -- is it worth the phone call to the prescriber to offer him an alternative, or should I just save some time and just go ahead and override this?

The severity level 3s are the moderate interactions, and those are the ones that really are -- keep an eye on this. Often in the inpatient environment, the patient is probably discharged before, really, the effects of monitoring would make this a safe choice. And there has to be that transition then when the patient is continued in a med rec standpoint; that if the drug-drug interaction adverse effect doesn't occur until two

or three weeks out, that that indeed needs to be followed up with the physician who's taking care of the patient in the ambulatory environment.

Now, you can ask, with the override rate of drug-drug interaction, so is it alert fatigue or can it be something a little bit more serious? This is a recent paper from the Journal of Epilepsy and Behavior, and I always used to think that -- I'm again a strong believer that there's just way too much information out there for the CPUs that we were born with to process all that information.

So here was a study that surveyed 500 neurologists -- these were all primarily board-certified -- and asked them about four recent MedWatches about anti-epileptic drugs and their knowledge of those. As it turns out, 20 of them did not recognize any of the four, and only 30 percent of those 500 neurologists recognized all four of the warnings.

Now, to me this is just a sign that it's impossible for an individual, even with a number of

years of practice in their well-defined specialty areas -- so these are drugs that they are presumably prescribing quite a bit -- to keep up with all the information that the FDA is looking at in the biomedical literature.

So this is a little bit about MedWatch changes, so profile these for the last five years with 2013 not yet being complete. You can see that the pace is increasing. So FDA's been busy. And I suspect that 2013 may be a banner year. Again, drug approvals are also going up in the last three or four years compared to what they were in the past.

So this is all information that a clinician out there ,whether it's in their narrow use of the drugs they prescribe in their specialty or a primary care physician who may see the whole spectrum of drugs and indeed be dealing with drugs that they've never prescribed initially and may not really have in-depth knowledge about.

So the phenomenon of alert management. Again, I've seen the studies, 80 to 90 percent

overrides in the drug-drug interaction alerts. So this is a three-pronged strategy that FDB has undertaken in the last couple of years.

The first strategy is again fine-tuning the content. So we have all these drug-drug interactions embedded, and one of the steps that we take is again taking a hard look, where can we tease out to create less alerts, perhaps downgrading what might be a contraindication in the package insert into something that is indeed a severity level 2, providing the characteristics match it.

Here, for instance, we have drug interactions that are based on strength breakouts. So lower doses of certain drugs are unlikely to cause an interaction. And then we have 75 of those that have been broken out. We have route breakouts. Often, topical formulations that are not systemically absorbed. There's no reason for that drug then to interact with another drug that does have systemic effects.

Then finally, taking a hard look at the

class effects that are mentioned in some package inserts when it may not be appropriate to include the entire class. So for instance, clopidogrel and proton pump inhibitors, in terms of that interaction, at least in the literature, we believe there's a difference between lansoprazole and pantoprazole and have indicated that as a moderate interaction, something to monitor.

Here's an example again, a further example of fine-tuning content, so selected macrolides interacting with selected statins. And we see that again the strength breakout of atorvastatin at less than 20 milligrams is a severity level 3, whereas with the other statins and at higher doses of atorvastatin, we give that a contraindication. So this level of granularity allows us to decrease what are contraindicated pairs that the clinician would normally override.

The second prong of the strategy to decrease alert fatigue is a product that was released about three years ago for FDB customers. There's about 100 institutions currently using that. And that's

the allowance for local customization. It was mentioned in ONC as an option. And really what we're finding is that when a severity level is changed, that there are some institutions that don't like it, complain about it, and some that again just would love to get rid of it.

So this idea that one size, one alert, fits every possible scenario, every single institution, whether an institution has monitors for all their patients or an institution is a small rural hospital that basically has a minimal amount of equipment, we feel is not appropriate and should allow for some local customization.

So here's an example, a mockup of a screenshot. It's very small, but the circle that I have shows some quick easy buttons. So the ONC high priority list. If an institution says, that's really where we want to start, they press that button, and then the ONC list is imported into their contraindicated severity level 1 drug interactions. If they want to exclude the low priority interactions, again they press that button

and those will be excluded.

We see this phenomenon of lists being generated as probably continuing. Whether that's a good idea or bad idea, I'm not 100 percent sold on it because I think the day-to-day curation of that knowledge is extremely important. And when I see pairs in lists that say QT prolonging agent against QT prolonging agent, that drives me crazy because even within those nuances, those are not all contraindications.

Again, there's a number of institutions that have done extensive customizations to our severity level rankings, either upgrading them or downgrading them or completely deleting them.

Here's an example of another custom severity level. So I mentioned that we have really, in essence, three levels. So we have custom levels of a 5. So these drug pairs, for instance, would be invisible to cardiologists, who theoretically are dealing with these drugs all the time, but would be visible to all other specialty prescribers.

The custom severity level even could be

site-specific, so whether it's ambulatory or whether it's inpatient for where the alerts would be triggered. And this is a Web-based tool. So when new data flows in from FDB, the levels that have been changed at the local level are not impacted.

Now, we think, with this sort of local customization, there is a potential to look at what's called crowdsourcing of information. So what do academic medical centers with teaching programs -- what sort of customizations are they making? What sort of changes are community hospitals making? What are ambulatory clinics perhaps making in terms of local customization?

This is something that we're looking to share with individuals who use AlertSpace, and I think it again further guides us in terms of fine-tuning our alert content for all the other users of knowledge database vendor drug interactions.

So we have this feedback loop. We have in the past had information that EMR vendors have supplied to us. So here are four institutions.

Here are their patterns of overrides that they're seeing and where alerts are accepted.

That again feeds back into allowing us to fine-tune our content. So we get reports back like this. We're able to identify the specific drug pairs that are involved. So seeing those are involved, seeing how often the rates are overridden, much like in Dr. Bates' institution, the ones that are routinely overridden and of less serious nature, these are the ones that we can look at our content to find again whether there is a dose adjustment or some sort of route adjustment.

Then finally, I want to talk about individual patient parameters. So the things to consider in any drug-drug interaction alert, is this a new exposure or is this a continued therapy? So if a patient's been on a pair that's been fine, the disease is controlled, they've been on there five years, and just because they're now being admitted for the first time and the drugs are being ordered, alerts are going off. And then of course the clinician says, "Well, this is what the

patient's been on five years. I'm not going to change anything."

We have laboratory parameters. So if potassium is going to go up, if an INR is going to change, it may not happen that day. It may be appropriate therapy in an inpatient environment, but it's something that if you could bring in those lab values as it is being prescribed, perhaps it's an alert that can be delayed.

Number of physicians ordering meds. So is it the same physician ordering the med who will be aware of the interaction? Or is it somebody doing a consult who may not be familiar or may not even be aware that the precipitant med is on board?

Service location is something to look at, again whether it's a clinic or if it's an intensive care unit, where again monitoring is pretty heavy, versus in an ambulatory environment, where the patient may not be seen for another six months or so. And then we talked about comorbidities, renal or hepatic deficits, and then the pharmacogenomics aspect of the patient.

Then again, for the physician, what specialty are they? Are they a specialist or a generalist? And their role, is it a hospitalist with years of practice experience versus an intern or a resident who really doesn't have that much experience and seen that many cases?

Finally, in terms of the drug, what's the probability of the reaction, the percent occurrence, the incidence, and the severity or the serious nature of the event. We talked about some standard symbols, whether it's a go for it, caution, or a stop.

Then again, finally, in terms of implementation, which again is very specific to the institution. So the knowledge bases have an incredible amount of granular data about the drugs, but how the institution, how the EMR vendor, decides to program against it and implement it is probably key in terms of that scatter plot that you saw of the override rates.

So who's looking at the alert? Is it the prescriber? So again, in some institutions, those

are just the severity level 1s, the contraindicated pairs. Is it at the dispensing point? So again, the pharmacist often is the one who's looking at that. Or perhaps it's at the EMR level, so the nurse administering the drug who also is now looking and seeing some sort of interaction.

What other modules are simultaneously implemented at an institution? Because there is some overlap. So pharmacodynamically, for duplicate therapy, is this a drug interaction or is this duplicate therapy? You could say it should be one or the other, but often institutions may not have both modules turned on. And maybe getting alerts from both modules, and that may again lead to alert fatigue. Or is it a side effect rather than being one of the other modules?

Then finally, drug disease, contraindications and precautions. And some of the work we're finding in there is if the problem list is not well-maintained and updated, then that sort of module will lead to tremendous problems. So EMR hygiene and maintenance.

Then the user interface again was touched upon. It's if I've seen this once, maybe I don't need to see it every single time. Maybe I need to see it every five times just so that I'm reminded of this drug interaction. Perhaps I've already approved this combination in the patient, so if I'm just changing the dose, maybe I don't need to see it again.

Is there some symbolic coding that can be used? Is there a way to bundle alerts and prioritize alerts? So again, depending on the EMR system, you may just get a long list, and perhaps the more serious alerts are buried towards the bottom because they're in some alpha order or by module.

But really, the ideal way would be to present the alerts that are going to harm the patient right up front, whether you color-code them or emphasize them or bold them. That is of ultimate importance that a knowledge vendor like First Databank has really minimal control over.

Screen size viewing. So at some point,

we're in the era of iPads and perhaps smartphones being involved in the e-prescribing and the clinical decision-making, so how much of that real estate can we get on board to make sure that drug-drug interaction pairs are ultimately looked at and decided appropriately? Maybe audio alerts is another option, though I know in many institutions the lack of sound is not a problem; that they're various alarms.

So what are some of the issues that staff at First Databank have with package inserts? And we talked about a couple of them. Labeling mismatches between two drugs. So a newer drug comes out, lists out a number of drug interactions. And then you go to an older package insert of one of those listed and it won't have it. So we adjudicate that.

Then there's the case of label inconsistencies, so even within one label, and I'll share an example in my next slide.

Imprecise label narrative. So if something says, "Use these two drugs with caution," to me as

a pharmacist, you should use every drug with caution. That word has very little meaning.

Outdated labels. So again, labels that are just too old to be of any use at all.

Then finally, broad class effect statements within labeling, so this entire class interacts with this agent. Not very helpful because some knowledge database vendors may just apply it to the entire class. We try and slice it up as much as possible as evidence allows.

So here's my Xenazine, tetrabenazine. It's used for Huntington's chorea. So here is a label with various sections. So if I just read the highlights section, "Do not prescribe," that to me is a pretty strong statement. That's almost like a severity level 1 contraindication.

You read Section 5.11, and you've got, "Should be avoided in combination" for QT prolonging agents. That to me sounds a little bit like a severity level 2 interaction; avoid it, maybe look for better therapeutic alternatives, but it's not a "Do not prescribe."

Then you read Section 7.5 in that same PI, and what you read is, "Causes a small increase in QTC prolongation," so 8 milliseconds. You read that; it's the only thing you read, so that's not too bad. That sounds like severity level 3, maybe, just monitor and use cautiously. And there I go, using that word "use cautiously" with every drug. Then Section 7.6 says, "May be exaggerated by concomitant use" of various other QT prolonging agents.

So when we look at a label like that, there's a judgment that needs to be applied to that. And in this case, it's a severity level 3 unless the other precipitant drug is a strong QT prolonger. And those are the sort of judgments that have to be made every single day, every single label.

Another recommendation I'd make to the FDA is, make sure the manufacturer has the label on your site. So this is again Xenazine, and "label not available." So I think you have the regulatory might to make sure that if somebody's got a product

that's out there and dispensable, the label should be available to look up.

In summary, it's not easy. It's not always fun. But I think as David pointed out, that's why there's probably only about five companies that are doing this -- and you should not try this at home unless you have vast, extensive resources and pharmacy staff that you can apply to this every single day; and that at least the three-pronged approach, while it is not guaranteed 100 percent success, I think it's at least moving the bar, so local customization, fine-tuning of content, and then also adding more patient-specific parameters, which we hope to be able to do in the next few years to decrease alerts.

Then finally, the evolving evidence database is again -- I don't think the label will ever keep up with what's available in clinical practice. And those are the things that my staff looks at and incorporates into the knowledge base, as other knowledge bases do also, and that I think is important to providing the clinician with the best

evidence and information they have for prescribing these drugs that interact safely. So thank you.

Clarifying Questions

DR. BARRETT: We're going to have some clarifying questions now. And again, I would remind all of you to state your name before you make your point. Marilyn?

DR. MORRIS: Marilyn Morris. I wanted to ask Dr. Wilkins a clarifying question. You talked about certification of the various patient record systems. And I was wondering, what does this mean with regards to looking at DDI information in the systems?

DR. WILKINS: Sure. Thank you. So the certification of the EHR product, there are functionalities that the EHR vendor has to have to be certified by ONC as a meaningful use-certified product. We have criteria that requires them to have the ability to perform a drug-drug interaction alert or a drug allergy alert. We don't certify how that's displayed or the content of those drug classes or drug objects in those systems.

So we leave that up to the vendor themselves to work in conjunction with the knowledge base to have that information. We are simply saying that for a provider to use a system that's meaningful use-certified, they should have the ability to do this.

DR. BARRETT: Dr. Ruth?

DR. DAY: Ruth Day. I'd like to thank the speakers, the recent speakers, about providing evidence about how these databases are used in everyday life. It's very important and quite impressive.

I do have a question for the FDB presentation. We know that your database is used by many clients, many different institutions. If you could just briefly give us an idea of how many patients or patients per year are benefitting from this use, and then go on to talk a little bit about customization.

The liability implications for local customization are really frightening in some ways and challenging in other ways, I presume. But do

you keep tabs on how the different clients do customize the database and what problems have occurred so that then you could step back and provide guidance about things that can and should not be customized?

DR. MATUSZEWSKI: So for your first question, how many patients are supported with the FDB drug knowledge, I can't give you an exact number. I can tell you that there's thousands of customers in a variety of different uses, everything from pricing analysis to use in clinical decision support. A number of hospitals and health systems, even retail pharmacies that serve millions of patients every single year. But I can't give you an exact number.

In terms of the AlertSpace modification, that's a relatively new product, so it's been out three years. About a hundred customers are using it now and making modifications. And yes, FDB does have records of those modifications.

I can tell you that institutions who use AlertSpace use it very gingerly. And gingerly is

they don't make wholesale changes because before something like AlertSpace allowed local customization, they just basically used severity levels for crude adjustments and just said, we're going to either turn everything off, which doesn't help you at all, at least for Leapfrog, or we're just going to turn off level 2s and 3s, or we're just going to provide level 2s and 3s to pharmacists for review and not for prescribing purposes.

So the legal liability, I would say that most institutions are not making wholesale changes, but are also taking any changes they make through their P&T committees or med exec committees, and being very careful about when they change a severity level 1 contraindication that FDB has indicated to downgrade.

Now, a number of institutions have actually upgraded. So things that have been considered severity level 2 based on evidence, they may have had a problem with before, some med errors, they've upgraded them for their entire staff.

In terms of completely eliminating alerts, whether it was a 1, 2, or 3, that again is based on some of the data I've seen, not done very often. But occasionally, for the nuisance alerts that they perceive their institution has been done.

I think if you asked me that question in about another year or so, we'd have much more data.

DR. DAY: And do they ever add any drugs?

DR. MATUSZEWSKI: At this point, there have been some requests. So something that's not identified in any of our monitoring of the literature or not identified in the label. We are looking to add that functionality probably in early 2014 because that's a whole nother level of use, where nobody can really pinpoint but they say that's a problem at our institution.

DR. BARRETT: Dr. Horn?

DR. HORN: I'll just make a comment on the customization. I applaud the vendors for their ability to add that. We in our institution started customizing in 2006 our DDI database, and at that time, we had about 8,000 drug pairs that were in

the highest severity category. I wish I had Karl's database; it would only have been 1600. I would have been done much quicker.

We went through every one of those drug pairs and reviewed the literature on every one of them and reassigned categories. There are now 16,000 drug pairs in our highest severity list that we get from our vendor. So it's not a trivial process to do this.

We have done it for about 12 other institutions, helped them through that process. And what we find fundamentally is that you reduce the number of alerts that are firing, obviously, because you downgrade the highest ones to something less.

But also we find that the number of irritating alerts, for lack of a better word, is markedly reduced, and the practitioners recognize that. They're not getting alerts for silly things any more. And that's exactly what we want. We want the alerts to fire that we believe have risk for patient harm.

The legal question is one that gets bantered around a lot. There was recently a symposium held on that various issue. I don't have the reference in my head, but I'd be happy to share it with you later, if you'd like to look at it. It's really wonderful.

Their bottom line was, there's really not a big deal here if it's done in a prospective, knowledgeable manner as opposed to, oh, let's just shut them off, which is a real big risk. But if it's done with knowledge and with forethought, you're probably reducing your risk because there's a huge risk if you ignore an alert that's in the system and it causes harm.

In fact, the only case that I've been called on, a medical-legal one, was exactly for that -- regarding the customization stuff; was a situation where they shut an alert off and then it caused harm. But if you have specifically modified an alert and done that with forethought, you're probably not going to have much legal risk. You can't eliminate the risk. You've always got the

risk. But I don't think you're increasing your legal risk at all.

DR. DAY: But the risk transfers to the customizer, I hear, not the original vendor. Is that correct?

DR. HORN: Yes. But the original vendor has no risk, either. It's like we have no risk in our book because of the learned intermediary rules. So if the providers all were reliable, there would be no books. There would be no software. There would be nothing.

At the end of the day, the risk is the physicians. And then they'll go after the institution because those are the deep pockets. So if your institution has a policy to evaluate the interaction, look at the evidence, and make a decision based on that, that should hold up quite well in a court as opposed to, well, we were just tired of getting a lot of alerts so we shut 80 percent of them off. That's not going to look very good to a jury in any case.

Then we also have in place a system where we

have a monthly review committee that does nothing but look at interactions in our database because we are continually getting updates from the vendor. So we have to continually look at the new interaction alerts that are coming in as well as the data because we do the same thing. As Karl pointed out, we raise and lower alert rates, or severity levels, based on data.

