FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY

ADVISORY COMMITTEE MEETING

Wednesday, May 15, 2017

12:24 p.m. to 4:05 p.m.

Afternoon Session

Omni Shoreham Hotel

2500 Calvert Street, N.W.

Washington, D.C.

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(12:24 p.m.)

Call to Order

Introduction of Committee

DR. WALDMAN: Ladies and gentlemen, we're going to start the afternoon session.

Good afternoon. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Lauren Smith Dyer. If you are present, please stand.

We're going to do introductions of the folks that weren't here this morning, so if you were this morning, you don't have to do another introduction. So for the FDA folks actually who were not here this morning, could you please introduce yourselves?

DR. STRAUSS: David Strauss, director of Division of Applied Regulatory Science in the Office of Clinical Pharmacology at FDA.

DR. GARNETT: Hi. I'm Christine Garnett.

I'm a clinical analyst within the Division of Cardiovascular Renal Products within OND.

DR. Z. LI: Zhihua Li, Division of Applied Regulatory Science, Office of Clinical Pharmacology.

DR. WALDMAN: Terrific. And we have a telephone panelist who, I believe, didn't participate this morning but is not yet on.

Is that true? Dr. Li is not yet on?

(No response.)

DR. WALDMAN: I'm guessing he's not yet on. Okay. So let me read the preamble that I read this morning.

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

look forward to a productive meeting.

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

We 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 this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

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

Conflict of Interest Statement

DR. SHEPHERD: Good afternoon. The Food and Drug Administration is convening today's meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee under the authority

of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., 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 the federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her

potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting 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 the purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today, the committee will discuss the use of MIDD for new and generic drugs, which has significantly increased over the past several years. This afternoon's agenda includes discussions of strategies, approaches, and challenges in MIDD with specific focus on the

mechanistic model-informed safety evaluation with the focus on drug potential for causing arrhythmias. The comprehensive in vitro proarrhythmia assay, or CiPA, will be discussed an exemplar.

This is a particular matters meeting during which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Walid Awni, Jack Cook, and Srini Tenjarla are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry.

Drs. Awni, Cook, and Tenjarla's role at this

meeting is to represent industry in general and not any particular company. Dr. Awni is employed by AbbVie, Dr. Cook is employed by Pfizer, and Dr. Tenjarla is employed by Shire Pharmaceuticals.

With regard to the FDA guest speakers, the agency is determined that the information to be provided is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation in our comments made.

Dr. Gary Mirams has acknowledged he is principal investigator on an Oxford Systems Approaches to Biomedical Science DPhil project and coinvestigator on a Netherlands ZonMw grant. Guest speakers will not participate in committee deliberations, nor will they vote.

We would like to remind members and temporary voting members that if the discussion involves any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and

their exclusion will be noted for the record.

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

DR. WALDMAN: Thank you. We'll now proceed with the FDA and guest speaker presentations. We have five presentations. We will begin with Christine Garnett.

As she told you, she's clinical analyst and QT lead, Division of Cardiovascular and Renal Products, Office of Drug Evaluation I, Office of New Drugs, CDER at the FDA. She's going to talk to us, today, about overview of the ICH E14 guideline and its implementation within FDA.

FDA Presentation - Christine Garnett

DR. GARNETT: Good afternoon. As you heard, there will be five speakers in the session and as the first speaker, the purpose of my presentation is to go over the ICH E14 guideline and its current implementation within the FDA.

The global focus on new drugs' ability to prolong the QT interval and cause Torsade really started in the 1990s when there were significant number of marketed drugs that were removed from the market because of drug-induced Torsade.

If you look at the time period, between the 1990s up to the mid-2000s, there were 38 drugs removed from the market. These are noncardiac drugs. Of those, greater than 20 percent of those drugs were removed because they induced Torsades postmarketing. What was disturbing to regulatory agencies is the safety risk was not appreciated premarketing.

As a response, the global community, under the International Council of Harmonization, issued two guidelines. The first guideline is the nonclinical guideline; it's the ICH S7B. This nonclinical guideline pretty much focuses in on the drug's ability to inhibit one cardiac ion channel, the hERG channel or that encodes the IKr current. It also emphasizes looking at the ability of the drug to prolong the QT interval in animal species.

The ICH E14 guideline is the clinical guideline which I will be focusing on in my presentation, and this guideline describes how to clinically evaluate a drug's ability to prolong the QT interval.

This guideline was first published in 2005, and since its implementation within the regulatory agency, it's been modified several times. The modifications have come through the Q&A. So if you go on to the ICH and you want to see the current thinking and the current implementation of that guideline, you'd have to go through the Q&A document.

The E14 guideline pretty much is about designing the conduct analysis and interpretation of clinical studies to assess a drug's ability to delay cardiac repolarization as measured by the QT interval on the surface ECG.

Now, the centerpiece of this guideline is the thorough QT study. And the thorough QT study is typically designed as a randomized, placebo- and positive-controlled study. It's typically done in

healthy volunteers with some drugs that might be done directly in patients, but most of the time, it's healthy volunteers.

The idea in the study is you were trying to evaluate whether a drug has a threshold effect on the QT interval at supratherapeutic doses. And the reason why supratherapeutic doses are included in this study is we want a dose that will cover exposures, the high clinical exposures, to account for if patients would be taking the drug and take it with a metabolic inhibitor or have impaired elimination organs. We want to understand what the effects of that drug is at the high clinical exposures on the QT interval.

The E14 defines a positive thorough QT study as one where the upper bound of the maximum mean QT effect exceeds 10 milliseconds. And the threshold is pretty much, when they wrote the guideline, tied in with the primary statistical analysis.

In this plot, what I'm showing is the double-delta QTc. This is the QT interval that's been corrected for both baseline and placebo over

time. At each time point, you get a mean and an upper confidence interval. If that upper confidence interval exceeds 10 milliseconds, that's considered a positive study, and if that all confidence intervals are below 10 milliseconds, that's a negative study.

What does a positive study mean? Well, a positive study means that a company who's developing his drug has to collect more ECGs later in development to understand the proarrhythmic risk of that product directly on the patients. So this 10-millisecond threshold is only a regulatory threshold. It does not mean the drug is proarrhythmic; it does not mean that the drug is dangerous.

It became really apparent when implementing the E14 guidelines back in 2005 that exposure-response relationship is very important to interpreting in these studies.

In this plot, what I'm showing is if you have a thorough QT study where the therapeutic dose -- and the therapeutic dose would be one where

it would be the highest clinical dose that's going to be moved forward into late phase development The upper bound is below that 10 milliseconds, so it's negative. However, at the supratherapeutic dose, the dose that encompasses these high exposures, it exceeds 10 and it's positive, how do you interpret that?

What we do is when we look at an exposure-response relationship, you could see then you could start addressing clinical pharmacology-relevant questions, and you can start thinking about what is the prolongation in patients at steady state. What happens in the patients that their drug exposures is increased due to food, due to drug interaction, or due to hepatic impairment. And we can start addressing how to monitor in certain patients who's at higher risk and how eventually to label a product.

We started looking at exposure-response pretty much right when the guidance was implemented in 2005, and throughout the years, I think the value of using this relationship within the

evaluation of QT interval, not just in the thorough QT studies but other studies, was really apparent. By 2015, we actually changed the guidance to be able to use exposure-response modeling as the primary endpoint in thorough QT studies.

I think the big significant effect of this change in the guideline is that now, sponsors can collect ECGs in their first in-human studies where they're looking at the QT interval over a wide range of doses, use exposure-response modeling directly in that study, and use that study as a substitute for a thorough QT study, and they wouldn't have to do this confirmatory safety study later in development.

Here, I'm just outlining what type of QT evaluation typically occurs during drug development programs. Nonclinically is pretty much following the S7B guidelines.

In phase 1, sponsors can collect high quality ECGs in that first in-human study over a wide range of doses. And if that exposure margin covers that supratherapeutic dose or exceeds that

supratherapeutic dose, then that study may be able to be used as a substitute for a thorough QT study. If, however, a sponsor has to conduct a thorough QT study that typically happens in phase 2 -- because the purpose of understanding the drug effect on the QT interval is actually to inform how much ECG monitoring is needed in phase 3, and that could come either from the thorough QT study or now, from the phase 1 study.