DR. BARRETT: Again, just a reminder, please state your name when you speak in the mike.

Dave Flockhart? Okay.

Dr. Zineh?

DR. ZINEH: Two questions for clarification, one for Dr. Bates, the other for the speakers. You mentioned a recommendation to make boxed warnings computable. What does that mean?

DR. BATES: Just that when a boxed warning is released, it will be helpful to consumers of them if they are framed in such a way that you can actually put them into an algorithm. Often the warnings include words that are vague. Caution is an example. A caution is not a computable term.

So we're looking for things like, "If the ALT is above a certain level, then do X."

DR. ZINEH: Thank you.

The other question is for all speakers. There is a question before the advisory committee on a framework to assess literature, drug interactions from literature. That framework doesn't necessarily talk about evidence, and it's probably beyond the scope of the conversation here, but it's implicit. That would be the next step.

So my question is, these knowledge bases, are there rubrics for putting things into the system and assigning severity? Are those publicly available, transparent, et cetera, or are those part of the proprietary nature of these platforms?

DR. MATUSZEWSKI: There is no rubric. There is no formula. So if in the span of six months, there are five case reports, or if there is a series of 10 cases that identifies a significant interaction, that would be then judged on its merits on the strength and the quality of the study publication, whether that indeed gets incorporated

into the database.

With drug-drug interactions, you're not going to see randomized, controlled trials. And often early reports, if they're serious in nature and the mechanism is well explained, that in itself in a couple of case reports may cause a severity level to change or for an interaction to be added in our database for the first time.

We even have referenced animal studies, but rarely would an animal study be of sufficient quality evidence to include in the database in terms of a new drug interaction. So the answer is, there is no secret, magic formula.

DR. BATES: I feel like the existing evidence frameworks don't necessarily translate that well to this particular domain, and so developing something new would be a real contribution. I think that the group that Dr. Malone has brought together has talked about doing that. Dr. Horn may have been involved in efforts like that as well.

DR. BARRETT: Dr. Venitz?

DR. VENITZ: Jurgen Venitz. Let me ask a follow-up question. How important is, in terms of evidentiary assessment, the knowledge of a mechanism? In other words, would you accept case reports, whatever, without any mechanism and incorporate that in your database?

DR. MATUSZEWSKI: "It depends" is too flip of an answer. If it was a strong study and the mechanism was applicable to other drugs and was now uncovered, I would say that there would be a reasonable chance that it would be included in terms of assigning a severity level.

I think one of the new evidence sources that we're looking at again is a drug metabolism and drug transport database and using that to refine our contents. So the more of that that's available, either from the labeling or from the literature, I think improves our ability to appropriately categorize a drug-drug interaction in terms of severity.

DR. VENITZ: But in the extreme case, if you had no evidence of any mechanism, but you have

either uncontrolled studies or case reports suggesting that there's an interaction?

DR. MATUSZEWSKI: Then I would say if the adverse effects from that interaction were serious and of a high enough frequency, that probably would be included without having the mechanism.

DR. VENITZ: Thank you.

DR. BARRETT: Dr. Au?

DR. AU: Jessie Au. My question is actually for the entire morning, what I heard. I heard prediction that you use in FDA to make your projection. I heard quantitative versus qualitative. And I also heard from several speakers now that the DDI situation is becoming more and more complex.

So looking ahead and looking backward, most of the DDI that we have so far are based on PK interactions, whereas the situations are easier to handle from a quantitative standpoint because the drug level goes up, goes down. You can project.

However, we are now in this beginning or already in the middle of the molecular medicine era

where we're dealing with molecular targets, which the plasma level really doesn't say much about that. It doesn't help us to understand the mechanism. And I would like to use this one example and then ask my question.

So just to give an example how fast things are coming at us, in the last seven years FDA approved seven drugs, molecular targeted drugs for renal cell cancer. It's coming so fast. And then if you look back a few years, eGFR inhibitors, of course, has been out there for a while now, and of course if one drug works, adding two drugs that work must be better.

However, a trial was done with 200-some patients, where it gave eGFR inhibitors and combined it with standard cytotoxics to non-small cell cancer patients. So instead of dying on average in nine months, they now died on average in six months when they got this extra drug. Okay. So now finally we know we can't just combine drugs.

So now my question here is, based on something like this, what do you do? Do you now

start to predict that you should not combine eGFR inhibitors with standard cytotoxics? And at what level do you get this information out?

Because it's not really quantitative. There's no way to quantify that except we do know, evidence-wise, patients are now dying faster because when we did a trial, we didn't know better. How do you handle that information in the FDA or in FDB? Do you actually get this information out there so patients know that they shouldn't be getting things if we don't know how they work? Since we're in the molecular medicine era.

DR. MATUSZEWSKI: I'll go first, and then FDA can give the final answer. So it's almost the beta blocker. If I give one beta blocker and I think I'm going to get twice as much effect by giving a second beta blocker, that's duplicate therapy. No? Not quite the same?

DR. AU: No, because the signaling pathway is more complicated than just beta blocker. Beta blocker, you have a finite target. When you talk about signaling, you have P transcription, post

transcription, post translation. You interact at so many levels. And if you do the equation and do the math, you can get antagonism sometimes. You can get synergism sometimes.

But that part of the research is still in the infancy. So you don't even have the guidelines to give out advice. But you do see the outcome of it; 200-some patients are now dying faster.

DR. MATUSZEWSKI: So in that case we probably would not include it in the database. If you have drugs that are given for the same indication, then that might again trigger some sort of alert; is a second drug necessary?

But in terms of the molecular pathways having detrimental effects, until that either appears in the label or in a publication that would make that something to be contraindicated, we wouldn't be picking up on that.

DR. ZINEH: I can try to address that. I think it's a little out of scope. The answer to -- I don't know enough about this example. But if this is observed in drug development, that's

clearly handled by not approving the combination.

If this emerges just like any other post-approval issue in terms of diminished efficacy in a subgroup, enhanced risk in a particular subgroup, that's handled through a variety of ways. It includes updated labeling, risk mitigation strategies, drug communications. In worst case scenarios, if we find out something that was untoward in terms of the risk/benefit analysis, drugs get pulled off the market.

So without knowing the specifics of your example, I would say there are a variety of ways to handle unexpected risk/benefit balances in subpopulations after drug approval.

DR. BARRETT: Maybe just to come back to the labeling issue, though. I saw in, Dr. Matuszewski, your pie chart here when you list the different sources of evidence. And of course, the labeling is only one part of this.

But I'm curious. Do you keep track of the extent to which the database matches the labeling? Or is that something that is at all part of this?

Certainly you allow some flexibilities at the end user level. But from the standpoint of the label as it weights the clinical evidence portion of this pie chart, do you keep track of that at all?

DR. MATUSZEWSKI: All the drug-drug interactions are then further detailed in a monograph. So all those pairs have monographs. So there would be reference to whether the interaction is based on the PI or other literature.

In terms of weighting with again a new drug on the market that has interactions, there often is PI is the only source. So you really don't have any weighting. As a drug's been used and on the market for a number of years, that's when the product information may become out of date, where again information from the published literature would override what might be in the product information.

So is there a weighting system? I would say there isn't. But again, the manufacturer's labeling is a very important thing that we look at every single time.

DR. BARRETT: But you're not keeping track of when you go outside of the labeling? That's not a metric?

DR. MATUSZEWSKI: Oh, we are. In terms of the references for a recommendation of a specific severity level, that would be included in the monograph. If you're asking me what percentage of the time --

DR. BARRETT: Yes. Yes.

DR. MATUSZEWSKI: -- that probably requires some extensive research, which perhaps if I get a student or fellow in the next couple of months, I might be able to look at it.

DR. BARRETT: Good enough.

Our last question will go to -- Dr. Horn? I'm sorry.

DR. HORN: I was just going to comment -- this John Horn -- on the question that was asked about the case studies. And these are a huge problem for all of us to try and make sense out of this literature. And some years ago, we developed something called the DIPS, which is a

Drug Interaction Probability Scale, which was designed to take where Naranjo started with the ADR scale and make that applicable to drug interactions; in other words, not just one drug but two drugs; and then whether those caused the ADR.

That's really what we use now in our evaluation. And one of the parameters of that scale is mechanism because if you don't have biologic plausibility, I don't care how good your study is, it's nonsense. And there's plenty of that in the literature.

So we're pretty cynical about case reports because usually they're not well done and it's a huge problem. But I think that case reports are a lot like other things; they're a good trigger, and the hair on the back of your neck goes up, and then you remember to watch for more information.

DR. BARRETT: Dr. Malone?

DR. MALONE: So, Karl and David, one of the things that both of you raised -- and Tricia, this applies to the ONC as well, and certainly to the FDA; I'd like to hear comments across all of

you -- with regard to the use of the term contraindicated, we see that term used, especially with drug interactions.

I'm wondering if we could have a little bit of a discussion amongst you about what sort of criteria you would use or do use to imply that because many times, people imply or assume that contraindicated means there was never, ever a situation where one would want to use these medications together, and therefore it would be inappropriate to use the medications together.

As we've done some of our work with the conference series that we've alluded to earlier today, we're struggling with that concept. So I'm sure you guys have all struggled with it, too. But I'm interested to hear your perspectives on the use of that term, especially as it applies to the drug interactions.

DR. BATES: This is an important area, and I guess what I would say is it would be very valuable to really, across the industry, have some agreement about what we mean by perform terms.

This really came out for me when we did a study in which we compared -- we basically looked at terms that radiologists used in radiographs to say whether something was present and when it was absent. And we looked at a number of reports. We found all the terms that they used. Then we had them rank them in terms of probability.

It turned out that amongst the radiologists, there was almost no agreement as to what any of those terms meant. And there was even less agreement when you compared things to what the primary care providers who are the consumers of the reports meant.

So unless we agree on what we mean, I think it's a big issue. And in domain after domain in medicine, after you develop some terms and everybody agreed about what they meant, you're better off. That happened in sepsis, for example.

When we use the term contraindicated, we mean that the two drugs should never be given together. But unless everybody else agrees about that, too, I think we're not where we want to be.

And it would be very helpful to have just a few terms and then get some agreement about those.

DR. WILKINS: I think it's a great question, and we should get some consensus. I would say, from ONC's perspective, we're looking at this from clinical decision support. How do we support clinicians to make these decisions? How do we provide them the right information for them to do their jobs effectively?

In the work that we do with electronic quality measures, we allow for exceptions and exclusions in different scenarios. And so we have the goals for these measures and what the outcomes should be, but we know that in practice, things aren't always cut and dried and that we, from our perspective, aren't in a position to say what that should be.

I think that we would approach it -- as we continue to work in the drug-drug interaction ream, we will continue to approach it from that angle and have ways that these systems can acknowledge, if we're doing this for certification, exclusions and

instances where the benefit outweighs the risk and we allowed providers to do their jobs without them being restricted in that way.

I think that what would help us, though, is if the knowledge base community gets better consensus on the severity ratings and how these drugs are categorized, that we don't have to put things back on clinicians to have to readjust severity ratings on their end.

I think that it would be useful for us to have more of that discussion, though. So I agree. But we would not -- I shouldn't say we wouldn't not; we are more interested in supporting the decisions that clinicians have to make in their context with whatever parameters they have to deal with as opposed to looking for hard and fast rules.

So I would say that we would take a similar approach as we have with clinical quality measures and allowing for exclusions, and allowing physicians to document how and when those take place.

DR. MATUSZEWSKI: I might just say that if

contraindicated as a section or a statement appears in the package insert, that is a major signal for a drug knowledge database to say it's contraindicated. That means, don't give it. Then if you put "should not prescribe together" in a black box warning, that's also a pretty strong signal that that's contraindicated.

Now, after those statements are made, can you look at breakouts in terms of dose intensity? Can you look out for route distinctions? That's where we would try and fine-tune the content if evidence was available to make that breakout.

But again, our definition of contraindicated is, you should not give these together. And unfortunately, the amount of overrides suggest that that may not be true.

DR. BARRETT: Final question to Dr. Muzzio.

DR. MUZZIO: Yes. A very good question. So when you evaluate literature to decide to include something or not to include it, do you pay any attention to who funded the work, the corporate relationships of the investigator? I mean, not

that I want to doubt anybody, but just out of curiosity.

DR. MATUSZEWSKI: In any good study review, the source of funding would be probably something that one would look at. Unfortunately, I think in a lot of the case reports, these are not things that are necessarily funded by industry, not likely to have bias implicit in their results, and if anything else, are independent, this is a problem at an academic level, report. So this is not about effectiveness or off-label use. This is really about negative things.

So I would say yes. I don't have a list with me, but there's probably over a hundred journals that are looked at in terms of drug-drug interaction information, case reports, or case series, and the source of funding would be something evaluated. We don't necessarily document that, but that would be considered. But I don't think that's a major source of contention at this point.

DR. BARRETT: Kellie, did you --

DR. MATUSZEWSKI: We would love to see more funded drug-drug interaction study.

DR. BARRETT: Did you have a comment?

DR. REYNOLDS: I was just going to respond to the contraindication question.

DR. BARRETT: Please.

DR. REYNOLDS: Our intent when we indicate two drugs are contraindicated, there are no situations where risk/benefit indicates the drugs can be given together. It needs to be based on some kind of evidence. Usually it's not based on a drug interaction study. Usually it's based on mechanism or extrapolation from another drug interaction study. But that is our intent, where it's more difficult is where in other sections of the label we say "Avoid" or "Should not use." That's a little more wiggle room there. But it's not the same as contraindication.

DR. BARRETT: Thank you.

We will break for lunch now. We will reconvene in this room in one hour, at about 11:55. Please take any personal belongings you may want at

this time. The room will be secured by FDA staff during the break. Panel members, please remember that you should not discuss the meeting topic during lunch among yourselves. Thank you.

(Whereupon, at 11:52 a.m., a luncheon recess was taken.)

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

(12:56 p.m.)

Questions to the Committee and Discussion

DR. BARRETT: Could everyone come in and take their seats, please? We're going to get started here.

We will now proceed with the questions to the committee and the panel discussions. I would like to remind the public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

I'd also like to recognize the FDA press person, Stephen King. Are you here? No? All right. Well, he's in the house writing "The Shining, Part 2." No.

So we're going to go through, and I will read the questions, and then we will go around the horn and get some feedback from the committee members. Again, just please, after we go through once, then we'll go and have additional discussion.

Please discuss the following with regard to

the format of drug interaction study results presentation in prescription drug labeling:

a) The level of detail on study designs and study results;

b) The advantages and disadvantages of presenting the drug interaction study results in a forest plot versus a table versus a narrative.

So would anyone like to begin? Or Jack, are you okay if we start down in order? Just your initial thoughts on those questions.

DR. COOK: Okay. The level on detail on study design and study results? Well, the design, I submit, is probably of minimal use in the label. I would expect that that be detailed at the FDA, and they can deem whether the results are appropriate or not. So I wouldn't spend a lot of label space on something like that.

I wouldn't say as far as the advantages or disadvantages of producing forest plots, tables, or narratives. Certainly the forest plot, we've started to use those more and more, not only in our labels but internally, to present a large amount of

data. And it puts it into relative context.

One thing I do like about it is you can make sure that your recommendations are consistent for at least consistent PK changes as far as dose adaptation. I think that's a little easier to do than in a table.

So I'll leave it at those opening remarks, and you can go left.

DR. BARRETT: Jim?

DR. KEIRNS: Yes. I have the same comment that Jack does about design. I think we probably don't have enough real estate in the label to have design, so we just have to trust the judgment of the people that put it in the label that actually it was a good study or it wouldn't be there at all.

In terms of the data presentation, like Jack, we're using forest plots a lot. We particularly started using it about three years ago when we saw a publication from OCP scientists. And in the example that Dr. Reynolds showed on mirabegron, I was intimately involved in that, and we were quite pleased with the way that worked out.

Now, one thing that was kind of interesting about it was that our proposed labeling for Europe was exactly the same as the U.S. But then at the late stage, during label negotiations, the reviewers in Europe said, "Oh, well, we don't understand this plot. Please replace it all with text."

So if you go look at the European label for mirabegron, it looks kind of old-fashioned for the presentation of DDI, whereas the U.S. label is what Dr. Reynolds summarized.

DR. BARRETT: Maybe just as we're going around here, if you would like to comment from FDA's perspective, just let me know because some of this, I think, maybe you want to make comment to as we go through the initial comments.

Kathleen?

DR. NEVILLE: I think levels of evidence, maybe not detailed, per se, but levels of evidence for study design would be helpful. And while I appreciate these guys' comments, we struggle with having practitioners understand what Cmax and AUC

is, never mind a forest plot.

If you're trying to get the average practitioner to understand what drug-drug interactions matter and what don't, I don't think a forest plot will accomplish that; perhaps in addition to tables and narratives, maybe. But as a standalone, I think that that would absolutely not achieve the goals that we're looking for.

DR. BARRETT: Kathleen, let me follow up, though. As a caregiver, what do you want to see in there? What do you see is the biggest benefit?

DR. NEVILLE: In the materials that were given in preparation for this, I found that tables and the narrative the most helpful. I think a more concise, like you said, high yield introductory paragraph is very helpful.

I've found that tables with what happens to the -- whether it's a victim or a perpetrator, and then potential. I know FDA can't dictate care, but potential implications for dosing is very helpful to the practitioner, especially my biases in the upcoming years.

As trainees get less and less pharmacology, they are going to understand the implications of DDIs less and less. So they're getting less statistics, too, so the simplest language. And like was mentioned earlier in some of the talks, perhaps not referring to AUC but to exposure, things like that that make it easier for the average practitioner who doesn't understand the level that we do clinical pharmacology, would help them understand the implications of drug-drug interactions.

DR. MORRIS: Well, I found Kathleen's comments very interesting. So I agree. I think the information that is presented should be very simple and straightforward. And maybe one of the most important aspects is changes in dosing regimens if something is completely contraindicated.

You have to say, what should you do with this interaction? This is what, I think, the physicians are looking for. Does the dose have to be decreased? What should it be decreased to? So

that sort of information is very important.