In this slide, what I want to do is give an idea of what the decision-making is around the recommendations for monitoring in phase 3 after a positive thorough QT study or after a positive phase 1 study. Pretty much, the decision is based on the magnitude of the QT prolongation interval at therapeutic exposures.

In the first scenario, the mean double-delta QTc at therapeutic exposures is less than 10. However, the study is still positive. The drug is still considered prolonged in the QT interval because at that supratherapeutic dose, it exceeds 10.

If that supratherapeutic dose provides a sufficient exposure margin, such that patients taking the clinical dose will never achieve those high exposures, we consider that to be a negative study, and no additional ECG monitoring would be needed.

If, however, that high supratherapeutic dose reflects concentrations that may be in a specific population, such as patients with renal impairment, then the sponsor has the option to come in with targeted dosing in patients who are at increased risk.

Now, if the mean double-delta QTc at therapeutic exposures is between 10 and 20 milliseconds, this pretty much always calls for intensive monitoring in late-phase trials. And the intensity of that monitoring will depend on the pharmaco-characteristics of the drug, the magnitude, what patients that will receive the drug, whether they have increased risk factors for Torsade, as well as whether the drug also has other adverse events such as the drug may cause

hyperkalemia, bradycardia that would increase a patient's risk for Torsade.

Finally, in the last category, if a drug in the thorough QT study has a very large effect on the QT interval greater than 20, we consider that probably a drug that does have proarrhythmic potential, and the late-phase trials most always have intensive monitoring, plus including risk mitigation strategies for the patients.

Now, when we think about the safety, the safety element that we really care about is Torsade, but we're using QT prolongation as the biomarker for Torsade. A lot of the decision-making we make is based on the magnitude of the QT prolongation as a surrogate for the potential for Torsade. In this, I just want to give an idea of our level of concern for Torsade based on that QT interval.

Pretty much at the QT interval, it's small, less than 10 milliseconds, the mean effect is in therapeutic exposures, there's pretty much low concern for a Torsade risk. There's an increase in

concern for Torsade risk as that QT interval increases. So between 10 and 20 milliseconds is the mean effect, we would consider how many patients within the clinical trials had a very high value such a QT greater than 500. This would increase our concern for Torsade with or without evidence of clinical adverse events.

Again, like I said in the previous side, we're definitely concerned for a drug that has Torsade if the QT interval prolongation and the mean effect would be greater than 20 milliseconds. Our concern for a Torsade risk is what we communicate within the package insert or the label of products.

I'm going to show you, just to give an idea, of what we communicate for three types of drugs. For my first example is for vandetanib. Vandetanib is a drug that's been approved for medullary thyroid cancer.

During clinical development, it was shown that the mean effect on the QT interval was over 20 milliseconds. There were Torsade events, as

well as sudden death in the clinical trials.

That safety risk, the risk for Torsade and sudden death, are very much communicated within the labeling, including the box warning for these adverse events. And I list in the slide all the different labeling sections where the QT is described. The label also has quite a bit of risk mitigation strategies included to minimize a patient's risk for developing the arrhythmia.

In my next two slides, these are going to be drugs that are positive, but their effect size are lower than what we saw for vandetanib.

The first one is paliperidone. Paliperidone is an antipsychotic, and in the thorough QT study, the mean effect size was between 10 and 19. And actually, it was closer to the 10 milliseconds.

In the label, they did get warnings and precautions. For QT prolongation, they had QT prolongation labeled in the adverse reactions because we didn't want the drug to be given with other QT prolonging drugs. And it described an overdose case of QT prolongation and Torsade in the

overdosage.

Last example is for tetrabenazine. Tetrabenazine, actually, the mean effect size was less than 10, but there was concern that in some patients, especially patients who are 2D6 poor metabolizers or taking a 2D6 inhibitor, they would have higher exposures.

This drug was also labeled with warnings and precautions. In this case, it was mainly, do not administer with other QT prolonging drugs. The same type of warning was also in the drug interaction section, as well as a study, the TQT study described in pharmacodynamics section.

When the FDA first implemented the E14 guidelines back in 2005, actually, what they did is they set up an integrated team to look at all QT studies coming in all across CDER. So we have one centralized review team, and it's called the IRT. And it pulls in from multiple disciplines, including clinical pharmacologists, clinical statisticians, we have data managers, and project managers.

The idea is that anything that's related to QT, whether it's the protocol, a meeting package, a report, it would come to the centralized team. And they would review it and provide advice back out to the review divisions.

The team is also very active in monitoring the ECG warehouse. Part of the review would be the sponsors would submit their digital waveforms from these clinical trials into a repository, which is the ECG warehouse, and the IRT would also monitor the waveforms during regulatory review.

Now, the IRT I think was quite unique in the setup within CDER because they pretty much use the knowledge management type of system to be able not only to do regulatory review, but also to advance the science for QT evaluation. And I see this type of model being very applicable to CiPA and how CiPA can also be implemented within the agency.

Pretty much, what's happening is when we wanted to implement this new guidance, which would be E14, CDER developed this interdisciplinary review team to develop the science. This team

works with outside collaborators to understand what the issues are. And then they also manage the technology. They developed scientific standards. They developed the databases. They have a database of all the thorough QT studies that come into the agency. They have review templates, as well as analysis tools to increase the efficiency of review.

Then they're very open to sharing what they have with the public through public meetings and presentations. And then by collaborating with these external stakeholders, then they could find other areas of interest, increase the science. And this is how we've gotten to quite a bit of innovation within this team in terms of study designs and analysis approaches.

In summary, the main points that I wanted just to remind the committee of, from my presentation, is that all new drugs undergo clinical evaluation to assess the effects on the QT interval. This can be done either on a thorough QT study, and now it can be assessed in a phase 1

study with the exposure-response modeling.

The magnitude of QT prolongation is really -- therapeutic exposure is what influences the late-stage monitoring. And the labels for drugs that prolong the QT interval are just really based on the agency's concern for the Torsade risk. And that's pretty much based also on the extended QT prolongation, the presence of other clinical AEs and factors that could modify the Torsade risk in patients.

Finally, the centralized review team, which I think is very -- CiPA could borrow that type of model, was really, really important for implementing E14. It has facilitated and managed innovation and organizational learning within the FDA.

Just to conclude, I just wanted the committee to think about that there is room for improvement in this QT evaluation. Overall, I think there's a general consensus that E14 is working. There have been no increases in the number of Torsade events with the approval of new

drugs since the implementation in 2005, and there's been no new drug that's been removed from the market because of Torsade since the implementation in 2005.

Where I see there is room for improvement is pretty much being able to do a better job at labeling. This is what's diagramed in the study, in this figure.

In this figure, what I looked at were about 300 thorough QT studies for non-oncology drugs over the last 10 years. Of those 300 studies, 39 of those were drugs that were approved with the positive thorough QT study; 22 of those were labeled with warnings and precautions, and of those, only 8 actually caused Torsade.

So I see where CiPA comes into this is being able to differentiate drugs that prolong the QT and cause Torsade like we saw for vandetanib versus drugs that prolong the QT and don't cause Torsade such as ranolazine. That's where I see where CiPA would really be helpful within this paradigm. Thank you.

DR. WALDMAN: Thank you very much.

(Applause.)

DR. WALDMAN: Our next presenter is Gary Gintant, senior research fellow, Department of Integrative Pharmacology at AbbVie. He's going to talk to us today about Goals of CiPA: The Comprehensive In Vitro Proarrhythmia Assay.

Guest Speaker Presentation - Gary Gintant

DR. GINTANT: Okay. Well, good afternoon, everyone. The title of the talk, Goals of CiPA. My goal in the presentation is to provide you some background so that you understand some of the electrophysiology, the underpinnings of CiPA, as well as discuss briefly some of the unintended consequences of the focus on hERG and IKr current that resulted from the S7B type of guidance, thinking along those lines; then the majority of my talk to describe CiPA, its goals and the individual components within the CiPA initiative; and then finally some ongoing efforts within CiPA itself.