With regards to study design, I agree that I don't think that needs to be there. But study results, I'd like to see maybe a link to information, so those individuals that want to look at this in more detail, what exactly did this study show? And these would maybe be for specialists or be for residents that really wanted to understand the interaction. So having a link to that information would be valuable.

With regards to forest plots, I really like the forest plot, so it shows the way I was looking at it. But what I thought was -- and certainly you could use, instead of AUC, exposure. That would be one way of doing it.

I liked where you have really the stippled lines, the variability that is within the normal range. And you can see if you're outside, if you're higher or lower. But then also, what should you do? So you have this interaction, so you reduce the dosage to 20 milligrams daily. So again, giving clear information on what you do with

this type of interaction. Contraindicated. Do not administer together. Something like this.

But again, some interactions are very complex, and I think those interactions you can't really describe by a forest plot. And that's where I think you really need to get into at least a table to describe in a bit more detail the interactions.

So that's how I felt it would be most valuable to practitioners.

DR. MILLER: A couple of thoughts. One observation I made, the drug interaction information and results come in a lot of different places in product labeling. I find that very confusing to follow through all the different areas.

If this is all a function of drug interaction, maybe there should be a concentrated effort to place as much of that information in that particular area, so you don't have to hunt and peck around for information. That's one issue.

As far as how you present the information

from a literacy perspective, using pictures, diagrams, to supplement some narrative information is an important aspect of that. But perhaps rather than having lengthy narratives, maybe a figure with some callout boxes that highlight key results or something like that may be a useful strategy.

Then the last point I'd like to make is that whatever result is presented, there has to be actionable information aligned with it. And the reality is, I'm looking at some of the examples from earlier slides, and it just simply says, well, this increases the plasma concentration.

So the prescriber -- how do you interpret that? How do you make that judgment about what action do I take now because of that? Or should I just be aware that that does that? So those are my three points.

DR. MALONE: Well, I'd like to thank the FDA for assembling this committee. I've been working on some of these issues for over 10 years with respect to how to evaluate the evidence and putting it into meaningful clinical decision support to

clinicians to improve patient safety. So a lot of these issues are fairly close to home for where I do my research and the types of projects I'm involved in.

I guess importantly, at this point in time I'm the principal investigator on a funded study from the Agency for Healthcare Research and Quality that has three different working groups that are addressing various issues with drug interactions and clinical decision support.

So I'm going to interject some of my comments with what I'm hearing from these working groups, some of the issues that they're struggling with, although my comments are specific to myself, not necessarily reflective of the entire working group.

But with respect to the level of study detail and study design results, the FDA label is a relatively static document. There's no page restrictions on how long that label is. There's no width or size restrictions. We see slim jims. We see huge poster-sized labels, et cetera.

So that the notion that we need to be restrictive in how much information we provide in the label to me is kind of silly in that when we try to evaluate the evidence that's included in the label relative to the strength of evidence we're seeing from other sources, many times these studies that are done premarketing never get published and they're black box phenomena. And I don't mean black box warnings; black box in terms of we don't know what happened. We don't know what type of study it was.

So I think the level of detail needs to be dramatically ramped up. And I may be alone on this, but if there was a reasonable expectation why we would want to keep this information hidden, I could understand it. But I see no reason for that, that we really do need to know the study design.

We don't know need to know all the details, just like we don't see all the details about randomized clinical trials in the package insert. But we need to have some basic information about the approach of the study.

With respect to the study results, most individuals who are looking at this information are usually not the practitioners. They're synthesizing it to a practitioner at some level, whether it be at the drug knowledge database level or some other intermediary that's going to take that information and synthesize it into, hey, listen, I don't think you should give these together, or, that's fine, I don't see a problem here.

What happens is when you are using terms that are subjective in nature -- we recommend, not recommended, may reduce the dose -- those general terms really become difficult to be actionable to the clinician. So the more detail that we have with regard to study results, I think it's key.

With respect to that, the notion of a narrative -- narratives are less meaningful, I think, than having the data in the tables and/or forest plots. The advantage of forest plots, relatively quickly interpreted. The advantage of a table if the data's there is that it's detailed

enough so that you can do secondary analyses in the long run if you feel like you have the information across multiple studies.

But because many of these studies never get published, having that raw source of information I think is critical for people trying to evaluate this to take it to the next level, meaning what should the clinician do.

So I would avoid narrative statements. I would argue to include as much information as you possibly can, especially given that the label has largely become not the primary source of information for the busy, active practitioner. It's the people who are working in the drug information centers, the drug knowledge database vendors, these other trained intermediaries that are taking this information and synthesizing it. Thank you.

DR. BARRETT: Again, please state your name before you start.

DR. MALONE: So that was by Dan Malone from the University of Arizona. Sorry.

DR. BARRETT: Thank you.

DR. HORN: John Horn. Yes. Thanks again for inviting me. It's been very stimulating and entertaining. And before I talk about those two specific things, I would just like to make two simple pleas. One is, I know we're not supposed to talk about where in the label the information is, but I can't stop myself.

(Laughter.)

DR. HORN: I have no objection at all to having it spread out. But the only thing I would ask is that all of the drug interaction information be put in the section labeled drug interactions. I go nuts having to go through the label having to find all of the drug interaction information. Okay? A simple thing. Please? Thank you.

The second one, everybody down this line has said, sometimes we need detail and sometimes we don't. I have a really simple suggestion. Put links in between the label and the review of the NDA because that's what I have to do. I have to go back to the NDA reviews to look at the data because

I don't believe what you guys write most of the time. No offense, but I want to know what did the study involve?

Now, I'm odd because I like that stuff, and other people don't. So you don't have to clutter the label with it, but put a link in. It would save me the time of going up online, downloading those huge documents, and flipping through 40,000 pages in order to find the one I want. Easy to do. It would make our lives much, much easier.

As far as the actual questions we're supposed to be answering, the level of detail in study design, as I said, if you can link it, that would be great. I think there's some minimal amount of detail that needs to be in the labeling so that anybody can get it. And that's why I really don't like the forest plots. The problem with those is, you can't see the trees because of the forest.

(Laughter.)

DR. HORN: You look at a forest plot, and first of all, I have a lot of trouble figuring out

where that thing comes down on the line. I want to have to get a ruler out because the bigger they get, the harder it is to figure out what they are. There's no dosing data. There's no duration data on those plots. Totally useless to me. I can't make anything out of that. I don't know what those numbers mean.

I'm sure the statisticians knowledge exactly what they mean, but have you guys actually gone out and asked a bunch of practitioners to describe what's on those things? Because I'll bet there isn't five practitioners in the world that knows what's on those things. They are very difficult to interpret compared to a table. Everybody can read a table.

With regard to the tables, again a couple of really simple things. Please alphabetize the listings in the tables. You've got lists of tables that are 40 drugs long, and I'm looking for one drug. Why do I have to go through 40 of them to find it? It should be alpha. Right? Simple. Do it. The tables usually contain information.

They've got the dosing of both drugs. They have the duration, usually, of both drugs involved. That's really the information I'm after.

Then we get to the outcomes, Cmax, AUC. I personally like that because the only way I can decide whether this is likely to be a problem or not is to know what the AUC change is. I'm looking for that.

What I don't particularly care for is the statistical presentation of that data. First of all, there's no easy way to look at it and ask the simple question, is this statistically significant or not? Now, of course you can figure out what the confidence interval is. You can figure it out. But we're talking about practitioners, like I used to be. I don't know how to do that with a confidence interval.

I would much prefer, instead of a confidence interval, to see the range of outcomes because we know there is a huge inter-patient variability in the outcomes of interactions. And that's a very important piece for me when I'm making a decision

about whether I want to do something about a particular interaction.

If I know that even though the average changes 40 percent, if there are people that are having a 200 percent change, that's important for me because some drugs a 200 percent change may not be very important, but for others that might be really important.

So knowing what the range of response is, is much more useful to me than confidence interval. I don't care about confidence interval. It really doesn't help me. And I know a lot of people out there who are less sophisticated than you all would be able to deal with, I think, just the simple range numbers much -- if you want to put the confidence interval in, that's fine.

Try and be consistent in your labeling. Just looking at the examples, we've got LS mean ratio. I think LS means least squares, but I'm not sure about that. I suspect if I gave that to my students, nobody would know what that meant.

Change in mean ratio. Why ratio estimate?

That's 1 minus the change in percent. We don't have to clutter the label with that. I can do that math. That's not hard. I'm not sure what difference that is compared to the others.

So those are some really simple things that would clean it up. And obviously, my preference is tables, not the -- the forest plots to me are just -- make me nuts. I don't like those at all. I just can't get enough information out of it to make any sense out of it. It's just not helpful.

I'll stop there. Thank you.

DR. FLOCKHART: I'm a forest plot fan, but I'll come back to that. I'm Dave Flockhart from Indiana University.

I think in terms of the first question, the level of detail, there were two things here, and I think we're walking between the two. One is, I think, we're not creating the label for a bunch of academic researchers. We're creating the label for practitioners.

I think it's perfectly legitimate to link it, to link it to the NDA or to link it to good

academic research. But Dr. Bates and others made very clear that 2 percent or much, much less of the people are actually going to be the people digging in.

I think, as a physician who practices with patients who have lots of drug interactions -- I see a very biased group of people, I think. But I think more pharmacists see them. But I think at the patient level is something I really think is very important.

We were given a series of tools this morning in the four excellent talks before this that allow us to prioritize interactions. And there's a lot of data on this. Whether it be the word contraindications, whether it be specifically some serious discussion at the FDA about what goes on the highlights section, or whether it be Dr. Bates' 15 or 17 really bad interactions, I think a really good thing for everybody would be a binary decision, drugs for which drug interactions might matter and drugs for which they might not. Just yes or no as a first thing, and something you could

translate eventually into some kind of symbol or something that would really be patient.

Now, that allows you to actually have to get cortical and think about what that level of risk would be. Some level of scientifically guided decision would have to be made about what goes into the interaction group and what goes into the not. Without getting into that debate, I think my only thing about it would be the general perception that we horribly, horribly, horribly overestimate these interactions at the moment because of the way the drug interaction databases that are commercially available have practiced over the last 20 years.

It is clear from the whole morning we have vast surfeits of information, and we have huge alert fatigue. And that is a public health risk, that itself. So every time you add more information, I think you have to think you're adding a public health risk if you add more information.

So I'm for proposing a binary decision. Also, I think then if one walks through it, the

next step is to alert people to who are the people that you're focusing on at most risk? Because even with bad interactions, the pharmacokinetics often doesn't mean anything.

I was informed in my own training by the legendary Dr. Abernethy here, who pointed out to me many, many years ago that there's a cimetidine/benzodiazepine interaction that is purely kinetic and not dynamic. And he measured both, and this is probably the first study that really killed that point.

But it's been made many, many times, even in the worst interactions that we have -- terfenadine/ketoconazole -- if everybody had died, half the population wouldn't be here. So there's a very, very small number of people who suffered in that particular context.

So it's very useful, I think, to put right at the top of the label that you care about, what are the risks? Hypokalemia. Which interacting drugs? Right up front. What are the risks that increase the risk of a person experiencing that

interaction? And then, of course, as was pointed out, what do to. Those three things -- do you care, who do you care most about, and what to do; those three things.

Now, specifically to forest plots. I'm a fan of pictures as opposed to -- I think a picture is worth a thousand words. I think most tables aren't read by people, that's the problem. And they're better, from a scientist point of view, but they don't get read.

They're fine to link to. But I think you need something for practitioners, and I think forest plots are up there as one of the best ways of presenting it. I have problems with forest plots, too, like John does.

I think log scales should be banned because your average medical student, never mind anybody else, can't appreciate the value of that. I think it's got to be really clear what the error bars are, and I'm a fan of the range as well, putting on the range on there rather than some estimate of the error that's clear to a statistician but not to a

practitioner.

But a range, I totally agree with John about that. A range is clear. And a range also deals with one really important thing, and that is that very often you're looking at the mean of something that is not normally distributed. It's not a nice, normal distribution.

There are people who don't experience the interaction at all, and there are people who experience a bad interaction, and there are people who even have the interaction experienced in the opposite direction.

So I think having a range is a way of communicating that without implying, by putting down there a mean with a standard deviation or a standard error, that it's normally distributed, I think that can be deceptive.

So to summarize, I think the scale should be clear. The size of the interaction should be clear. And it shouldn't be presented in a way that is deceptive in terms of the error. But I do think a picture like a forest plot is something valuable,

and they communicate very quickly that there's a big difference to an arm.

One last point about it. A pharmacokinetic change on a forest plot to me is pretty useless. It's got to be some respectable clinical outcome derived hopefully -- and this is a fantasy, really -- derived hopefully from some kind of randomized thing. But the problem with that is we'd all go bankrupt if all these things were randomized, controlled trials.

So to Dr. Abernethy's point early on, I think we should entertain a discussion about what other data, beyond tightly controlled, what observational data might be included in that. And I think one could usefully come up with a series of criteria of what are valuable observational data and what are not.

There is such a thing as a really, really good case study that's very carefully conducted; not all case studies are simple, quick observations. So I think having a discussion about that would be something valuable.

I'll stop there and shut up.

DR. POLLI: James Polli. My major comment is very similar to what David was talking about when he first started talking. So he saw them, and his first comments were -- he talked about how the label has several stakeholders.

I think that point was made very clear from this morning, sometimes in a painful way. Dr. Juurlink talked about how most practitioners, most physicians, prescribers, don't use labels frequently. Meanwhile, the gentleman from First Databank says it's the most important information for what they do.

I guess during the course of the morning I was mostly thinking about prescribers, pharmacists, and actually also patients. And I guess my major comment would be, I have a hard time thinking about this question because it seems like a single label that's black and white PDF, found at dailymed.gov, it's clearly not working for all stakeholders, it seems.

So to me it would be great to have labels

for different stakeholders. And you do have, at least for some drugs, a label for patients, which we maybe didn't talk too much about.

As far as study design, I think most stakeholders probably -- I agree with Jack, probably not very interested. If it's not done well, then don't include it. Study results, I agree with Michael in terms of actionable. Seems to be extraordinarily important for several different stakeholders.

As far as representation, I think I had the same experience as Kathleen. I like graphs, but as I was reading through the materials, I said, I think I like tables and simple text a little bit more than I had originally thought of. I like the idea of a binary decision tree, at least for some stakeholders.

MS. CABALLERO: Rose Caballero, representing consumers. I'm from San Antonio, Texas, and I've been sitting here listening to all these discussions. And when you consider that all the physicians/clinicians are confused by the results,

I'm sitting here thinking, where do you think the patients are? Certainly, if they were to look at one of those reports, how do you think they're going to interpret it?

So what my hope is that as you look at finding ways of making the reports easier for physicians and more physician-friendly, that that will trickle down to making consumer reports simple. KIS, Keep It Simple for patients to be able to look at and see and question themselves and ask their physician, "Is this something that I should be using? How is it going to benefit me? Is there any concern for me? Is there any risk?"

So you mentioned the forest, you'd get lost in it. Well, imagine what the patient's going through with all those trees. So my concern from the consumer aspect is, I would very much like to see reports on it because as a consumer, usually the only report that the consumer can get -- yes, there is dot gov, but there's not too many consumers that realistically go to that site to look up reports.

Pharmacists from certain pharmacy chains do give out a written report, attach it to the prescription and give it to the patient. I would venture to say very few take the time to read it to see what the medication is for, what they should look for, for side effects.

There's consultation that is available. Sometimes they'll take the pharmacist up on it if they want to have information because they'll usually say, "Oh, no. My doctor already told me how to use it." And what the doctor may have told them is, "Take it three times a day before meals," but they just heard "three times a day."

So education-wise, there's still a lot missing for the consumer. I can tell you that. So my hope and what I'm looking for is that there'll be more information made available for a consumer. Thank you.

DR. BARRETT: I think you're really hearing an issue of audience, and that comes through a lot of these discussions from the standpoint of who reads the labels. Hearing just the diversity, we

haven't even gotten halfway around the room, and it's just amazing.

I'm going to add to that because in terms of the level of detail on the study design and results, I would be really reluctant not to have that in there. And maybe some of this is from my work in pediatrics, but I know I could say when you're looking for any information at all, and particularly if you're going to pull in data from the literature now, some of those studies will not fall in the category of very well-defined, or perhaps not in a large number of subjects.

But you're still going to put it in there because it's the best information we have. But it will be quasi-dynamic, and as new information becomes generated, it will be replaced. But I would still like to know the details for who this study was in, at least the duration of therapy, the number of patients. Are these critically ill patients or are they healthy volunteers?

That, I think, is important, maybe not from the standpoint of a rapid-fire assessment from the

standpoint of the caregiver, but anyone who's judging the validity of that information at any point in time needs to know that detail, especially when you see your changed control when new information becomes available. Other parts on the label, particularly the clinical trials, are described in more detail. So I think there's some level of consistency by keeping that in there.

In terms of the actual results, on this side I think again you're looking for interpretation. The results are there. There is lots of numeric data. This is always the compromise in terms of being able to recapitulate it in the label, that it's informative but understandable.

Again, recognizing that, we would love this to be simple, but it's typically not. There's still a lot of information that you're capturing that we have uncertainty about. And I think the great role that the FDA does in collaboration with the sponsor is to do your best job at summarizing this in reasonable detail. But I think it's just a QC check, that it's vetted against the caregiver

that they can interpret this and make sense of it, that you are delivering a message.

So on that topic, I guess what I would say is I would prefer some narrative interpreting these results specific to dosing. And I agree. I think the clinicians don't think in terms of even concentrations.

You may have this evolving section of the label that describes the pharmacokinetics. So you've seen it in the beginning part of the label, so I don't think we need to -- you want that consistency across this. So if you're going to describe pharmacokinetic metrics, then it's not unreasonable to use that later in terms of judging the results of a DDI study. But having said that, the caregiver is past that. They want that quick information, and talk to me about dose.

The other thing that we haven't mentioned yet is the therapeutic window. The problem I have with the forest plot is not that it's not a quick assessment, but it doesn't speak in the context of a therapeutic window.

For some drugs, one tree, so one presentation, may be fine. But you really need to look at that in the context of, what's the expected variability in the exposure for that drug? Should I be concerned or not about it?

So it's an issue of providing, I think, the narrative that interprets the data. That is really the key in my mind.

DR. VENITZ: This Jurgen Venitz. It's still me. And I think the question comes down to, who is your primary target audience for the label that we are talking about? And my personal opinion is it is not the practitioner. It is not the patient. Because I think they get their information from secondhand, the curating databases that we were talking about earlier today that involve more than just label. And they condense it in a way that makes it usable to the practitioner.

So I don't think your target is a practitioner. I do think your target is the kind of people sitting around this table that try to make sense of it and find out or figure out how to

make it palatable.

I'll give you an example and little anecdote. A couple of years ago I did a lecture to a bunch of specialists, medical specialists, on drug-drug interactions. We talked primarily about metabolic drug interactions, and by the time that I was done, they all enjoyed it; at least, apparently they did.

One person approached me, and he told me that he finally understood why all those new drugs were tested in combination with ketoconazole, a drug that he had never used and he never anticipated using. But he now understood that ketoconazole was not really used as an anti-fungal. It was used as a prototypical 3A4 inhibitor.

So it's that level of sophistication, pun intended, that you're going to have to deal with. So it's not just a matter of whether we're using forest plots or geometric mean ratios. There's a much more fundamental lack of understanding in the practitioners that you have to assume. That's why they need to use databases.

So in my mind, there should be detailed information on drug-drug interactions. And I would make the argument if you are a practitioner and you read the reproductive sections of a label, I'm not sure whether they would understand that either.

So I'm not picking on drug-drug interaction. I'm just saying the labels have evolved to something that goes beyond an instruction manual for a primary care physician to figure out how to give the drug. They use other sources to do that.

So as far as the specific information is concerned, I'm a fan for tables because they are more informative. They also get me away from this comparative aspect that the forest plot has. I like to look at not only mean ratios, I do like ranges. And I think you heard that comment before because the 90 percent confidence interval just tells me how confident am I that the mean actually falls into that particular range. It doesn't tell me anything about the range of inhibition, if that's what is concerned. So I would like to see the range expressed rather than the 90 percent

confidence interval on the exposure metrics.

In addition to that, lots of times the half-life is not mentioned, which sometimes helps me figure out whether the drug is really affecting absorption versus elimination. So that's something I think on a case-by-case basis.

But in addition to the exposure changes, I do think you should discuss briefly, maybe in a narrative or maybe in a comments section, what the presumed mechanism is as well as what the potential consequences are clinically.

So I would put all the high level information that a practitioner might need in the highlights section. That's really stuff that they ought to know and ought to understand.

I think it's also important -- we didn't discuss that in any detail other than during some of the presentations earlier on today -- when I teach this material to my students, I tell them, "There are two things that you need to know. You need to know the odds and you need to know the stakes. Then you can gamble. Otherwise, you

gamble but you're not rationally gambling." All right?

So you need to know what the stakes are. In other words, are you worried about lack of efficacy or loss of efficacy? Or are you worried about toxicity for whatever interaction of whatever special population you're looking at? And that's stuff that should be up front in the highlights section so the practitioner understands, this is what I'm gambling with. And then the highlights section tells them enough to rationally gamble, and if they need to know more, whether they need to use those databases.

Yes. I think that's it for right now.

DR. AU: I'm Jessie Au. So I've been a pharmacist. I've been an academic scientist generating the type of data that you see. Now I'm a drug developer. In all three roles, I care about drug-drug interaction because you can imagine, if my new drug had an interaction that would kill a patient, that's the end of my drug.

However, it's really the fourth role that I

see that I would like to offer my opinion on, and that's the end user, is the patient or as the mother of patients. More and more now, we don't even go to pharmacy. We just get our drugs through the mail. So I get a package insert. Then I say, "Shoot, I can't read it. I don't have my reading glasses. I don't know where it is." And there's a long list of things.

So I think that end user, other than this lady here, is really not being represented in this particular meeting. And I think if you look at the reality of healthcare delivery nowadays, everybody's in a rush. I cannot tell you how many times my physician misprescribes drugs for me -- wrong dose, wrong drug. Happens all the time, because they didn't have time. Pharmacists, they don't have time. Technicians hand out the drug.

So ultimately, you're really looking at the patients. And I think now we are talking about -- even the Baby Boomers are now in their 60s. So yes, they are becoming more and more

technology-savvy. I think we have to find a way to communicate with patients so they can take care of themselves. Right? You cannot rely on the healthcare delivery system to work perfectly.

As a scientist, however, I do like high level of information. So on your question number 1, I say, yes, give all the details on your study design, study results. I think it should be there. However, I think the communication to patients can be done a different way, maybe not so much information on the one page that they get from the pharmacy.

Also bear in mind that those names, those chemical names, are very intimidating. And I say that as a PhD in chemistry. Right? So I have a problem with all those names.

However, a patient always know what disease they have. They know the hypertension, the type 2 diabetes. They know all that. So if you can at least say you have these other conditions, make sure that you check on this website for more information relating to a drug that you may be

taking that may have a drug-drug interaction. So I think that would be a good way to communicate to patients.

In the package, however, it should be simple. It has to be, like you say, the high level. Contraindicated, you may end in death, that's a black box warning. They should know all those things. But they have to have a way to get the information when they need to. So that's the first question.

The second one about the forest plot, I like pictures. So a forest plot to me is really easy to read. There's another plot called waterfall plot; you're not even talking about that here. I'm used to reading plots like that, and it's very easy. I take one look and I know what the data means, and obviously, because that's my work.

However, I think plots are easier to get to. You have all this explanation on the side. I really like the forest plots. So I think the table will get lost. The forest plot will not.

DR. MUZZIO: Fernando Muzzio, Rutgers

University. So I'm neither a prescribing physician nor a pharmacist, so I'm going to give you a perspective from the point of view of perhaps an engineer, and somebody who teaches experimental design, and somebody who has an 85-year-old mother and a 96-year-old father-in-law.

So let me start with the last because as fate will have it, both of these people happen to be in the hospital right now for separate reasons. And both of them in the last 30 days were given the wrong medication. I think it's a fact we all know that older people are the people most likely to be taking multiple medications.

Now, in the case of the people in my family, none of the doctors that see them actually know what it is that they are taking because they go to three different doctors. The doctors don't talk to each other. These people are both memory-impaired, so they cannot recite the six or seven or eight things they are taking. And they don't get all their things from the same corner pharmacy. Yes?

So there is no place right now where all

that information is except in the mind of my wife and my sister. They are the two that actually keep track, neither of which is a doctor. Right? My wife is a pharmacist.

But in both of these cases, we figured out they were getting the wrong medication and there were interactions because somebody in the family took the time to actually read the labels and found that, oh, my God, they shouldn't be taking this if they are taking that.

So yes, you might think that you're only writing this for the doctor, but in fact, I think these kind of situations call for a lay person being able to, at least on a very basic level, ask the right question. Okay?

So moving on now to on a more scientific basis, I don't understand question b at all. From the perspective of somebody who's actually written a lot of papers, some of the papers I write also have multiple audiences.

They go to the PhD student, who's really going to read it closely; to the professor, who's

only going to look at the abstract; to the person in industry, who's only going to look at the pictures, maybe. What's wrong with that? We are talking to multiple audiences.

Why don't we use multiple ways of conveying the information? Some people capture the information better in a picture, some people get it out of a table, and some people actually want to read every word.

I actually really, really like the suggestion about maintaining a website with all the appendices and all the other stuff that the statistical geeks like me are actually going to want to know. When I teach experimental design, I teach to my students, but it's ridiculous to look at whether a variable is statistically significant or not if you didn't look at the design because you can look at only main effects or you can look at interactions. And guess what? Your conclusions about what's significant will change. So if you don't know the design, you know?

So I hope that there are ways in which we

can use modern tools to convey information to make the information available in different formats to the different audiences that might need it for different reasons.

DR. PAU: Thank you. Alice Pau from NIH. I guess I'll give a background. I use the package insert probably every single day as two purposes. I'm a clinical pharmacist; I do take care of patients in our clinic, and get asked questions almost every day about drug interactions.

I don't memorize all these drug interactions, and in many cases are drugs that I'm not familiar with, so I have to go and look it up. And that's where I find discrepancies between different labels that don't have the information in all of them.

Secondly, my other role is to write treatment guidelines for HIV, which, as we heard over and over again, that there are multiple drug-drug interactions. So I go to the labels to look up the information so that I can translate that into our guidelines.

So for that purposes, there are two things that I think are important. Dr. Horn said, and I totally agree with, please, please put everything about drug interaction into one section. Many times on a daily basis when I look at these, I missed one section or another because I have to go from one place to another to a third place, and sometimes I missed some information that could be crucial.

It could be very easy to have a section just called drug interaction and have all the information in there, and particularly important, to try to translate the clinical or the PK data into recommendation because you have one place that give you the data, and then you have to go to another place to look and see what the recommendation truly is.

The other thing that's also difficult when I look at these tables is that if you have a drug interaction study that is done that is going to look at interactions of the two drugs and have PK data on both drugs, why not put them in the same

table of drug A, drug B, this is the end result of drug A and this is the end result of drug B?

Right now we have to go to two separate tables, the first one to say, this is what it does to the sponsor's drug, and then you to go a second table to say, this is what happened to the other drug, when they can be put in the same table.

When we make decision, we make decision together to decide on what to do and not separately have to go two different tables. And if you look at the clinicians on a daily basis, they might not have time, and oftentimes what will happen is that they go to just one table, expect that that information is there, and then stop right there and not go to the second one.

So I would really recommend putting everything into one place all at one time, including both the data. And I like data because I need them. I also like the data to know that is this a study that is a single-dose study versus multiple-dose study. How many patients? Is it healthy volunteer versus this being used in

patients? Because there might be a difference.

The second thing that I think that I have not seen in any of the labels are relating to what is the role of therapeutic drug monitoring. There is no mention -- and there are many drugs that have commercially available drug concentrations that can be monitored, and we use them all the time in my clinical practice.

If I'm using rifampin or rifabutin with a drug, I always would monitor the drug level to make sure that I'm getting the right drug level. There's no mention whatsoever if there is a role of therapeutic drug monitoring. I put in my guidelines I recommended for the clinician to do it. But it is not anywhere in the label to be seen.

The third thing I wanted to mention is that most of the information in the label relate to, as we mentioned before, studies that were done by the sponsor. I want to give an example, atazanavir with PPI or atazanavir with antacid.

The current label has very difficult to

interpret information about how to take them together at the same time. You have space it by 2 hours before, 12 hours before, whatever. In fact, when the label was going to be put out, I was given the language to review, and I drew a line of a 24-hour line and see how I'm going to teach my patient how to take the medicine. And I was totally confused. And I don't know how a pharmacist or a doctor can teach the patient, what does it mean by taking this drug 12 hours before that drug, not to take it 2 hours later?

Since then, there have been multiple drug interaction studies with atazanavir and PPI that were done by individual investigators using different strategies -- different time, different doses -- and come up with different results. None of those got into the label.

So the question is, for the consumers, if there are other results, other ways of taking these medications that might be easier for them to do, and those information are not available for them, how can they get that information outside of it?

So I think those type of information is very important.

Lastly, about what information are not necessary -- well, I talk about these. So for me, as far as the forest plot versus table, I like table better than forest plot. I mean, I actually -- reading the material, and I share it with multiple of the clinicians in our clinic and ask them, do they like the forest plot? They say no. This doesn't give me the information.

The main reason is part of it is, especially if you are talking about the forest plot of the multiple different other drugs that has different therapeutic windows, there are different significance in terms of the interactions, it's very difficult to interpret what that really means.

I guess we are more used to numbers, and that's the reason why I like the table much better. And the table being able to give us the information about the study design also helped me as well.

DR. DAY: Ruth Day. Concerning format, all forest plots are not equal. All tables are not

equal. All text or narratives are not equal. We can see this even in the briefing materials that we were provided.

There are two examples of a table early on, and the first one's okay; the second one's better. It's better because it has obeyed various cognitive principles about how people process information. On your own time you can look at these and see if you can tell the differences, but one major thing is that there is some chunking that is done in the second table.

Chunking basically means take like things, put them together, and separate them from other things so they don't all run together. And this is a principle that's been around for over 50 years. It works for understanding numbers and remembering them all the way up to this kind of complex information.

The forest plots that are provided, the first one's okay; the second one is better. It has various cognitive enhancement. So it's not that this table is better than that forest plot, but

let's look at what are the options for making a good table? What are the options for making good forest plots, and text or narratives?

So in looking at some of the examples in the briefing documents, sometimes there's way too much in the paragraph versus separating it out into two chunks. That would make it better. But one of the major problems within drug interaction communication has to do with the long list of drugs that are relevant to whatever's being said.

So often there's a sentence where basically there's a head of the sentence, like a subject, and then at the end there's something at the end, like a predicate. And in the middle, there's this incredible long list. And by the time you go through everything and try to maybe pronounce the names of the drugs to yourself, you get to the end and you forget what the beginning was. Was this something that you should be cautious about, or is this something else?

There's a very easy fix for this, obeying cognitive principles. And that is, you start the

sentence, and then you don't have to bullet and list all of the drugs involved. Just indent them a little bit. Set them off in some ways, and then continue the sentence. Okay? So you can see the beginning of the sentence and the end of the sentence. You know the meaning of the sentence. Then you can see what ones apply to that.

So if we want to know which is the most best way, if you'll pardon the expression, I think it's the wrong question to ask. It depends on how we go about finding the answer.

One way is to have a panel of experts, such as we are here today, and it's incredibly valuable. And I know FDA will make giant charts of all of our comments and compare them. I've seen these, being in work groups and so on. And they will compare all of our comments and sift through and see what they want to do about it.

But what we're basically getting is a contrast between cognition and meta-cognition. We've been talking today about meta-cognition. I like this. I like that. I do better with this. I

think you need that.

So there is a gap between cognition and meta-cognition oftentimes. Cognition are the processes of attention and comprehension and memory and problem-solving, et cetera, whereas meta-cognition is how we think we do those things and how well we do with different things.

In research in my lab, we often find that people's meta-cognition is higher than their actual cognition. They don't know as much as they think they do. They don't understand as much as they think they do.

So I think that in addition to this incredible, valuable experience of getting the meta-cognition of experts is to actually get some evidence by testing. So I would recommend cognitive experiments where we take alternative representations, which could be forest plots, tables, text, and other kinds of things.

We've developed various kinds of spatial displays in my lab that increase comprehension by 80 percent, sometimes even 100 percent. You can

also have hybrids. It doesn't have to be one or the other. You can have hybrids.

Then people read. By the way, these are alternative representations, and what that means is they have all the same information, the exact same information, but just shown in different alternative ways.

So then people, and who are the people? They can be the physicians. They can be the pharmacists. They can be the patients, whatever. The people read. They can keep it in front of them. It can be open book or closed book. And then you test their knowledge, you test their comprehension, and then you test problem-solving using real world scenario problems.

So it could be you have a patient with X, Y, and Z and so on, or you could be a mother with a kid with a certain condition, and so on and so forth. And from this we can get evidence as to what the most effective ways might be in different situations and, of course, for different kinds of people.

So to finish up, there are systemic individual differences in cognition that cut across this content area where some people are very language-based and they want the text. And they may like the tables because there's more text in it. And there are other people who are more language-optional. They can use language, but they like more spatial displays as well.

This happens not only among experts, but it happens among lay people as well. And so we have a lot of stakeholders here, and the FDA does have initiatives now on communication to patients, the type leaflets you get in the pharmacy or that are patient-directed or by mail. And the new initiative is calling these things patient medication information. The ones that are currently out there are called consumer medication Information. They might be four, five, six, three pages long, and the idea is that maybe we can get it down to one page. And so how can you put everything into one page or a limited number of pages?

We've just completed a study -- it was nationwide -- for patients from coast to coast, 1400-plus patients, with alternative designs and effects on their comprehension and problem-solving and so on. And we get huge differences. We can get increases in comprehension and knowing what to do in certain situations by over 100 percent.

So those are my comments.

DR. BARRETT: My esteemed members of the FDA, you've heard a lot of discussion on question 1. Was that an adequate level of detail? Can we move on to the second question?

DR. ZINEH: Yes. I think that's great. Thank you very much for the thoughtful comments. I guess I would just have one question for the folks who recommended this kind of lean approach to the label, where then you can go get supplemental information.

That's a cumbersome process for us because it's not like, the day you finish your review, it goes on the Web. There's a redaction process. There's all this legal stuff that has to happen

before reviews become public.

So you actually run into a situation like you did -- I forget who the presenter was that showed he or she tried to get a label and it wasn't at the drug at the FDA website. That happens sometimes. But that certainly happens for reviews and supplemental materials.

So if there's a lag time between completing that in-depth review, if you will, the evidentiary backbone for the lean recommendations in the label, if there's a lag time of six months, a year, et cetera, does that matter? In other words, is that information so important that you really would like to have it at the time that you put the so-called actionable information in the label?

DR. COOK: I think there may be two different things here because I think the example was given with the SBAs. And if you go on drugs@FDA and go to there, there are things all the while that never get updated there as opposed to using something like DailyMed that has it.

Maybe it's more -- I wrote this

down -- more of a cry of making it easier to find the information. And I like this idea of being linked. And you can think of the label maybe as the start of the basic information. Maybe the question whether you like forest plots or whatever -- I think there was a great answer by Dr. Day on how you should go about that. Maybe the real important question is, what's that first level that you want to have out there for whomever the audience is targeted and the ability to drill down and find the information?

We can make that information available. I don't see the FDA having a problem of disclosing -- I know at Pfizer we tried to do all our drug interaction, our clinical pharmacology studies on -- I'm going to get it wrong -- clinicalstudies.org or whatever it is, even though it's not a requirement. We vacillate back and forth on whether we should do that or not because we don't see a lot of other people joining in on that.

But we can make that a requirement and get

that information out there so you could presumably link in and drill down and at least hit everybody. It may not be at that base level that we want, but maybe that's the way to go about it is decide what we want as a base level and have people drill down.