We'll start with some very basic electrophysiology. The focus here is on

repolarization, cardiac repolarization, which represents the integration of multiple inward and outward currents that define what's called the action potential duration here, the waveform of the electrical activity recorded from a single ventricular cell within the myocardium.

Of course, it's the integration of the cellular activity that defines the QT interval on the ECG and delayed repolarization in QT prolongation that Christine was talking about.

We have drugs, certainly, that will decrease in that outward current, and it's really net outward current that defines the extent of polarization and the delays in repolarization of the drugs. And certainly, by reducing an outward current, we see delayed repolarization both on the cellular level, as well as on the ECG. From this, we understand quite thoroughly the cellular mechanism that caused delayed repolarization that lead to proarrhythmia, including the Torsade with the example.

Looking under the hood a little bit more

closely, here again, we have an action potential. And one must recognize that the action potential is the sum or the symphony of multiple de- and repolarizing currents that is repeated with each cycle, with each heartbeat.

Here are the some of the predominant currents listed here. Inward currents are downward. Outward repolarizing currents are upward in the traces. One can recognize that hERG or IKr current circled is one prominent repolarizing current. And obviously, block of hERG is associated with delayed repolarization.

However, more well-appreciated, that block of hERG alone is insufficient to predict delayed repolarization because, indeed, it's the net sum of the multiple currents that define the shape and the duration of repolarization. And this is one of the things that CiPA explores as part of the paradigm.

This represents a bit of a change from the ICH S7B, which really was what I call a hERG-centric approach in which there was much emphasis placed on analysis of only one ion of current, the

IKr or hERG current.

As Christine mentioned, ICH S7B, along with E14 was successful. No drugs have been removed from the market due to Torsade since 2003. However, again, hERG is not very predictive of QTc effects itself for a surrogate marker for proarrhythmia.

hERG is very convenient in the fact that during drug discovery, a finding of hERG block or IKr block with early drug candidates often discourages compound progression, and it's been referred to as throwing baby out with the bath water. People will maybe leave the promising compounds on the bench and move to other ones if they don't have this IKr or hERG blocking effect.

This triggers additional costs for new synthetic efforts to remove the hERG liability, as well as slowing efforts towards drug discoveries. And it's been argued that some drugs that are on the market today may not have been available if the hERG assay results were enforced early on, for example, pentobarbital, verapamil, and ranolazine.

Then one last thing to consider before I move on to the components, we know more, or we have a greater appreciation for what constitutes or what defines repolarization. Now, with the advent of automated patch techniques and platforms, we now understand that drugs not only affect hERG current but other cardiac currents, as well.

I'll just talk about the pie chart here, and this pie chart compares for 55 compounds, the potency of a drug to block hERG current, which is red, the drugs that block hERG current more potent versus the hERG drugs that block calcium current.

You can see that some 66, 67 percent of the drugs are equal potent or more potent to block the L-type calcium current and inward repolarization current during the plateau as compared to blocking hERG in outward or competing current that helps to define repolarization. And this provides or gives evidence for meeting a more comprehensive mechanism-based assessment of integrated effects of drugs on repolarization.

Now, we get to CiPA. The goal of CiPA is to

develop a new in vitro paradigm for cardiac safety evaluation of new drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential. The focus is on proarrhythmia, not simply QT prolongation to improve specificity compared to preclinical hERG and clinical QT studies.

How this is done is to define drug effects on multiple human cardiac currents, characterize with models effects on human ventricular electrophysiology, and then verify effects using human stem cell-derived ventricular myocytes along with QT evaluations.

These four components are illustrated graphically on this slide here. We start with looking at effects of drugs on ionic currents, expressed in heterologous expression systems. Again, these are human currents.

We take this data and use them as input to in silico reconstructions of human ventricular electrophysiology to define the extent of repolarization to look for these interruptions in

repolarization called early-after repolarization, which have been linked to Torsade. These two components are used to characterized or classify drug effects.

Then we move on to the right two panels, the purpose of which are to check for missed or unanticipated effects. Here, we're looking at effects on human stem cell-derived ventricular myocytes, and then finally looking for unanticipated electrophysiology based upon clinical evaluation of ECG.

I'll go through each of these in turn. First, drug effects on human ionic currents, this is the work of the Ion Channel Working Group, whose goal is to characterize the effects of drugs on 7 prominent ionic currents that are recognized to play a prominent role in defining repolarization. So we have 3 repolarizing currents and 4 repolarizing currents in red and in green respectively.

Part of the task here is demonstrate that one can reliably and reproducibly characterize

block of these ionic currents and heterologous expressions. We're using automated patch platforms for higher throughput and reducing the variability. Again, these 7 currents that are listed here were selected based on the experience of academia, industry, and regulators.

Right now, there's an ongoing high throughput study with the Ion Channel Working Group to assess the variability and reproducibility of these high throughput screening platforms for defining the drug effects; looking for differences across and between platforms and between sites using standardized protocols and standardized concentrations for the drugs tested.

We're generating key ion channel data, IC50 values for current block predominantly for the calibration and validation of reconstructions by In Silico Working Group. And then the hERG current response are going to be shared with the In Silico Working Group for further characterization and modeling of IKr block kinetics.

In phase 1, we're looking at data set and a

calibration set of 12 drugs. That's due, actually, the end of first quarter of this year. And then we'll follow up with a phase 2 with a blinded validation set of 16 additional compounds. We'll have a total data set of 28 compounds.

Moving on to the In Silico Working Group, the goals of this group are to define a proarrhythmic risk metric based upon drug effects using this in silico model of a human ventricular cardiomyocyte.

This metric has to be mechanistically-related to the cellular proarrhythmia effects and experimentally verifiable. The model that's being used is the O'Hara-Rudy model selected by experts, and this model was based upon experimental data derived from data from human tissues. The hERG or IKr current has been modified with a Markov model to add a greater validity to the model.

The data from the human ionic current assays will be used in the model to assess the relative Torsade risk, and the idea is to be able to

separate these 28 reference drugs into three distinct categories: high, intermediate, and low/no risk proarrhythmia, normalized on clinical exposures. And the results will be compared to these clinically-assigned risk categories. Gary Mirams and Zhihua Li will talk about this in the next few presentations.

There were 28 drugs, which we refer to as CiPA 28, are listed here. We have, in red, the high Torsade risk compounds of which there are 8, then I think there are 10 for the intermediate and the remaining low Torsade risk.

These compounds, they are drugs that were assigned based upon the work of the Clinical Translational Working Group and based upon their experience with these drugs, reports in the AERS database, other publications. These will be the gold standard by which we will compare the CiPA results.

The next group is the group that's evaluating drug effects on stem cell-derived human cardiomyocytes. This is the CiPA-HESI Myocyte

Working Group. The role of this group is to identify potential gaps in cellular electrophysiologic effects not detected from the ionic currents or in silico reconstructions that may impact the Torsade risk assessment.

It relies upon the ability of these myocytes to recapitulate the integrated effects of those systems that influence the drug electrophysiologic effects found in the myocytes.

Here, we're talking about some things that the channels may have missed, the Ion Channel Working Group may have missed: modulation of the channels or the currents by receptors or second messengers; additional transporters that aren't in the model itself, as well as exchangers; maybe some calcium dysregulation.

How the group will do this is to report on drug-induced repolarization abnormalities in these human stem cell-derived cardiomyocytes. Electrically, the studies are using high throughput techniques using either multi-electrode array approach, by recording the extracellular field

potential from cells at the bottom of wells in, again, high throughput platforms or voltage-sensing dyes.

Here, we see prolongation of the field potential duration with increasing concentrations as the QT prolonging drug, cisapride, and here, prolongation, with the beginning of an early-after depolarization with the IKr blocking drug, E-4031.

Some other indices that are also being measured are changes in rates, spike amplitude; again, the appearance of these early-after depolarization is recognized as triggers for Torsades proarrhythmia. Here's another example of what an EAD looks like from a micro-electrode recording, and it's thought that these give rise to the Torsade.