One of the things I was worried about is I hear a lot of people wanting to look up their drug. And gosh, I'll admit, in industry we don't look at every potential drug that there's a drug interaction with. In fact, we know there are lots of them that we don't do it with because we use a class, ketoconazole, go for all 3A4.

So that's an important part that I didn't see discussed at all, is the extrapolability of things to other drugs and how should we be getting that across so somebody doesn't get the false belief that I should look at the label. I don't see my drug listed, or it's a new drug, and of course it's not going to be updated by one of the labels just yet. How do we make sure that people have the right information to know that they ought to be concerned about it?

DR. KEIRNS: I'd like to comment about the availability of details of study design and study results. My position is, for newly approved drugs, it's readily available. All you have to do is look in the right place for it. Now, it may be that you don't know what the right place to look for it is. With our programs, with a newly approved drug we try all of the relevant clin pharm studies, all the DDI studies.

Now, it takes a year or two to get that done because the journals are not terribly enthusiastic about receiving these things. They say, "Oh, that's not really interesting. It doesn't fit our profile."

We had an approval a year and a half ago. We've actually gotten all the clin pharm studies published now. In some cases it was the second or third journal that we submitted to. And of course, we kept going down and down in impact factor. But they were all in peer-reviewed journals, so that was available.

As Jack alluded to, there's the clinical

results database. My understanding is that we're obligated to put all the results there 30 days after approval. So that should solve the problem, that the results of the study will be there. It's a legal requirement, is my understanding. Now, maybe there's an exemption for clin pharm studies. I wasn't aware that there is.

I guess the third suggestion I would have is, ask the company. We would readily provide the data if somebody wants it if somehow you can't find it or it hasn't appeared, and I imagine other companies, for the most part, would do the same thing.

DR. BARRETT: Well, if you're satisfied with question 1, we're going to move on to the second question. We're going to change the format this time because I don't think the around-the-table approach will let us finish today. So let me read the second question, and then as you want to make comments, please identify yourself and we'll get you in.

Question number 2: How do you recommend

that complex drug-drug interaction information be presented in prescription drug labeling? Examples of complex DDI information include the following:

a) DDIs that differ between poor metabolizers and extensive metabolizers if the drug is metabolized by a polymorphic enzyme;

b) DDIs that change over time;

c) DDIs that differ, depending on organ impairment, kidney or liver;

d) DDIs in patients who take three or more drugs, but DDIs were evaluated in pairs.

Please.

DR. HORN: John Horn. I'll take a swing at the first one because that's the first one. This is actually pretty easy, I think. The only thing you really have to think about here is whether the polymorphism affects the object drug or the precipitant drug. And once you've got that decided, then it's a matter of just thinking through it. And there's lots of data out there now, so this is not tough.

So if you're a PM, you can't affect the

object drug any more because you're already a non-metabolizer. So PMs for the object drugs don't have interactions with that enzyme.

If you're a PM for the precipitant drug, you're going to have high concentrations of precipitant drug, and you'll have greater effect. And you can just flip that rationale around, and it works exactly the same way if you're talking about somebody who's a PM in the opposite direction.

So it's fairly straightforward if you have complete inhibition, if you're a true PM. Now, part of the problem is in the data now as it exists for the genomics, there's a lot of these partial metabolizers out there. And they still will have some effect when you give them an inhibitor of that enzyme. And there's lots of examples: 2D6, where there's partial activity. So if you're a true PM, there's no enzyme, so you can't inhibit it. It's just simple.

Now, the only thing that gets more difficult is if you have a multiple pathway drug where you're a PM for either a primary or a secondary pathway,

and then you come in with an inhibitor of the alternative pathway. And in those settings, you can produce remarkably big interactions.

So it all follows the same sort of logic that we use with any interaction. It's just that you've added in one additional piece of variability. And I actually think that much of the variability that has been unexplained to date in the data is pharmacogenomic. I think a lot of it would be explained if we knew the genetics of those patients that were in those studies.

DR. BARRETT: In terms of the presentation, though, exactly what you would -- so how to present it.

DR. HORN: Yes. The problem is how to do that easily in the labeling. And I think right now it's not easy to do because we just don't have good data.

DR. BARRETT: But Dave knows.

DR. FLOCKHART: This is about how to present. And I totally agree with everything John said about it's not rocket science to actually

divide this up. But I come back to what I said before. I think not everybody responds the same way to a drug interaction, and including pretty high up in the label, what are the factors that increase the risk, or decrease the risk is reasonable, I think. In fact, it's more than reasonable because the vast majority of interactions don't occur. They don't actually occur in people, even though we warn them.

So I think including a table of things that a clinician, a patient, or a pharmacist can understand about what increase there is -- and it would include genetics, I comply agree -- they would also include time, and they would also include the administration of multiple drugs.

DR. BARRETT: So you have a narrative before that that talked about who the vulnerable population was?

DR. FLOCKHART: Precisely. That's what I'm trying to get at, to have included who is most vulnerable to this interaction as a relatively high level thing in labels.

Just to address the conversation before, I'm not opposed -- I think it's very, very important, actually -- to have detailed information about study design and so forth available to someone who wants to look deeper. That might not just be researchers; it might be educated patients and so forth, people doing health policy-related stuff.

But to me that can be linked. And I'm struggling with what Issam's problem is in terms of that. If it's all approved as one label -- maybe we're struggling with words here. Why is it so hard to look at some data and present others to different people? To me it's all just a question of all the data is there.

DR. ZINEH: It's a question of business informatics. It's not a question of -- it's not a problem, per se. It's how you do it. It's just like everyone has logistical informatic challenges. I think that's where we're going with this.

The other problem with that model -- and I'm not saying it's not a good model; it's compelling. The other problem is if someone gets a package

insert in their mail order, how are you going to link that to information?

So I don't want to create the impression that it's not something of interest because it's been brought up in several scenarios, but it's an informatics issue, is what I would say.

DR. FLOCKHART: Why give the patient the label at all if they're not going to --

DR. HORN: This is John Horn. The person who gets the label in the mail order, like I do, if I was a consumer, I wouldn't -- I'm not the person who's ever going to link anyway. So the linkage is really for those of us who want to do something else with the data or want more, additional information.

Really, the label shouldn't go to the consumer. They should be getting the patient package insert. You guys have done a great job with those, and those probably have more than enough information for most consumers.

DR. VENITZ: I would just make a general comment, and I think it regards both number 2 and

number 3. It's important to distinguish between what is evidence, meaning what was actually done, empirically studied, and what the conclusions were as opposed to what was extrapolated, whether that be from in vitro or any kind of the simulations. And I think that applies both for number 2 and number 3.

So again, given the fact that I think the label is your main communication tool to high level practitioners or to researchers, you want to be as close as you can to the actual database that supports time dependence.

Number 2d, I would just make the statement that we have to confess we typically don't know what happens with anything other than two drugs together. Everything else is a guess. So I don't know how much opportunity you have that actually three drugs are studied together. So we use information based on two-way interactions, and then we extrapolate what happens when we have fivefold interactions.

DR. PAU: So with regards to the first

question over there, or actually 2a -- I'm looking at page 15 of the briefing material for fesoterodine -- I look at that paragraph, and I was trying to write it out myself to figure out how I understand it. Then when Kellie presented in her slide using different lines to write it all, I understood it much easier.

So this is again the way you present that information. If you really want the clinicians, pharmacists, or even consumers to understand what the paragraph means, it has to be in a way in which it could be easily digested and understood because that paragraph I was looking through, I said, okay.

So I actually had to write it out to say what does that really mean in terms of a poor metabolizer comparing with someone who is not a poor metabolizer, with ketoconazole or not with ketoconazole. But it was so much easier when Kellie showed it in her slide. So I think it is just a way of conveying the message if you want to put that kind of detail in the package insert itself.

Then it goes into the complication of, we don't even have a way really to identify who is a poor metabolizer at this point. In the general practice circumstances, the data, and you're prescribing the drug.

So is this useful for the prescriber if they are picking up the prescription to write that prescription today and you're going to use it for the patient?

DR. DAY: Ruth Day. In thinking about these various cases, why don't we rely on existing ways that people think about such things, even in everyday life? So if you have metabolizers who are poor, moderate, and extreme, you got three categories. Why not think about histograms, where you have along the bottom degree of metabolizer or type of metabolizer, from low, medium, to high, and then an appropriate measure on the Y axis about what's going to happen?

For changes over time, time, we think of a timeline. We heard that here today. Have a timeline starting it now, administration, and

relevant points of time there, and look to see what goes up and down. It could be a line. It could be a bar chart.

As for representing multiple drugs being taken, let's at least start with three and get a good representation for that. There are lots of good 3D representations for things that people see in everyday life, and perhaps we could build on that. So let's think about how people process information in these various situations to begin with.

DR. BARRETT: My own comment on this would be I'm kind of defaulting to Dave's opinion in terms of identifying vulnerable populations, being able to describe them in the context of these more complex patient subtypes.

So specifically, patients in which polypharmacy is an issue and a problem, there could be a section that discusses this because if you knew a particular triple combination that was problematic, or four-drug or whatever, then you would provide the adequate detail, and perhaps

you'd have data to support that.

But in the absence of that and where you suspect but don't have necessarily good clinical evidence, I think it's still reasonable to say, patients receiving antiretroviral therapy, including X, Y, and Z class, it would be very reasonable to expect an X-fold increase or whatever the wording is.

But again, I would default to wording that is linked to clinical relevance even if it's based on some rule of thumb with increase in exposure. But again, I think that it should be stated in whatever, in that text, whatever it is, a 40 percent increase in AUC.

But I think you have the quantitative interpretation, but you're still highlighting the fact that you think this is clinically relevant in terms of the polypharmacy that may exist. But it's really, I think, tied to patients who are vulnerable to drug interactions, and that really also addresses the issue of the organ impairment as well.

The same thing with DDIs that change over time. I think you're trying to provide an expectation; if you're taking this drug for X amount of time, you might expect to see whatever, however you're going to describe that interaction.

But I think if you address the wording from the standpoint of an expectation, that, I think, is ultimately more valuable than summarizing just the results of whatever small study you have. I think it's the interpretation that has to be clearly stated. I'm stranded on an island somewhere. Should I really care about -- what's the information I'm going to have in that label that tells me if I should be concerned or not?

So I think, at a high level, that's what you want to see. And then the drill-down is there. Again, I know we're trying to be pithy when we can in terms of the good, relevant clinical information quickly. But I think the adjoining detail, at least in a highly summarized form, has to be there right next to it. That's my opinion.

Please.

DR. NEVILLE: I was just going to make the comment that I think this then goes back to a comment made earlier, that if we're looking at all this, it needs to be in one place.

So if we're going to talk about poor metabolizers versus EMs versus changes over time, it would be extremely helpful just to have drug-drug interactions in other relevant information section. And then you do have the latitude to do everything you're talking about instead of searching throughout the whole label.

DR. MORRIS: Yes. I just wanted to follow up to some reviewer comments, Jeff. And I agree with Kathleen. It's very important to have this information in the drug interactions section, and enough detail so that someone can understand the changes that would be expected.

But again, it's very important to have specific recommendations if at all possible. It's interesting to know the changes that might occur in poor metabolizers. Okay? But what does the practitioner do? Do they need to genotype? And

if so, where do they go from there? Is there a recommended dosage that they need to use?

The changes in DDIs over time, what is done? Is there a change in therapy that's needed, or is this something you just look for over time?

Organ impairment, extremely important. That probably needs to be in the highlights because people want to know that right at the beginning if they need to change dosage with organ impairment.

Then multiple drugs -- again, specific examples of those drugs that would be taken by that patient population, very important information. And again, what's the recommendation? What needs to be done with that particular patient?

DR. MILLER: I'm going to echo some of what Marilyn said, some of what Kathleen said, some of what Ruth said. The information in there is good, in the example that Ruth went over, pointed us to is very, very dense, and it's just a matter of stylistic presentation.

If you had all that information in one spot, you'd say special considerations under drug-drug

interactions, and if you have a patient who is at risk for these conditions or these circumstances, this is what you need to do. This is why, and this is what you need to do.

DR. HORN: This is John Horn again. I think that maybe one way to think about these for difficult issues you've got here is to maybe break them up because as Dr. Flockhart mentioned, having a section -- we call it risk factors in our book -- but it's mitigating or risk issues that make the interaction more or less likely to cause problems. And we've been doing that for years and years and years and years because most of it is pretty easy to figure out. So that's stuff that you could do pretty easily. That's really pretty straightforward.

DR. FLOCKHART: It's not in labels.

DR. HORN: Pardon me?

DR. FLOCKHART: It's not in labels.

DR. HORN: Not in which?

DR. FLOCKHART: Labels.

DR. HORN: Labels? Not in labels, right.

So that would be something that could be put into a label pretty easily. It wouldn't take a lot of difficulty. Some of the other stuff like the polymorphism effects, we just don't have very good data and not very much data. So it's probably too early to really jump into that pool.

One of the things that we've done is we made an arbitrary decision, which I know we can do much more easily than you can. But if the FM of the drug is less than 50 percent for that enzyme, we probably don't care much about it unless it's a pretty narrow-ranged drug. Maybe 30 percent for some of the drugs.

There are cutoffs that we use to make those kinds of decisions. But I think, again, we're probably just early. The drugs that change over time, I'm trying to think of these. And besides the bosentan example in here, ritonavir is a great one, which makes us all nuts because it's an inhibitor/ inducer.

But there's a little data that suggests verapamil's P-gp inhibition becomes induction over

time. But I've got three fingers used up, and I can't think of any more examples.

DR. FLOCKHART: Efavirenz.

DR. HORN: Efavirenz, yes. So we've got four now. So this is really not a huge number of issues, and I'm not really sure how you deal with that. I think that the problem -- clinically, the issue of the change from first dose to steady state, I don't care what happens with the first dose. It's almost never going to be a clinical issue. It's what happens at steady state.

So if a drug goes from an inhibitor to an inducer or from a modest non-inhibitor to an inhibitor over time -- rifampin's a great example. It's not an inducer with dose one; it takes a little time. Erythromycin is not an inhibitor with dose one because it's the metabolite that inhibits.

So we don't really care what happens with dose one. So I think in those kinds of things, I would just focus on what happens at steady-state because that's what is going to eventually affect the outcome of the patient.

DR. HUANG: John, you mentioned some of the cases where we have multiple factors, multiple inhibitors or multiple inhibitor plus conditions. You indicated it's very important to look at the quality of data, what data we have. And I think you mentioned that we probably are ahead of ourselves. We don't have that information.

But we are seeing more information in submissions. Not only the sponsor has conducted multiple -- well, started with individual studies to look at individual factors, and then either by doing combined studies, as Kellie has mentioned one of the examples, or a lot of in silico predictions.

So there are more and more that we have seen: combination of renal impairment with drug interaction; combination of interaction drugs; inducers plus inhibitors, and many others. So I've heard some comments about starting with maybe a 2 by 2 or a 3D exhibit.

So I wanted to clarify from those who think that's a good idea. Are you recommending that we put the information, the results, in that kind of

decision, 2D, 3D? Or maybe the actionable recommendations in 2D or 3D, which may be more helpful? Because not everybody is looking forward to 2D, 3D, forest plot-like information.

DR. DAY: Well, that would be up to you, of course. But you might want to prioritize in various different ways, the most serious or the ones that have management implications and so on, and maybe not for all of everything because there can always be an additional second to say, "other," with less significance or whatever.

DR. HORN: If I can just quickly respond, the idea multiple drugs is a question I get all the time. And we've tried to look at that data. There is a little out there, and I'm sure you guys have seen it as well.

As I see that, the biggest problem is when you've got a multiple pathway substrate object drug and then you give inhibitors of both pathways. There's some great stuff with some of the oral hypoglycemic agents, for example.

If you give multiple inhibitors of the same

pathway, the problem is you're attacking the same pathway, and you can only do so much to inhibit that pathway. I always use the example, you can just fill the bathtub up with inhibitor and it's not going to do any more inhibition.

So multiple inhibitors of the same pathway, unless they're both modest inhibitors, you don't get much addition. You get another 10 or 20 percent, but it's not much to write home about. So those tend to be not that exciting.

The inhibitor/inducer one is really interesting because that's probably order of administration-dependent. And those are very difficult to -- I don't care how good your silicon is, I don't think you can do in silicos with those. I don't trust any of that stuff anyway.

But it's really, I think -- these are really, really good questions that require neatly, nicely done studies under controlled conditions to really try and get some ideas about what the mechanistic issues are. They're wonderful questions. But again, I'm just not sure that's

something I'd put in a label because, man, there's just no way to predict what will happen, I don't think.

DR. BARRETT: Dr. Au?

DR. AU: I'm going to present an opposite viewpoint. I thought the number 2 question is really interesting because it's really tough, which makes it fun to think about. And I also link that to question 3 in my mind because to me, the most important information I should get from question 2 -- as a consumer, it doesn't matter who I am -- is quantitative measurement.

Of course we know, if a drug is excreted by kidney, renal function is going to be a problem. We knew that in the '60s already. So I need a number. So now here comes the in silico analysis.

A lot of people think everything has to be in the lab, and I used to think that, although now I use more and more predictive models to even predict clinical trial outcomes. That's what we do now a lot of times.

I think everything in balance can be

predicted if we know what we're doing. For example, if you have a metabolism changer, you get a Vmax Km. You plug in your PVP. You should be able to analyze. You have the blood level; you should know how much metabolism will be suppressed.

So linking it to question 3, I'd like to see more prediction. You're not going to get all the data that you need. However, now science has gotten to the point that we start to look about, as long as a black box, but with little holes everywhere with light shining in.

So can we not take even two-dimensional data sets, things you generate in monolinear culture, understanding limitation on changing it to a 3D system. There are going to be problems in drug delivery and whatnot.

However, not worrying about that, but just say, can we not get a confidence interval? If I predict this interaction to be X percent, I can say with some confidence that if you are in this category, that's how many percent of your dose you need to have dose adjustment like you do with the

forest plot, 20 percent you need to start thinking.