A pilot study was completed a little over a year ago maybe. The goal of this was to evaluate the ability of these myocytes to detect electrophysiologic effects. It was a 12-site pilot study with two commercial cell lines with 8 blinded drugs, using the two approaches I mentioned.

Four of the compounds were specific to specific ion currents, sodium current, L-type calcium current, IKr, and then another potassium channel IKs, and then 4 test compounds representing the high, intermediate, and low-risk categories.

At the bottom here, we see graphs before the compound showing percent changes in field potential duration corrected for changes in heart rate. One sees, with increasing concentrations, what one would expect: increases in the duration of the field potentials with moxifloxacin, with flecainide, as well as with quinidine, although the effects were more variable with quinidine, and a decrease in the field potential with nifedipine.

This gave us encouragement to go forward with a validation study, which is ongoing, again using the same techniques and funded by a Broad Area Announcement Award from the FDA.

Here, we have our core group evaluating a blinded 28 CiPA drug set with high, intermediate, and low risk across the two different cells and the two different platforms.

Again, the focus is on delayed repolarization and cellular proarrhythmia, EADs, where there is, of course, input from industry, cell platform providers, academics, and the intermediate results since the drugs are still blinded. But they will be unblended. In April of 2017, there's going to be a meeting of all those involved.

The last component of CiPA is the phase 4. This is the ECG Biomarker Working Group headed by the FDA, as well as the Cardiac Safety Research Consortium. The goal, again, is to detect unexpected electrophysiologic effects, but in this case now, we're looking for clinical effects compared to the preclinical data expectations from the ion channel combined with in the in silico reconstructions and the human-derived cardiomyocytes.

Here, one might pick up human-specific metabolites, effects of protein binding, maybe particularly CNS/cardiovascular effects. But again, you've moved up now. You're looking at the

highest level of an integrated response certainly in the humans and in the clinic.

Besides evaluating for early in phase 1 studies, QT prolongation with more extensive exposure-response modeling than may have been done in the last past five years or so, the idea is also to look for changes in the QT morphology, which may reflect a different mechanism by which QT can be prolonged; for example, whether it's simply a hERG blocker or whether it's a mixed channel blocker based upon, for example, the J or Tpeak, or Tpeak to Tend differences in different parts of the QT waveform. More details on this will be provided by David Strauss.

In summary, CiPA is a proarrhythmic risk assessment based upon a mechanistic understanding of integrated cellular-emergent drug effects on multiple human cardiac currents. The present expectations of CiPA is that it will reduce unwarranted attrition of early drug candidates, sending more drugs to early clinical phase 1 trials, enable rapid progression of lower risk

Torsade-type drugs due to phase 1 studies, and also eliminate the need for a thorough QT studies in a later drug development.

With regard to the stem cells -- and I'll mention future expectation -- the present certainly is to identify potential gaps in the cellular electrophysiologic effects of drugs not detected from the ionic current and cellular reconstructions that may impact the risk.

In the future, as these cells get better, they may eventually replace the in silico or computer reconstructions. They'll be our biological integrator, and they'll also replace, for the most part, dedicated animal studies because we will be dealing with the intact human systems in a dish.

With that, the acknowledgements, this has been a volunteer effort from multiple sources: Health and Environmental Sciences research, HESI; CSRC; the Safety Pharmacology Society; a number of global regulatory agencies that have been involved listed here; as well as the numerous contributions

from industry, academics, contract research organizations, and multiple academic groups.

With that, I thank you for your attention. The coin here is a Roman coin in recognition of the Ides of March, which is today. And I turn it over to the next presentation, which is Gary Mirams here. Thank you.

DR. WALDMAN: Thank you very much.

(Applause.)

DR. WALDMAN: Our next presenter will be Gary Mirams, Sir Henry Dale Fellow, Centre for Mathematical Medicine and Biology, University of Nottingham, the UK. And he's going to speak to us today about the Background and Rationale for Mechanistic Cardiac Electrophysiology Models.

Dr. Mirams?

Guest Speaker Presentation - Gary Mirams

DR. MIRAMS: Thank you. Good afternoon. This talk is a quick introduction to these models, and why they've become a central part of the CiPA initiative, and why we think that's going to be a good idea for predicting arrhythmic risk.

Why use these mathematical models at all? I'll start with a couple of quotes that kind of explain it. "Mathematical Models in analytical pharmacology are not meant to be descriptions, pathetic descriptions, of nature. They're designed to be accurate descriptions of our pathetic thinking about nature."

The model is not supposed to be perfect, but it is supposed to be a perfect representation of how we think things work.

"They're meant to expose assumptions, define expectations, and help us devise new tests." In the context of CiPA, defining expectations is the crucial thing. I'll explain a bit more about that in a second.

Another one from John von Neumann, "If people do not believe that mathematics is simple, it is only because they do not realize how complicated life is." These mathematical models are not a really complicated way of doing this. There are actual a very simple way of looking at it.

Just to motivate why we're thinking about biophysical models, rather than statistical models, which you might be more familiar with, a little thought experiment.

Imagine dropping a 1-kilogram mass from between 8 or up to 12 meters off a tower, timing how long it takes to fall to the ground. You might get some data that looks like this. The higher up it is, the longer it takes to fall to the ground.

Then the statistician would put a nice red line through that, and that would be perfectly good if we were only going to be interpolating between 8 and 12 meters. We can just use this straight red line, and that's fine.

But if we extrapolate a bit further out, we might get some clues that this isn't a brilliant idea. Here, I just extrapolated that red line out from naught to 20 meters, and suddenly we find that the drop from naught meters actually takes quite a while.

What's gone wrong here? Well, if we actually had a hypothesis for the underlying

processes, in this case just acceleration due to gravity, we can make a physical model for what's happening. Here, it would just end up being this half GT-squared, and we'd get a line that looks more like this.

So because we captured some of the physics of this situation, this would be reliable for extrapolation outside where we've trained the model. This is the crucial benefit of using a physical-based model, rather than a statistical line of best-fit kind of model.

But it's also worth pointing out, at this juncture, that there are still things we've ignored here. There's air resistance that would actually change this red line a little bit. It might not be perfect so the air resistance would change, and we'd end up being slightly off the red line. We'd still be a lot closer than using this physical model than we would using a statistical one.

We'll get on to the fact that CiPA has, in effect, ignored air resistance, but hopefully captured the acceleration due to gravity kind of a

concept here.

This is one-slide introduction to electrophysiology modeling. At the lowest level, we have this voltage-gated ion channels. We typically have these kind of models with close states, open states, inactive states. The transitions between these are voltage-dependent, so as the voltage changes, the probability of the channels being open changes.

At the cell level, we model the cell as simply a capacitor. This equation just says the voltage changes according to the capacitance of the cell membrane and the sum of currents going across the membrane.

In a typical model, there would be lots of different kinds of ion channels, all adding up to show you how the voltage changes across the cell membrane. The interesting thing here is that the voltage depends on the current, and the currents depend on the voltage. It's all in one big nonlinear feedback system. And this is why a mathematical model is more helpful than just

thinking through what might happen in your head.

These models can be taken up to larger spatial scales. We can plug in diffusion of charge spatially and get these models like this one of two-dimensional or even up into three-dimensional all-body simulations now. These simulations might need a super computer. The ones at the cell level will be faster than real time on your laptop.

Again, it's worth saying here why CiPA is not going to try and do a whole organ, whole body simulation. Even if we've got perfectly realistic geometry, cell properties, and all the rest of it, these are only going at real time at the moment. And if we actually were simulating Torsade, we might have to simulate for 10,000 patient-months, years. And we'd have to do 10,000 years of simulations if we're going to do a perfectly realistic simulator. So we're always going to be looking for a marker for in the simulation, rather than trying to reproduce exactly what reality is doing.

Now, I'll just explain what the

cellular-level models look like. These started with Hodgkin & Huxley in 1952 with just these two-ion currents, sodium and potassium, and a small leak current. This was the first biophysical model of membrane excitability. It incredibly well-captured what the voltage waveform looks like, and that emerged out of the properties of the currents.

This was applied and adapted to cardiac cells by Denis Noble in the late '50s and published in 1960. These models have a very long history. Ever since, they've been intertwined with experiments. The models and experiments have really gone hand-in-hand as we learn more and more about cardiac electrophysiology.

Forward to 1991, this is the Luo-Rudy model. You can see it's still only got 6 currents in it, and it's still fairly simple. This is of limited use for drug action because we don't have individual ion channels tied to ion currents as all of the potassium currents are lumped into one description here.

Just go forward seven years, and by the

1998, the molecular biology revolution has come along, and we can now start to associate individual ionic currents with individual ion channel proteins. This model now includes separate IKr and IKs, for instance.

Forward to the modern day, this is what the models look like now. They have the intracellular calcium store, a sub-space in the membrane, and about 20 different ion currents.

This is the model that CiPA is based on at the moment, the O'Hara-Rudy model, which was almost entirely reformulated based on human data rather than animal data.

Why are these models going to be of any help? Well, it's all to do with putting together these multiple ion channel effects and predicting the overall effect on cellular electrophysiology, which is not something that's easy to do in your head.

Here's a simulation. If we say verapamil only blocks hERG, simulate at higher and higher concentrations, we'd get prolongation of the action

potential. If we say it blocks hERG but also calcium, then we get completely the opposite effect. And the simulation allows us to vary the degree of block and see what the consequences would be at the cellular level.

In CiPA, this is the basic idea that we get the patch clamp data, ideally from automated patch machines or up to these 7 currents. We use these as inputs into the mathematical model, the in silico reconstruction.

We then run simulations and work out a metric that classifies the level of Torsade risk, and Zhihua Li is going to talk about that next. Then we can check predictions, again, to the stem cells. So this is an important part, that we work out what we think the drug does to the ion channels, see what the consequences of that will be in a mathematical model, and then we compare those predictions from the model with the stem cells.

This step is important because if we're missing something crucial, for instance, the drug blocks another ion channel that wasn't screened, or

the drug interferes with trafficking, or something more complicated, we need to pick up that there's a mismatch, and go back and see if we can work out what's happening.

This flowchart will look something like this. You'll have the screening panel, put it into an actual potential model, run simulations at different concentrations, work out how the risk varies depending on concentration, and then compare that with any later safety tests, be they stem cells, later in vivo preclinical things that the pharmaceutical companies are already doing, or the phase 1 ECG.

Ideally, by the end of this process, we not only understand what the QT action is, we understand why we get that QT action. We, therefore, have more confidence in associating proarrhythmic risk.

In terms of the validation plan, at the moment, the In Silico Working Group has been using the data on 12 drugs, check that they can get the proarrhythmic marker, which separates the risk

profiles. And in the next phase, which will be coming along this year, they'll try and use 16 drugs, as Gary Gintant explained, and see how well the model predicts their risk categories.

That's it for me, just acknowledgments from the University of Oxford where all these people have helped with my thinking on this subject over the years, and a few resources down the bottom there that are open-source tools to let you play with these models and see what they do under drug action.

I'll now be handing over to Zhihua Li, who will tell you more about what the In Silico Working Group has been doing to develop the proarrhythmic risk markers.

(Applause.)

DR. WALDMAN: Thank you. Our next speaker is Zhihua Li. He's a staff fellow at the Division of Applied Regulatory Sciences at CDER at FDA. And as Gary said, he's going to speak to us about CiPA In Silico Modeling Development Strategy and Results. Dr. Li?

FDA Presentation - Zhihua Li

DR. Z. LI: Thanks. Thanks, everyone, for coming. Today, I would like to give a brief overview of the In Silico Model Development Strategy and Results.

As mentioned earlier, the O'Hara-Rudy cardiomyocyte model was chosen as the consensus base model for CiPA. The model development was divided into two stages: a training or collaboration stage where we used 12 drugs to train the model and another validation stage where we used 16 drugs for independent validation.

The model development for CiPA identifies a mechanistic metric that's related to early-after depolarization, or EAD, which is the cellular basis for Torsade, rather than action potential prolongation, which is for QT prolongation.

Now, here this is the 28 drugs tested by CiPA. They are categorized into three categories: high, intermediate, and low. Twelve of them are for training; they are shown on top. The remaining 16 are for validation. Right now, we have finished

the training stage, so today, all the data I'm going to present is going to be about the 12 training drugs.

This is the diagram of the basic CiPA model, O'Hara-Rudy. It has different components, each component representing a different ion channel, ion current. Several of them are selected by CiPA to focus on, and they are labeled by the red bars.

Now, after we took the base, the cardiomyocyte model, we made several improvements so that it can be used for CiPA. We first made the hERG or IKr component temperature-dependent. We then introduced drug-hERG interactions, and we optimized model parameters based on experiments.

In the next few slides, I'm going to give some details about the three improvements. First, temperature, because O'Hara-Rudy model operates at a physiological temperature, while the industry generates the hERG data, O'Hara-Rudy obtains at room temperature. A dynamic temperature-dependent hERG model is required.

For that, we developed a modified hERG model

that can reproduce temperature-dependent changes in major channel gating processes. This work was published last year.

The second improvement is dynamic drug-hERG interaction. Again, the rationale is because the same drug may show different block potency under different conditions, for example, under different heart rates. A novel model was developed to capture this dynamic drug-hERG interaction.

Shown above is the simplified diagram of this model. For time limits, I'm not go to into details. The left part is the hERG model, and we see drugs can bind to two sites or two states of the model, resulting two drug-bound states when channels open. When channel is closed, these two states can collapse into one state, which means a drug can be trapped within the closed hERG channel.

This trapping phenotype, represented by the red arrows, is often overlooked by published hERG models, but it turned out to be very important for many high Torsade risk drugs.

The third improvement was optimizing model

parameters using experimental data. Here, I'm using one piece of data as an example. We show here the human cardiomyocyte action potential duration recorded under one drug, L-type calcium current, or ICaL blocker, nisoldipine.

Here, the points are the mean data across 4 to 5 hearts with arrow bars. The dash line is the model prediction before we optimized the parameters. The solid line is after model optimization.

Clearly, the optimized model was able to reproduce the mean data better than the original model. And we see this not only for this current; similar improvements were seen for other major potassium currents, for example, IKr or hERG, and IKs and Ik1, and also late sodium current, INaL. This piece of work was being wrapped up with a manuscript and will be published soon.

Now that we have an optimized or improved base model, we began to develop a metric to differentiate different TdP risks. But before that, I would like to briefly revisit the key

mechanisms of Torsade, the imbalance of inward and outward currents.

Shown here is the action potential, the black trace. Action potential is basically membrane voltage during a heartbeat. You can see that it shoots up first, and then it enters this so-called plateau phase before it returns to the baseline, which is called repolarization.

The plateau phase is modulated by two opposing classes of currents, inward currents, which include L-type calcium and late sodium current, and outward currents, which include four different types of potassium currents including IKr or hERG current.

If for some reason the ratio between inward and outward currents increased, for example, if inward currents are enhanced or outward currents are blocked, you may see this red trace action potential, which is widened and prolonged. If this ratio is further increased, you will see this bump I showed before, which is called early-after depolarization or EAD. This EAD can lead to one or

two premature beats, resulting in Torsade de pointes on ECG.

From this, you can see that the balance between inward and outward currents are the key to the generation of EAD or Torsade. We developed a metric, the net current between inward and outward currents to reflect their balance. Mathematically, this metric, Inet, is the sum of all inward currents and outward currents because they have different directions or different signs. This actually reflects their balance.

Now, this is the performance of this metric over the 12 drugs. The X-axis is the concentration normalized against each drug's own Cmax, maximum clinical exposure. The Y-axis is the metric change of qInet. Change of qInet is basically the percentage change or integral of Inet between drug and the control.

Now, trial drugs, the red drugs, are high TdP risk. The blue ones are intermediate. The green ones are low risk. We can see that, overall, throughout all the concentration we tested from

1 to 25x Cmax, the three categories are all separated.

By the way, the simulation was done when we paced the heart at 2000 milliseconds or 30 beats per minute to mimic bradycardia because bradycardia is a known factor for Torsade. We also tried this for fast paced beating, or normal beating, or even tried the long-short-long pattern mentioned this morning. We found that bradycardia, as a trigger, is the best simulation protocol.