So I'd like to offer the other side. I really think in silico is an experiment; just the experiment's done on a computer. But it's an experiment by itself. It doesn't have to be in test tubes. Because once you know rate on studies, everything about it is really governed by kinetic processes. And look at all the bridges and roads that you drive on. Your engineers designed them based on those equations. So we drive on them every day. We don't worry about falling in the hole because we believe they can do it.

So anyway, I think we are at that point to start thinking more. The in silico analysis can help us to answer problems in a complex biological system.

DR. BARRETT: Dr. Au has given us a good segue to question 3. But before we move on, is there any last comments to question 2? Yes?

DR. DAY: Just very quickly, we've talked a lot about categorizing the drug interactions by severity or seriousness and by body system affected

and so on and so forth.

There hasn't been much discussion, so I'll just put it on the table, about frequency of occurrence, so likelihood and probability is one part of it. But the other part of it, what are the co-administrations that are likely to be happening?

So if a person has health condition A and they're going to get this drug you're looking at now, they're likely to be taking these others, and so on. So that would then drive what ones would get special treatment for display options, going back to your question.

DR. BARRETT: Any other comments on question 2?

(No response.)

DR. BARRETT: Are you okay, FDA? All right. So we're going to move to question 3, then.

Some DDIs can be predicted based on in vitro studies, other in vivo studies, and in in silico analyses. In those situations, what information about predicted DDIs should be included in prescription drug labeling? Should the labeling

list all potential interactions or a subset, based on drug class, likelihood of co-administration, or severity or interaction? Any takers? We know how you feel, John.

Please, Dr. Malone.

DR. MALONE: I would just make the quick comment that if it's an extrapolation based upon either a simulation or nonhuman studies, that those be clearly stated and kept separate from actual experiences, empirical data in humans, just because there is some examples where the extrapolations don't hold out.

We always want to have a reasonable doubt until we have firm evidence that something does occur. So I know that that has been a thorny issue for our evidence work group, trying to figure out fact from faction, and when extrapolations are reasonable and when they're not.

DR. HORN: I totally agree with Dan. But I think maybe there's a line we can draw here. What are we extrapolating? That's the question. And if the question is, if we know we have a potent

3A4 inhibitor, can we extrapolate that we'll interact with every other 3A4 substrate in the world? Yes. I absolutely agree with that. And we do that all the time.

So I'm totally in favor of what you guys have done with the labeling, where you include lists, and we saw some of those today. Here's the potent 3A4 inhibitors. All of these are going to interact. We don't have data on them, but you can take it to the bank because if they don't interact, there's something seriously wrong with the whole theory.

So I don't have a problem with that. I have much more of a problem with in vitro inhibitor/ inducer data, but not for substrate stuff. And this doesn't even necessarily have to be in vitro for the substrate stuff.

Now, where I really have a difficulty with the extrapolation is when you do it for dosing, both from personal experience and looking at the labeling. Many years ago when I was young and not too bright, I spent six months trying to do

predictive, prospective dosage adjustments for theophyllin and digoxin in patients getting interacting drugs. I had about 125 subjects.

You know how many I got right? Zero. Not one. Never. Never hit it because there's just too much variability. Yes, sure, the computer tells you exactly what the answer is. Sorry, doesn't work.

So I don't like that. It's fine if you can say, on average, there will be a 50 percent increase. But you'll never see the 50 percent person. You're always going to get the people on both ends of the curve.

So I have much more difficulty with extrapolation for dosing recommendations unless you've got real data, and then it's not extrapolation. But for trying to decide whether two drugs may have an interaction, I think that's absolutely rock solid.

DR. MUZZIO: I guess I'm one of those guys that designs those bridges using those equations that you feel comfortable driving on. Right? So I

want to talk about models for a minute.

First of all, there is a different between extrapolation, interpolation, and prediction. Yes? Those are different things. Because you used the word extrapolation throughout, and I think you meant not necessarily extrapolate, which means predicting outside the range, but in some cases you are interpolating because you might have data on the right, on the left, and you're trying to figure out what happens in the middle. Right? As opposed to predicting, which is basically what models do.

About models, so there is first principle models, where we understand the physics and the chemistry. Yes? Very basic stuff. Different from mechanistic models, where we may not understand the first principles, but at least we think we've figured out the mechanism, right? And we should be able to validate it; from statistical models, just, okay, we've got a bunch of data, and now we're interpolating, and we warn people, don't extrapolate. So not all models are created equal.

The quality of a model is determined by its

ability to predict, and that is called validation. So if you have a predictive model that has been validated that rests solidly on at least a mechanistic understanding of what's going on, that's one story. But if you've just got a bunch of data and you create a correlation and you're calling that your model, well, yes. Then what's in part of your experimental design when you were developing that response?

So to answer the question, my question is, to the questionnaires, what kind of models are you talking about? And what do you do about making sure that the model is scientifically sound, as close to first principles as possible, and has been validated? Then we can talk about what information you use.

DR. BARRETT: I think that's a great comment. And I'll just chime in and give my two cents on this, as someone who is also involved in modeling work.

We have the great advantage of a lot of historical data with many drugs. So I think in

terms of validation for a lot of the drugs where we do have good drug interaction information, these models have really gotten much better in terms of predicting not just the mean or the median but the extremes of the population.

Now, again, I would agree completely. Not all models are created equal, and we have to set standards because the operating characteristics and the requirements for those types of models should be held to very high standards if it's going to make the label. So I agree completely.

But where I think we can demonstrate that, I think it's perfectly valid to put it in there, especially with the qualifier of the source of where it came from and the conditions on that. Again, you don't want to do a PhD thesis in the label, but I think there is an appropriate amount of wording that can get people comfortable with that.

Again, when you look at labels, how they've evolved, was this any worse than the studies that went into some of the historical data where we knew

nothing? So again, I think the data is on the side of the modeling in terms of enough historical data to show that this is a reasonable approach. And perhaps we can address some of these vulnerable populations with the modeling as well.

There's no reason that this has to stay static, and as we collect data in these vulnerable populations where we've made predictions, they should be updated and revisited. So I don't think this is a place where once it makes the label from whatever form, that we don't challenge it down the road. Nobody's saying it has to be perfect at the beginning.

But I think it's better than knowing there's a problem and not being able to address it quantitatively, and even potentially using this in combination with simulation to consider dosing adjustments. Whether or not that makes the label, I think, is something that needs to be vetted against the information value of it.

DR. ZINEH: Can I follow up on this point that's being made?

DR. BARRETT: Please. Please.

DR. ZINEH: This question of believability of data, is essentially what it boils down to, is a big problem for drug interactions to begin with. And I think I made the point that the way drug interactions are studied is very reductionistic.

You take a couple dozen patients, you expose them to what you think is a worst case scenario. No patient experience those things in isolation; you always have some background physiology that you have to take into account, diseases that are untested in drug-drug interaction studies, et cetera.

So in some sense there's always going to be uncertainty around what the relevance of the drug interaction information that's generated empirically is to the population of interest who's going to get this drug. So I think let's accept that.

In terms of on the model side, you have the same kinds of problems of generalizability, probably for a different set of reasons. And so I

guess my question back to the panel is, let's say you believe in some model, some mechanistic model or predictive model, where you get to the point where you believe it enough that it makes the label. So forget the evidentiary requirements to meet that bar for now, but let's say it makes it into the label.

Should there be an exceptionalism around those kinds of recommendations that are specific to model-based, let's say, dose recommendations or monitoring recommendations or whatever the case may be that you don't have for empirically derived drug interaction information? In other words, what's the justification for calling those out as model-generated if you believe it enough to put it in the label?

DR. VENITZ: As long you identify them as model-based as opposed to empiric?

DR. ZINEH: My question is, why would you do that? What's the value in -- doesn't that create the caveat that you're not confident enough in those data?

DR. VENITZ: Why would you characterize something as in vitro versus in vivo? Because you want to indicate the source of your information.

In this case it's based on a model that was found off the extensive review by your reviewers as an acceptable or valid model for that particular purpose, but you want to indicate that it's based not on a 12-healthy-volunteer crossover study, but it's based on in silico modeling. I don't see anything inappropriate with that. You're just indicating the source. We do that all the time.

DR. BARRETT: I agree. I don't think this is like Barry Bonds' home run record. It doesn't need an asterisk here.

(Laughter.)

DR. BARRETT: Because again, it's just transparency of the information.

DR. MUZZIO: Actually, there might be a simpler reason to not only disclose that the information comes from a model, but actually to disclose the model itself and the assumptions that were made and the parameters that were used. And

I'll give you that reason.

The reason is that it might be very expensive to run another clinical study. But it should be very easy and cheap for somebody else somewhere else to rerun the model and improve upon it and consider the conditions and propose a better model.

There are lots and lots of fields in engineering where the minute we started getting decent models and we made them publicly available, lots of people started doing those things. I'll give you an example. Airplane design. It's incredibly expensive to build a wind tunnel. But once competition of free dynamics became available, a hundred different departments are designing planes and learning a lot about it.

So if we could actually develop a library of models that we like that a lot of smart people could play with and improve upon and maybe test against other things, you might find that things move forward very quickly.

DR. HUANG: Just to clarify, you think it's

very important to put the source of the information, for example, based on model. So it doesn't matter whether the model is so-called validated or qualified based on our knowledge or historic data?

Because my point is, maybe a lot of time the model may not be validated because patients have so many variables that there's no way that there is one gold standard that your model will predict. Or I don't know what's the model that, John, you were referring to.

But that's why I'm saying when you have the model, you actually consider all possible variables. If you look at the drug interactions, say, ketoconazole, okay, the drug most patients most use. But we have a lot of information in the literature.

If you look at their extent of interaction reported, they have a lot of range, more than an order of magnitude difference. Why? Because -- well, the main reason for these type of studies -- many of them are in healthy

subjects -- study design.

So it's very hard to say if this model is not qualified because they do not meet the so-called gold standards, which is the human study, which has a lot of variability in that.

DR. BARRETT: Dr. Au and then Dr. Venitz.

DR. AU: I think when you do a model, it has to be transparent. Actually, I had the same reaction when I read your briefing material, that when you predicted something, you didn't tell me you predicted it. And you also didn't tell me what model you used, nor did you tell me your assumptions.

When I look at a model paper -- for example, we just published one predicting how nanoparticles will move in a body, so within a month I got tons of email. People want to play with it. Right? But they all know, and I would tell them, "These are limiting assumptions. It won't apply at a later time because I have not allowed steady state to occur." So I give all my assumptions so they know what risk they're subjecting themselves to.

So that's what you have to do. With this model, you have to tell me, how's your compartment look like? What rate constant did you get it from, the reference? What's your Vmax Km? And if you have outliers, you can play with outliers. That's the beauty of models. You can plug in any imaginary numbers and say, oh, wow, this is going to be really bad if you have this kind of Vmax Km. And you can issue whatever statement you think appropriate.

But I think that transparency is a must. You cannot just predict without telling me where you're getting your numbers from. Right? We have to be able to judge. If you get a number from a journal that I would never read, then I'd go, "Ooh, okay. I don't trust this model." Right? So you've got to get us that information.

DR. HUANG: I was going to ask, so just to clarify, this is very similar to question number 1 when you think it's important to have study details, experimental design. So there's no extra requirements for a modeled interaction?

DR. AU: (Nods head affirmatively.)

DR. HUANG: Thank you.

DR. VENITZ: I wanted to make a separate comment, and that had to do with class labeling, one of my pet peeves. I'm not exactly sure what you mean by that. I'm assuming you mean pharmacological class. Right?

I would be very reluctant to go beyond the evidence that actually exists unless you really know that chemical similarity within a pharmacological class is actually supporting the notion that if you inhibit one statin, you inhibit all the other statins, which it usually is not. Okay?

So I'm trying to get you to make a distinction between chemical similarity and pharmacological class. Usually drugs are classified by pharmacological class, but they chemically may behave very differently relative to drug-drug interactions. So I'm very sensitive.

DR. POLLI: Issam's question, Jurgen wants to know everything, John wants to know everything,

and that's great. There are other stakeholders that don't have the time to know everything.

So if you're confident that something can go in the label, I think there are some stakeholders, they won't be so interested in the methodology that was applied to reach that label. Some of the speakers from this morning talked about alert fatigue. I think one of the speakers was kind enough to talk about non-interruptive drug-drug interactions.

So I think there are certain stakeholders where the labeling just needs to be simplified. Meanwhile, there's other stakeholders that will want to know everything. And some stakeholders are willing to trust your opinion about what should go in the label in the end.

DR. BARRETT: Jack?

DR. COOK: Thank you. Jack Cook with Pfizer. So I'll go back and defend what I think was your first premise. I do think there are some individuals -- because we heard it earlier -- who I think it's more likely Barry Bonds' home run

record, where they don't want to believe anything that's in vitro or something like that.

Based on the premise that you set up, if I really believe it as a sponsor, I want to treat it as the same way because I want people to pay attention to what I think we know about the drug. So I agree in principle that it's great to provide the information. How do we convince people that you don't dismiss the information?

One of the ways we could start gathering more information would be to change slightly how we analyze phase 3 studies. And I've suggested it before, and like a lot of my ideas, I'm laughed at. So for drugs that you actually think it would be safe to co-administer because they'll be tolerated at a higher level, to go ahead and allow those in your phase 3 studies. But I'd like to put them in a different group, such as the higher dose group.

So if I have two doses in phase 3 that are twofold apart, maybe I allow certain drug interactions. And then I treat them as a statistical model, not being at dose X but at dose

2X. And you could actually gain information about that. But within our confirmatory world, I usually receive much resistance about that.

So the type of patients we study in phase 3 are very clean and they don't have as many drug interactions as the entire population. And we lose that ability to help decide what level these interactions should be at. And I'm not talking about the ones that are contraindicated, but the ones where I think it would be reasonable to explore tolerance because I think that they'll be reasonably tolerated and I can start to get that information.

I'm going to do the simulations -- because a lot of times I believe in that -- to make sure if they take two or three or four drugs, that it ought to be safe in those individuals, and we'll write our protocols accordingly.

But at least that is in a monitored population where I'm looking at safety, as opposed to when it's launched and I'm not as sure how well those patients will be taken care of. Thank you.

DR. BARRETT: I guess, in some context, all of drug development is in some way a model of what happens in the mainstream population anyway. And most of these studies are again done in healthy volunteers in a very acute fashion.

The purpose for doing them is a little bit different as far as an in vivo quality control in the performance of those. So getting at Jack's point, and this is why I brought up the pharmacoepidemiologic aspect of the case control study, when you take a look at surveillance data, where do we value in the clinical relevance? Because I could say in a number of situations where we've taken a look at this, at the University of Pennsylvania from a huge, huge amount of data in the actual patient populations, some of the suspect drug interactions just don't pan out clinically.

That's not to say that nobody's pulling any samples from them, so we're not assessing the PK portion of it. But from the standpoint of the clinical relevance, it doesn't necessarily hold up.

So again, we've got a rolling situation

where we're assessing drug interaction potential for its relevance along the way. I view the modeling part of this as some part of that continuum. And again, I think you have the benefit of being able to construct these from a lot of historical data and from the data that's generated all throughout, and again, implicit upon those doing it to be rigorous from that standpoint, with some amount of verification.

So again, it's not an issue of the asterisk, per se. You just simply disclose the fact that that's the origin of it. But obviously it implies, just like the phase 1 studies, that you did it well. So I don't see any difference from that standpoint.

We're probably at a place where we should take a bio break, if everyone is okay with that. Then we'll come back and summarize and go on to question 4. Take 15 minutes.

(Whereupon, a brief recess was taken.)

DR. BARRETT: I'm going to take a minute to summarize just what I heard on the first three

questions, and we can have comment to this.

But it's clear that the committee, there's a lot of diverse opinions regarding the requirements, the complexity that should be as part of the label with respect to drug interactions, the level of detail, how the information is presented.

One of the issues that seems to be very relevant, though, is in fact the audience who in fact the label is written for. We recognize that it's a little bit out of scope, but that's probably one of the key factors driving a lot of the variation that you see from the various members of the committee.

It's clear that everyone recognizes on the panel the need to provide informative information, adequate quality, but also to have this be interpretable and then be easy to find. So I think, as much as we could get some level of consensus, the organization should be such that the material is easy to read, easy to find, and states the current understanding in terms of the importance or the clinical relevance of the drug

interaction.

There's varying opinions on how in fact that should be conveyed, and most of this revolves around, really, the intention of the target audience for the label.

So I don't know if anyone wants to comment to that summary before we move on to question 4. Are we able to do that?

(No response.)

DR. BARRETT: Okay. Question 4. What statements about the management of drug interactions are most useful and least useful? Please, Alice.

DR. PAU: I just want to mention something that had been brought up by several people. I was going through the reading material that we have. There are certain terms that are used, somewhat interchangeable, but we don't know exactly whether that is what was meant to be.

Looking through, there's a statement that says they are "contraindicated" drugs, and then one of the tables says "should not be given together,"

and then "should be avoided." And of course, there's others. There's use with caution.

My question to maybe the FDA is, do you have a specific definition that is easy for the consumers and the clinicians to know? Is "contraindicated" at a higher level than "should not be used together" and a higher level than "should be avoided"?

To me, "contraindicated" seems like there's a legal implication to it. It is something that is easy for me, if I recommend the two to be used together, that I will get myself into trouble. But if it says "should be avoided," there might be some room of negotiation of clinical judgment.

In communicating that information to clinicians and translating into practice, sometimes there are cases where I think that two drugs in those categories need to be used together because of benefit. But I worry that people don't want to use them together because of the way it is put in the label.

So my question is, are there any definitions

out there that the FDA uses in putting that language in the label? And if there is not true definition, how do we determine how those are put in?

DR. REYNOLDS: Contraindication is the only place where we really do have a definition, and that's, as we stated before, risk/benefit. We don't want those drugs given together.

The "should not be given together," "should not co-administer," "avoid," "recommend avoid," "recommend should not use," "recommend should avoid," all of those, unfortunately we don't have a good definition.

I think talking with the individuals who are pharmacists and physicians who work on labeling, they are moving in that direction where they're trying to get us more consistent. We're not there yet. So right now what we have in labels are opinions of different groups. So it may not mean the same thing to everyone. But it's not as high as a contraindication because if it was a contraindication, it would be in the

contraindications section.

So sometimes when we have the "should not co-administer," there's a little bit of other wording around it that there may be cases where the risk/benefit indicates you need to give these two drugs together, which is what it really means. But I agree those terms are confusing.

DR. PAU: Yes. I think it would be helpful, if you really mean that, to add that separate statement to it so that it will allow the clinicians to make their clinical judgment based on risk/ benefit.

DR. BARRETT: Marilyn?

DR. MORRIS: I would say the most useful information is specific dosage recommendations, as I've mentioned before. That's the most useful information. It really tells the practitioner what to do, decrease the dose to 20 milligrams per kilogram. And also, definite contraindication.

Again, I agree with the last speaker, who said some of the other information, you're not sure if it means the same thing, if there's certain

times when you might want to still administer the drugs together. So maybe that should be clarified.

DR. DAY: Ruth Day. I recommend that we exercise caution about exercising caution. I have heard that term come up in so many advisory committee meetings. I serve on most of them at one point or another. And people often ask, "What does that mean? Should I slow down and do it anyway?" Et cetera.

(Laughter.)

DR. DAY: So FDA might want to review all these terms and see if some should be -- well, I don't know -- dis-encouraged, right. Discouraged.

DR. ZINEH: Can I interject here and just maybe hear some thoughts on what alternatives to this might look like? Because what you're hearing is the inherent tension between being overly prescriptive and allowing the practice of medicine to occur.

Where it's very obvious, we do things like put it in contraindications. When you should actually -- when we want something to be a speed

bump to the prescriber, you may start to see some of this softer language, although it's not super-soft. Right? It raises people's attention.

So if things like "exercise caution" or "should be avoided" or things like that are not adequately informative, what would some alternatives to the full stop be?

DR. DAY: I think that one might just be eliminated, perhaps. But some of these can be turned into actionable terms. So it could be about monitoring or something of the sort. So if it could be turned into monitoring, that would be a good way.

But there are a lot of ways to have a series of terms that are arrayed in degrees of severity or any other dimension. And part of the problem here is that all these terms do not fall along a good scale.

So I am sorry to be professorial, but there are four kinds of scale. There's nominal, where you just name things. There's ordinal -- they're ordered in a way, and I'm not sure people can tell

which ones are worse and better here. And then there's interval, and then there's ratio, where each one is spaced in a certain way.

So I think taking a look at what are all the terms that are being used and seeing if you can locate them on a scale, and then see what scale you might like to have -- is it a five-item scale or something of the sort -- and then figure out what some good terms for those things might be, and take the ones that are incredibly ambiguous and just not use them, or turn them into an action kind of term.

DR. BARRETT: Please. Doctor?

DR. MUZZIO: I have a little bit of a feeling that we are trying to address this situation as if it only happened here for the first time. Scales of risk, degrees of risk, are common in lots of other contexts. People come up with, this is highly risky. This is kind of risky. This is maybe risky.

Look at what people do in a variety of contexts in risk management, from business to homeland security to whatever else. And you can

come up with a scale where you tell people, this is orange. This is yellow. This is whatever.

I'm trying to be quasi-humorous, but you understand what I'm saying. Right? I'm getting at that it's not that hard to say some things are potentially very, very dangerous, and some things are not.

In fact, risk has been defined, in the context of manufacturing in the new GNPs, as the product of how likely something bad is and how bad it is when it happens. And that's one useful way to look at it.

So in terms of useful things to know, by the way, from the patient point of view, I'm a little worried about the whole thing about how patients can handle generic versions of things because everybody would know Tylenol, right, but not necessarily acetaminophen. Right? And that's the best known, maybe. Right?

So there are lots of factors that -- again, I'm thinking about my mother and my sister living with my mom's seven medications, and do they know

that the generic version of this is that? Especially because sometimes they're marketed under brand names, too. Right?

So I don't know what you can do about disclosing a whole family of things in a way that people would understand it. But it would be good to think about it.

DR. BARRETT: When I think of management of the drugs, I think what I'd like to be able to say in the labeling, if I had the information, was that if you waited with one drug and gave the dose six hours later, that you could give certain combinations, perhaps, in place. Or I could substitute one for another drug in the same class.

So when I think of something useful, it's how do I maintain my therapy with the drugs that I have been prescribed or other drugs I could have been prescribed that would still allow me to stay within my therapeutic window?

We've done studies where you have variation in dosing practices, and you take a look at the observance of adverse events or adverse drug

reactions that can be correlated with the co-administration relative to more staggered dosing. And you can clearly see this.

But when you have existing protocols or existing practices -- and maybe this is outside of the label -- and I could see a potential benefit in relative risk by just staggering the doses, why wouldn't you do that?

Partly the evidence I need to show that, which is not really what you're asking, but if that information was available, I'd like to see that in the label in terms of being able to take two medicines which maybe the risk was greater if I gave them closer together than if I staggered them, if that was in there. That would, I think, be very useful information.

The other thing is, again, other lifestyle issues associated with the drug interactions, that would be helpful to be in there. We're again at the level of the patient, where I know it relates to dose.

Anybody else? Please, Kathleen.

DR. NEVILLE: So, Issam, I appreciate what you're saying about not wanting to be prescriptive. But I think the agency has done a masterful job in the past of issuing, over time, nonbinding guidances.

So while it's a fine line, I think it's an easy line when it just takes one sentence or suggested dose changes so that you're not prescriptive. But I completely agree with Jeff that there are so many things that the practitioner needs guidance on out there, including lifestyle, including levels of inhibition of various inhibitors, that sort of thing.

One of the things we often talk about is nobody uses the label like they should. They use other databases. Practical information guiding, not prescriptive information such as this, I think would cause people to use the label more.

DR. MILLER: Michael Miller. I go back to an earlier slide that says the goal of this information is to inform the healthcare provider. So I think when you write that language, you have

to ask yourself, what would a healthcare provider do with this information? How would they use that to manage a patient and to optimize the safety of their care and optimize the therapeutic effect of their care?

I think it speaks to the importance of end user testing, and once you define who your end user is, to go out and say, okay, these are the kinds of directives and guidance we're going to give. How does the end user understand how to use -- are they all on the same page in what our terminology is?

That's a literacy principle. We don't want to design information in the context -- these are all very, very smart people around this table, and we're talking in our language. Okay? There's a world of people outside of this room that don't understand that language.

That ranges from clinicians to patients. And we're here in their interest, and we have to talk in their language. And if we put complicated things in the labeling, for a busy clinician to then translate that -- if we give them guidance in

a complicated way that they don't understand, how can we expect them to translate that into plain language that the lay public can understand when they're trying to manage a patient?

So I think we have to look to that end user, whoever the end user is. And as we've talked about, there's a lot of end users of this information.

DR. MALONE: Dan Malone. I think the most frightful words to a risk manager is "be careful." And hence, for drug interactions, I think the most frightful word is "monitor." Monitor the patient. Well, monitor for what?

The more specific information that's delivered to the clinician vis-a-vis all these other comments, the better off they are. So I think that if we can be specific about things that need to be done or things that should be taken into account, then you're better off than leaving it as a very general statement that allows for "latitude" but provides no information in terms of how to be careful.

DR. HORN: This is John Horn. I'm looking at page 19 from the material that was handed out, and this is from the axitinib label. It discusses 3A4 or 3A5 inhibitors, and the last couple of sentences say, "Subsequent doses can be increased or decreased based on individual safety and tolerability. If co-administration of the strong inhibitor is discontinued, the Inlyta" -- or however that's pronounced -- "dose should be returned after three to five half-lives of the inhibitor to that prior to initiation of the strong inhibitor."

Wow. Right on, people. That is very specific, very clear, and handles both the onset and the offset of the inhibitor. That is perfect. Very good. You've done it. So you know how to do it, obviously.

So just saying, "Be careful, monitor," is not enough. This tells you what to do. And if you need to say, "Gee, maybe you ought to get a blood level to check this," plasma level monitoring, be specific. Monitor, somebody mentioned, liver

function if that's the side effect.

It's not hard again to figure out what to monitor. And most physicians know that for the object drugs. But adding that kind of language, I think, is wonderful. That's exactly what I would want if I was telling a physician, which I do a lot, on what to do. This is what I would say.

In two sentences, I would tell them what to do. That's it. So I think that that's not a lot of bulk that you would have to add to the labeling. But when you have that kind of specificity, put it in there.

The whole idea of contraindicated, let me just give you my one cent's worth of that. I don't think anything is contraindicated because the risk/benefit ration is what we're talking about here. And for drug interactions, the risk is when people don't know there's an interaction.

If you know there's going to be an interaction and you adjust the dose prophylactically, or you measure plasma concentrations or monitor, the risk to the patient

is almost zero. It's very difficult to hurt somebody if you're watching them. It's very easy to hurt them if you give them the drugs that interact and you don't know they interact and you don't do any monitoring.

So monitoring is a really important management tool, but it's also the most important risk management tool, risk-eliminating tool, that we've got. So anything you can do to enhance that, I think, is going to be really beneficial for the labeling.

DR. NEVILLE: For what it's worth, I was just going to echo that because that's one of the few sentences I read where I went, oh, my God, that's it right there. And it cites other places if you want more detail.

So if you don't need the detail, you don't have it; but if you want it, you have other places you could go. So I thought that was one of the best statements in the whole 27 pages.

DR. BARRETT: Marilyn? Did you have something, Marilyn? No? Okay.

Please.

MS. CABALLERO: I'd like to address just what you just finished saying, Dr. Horn, and that has to do with what I'm hearing here, is the mission of FDA is to serve and protect the public.

If was wondering whether -- you addressing the needs that the clinicians, the practitioners, need, and that is to understand the effects and how the medication works and be able to read the warnings better so that they in turn can know which medications to best treat the patients with, the ultimate outcome, what I see here, is the outcome for patient safety is going to be so much more enhanced by what you're trying to accomplish here.

So to me, this is a win/win for the clinicians because they'll be much better prepared, and it's definitely a win/win for the patient, who ultimately is going to benefit the most out of what you're trying to do here. And I see such deduction, and I applaud that as a consumer member. Thank you.

DR. BARRETT: Shiew-Mei, you look like you

want to say something. No? Okay.

Please.

DR. PAU: So one question I have is, we talked about monitoring, and in some cases there are alternatives to a specific combination. There could be an alternative from the same class, statin being one of the examples.

I was wondering whether -- and in most of the recommendations, it mainly says "should be avoided" or whatever. But I'm not aware of whether many of them, if there are alternatives, that there are guidance for the clinicians, what else they can use in those cases. And is that a role of the label?

DR. ZINEH: This is a great question. Jack is over there laughing. I think he's going to say exactly what I'm going to say. So maybe I'll -- if I get it wrong, amplify.

I think one of the major sensitivities around FDA labels is endorsement of any specific therapeutic modality. Remember I said at the top of the day that the label guides how people can

promote certain drugs, or all drugs, essentially. So you have to be very careful about comparative claims. That's just one example of the thing that you'd want to be very cautious of.

For that matter, the same is true, probably, of linking out to a platform. So there was some early suggestion that FDA could do an abbreviated label and then link out to perhaps some third party curated data or database, knowledge base.

There are some implications for that as well. Is FDA endorsing platform A, B, C? There are some sensitivities around that as well. So I appreciate that point, and I think it raises some of the difficulty in crafting labels to be absolutely informative to the end user.

Jack, did I hit it?

DR. COOK: You did. But I would really like it if everybody said, in case you have this drug interaction, use this Pfizer product. I think that would be phenomenal.

(Laughter.)

DR. HORN: This is John Horn. If you do

that, no one will buy our book. So please don't do that.

(Laughter.)

DR. BARRETT: Shiew-Mei, please.

DR. HUANG: This is why it is important. At times you will see we will put in the labeling that this drug has no interaction with a certain drug. But we wouldn't compare it to the other drug that has severe drug interactions.

But obviously, we will put that in when you see the other drugs in the same class has interactions. We will just state the fact, but not say the other drug. Or you can look for the labeling yourself.

DR. ZINEH: I think that's a very important point that Shiew-Mei is making. Pertinent negatives are also actionable. They're very important, I think, to the prescriber and to the patient. So if you know what doesn't interact, I think that's actionable.

I go back to the recommendations of really putting only the actionable stuff in the label.

But remember, the label is deconstructed. In one part you're talking about drug-drug interactions. In the other part, you're talking about organ impairment, kidney function, hepatic function, et cetera.

It's up to some interpreter to synthesize all that to make it relevant to their patient, the person that they're seeing in front of them. So it's very difficult to in some sense decide what is actionable because that's going to be different, depending on what the constellation of features are for any given patient.

DR. BARRETT: Thank you. Please.

DR. MUZZIO: Just for clarification, you don't mean has no interaction. You mean has no known interaction. Right?

DR. ZINEH: No. I mean based on the tested -- no. Has no interaction based on what the empirical evidence suggests from the experimental testing.

DR. MUZZIO: But which is what I'm saying. Has no known interaction because the universe of

data is finite.

DR. ZINEH: I guess the null hypothesis was accepted.

DR. MUZZIO: Which is not proof of lack of existence of an effect. It's only proof that the effect hasn't been observed with the available data. Those two things are different.

DR. ZINEH: But my point is that you're doing a dedicated study to rule in or out an effect. And so that's the scenario I think that was being -- that we're talking about here.

DR. HUANG: Yes. I think in some cases --

DR. BARRETT: Guys, let me just stop here because Yvette's going to start punching me. Please just look here, and I will direct traffic. I'm just the messenger. No, just kidding.

Okay. Please.

DR. MUZZIO: But again, the most you can do is fail to prove that an effect exists. You cannot prove that an effect does not exist. So if you had infinite data and you have seen every person on earth, you might be able to say, "We checked

everybody and the effect doesn't exist for anybody." But you don't really actually ever know that the effect never exists. You just know that with the data available, you haven't observed it.

DR. ZINEH: I think that's true for all experiments.

DR. HUANG: I was going to say sometimes we report that for a certain drug pair, there will be no interaction, or at times will be specific, indicating that for CYP-based, and then we'll list which CYPs -- CYP3A, 2D6, and so on. This drug is not a substrate. It's not an inhibitor. It's not an inducer or transporter-based.

So it's very detailed and it's always under certain conditions. When we say this drug has no interactions, that's based on PK many times. But the pharmacodynamics, we will also have certain aspects included in the labeling. That's why the labeling is very detailed.

DR. BARRETT: Any more comments on least useful/most useful before we move to the next question?

(No response.)

DR. BARRETT: Okay. The final question. Under what circumstances should DDI results from the literature be included in the prescription drug labeling? Please discuss the factors that should be considered to determine whether literature reported DDI results are included in the labeling qualitatively, general description of the DDI, or quantitatively, the quantitative information may be used for dosage adjustment.

Dr. Au?

DR. AU: Jessie Au. I was wondering, in my work I always have to try to reproduce someone else's work, and oftentimes it cannot be done. So we say, okay, we are not good enough.

But how do you judge? Let's say you have certain papers say one thing and certain papers say another. It happens all the time. The study design, that sort of goes back to number 1 -- study design dictates what outcome you're going to get. How do you make that judgment? And this is qualitative, and then you have quantitative to deal

with as well.

So I'm discussing. In a sense, I'm just presenting my side of the problem. And I try to reproduce someone else's work, but you don't even do lab here. So you cannot go in there and do it. Right?

DR. BARRETT: Dr. Abernethy?

DR. ABERNETHY: Well, certainly if there are considerable data on either side of a question, that seems like that weakens greatly the likelihood or the confidence one has in either finding, meaning, I think, that you discount it quite a bit.

But I think a part of your question is, so you think you have one very solid study, and you know and you say, that was well-conducted. It looks like it's analyzed properly, and the rest. Is that enough? Or do you really want an independent replication?

DR. BARRETT: Dr. Cook?

DR. COOK: I actually liked Dr. Zhang's presentation where you went through that. I also think if you can publish on that, that might set

the standard for investigators to actually provide the type of data that you can look at and make those judgments for us, or you can get the thing that you want.

Again, I think that's something that -- the higher quality data will be something that sponsors encourage because if it is something where you question the results of the study, that actually creates more work for us rather than understanding why the interaction occurred because we've got to do the study over again to make sure that it did occur.

DR. BARRETT: Dr. Venitz?

DR. VENITZ: Yes. I think the framework that you presented, Dr. Zhang, makes sense to me, and I think you've worked it out to a level of detail that maybe escapes me at this time.

But there are two things that you might want to consider adding. The first one would be, what is the a priori expectation? Was this something that you expected based on what you know about similar drugs or not? If it's not -- in other

words, it's something that is totally out of the blue, totally unexpected -- you might put your burden of proof very high to demonstrate that this is real. Okay?

As opposed to, well, you've got other drugs that have similar drug interactions, and you just happen to get a report in that says this one has the same or similar interactions. That to me is much more in line with the expectation.

The second one -- I think you alluded to that when you presented it -- is, do we understand the mechanism? As you could tell, I asked several times, what makes a drug interaction for the curators? What makes them more important?

Well, even if it's a case report or a series of case reports, if there's a mechanism that is plausible that already elevates the suspicion that this is real, not just something that just happened coincidentally. So the expectedness and the mechanistic plausibility should be part of whatever we end up using.

But overall, I do like the decision tree

that she came up with.

DR. BARRETT: Dr. Keirns?

DR. KEIRNS: Jim Keirns, Astellas. The discussion about this topic that we had this morning got me to thinking about how we might engage the sponsors more in this process.

We were talking about the situation where an independent investigator has done a study that they believe shows some clear result; perhaps it has some safety implications. And I think typically now, if they've published their paper in one of the journals that I routinely scan all the table of contents, I'll follow up on it right away.