Also, we found another related metric, which is called change of qInward. Again, the X-axis is a concentration. The Y-axis is the metric, which is the percentage change of integral, of inward current only, which includes late sodium and L-type calcium current. Again, we see that the three categories are separated at high concentrations.

Three out of the four high-risk compounds developed EAD during simulation, shown by the stars here, which indicates this is very mechanistic metric. You might ask now, we know the balance between inward and outward currents are important;

how come you can still separate drugs by using only the inward currents? This is because due to the interaction between inward and outward currents, the change of inward currents actually carries the information of outward currents and reflects the shifted balance between them. It's not a direct measurement. That's why it's not as good as the net [ph] current before, but it's still good.

Now, we have two good, new metrics, the Inet and the inward currents. We wanted to do a systematic comparison with these two and other commonly used metrics. And here, the axis, again, is the drug concentration for the trial drugs normalized against its Cmax. The Y-axis, each row is one metric. We have the two new metrics on top, followed by some APD-related metrics, which are basically QT prolongation-related metrics and other metrics below.

Each square is the mean classification error across 12 drugs. This is the training stage, so we want the metric to be able to achieve zero training error, indicated by the white square.

Now, you can see that over all this metrics, only the two new metrics can achieve zero training error. All other metrics, including this QT prolongation-based ones, cannot achieve zero error, which means they always make a mistake when classifying just one or two of the 12 drugs.

Finally, what about experimental uncertainty? We know experimental data have intrinsic and extrinsic uncertainty. This will lead to uncertainty in metric calculation and TdP risk assessment. Thus, each drug at a specific concentration should have a range of possible metric values versus before for each drug at each concentration. I want to give you one metric value.

For this, we developed a method to translate experimental uncertainty, for example, variability of IC50s into uncertainty in metric calculation. Here, we have 12 drugs again. This is a simulation done at 2x Cmax. Previously, at this concentration, each drug has only one metric value, but now each drug has a distribution of possible

metric values.

The width of the distribution will reflect the uncertainty in the IC50s for similar data. We can see that even though there are some overlap between the distributions, the peaks of the distributions, which reflects the most probable metric value for each drug, are still separate along these three categories, indicating our metric, the Inet-based metric can still separate the three categories.

In summary, we took the consensus-based model, ORd model, and further enhanced it with temperature-dependent dynamic drug-hERG interaction and optimized model parameters.

We identified the two promising metrics using training drugs. Their performance needs to be assessed using independent validation. Method to incorporate experimental uncertainty established; method to capture inter-subject variability also being considered. And finally, the experimental quality criteria, data format standard and efficient route for sponsor data

submission are being developed in collaboration with industry collaborators.

CiPA is truly a global collaboration effort. I have many people to thank. Due to time limits, I cannot go through the names here. Our next presentation is going to be from Dr. David Strauss. Thanks.

(Applause.)

DR. WALDMAN: Our last presentation will be by Dr. David Strauss, division director, Division of Applied Regulatory Science, CDER at FDA. He's going to speak to us today about Phase 1 ECG Analysis under CiPA, Integration of All CiPA Components, and the Potential implementation strategy.

Thank you. David?

FDA Presentation - David Strauss

DR. STRAUSS: Thank you very much.

We've heard an overview of all of the four components of CiPA. I'm going to, first, talk about the last component, evaluation of unanticipated effects in clinical phase 1 studies.

The goal of this component is to use human phase 1 ECG data to determine if there are unexpected ion channel effects compared to preclinical ion channel data. This might occur because of a human-specific metabolite or protein binding.

The ECG biomarker working group looked at potential new ECG biomarkers and identified there would be a need to add additional information beyond QTc if we were going to introduce any new methods. Key criteria were the ability to differentiate multi-ion channel effects during repolarization, that the biomarker can be corrected for heart rate if needed, that there's sufficient power to detect changes in small sample sizes with exposure-response analysis as would occur in early phase 1 studies, and that analysis algorithms would be available for widespread use.

We started investigating this by performing an analysis of approximately 500,000 digital ECGs from a large number of prior thorough QT studies comparing to submitted nonclinical ion channel

data. And we identified an ECG biomarker, the so-called J to Tpeak interval that I'll explain on the next slide, that could differentiate drugs that selectively block hERG that are usually associated with Torsade risk, from drugs that block hERG and inward currents, late sodium and/or calcium, and have low Torsade risk.

This graphic shows the body surface ECG on top and ventricular action potentials from the heart on the bottom. The first component is the QRS, depolarization, corresponding with the peak sodium current.

The next part is this J to Tpeak interval going from the junction, the J point between the QRS and the ST to the peak of the T wave. As Dr. Li presented, this is when the calcium and late sodium currents are present. Later in repolarization, the hERG current becomes active and extends into the Tpeak to Tend interval.

We had incomplete ion channel data on many of the prior thorough QT studies, so we went on to conduct two prospective clinical trials involving a

total of 8 drugs and 3 drug combinations. I'm going to go through two slides, one from each study.

This slide, if you focus on the right-hand side, shows data for two drug --

(Pause - technical difficulty.)

DR. STRAUSS: All right. Both of these drugs prolong QT, and by only looking at QT, you cannot tell them apart. However, dofetilide, the selective hERG blocker, prolongs QT by prolonging both the J to Tpeak and Tpeak to Tend intervals.

In contrast, ranolazine prolongs QT by only prolonging Tpeak to Tend and not J to Tpeak. And this is consistent with the late sodium current, shortening the J to Tpeak interval and returning it back to baseline values.

We went on to investigate this further in a drug combination study combining dofetilide with lidocaine and mexiletine, the two late sodium current blockers. These graphs show the dofetilide concentration on the X-axis and the change on the ECG measurement on the Y-axis for QT, J to Tpeak,

and Tpeak to Tend, respectively.

Later, late sodium current blockers were administered. It shortened the QT interval as hypothesized, and it did this by shortening the J to Tpeak back to a baseline value without affecting the Tpeak to Tend interval.

In summary, from our ECG biomarker analysis, which went beyond what I presented today, we examined 12 potential ECG biomarkers in comparing them to ion channel data. Multiple ECG biomarkers could be applied in exposure-response analysis. However, area under the curve analysis show that the J to Tpeak interval was the strongest predictor of the balance between inward current or late sodium current block in the presence of hERG block.

This measurement also had similar inter- and intra-subject variability and heart rate relationship as QT, and other ECG biomarkers had a variable heart rate relationship. Software that we developed to make these measurements has also been released as open-source software, and there are six publications at the bottom that detail much of this

work in more detail.

We are performing another prospective clinical validation study that will apply this method in a small sample size, early phase 1-type clinical study to verify that a combined assessment of QT and J to Tpeak can differentiate between drugs that are selective hERG blockers versus have balanced block of hERG and late sodium and/or calcium. We'll include 6 drugs that is a combination of selective hERG blockers, hERG plus late sodium, hERG plus calcium, or the combination of all three. This will be completed in 2017, and it's actually starting to recruit subjects today.

Now, how do the components fit together? I'm going to walk you through this slide slowly, which will tie the four parts together. At the top, we have the output of the in silico proarrhythmia model in a continuous metric, going between low, intermediate, and high risk, as Dr. Li presented.

We, first, focus on the low-risk predictions. This can primarily be due to two

reasons. One, there's no hERG block or other relevant ion channel effects near clinical concentrations, or we have balanced ion channel effects like ranolazine or verapamil.

Focusing on the no-ion channel effects, the stem cell cardiomyocytes can be -- the assays can be performed to look at repolarization effects. If there are no repolarization effects, this is consistent with low risk. If there are repolarization effects, this is a potential discrepancy.

We would want to understand the mechanism, but this does not mean there is Torsade risk. We'd want to proceed to phase 1 studies where QT exposure-response analysis can still be performed. No QT prolongation is consistent with low risk.

The presence of QT prolongation is a potential discrepancy. An integrated risk assessment could be performed assessing J to Tpeak and Tpeak to Tend, asking questions such as if the effects are due to a minor potassium channel, a metabolite, hERG trafficking, or a non-acute

effect.