Otherwise, what's going to happen is that once a year, we do put together an NDA annual report. Somebody in my company runs a literature search, and I can tell you, with a drug that's been on the market for a long time and is widely used, they'll give me about 200 pages of abstracts of all this stuff. I go through it. And then if I see it, ah. Well, that looks like something we ought to follow up on. But it could easily be a year

before I see it.

So what I was thinking, if we could somehow get the word out to the independent investigators, is that companies are quite open to getting reports of safety issues. We have this mechanism where it can be submitted and then it will be evaluated.

I can assure you that if our pharmacovigilance department gets one of these reports that says something about a drug-drug interaction, they're going to call me either the same day or the next day and say, "Jim, help us figure this out."

So I think there is more of an opportunity for communication, whereas I think perhaps the scientists outside may not really realize that the scientists in the companies would love to get this information as soon as possible to actually grapple with it.

DR. BARRETT: Let me follow up on that question before we move on. I was in a situation where we published some information about the potential for drug interaction in children, and I

got contacted by a sponsor in a very distant way.

I was sent a form in an email. Basically, fill out this form. And there was no dialogue, no chance to explain anything. It was just -- I'm just saying that there's either end of the extremes as far as this goes. So I definitely think the dialogue is valuable and should occur. But I would say there's big variations.

DR. KEIRNS: Yes. You have to realize that the pharmacovigilance folks are dealing with -- and there's also the complaint departments, if you will, in the companies who are dealing with stuff. And they have their procedures.

Yes, they may look kind of ham-handed to you. But I believe, actually, that once the information gets into the company, it does get looked at by people who will understand what you're doing and will follow back up with you. I know that's true for the company I work with, and I think it is for many others. I can't promise it's true for every company.

DR. BARRETT: Sure.

DR. MORRIS: I like the proposed decision framework that was outlined. My only comment was with regards to as we're going down the yes column. So first of all, are study results likely to have a clinical impact? Is the study design adequate to understand DDI? And if both are yes, you go to evaluating the full study report.

But I think at this point, too, you'd want to look at whether or not the study results are consistent with other public literature or anticipated based on what is known about each drug. Again, this goes to the mechanism of the drug-drug interaction, and it's consistent with what we know about interactions.

So because this is based on one full study report, I think you still want to go to the literature and make sure that you're consistent with the results that have been published even though you're going down this yes column. But otherwise, I think this is a very good approach to looking at published literature and getting this out into the package insert.

DR. BARRETT: Jack?

DR. COOK: One thing that I wonder if it's a trap -- when we keep saying, is this a known mechanism and the various variations, is it's already stuff that's likely in that label.

So should we publish every drug interaction with a 3A4 inhibitor and midazolam on midazolam's label? I'd like stock in the paper Companies if we're going to decide to do that.

DR. BARRETT: Dr. Zineh?

DR. ZINEH: Yes. I have a point of clarification. It's a question based on what was just said. If you introduce that question upstream on the decision tree, you get into this possibility of bias -- intellectual bias, publication bias, et cetera -- because you're only dealing with the things that have corroborated your previous understanding. So I guess my question is, is anyone worried about that?

DR. PAU: I'm not answering your question. But I just wanted to make a point. I like the decision tree that you put together, and it's good

hopefully to be able to let people that are out there doing PK studies in academia and other places to know that whatever they are doing, trying to make sure that they have the sound study design to do what might be expected.

I'm not saying that they should be aiming at changing a label. But at least if they a priori put together a design that would be able to lead to some changes, that would be good.

My other point is that using the example that is close to my heart, which is efavirenz and rifampin, the study was done maybe 2004, 2005, showing that there is about a 25 percent reduction in efavirenz level. Nothing was done. There was no change in label.

Subsequently, there have been multiple studies that have shown that despite the interaction, there's no change in efficacy. There's some PK studies that came out. And out of the blue all of a sudden, there was a change in label to increase the dose to 800 milligrams, which no one follows at this point as far as I know.

Then at the same time, there are other studies to go against that recommendation.

My question is, where there are multiple studies like that that are not done by the sponsor, when will it take for it to get to the level -- where it's not only one study but multiple studies -- to get to the level where there will be a label that will be changed back to where it was before? Would there be action to be taken when there is differences in data or differences in findings?

DR. ZHANG: Let me just try to quick response to that. I think, yes, when we deal with those conflicting data, I think really we are also in the same position as everybody else to judge the information. And one criteria, we probably will use as more risk/benefit -- if it would be wrong, what could be the risk we will run into? So we have to take one position, and let the time tell us whether we made the right or wrong decision. I think that's the generic answer, but in that particular case, I don't know the details.

DR. BARRETT: Dr. Venitz, do you want to --

DR. VENITZ: Yes. Issam, I do think what you're dealing with is basically a patient problem. You have a priori expectations, and they may be completely flat. You may know nothing. Then the entire burden of proof that there is a drug interaction that you care about has to be on the experiment, the study that you're looking at. However, if you have some prior expectation, then the level of evidence that you need to get to the same level of confidence post hoc is less.

Now, the whole thing is obviously complicated by the fact that you have to realize, as I said before, what the stakes are. So sometimes the stakes are very high; even though the evidence is not as conclusive as you'd like, you may decide that you're still going to label it, which I think is what you just said.

But I do think fundamentally you're approaching this as a patient. So you have some a priori expectations, no matter where you put them in your decision tree.

DR. BARRETT: Dr. Miller?

DR. MILLER: Michael Miller. My only concern about the algorithm is the criteria you use to make judgments at each decision point. When we evaluate studies in the clinical realm, there are often rubrics, frameworks, for judging studies, looking at design issues, sampling, all those different approaches. Measurements.

I don't operate in the space in evaluating pharmacokinetic studies, but I'm sure there's probably some framework for doing that. And it would be nice to know that when those decisions are being made, they're based on a set of consistent criteria across the board. And right now, as I look at that framework, I can't tell. I may be missing something, but that would be my only challenge to it.

DR. NEVILLE: I would just urge you, as we're going forward in this process, to keep pediatrics in the forefront of your mind because especially with all of the recent legislation, I think we want studies that are no less rigorous,

but there may be fewer. And yes, some of this stuff can be extrapolated, and yes, in general children are on less medications number-wise so they should have less DDIs. But the DDIs may be different. So as you're developing this framework, I would hate in five years as a pediatrician to have to go back and reinvent it.

DR. BARRETT: If I think back to the progression of questions you have here, under what circumstances should results from the literature be included, to me this gets at some of the points that were discussed here. If it doesn't add value from the standpoint of a different population or different set of circumstances, I really think that could be factored in.

It's easy to do that in an unbiased way based on the fact if information exists or not. If it is new information from a new population, new dose level, or outside of the experience that's currently in your labeling, then it should pass that first hurdle as being potentially considered, assuming that the rigor is there.

Again, in terms of the factors on whether or not it's included, I think again the reasonable setting under which the drug is being done, assuming that there is IRB approval -- all that obviously should be there. But reasonable numbers of patients in terms of the trial, the design that makes sense based on the kinetic attributes of the molecule, those are what you would expect to be there. But I think that should be formally stated, that it has to be a trial founded in good science relative to the attributes of the drug molecules in question.

I think one of the other issues is when we have a chance to learn something -- we do these studies that are based on prototypes in order to be more expedient and make some generalizations. But where we can verify this with an actual in vivo study, that's very reasonable to include in there, and I think it adds value as a confirmatory DDI study, that we were in fact able to generalize based on this probe or not. So I think that certainly would be a situation in which it

certainly would add value.

Again, other settings, particularly in disease populations I think have a huge benefit, even if they're done under a non-traditional, more observational setting. And that maybe is in the category of a qualitatively described drug interaction. But I think it's very valuable to have data in the target population where maybe you're also considering on whether or not the disease state does in fact make a patient population more vulnerable to a DDI.

DR. MALONE: Dan Malone. There are a couple issues I just wanted to make sure that were included in the discussion, and one is the notion that these well-conducted studies are usually done in normal volunteers. And we're looking at surrogate markers of outcomes, not necessarily clinical experience, where patients may be placed at risk.

It's really difficult to conduct those studies. David Juurlink, who presented earlier, has been doing some of that excellent work where we

have really good information about the risk associated with harm with co-administration of drug pairs.

I think that information is useful to practitioners and useful to those people who are going to consider prescribing those drug pairs under the knowledge that there's a risk associated with it.

The second point I want to make is that when we've done studies to evaluate the quantity of evidence associated with any series of interactions, and I have in front of me a study that we have not yet published, we've looked at it with respect to the azole antifungals and statins.

When you summarize that evidence, the vast majority of it falls into the case reports. And not to promote the gentleman to my left, Dr. Horn, but the only instrument we have available to evaluate case reports is his instrument. Well, maybe I should promote you. But anyway, he's a good friend.

But the point I'm making is that when we

evaluate these case reports, it makes sense for us to use some sort of tool to say, what's the likelihood that this is a valid case report, and separate the wheat from the chaff, so to speak.

Then the final comment I wanted to make was on slide number 56 of the FDA's presentation this morning, Dr. Zhang presented this decision tree. It's on page 28 of the handout. I guess I just have one minor disagreement with the decision tree, and this asks the question 2c, are DDI results consistent with other public literature? If it's yes, then include it quantitatively. If it's no, include it qualitatively.

I guess I have a difficult time understanding the rationale for qualitative inclusion of negative studies versus quantitative inclusion of positive studies. In my mind, I would think both you'd like to have in both quantitative ways so that -- one study in and of itself it never sufficient. I think the FDA has made that abundantly clear in terms of drug approval, and hence a negative study on a drug interaction or a

positive study in drug interaction, depending upon how you look at it, wouldn't sway us one way or another. But yet we'd want to be able to look at the data.

So I'm just curious why, under 2c, there was that distinction between qualitative and quantitative data, and if I could argue for including it quantitatively, I'll go there. So thank you very much.

DR. BARRETT: Lei? Did you want to address that?

DR. ZHANG: Yes. Sure. Thank you. Actually, this qualitative/quantitative discussion not just only applies to literature DDI. Could be any DDI studies. So the reason we put it here, I think at FDA we heard all the comments.

We want to strive to give more definitive, more clear recommendation, which is quantitative's ultimate goal. We want to strive to put it in the label if we could, so give a more clear direction to the physician what to do with drug interaction.

I think the reason we want to make this

subtle difference here is just due to the study report details. If there's not enough detail, there's not enough detail if we believe this DDI is very likely to be true, then we are willing to take that risk to take that data quantitatively.

But if there's no such mechanism, we will be less likely to trust that data. Just we want to wait for a better study report or better study to get to answers that definitive quantitative change. That's the difference here.

DR. MALONE: I totally understand that. But question 2c doesn't ask that question. It just says, are the results consistent? It doesn't say, are the results reliable, valid? So that's why I'm drawing that distinction in my mind.

DR. ZHANG: Yes. That question is already answered in 1b. Already overall we believe the study design is okay, so that already is a yes. So we already believe the study design is okay; it's just not enough detail for us to further judge the analytical other aspects, PK aspects, of the study. I think that's the difference here.

DR. ZINEH: But your point is that this is not a methodological criteria. It's just how close is it to what you expected. And if it's unexpected but you believe it, why are you treating it any differently? And I think that's a fair point for future consideration.

DR. ZHANG: So your suggestion is mainly you don't want to make that distinction; you just want to accept it quantitatively?

DR. MALONE: Well, I'm not saying accept it, accept the evidence. But I'm saying consider treating both in the same fashion. So if you're going to use one quantitatively, you should use the other quantitatively. If you're going to allow the reports of the positive study quantitatively, you should report the negative study quantitatively as well, is all I'm saying.

DR. ZHANG: Okay.

DR. COOK: Just a point of clarification. I don't believe it's necessarily a negative study showing no interaction. It was more about, was the mechanism known and expected or unknown? I'm

probably reading too much into the table, but when I first read this, known and expected would be I know something about this.

This is probably a medication that will quite often be concomitantly given. It's probably worth updating the label as opposed to, yup, there's another 3A4 strong inhibitor; I've already got a whole bunch in the label, not likely to be given. But gee, include it.

So that's how I differentiated the two. I think the point is still good if the data can be presented quantitatively. Even though you don't know the mechanism of action, it still might be of use. It's probably not extrapolable because we don't know why it was caused. But if it's a decent study, then it's at least providing something for when those two drugs have to be given together.

DR. BARRETT: Marilyn?

DR. MORRIS: Marilyn Morris. I think I'm looking at this maybe a little bit differently. What I see here is you have a study and you don't have all the data for that study. So you can't

thoroughly investigate the study design and all the patient results.

The study results are not consistent. And I don't mean consistent with just the findings of that drug. I mean consistent with the findings of related drugs with regards to, really, mechanism underlying this interaction.

So I guess I wouldn't feel comfortable in using that data if that was the case without some further information, maybe even in vitro studies to confirm, maybe, a potential mechanism, or something of that nature, maybe some modeling studies. I guess I wouldn't feel that that information is -- I wouldn't be confident in using that information at that point.

So maybe what you're presenting is somewhat different than I'm interpreting it. But that's my feeling with regards to this.

DR. BARRETT: Dr. Day?

DR. DAY: We've been discussing whether a study gets into the label or not. Does FDA have a policy about the weight of the evidence overall

across studies? Now, I know you can't go out and do a meta-analysis yourself, and meta-analyses in and of themselves have problems, and so on and so forth.

But is there a general policy just to never mention that there is a huge amount of data, however that would be said, versus there are some studies that show this but others the opposite? So what about the weight of the literature in general?

DR. ZINEH: Yes. That's a great question. The answer is there's not a general policy. The practice is that appropriate caveats to the interpretation of the information are typically included.

I don't think we see that too much in the drug-drug interaction arena. Where we do see that is where there are maybe postmarketing or post-approval studies that suggest some safety problem or some failure of therapeutic response in a subset of the population, and the data emerge after the drug is approved. You really have to create a synthesis of that information and really describe

in great detail, usually in the clinical trials section of the label, what's the granularity around the data.

There's no weight of evidence criteria per se, and to our knowledge, this is actually the first decision tree that we know of for any discipline in the FDA and CDER in terms of deciding what might go into a label in terms of published literature.

DR. BARRETT: Dr. Muzzio? Oh, okay.

Please, Dr. Horn.

DR. HORN: This is John Horn. As I read this, part of the results consistent with other public literature, et cetera, I can't help but think of the four or five theophylline/erythromycin studies, all of which showed no interaction, and then the sixth one showed an interaction. So under this criteria, you'd throw the sixth one out, which was actually the correct one.

That's, I think, a little bit of a risk that you have to keep in mind when you use this consistent -- I don't particularly care for that

because there's a lot of inconsistencies in these studies, and it just makes me a little nervous when you do that.

So I'll tell you what I use. What I teach my students is that if you see a drug interaction study that doesn't make sense -- it's not consistent -- there's exactly two possible reasons for that. One, you're too dumb to understand why it doesn't make sense, and two, it's wrong. That's it. There's no other options.

So if you see one that's inconsistent, it's either wrong or it might be correct and we just don't understand why.

DR. ZINEH: Just to clarify, in that scenario that study would not be thrown out. If that study had face validity, it would be described, according to this, qualitatively. But what we heard is that there's probably no reason to treat that study, assuming that again it had methodological rigor on face, and better yet if we can get our hands on the data -- there would be no reason to treat those differently from positive

studies. You'd want to describe the quantitative aspect of that.

Is that fair, Dr. Malone?

DR. HORN: And I liked the work. I think it's very useful.

DR. ZHANG: Actually, I have a question for the database curators or vendors. How do you treat those? I know internally you must have your own criteria, your board, to discuss those things, like how you treat those case reports versus literature study versus observational study, what kind of criteria you may come up with to share?

DR. MATUSZEWSKI: Well, much like the FDA, we don't have an algorithm or an evidence weighting system. Again, if there is a consistency, it's a number of case reports. And again, if the case reports have enough detail and they look like they're rigorous enough, then that would be an indication that we should give it some type of notification in the database.

It might not be a contraindication. It might be perhaps at either a level 3 or a level 2,

so either with some monitoring or perhaps use very carefully, avoid if possible but the risks may outweigh the benefits. But if they don't, then again, that's something you could use.

So case reports, a single case report might not trigger addition in the database. But if there were a number of them -- again, a case series, if it was a case control series -- that increase in terms of comfort would be potentially something that could be added to the database and we wouldn't wait for it to necessarily appear on the label.

DR. BARRETT: Any final comments to the last question?

DR. FLOCKHART: Just I think it's a very well worked-through rubric. And it does, as some indicated at the beginning, represent a skeleton for other approaches to not just drug interactions but adverse effects, so drugs' off-target effects. I think you could use this in other contexts as well.

DR. BARRETT: Dr. Zineh, would you like to give us an assessment of the interaction or in

fact, challenge the committee to have discussion on any other points that we haven't adequately addressed in your mind?

DR. ZINEH: No. Well, first of all I want to again, on behalf of our office and the Center, thank everyone who served on this committee today. We made the predictions at the beginning of this day that it was going to be fruitful and inform many of the things that we were going to be doing moving forward. And I think it's fulfilled that promise.

To my mind there are some dominant themes that stood out. The issue of who the end user of the label is, is clearly the major issue. And I think that's what's been the major driver behind figuring out these best practices, that heterogeneity in who the end user is makes it difficult to come up with best practices, and I think this committee did a great job in helping us get some thinking around those issues.

I don't believe that any of our questions are outstanding. I think that the group has done

an adequate job in addressing those. And we just again appreciate the efforts.

Adjournment

DR. BARRETT: Again, on behalf of the committee, I think we were all very appreciative of this issue being raised by FDA. And it's clear to see the passion of the FDA in gathering the material and really focusing the questions in a very meaningful way.

I think you saw the passion from everybody here that we all felt that this was all along the right path of improving the labeling, both from the standpoint of the sponsors, the academic medical research community, regulatory community. So I applaud you for the efforts in synthesizing this and making it easy, I think, to have this kind of dialogue.

So with that, we will adjourn the meeting. Please remember to drop off your name badges at the registration table on the way out. Thank you.

(Whereupon, at 4:02 p.m., the committee was adjourned.)