With the balanced ion channel effect drugs, the stem cell-derived cardiomyocyte assays can still be performed. Although as they are not perfectly "mature" in their balance of ion channels, there wouldn't be too much weight placed on this assay.

We would expect potential QT prolongation with these drugs, and so we would look at the J to Tpeak interval. The absence of J to Tpeak prolongation would be consistent with a low-risk drug, whereas the presence would be a potential discrepancy not consistent with low risk and would likely require enhanced ECG monitoring in development and appropriate labeling.

For intermediate or high-risk Torsade drugs, if the decision is made to progress to human studies, the QT analysis can still be applied in exposure-response analysis in phase 1. QT prolongation would be expected, and it's still consistent with intermediate or high risk that would've been predicted from the model.

The absence of QT prolongation would be a potential discrepancy, and after an integrated risk assessment, assuring that an appropriate supratherapeutic exposure was achieved and the study was adequate, the risk could be down classified.

In summary, CiPA is intended to be a fit-for-purpose assay. It will utilize an in silico mechanistic model to serve as the prediction of proarrhythmic risk of a drug in comparison to known clinical comparators. An additional preclinical check with stem cell-derived cardiomyocytes will be performed to ensure that drug effects on repolarization are not missed. ECGs will still be assessed in phase 1 clinical studies that are already being performed with exposure-response modeling.

I'm now going to quickly go through the questions, followed by one background context slide. Question 1 for the committee will be:

For a QT prolonging drug, will this mechanistic model-based approach be fit for the

following two applications:? A) determining whether ECGs need to be collected in phase 3; and B) informing proarrhythmic risk language in drug labeling?

As Dr. Garnett [sic] reviewed, currently, a positive thorough QT study often results in further ECG follow-up in late phase studies. The extent of follow-up is influenced by the magnitude of QT prolongation; although that does not necessarily correlate with Torsade risk.

If QT prolongation is substantial, the goal of ECG monitoring is to protect patients in later trials and obtain further information on the frequency of substantial QT prolongation to understand the potential proarrhythmic risk of the drug.

QT prolongation at therapeutic exposures results usually at a minimum in labeling in the warnings and precautions and advising to avoid use with other QT prolonging drugs or in high-risk patients.

Question 2. Does the committee agree with

the proposed approach for validating the new paradigm that involves assessing 28 drugs classified into low, intermediate, and high risk by an expert panel, and if not, what else should be done?

To recap, a set of 28 drugs with well-defined electrophysiology and known clinical characteristics was identified by a team of expert clinicians, safety pharmacologists, and cardiac electrophysiologists from regulatory agencies, industry, and academia.

They were categorized into high, intermediate, and low risk of Torsade based on published reports, analysis of the FDA adverse event reporting system data base, other data sources, and expert opinion.

The set of 28 drugs was divided into training and validation drugs. The validation will include assessing all of these drugs in both the ion channel, in silico assay, and the IPSC, the stem cell-derived cardiomyocyte assays.

For the CiPA phase 1 ECG approach, analysis

has included an assessment of a large number of thorough QT studies, two prior FDA-sponsored clinical trials including 8 drugs, and a confirmatory prospective study involving 6 drugs to be completed in 2017.

The final question is, as this new mechanistic model-based approach is implemented, should the FDA collect the world's experience to facilitate future enhancements as was done by the FDA with the ECG warehouse for QT studies?

As occurred with implementation of the QT interdisciplinary review team and digital ECG warehouse, FDA intends to expand to a proarrhythmia interdisciplinary review team and collect digital waveform data from in vitro experiments to collect the world's experience and further refine the paradigm over time.

We anticipate that this will inform enhanced in vitro laboratory protocols and improve the computational model over time, similar to the evolution of QT studies, to implement exposure-response analysis and design more

efficient studies.

In summary, we expect that CiPA will result in standardized nonclinical, mechanistic-based studies to determine proarrhythmic risk that can be applied early in drug development to aid in compound selection, as Dr. Gintant presented.

Proarrhythmic risk will be calibrated against consensus clinical comparators ranked according to clinical experience.

Compounds with hERG block and/or QT prolongation that might be dropped development under the current paradigm could have a clearer path to advance if they are shown to not be proarrhythmic. QT prolonging drugs on the market that are not proarrhythmic could have their labeling updated to reflect this. And this can be a model for other comprehensive, model-informed, mechanistic-based approaches to be applied in other drug safety areas.

In conclusion, the CiPA teams have presented multiple times to the ICG S7B/E14 discussion group the rationale and approach being taken under CiPA.

The CiPA Steering Committee is optimistic that this interaction will speed acceptance of this alternative pathway for assessment of proarrhythmic potential for regulatory purposes.

The CiPA Steering Committee is also optimistic that the work outlined here can be completed by the end of 2017. After implementation, we are interested in carefully evaluating approved drugs that show evidence of being QT prolongers without Torsade risk, with the expectation that the application of CiPA will result in drugs having their current labeling changed to more benign language, if appropriate.

I'd like to thank the many people involved within and outside the FDA. Thank you very much.

(Applause.)

Clarifying Questions

DR. WALDMAN: Thank you very much.

We're at the point in meeting where we will have clarifying questions to the FDA and guest speakers. Let me ask the assembled, are there any clarifying questions for the FDA or guest speakers?

Please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter.

If I can start off the questions while you guys are thinking about your questions and queuing up your hands, David, this is for you; although anybody can answer. This is not my field, and I may be asking really naïve questions. I apologize for that in advance.

There are two scenarios that I was thinking about as you were speaking. One is the, for lack of a better phrase, the false-negative situation, and the other is the false-positive situation.

It seems, to me, that the CiPA paradigm doesn't take into consideration intrinsic and extrinsic factors of the patient that could potentially influence electrophysiology, so co-morbid conditions, concomitant medications.

My concern would be for a drug to make it through the paradigm, make it through screening, make it through phase 1, absolutely clean, and the determination is, okay, we don't need cardiograms

in phase 3, and now go into a patient population with the disease, comorbid conditions and concomitant medications, and reveal an electrophysiological effect and Torsade, for example. That's a false-negative scenario.

The false-positive scenario is a drug that gets identified in the paradigm, gets into phase 1 and further clinical trials, and has no electrophysiological signal in the patient populations.

Does that drug now carry with it the burden of a labeling change into the future, ultimately, if it gets approved, because it showed something in the paradigm that didn't play out in the patients? Those are two questions. Sorry.

DR. STRAUSS: Yes. Thanks for those questions. David Strauss.

I think before I directly answer the questions, it's important to point out that with the current paradigm where we just focus on hERG, one ion channel, and QT, the primary problem has been false-positives, not false-negatives.

That has actually been one of the main driving factors for CiPA. All the excellent points about there can be patient variability, drug-drug interactions, I mean, all that is true in the current paradigm also, and we haven't had too many problems or we haven't had problems.

With that caveat, I think that if I focus on the false-positive first, you're asking if there's a drug that comes out as predicting it's proarrhythmic, but in phase 3, you don't see any Torsade events. That's common currently because Torsade is extremely rare, except for the highest risk drugs, dofetilide, quinidine. It's still only in a 1, 2 percent range.

So yes, a drug could still carry Torsade -- or we think this drug is high risk even though we didn't see it in clinical development, but I think that would be appropriate since it is such a rare event.

For the false-negatives, your question is if we -- can restate your specific question for that?

DR. WALDMAN: Yes. The drug gets through

the CiPA paradigm, and it's clean.

DR. STRAUSS: Right.

DR. WALDMAN: So then the decision now is, okay, I don't need to collect cardiographic information in phase 3; I don't have to do that. But it turns out that when it enters the patient population with the pathophysiology, the concomitant medications, the comorbid conditions, now an electrophysiological effect is revealed --

DR. STRAUSS: Right.

DR. WALDMAN: -- that you didn't pick up in the paradigm because the paradigm doesn't really consider those things.

DR. STRAUSS: Yes. We are able in the in silico computational modeling to take into account different electrophysiology effects. We're investigating the use of a so-called population of models approach where you vary the ion channel conductances of each of the currents. And instead of just running one simulation, you run a whole spectrum of them.

So we can get a spectrum of -- Dr. Li

presented the uncertainty quantification, and then we can do that with a population of models that represent different patient characteristics in addition.

We have some ability with the modeling, do both models, different exposure levels. We will do that, and we showed that here, but then also to model potential differences in the electrophysiology on an individual patients' basis. And we will see if that helps in the risk stratification.

Ultimately, it's important to point out that we're not performing personalized medicine here. We're not trying to predict risk in an individual patient. We're trying to predict overall general risk for a compound.

DR. WALDMAN: Thank you very much.

Dr. Awni first, and then Dr. Carrico.

DR. AWNI: Walid Awni. This is a question for Dr. Strauss. I'm just trying to actually understand from the mechanism of drug development how this fits. You do your experiment, in vitro

ion current experiment, you get your data. You find the signal, all of them that you say, hey, there it is.

So then everybody will be doing an in silico modeling of that time point, and then do the stem cell? Because then you could go to the human. Ultimately, you're going to go to the first in-human. If you are trying to save, let's say, that the drug that get kicked out of the drug development process because they have hERG effect, I'd say, hey, there might be a different reason, and we shouldn't kick them out.

That means that a lot of that work will happen before you go to the first in-human, and when you get to the first in-human, you say, hey, we saw this, we have this mass, or, we didn't see anything?

I'm just trying to see where would you see all of that work fit in the drug development.

DR. STRAUSS: I could make a brief comment, and then I think it could be good for Dr. Gintant to make a comment from the industry perspective of

how he sees this might be used in pre-regulatory setting because sponsors can use this however they want before they come to FDA for their internal decision-making. And different companies may use it earlier, later in the process, during screening, or final compound selection. That's one point.

Would you want Dr. Gintant to comment on that briefly?

DR. AWNI: Yes.

DR. GINTANT: Industry is already moving toward this, at least looking at multiple ion channels, rather than simply hERG. There's a bit more I think reticence to moving to the in silico reconstruction simply because there's less familiarity with it, less understanding of what it can do.

Certainly, the industry is already moving towards this because they recognize that for mechanistic-based assessment -- and we want to move the same good compounds forward and not get surprised later on.

DR. AWNI: I'll just follow up just one

second because the simplicity of the decision at the earliest time point -- because you don't want to spend resources on it. It's very important. That's why the hERG experiment has been very valuable.

Although you killed some drugs, that's fine -- or not the drug -- some compound -- you move on. That's where I'm kind of like how simple could it be implemented, which tells me -- the other question for Dr. Strauss, the team is looking at all the pieces. Would the team come back and say, you know what, the only thing you need to do is just 1 and 4 because 2 and 3 could be quite different resources for a small company, a big company. You don't need to do it except for these special cases.

DR. STRAUSS: In this next year, we'll have a lot of validation data, and there are a few things that might happen. With the ion channel screening, right now, we're assessing 7 ion channels; that may go down to 4 ion channels that are critical, so that could be reduced.

We'll be able to see what the complimentary value is of the -- the ion channel in silico is really a combined approach. And once you have the ion channel data, it doesn't really cost you much to put it in the model.

We'll see how well the stem cell-derived cardiomyocyte data in this full multi-site global validation study performs. And it's possible that draft flowchart I presented of how things could fit together, our thinking, the group's thinking may evolve.

DR. WALDMAN: Terrific.

Dr. Carrico and then Dr. Roden?

DR. CARRICO: This is Jeff Carrico.

Dr. Strauss, I'd like to go back to the discussion about the false-negative, and taking into account that a lot of things can happen, and we need to talk about them and discuss them and everything, and also taking into account what you said about how the model can be played with, and the rarity of Torsades, could you talk a little bit about whether or not you see that -- again, taking

into account that we're discussing CiPA, to this extent, for its use, could you address whether or not you do see the opportunity for false-negatives, or is that something that just fits into the something-could-happen category?

DR. STRAUSS: Yes, it could happen, but we're not that worried about it. It has not been a problem over the past decade. We think that the current approach has likely been a little too conservative.

Yes, it's something that we will always keep in mind, and we do not want false-negatives, but we're not that worried about it.

DR. WALDMAN: Thank you. Dan?

DR. RODEN: I have about 10,000 questions.

(Laughter.)

DR. RODEN: I'm going to try to limit myself to the high points, and at some point, you and I, and others can get down in the real dirt, which is probably not important for this meeting.

So this is Dan Roden. These are clarification questions. I have other questions

for later.

The modeling is ventricular myocytes. Most people think Torsade originates in the Purkinje fibers, so I'd like a modeler to address that particular question. I'd also like to know why the models are done at 30 beats a minute, a heart rate that nobody ever sits at for long. They might sit there for a second or two.

So I think you need to think about why you're doing the models at 30 beats a minute and not 60 or 100 beats a minutes, or modeling disease.

I think a potential false-negative is a drug that is a particularly bad actor in the presence of heart disease. In particular -- and this is almost a personal belief, but there's lots of data to support me -- in the presence of atrial fibrillation and the conversion after atrial fibrillation, that's a very high-risk period for these drugs, and one way to bring them out.

Then I guess a generic question is, if we're talking about not doing the thorough QT, are there data, do you have a sense, is there a way to get

data on how this particular paradigm performs compared to a thorough QT paradigm?

I'm agnostic, at best, about the thorough QT study. I'm not sure it's all that helpful. It's certainly cumbersome, and some way to replace would be great. Do you know whether the thorough QT has actually helped anybody and whether this will help more?

Those are my clarification questions. Just wait until we get to the other questions.

DR. Z. LI: There are several questions about modeling. I think the first one and the third one, they can be combined together. The first question was some animal study that shows that Torsade or EAD more easy -- you can easily see them in Purkinje fibers; why did you use a endocardial myocyte rather than Purkinje fibers?

The third question was, we know that some diseases, patients are more prone to EAD or Torsade, but now, we are using a healthy human heart with healthy human myocyte; why do we do that?

I would like to combine the two questions into one to try and justify why we choose the model or the myocyte we are using now. The purpose of CiPA is not to predict at which beat EAD or Torsade will develop. If it was that, you would have to consider all kinds of things, underlying diseases, genetic background, et cetera, et cetera.

The primary purpose of CiPA model is to rank order drugs in terms of their tendency to cause EAD or Torsade. We found that by using a healthy human myocyte model, we can find a metric that measures the distance of the drug at a certain concentration to EAD generation. And we can use this distance to rank order drugs, so that we believe that this order is the same between different myocytes and the different conditions.

Also, another thing is the purpose of CiPA modeling originally was to try and to replace TQT study. A TQT study will recruit healthy human patients to -- we use QT signal from healthy patients to help us to make real good decisions, so that there's some parallel here.

The second question was about a choice of beating frequency. I said that we used 30 -- I showed the data for 30 beats per minute to mimic bradycardia. Admittedly, this is a very, very extreme slow beat, but we found that actually with our current base metric, the Inet-based metric, the metric performs equally well in 30 or 60 in slow beat, lower beat, heartbeats. When the heartbeats slow down a little bit, the separation is slightly enhanced, but we can achieve the separation in normal physiological conditions.

I think the third question is about TQT study. Maybe I can defer that to David or Christine.

DR. GARNETT: For the thorough QT study, the current paradigm right now is sponsors could collect the ECGs in the phase 1, which would now be considered that fourth component of the CiPA.

In the phase 1 study, if it goes over a large exposure range, which includes not only the therapeutic exposure range but in excess to account for high exposures those patients may see, we will

be looking at those electrophysiological effects of these new biomarkers over these wide range of concentrations in that phase 1. And that would be your definitive assessment of the mechanism within a human model per se, not just in the in silico models.

DR. RODEN: Do you have any sense whether the thorough QT, as currently performed, actually gets drugs that would be dangerous off the market? There's no way to know that. Because there's people stop developing a drug based on the --

DR. GARNETT: That's right.

DR. RODEN: So, we don't know.

DR. GARNETT: Well, the way the thorough QT study is implemented is if you come out of nonclinical development, and you know you have a prolonger, but because of benefit-risk such an oncology product, you're going to move it forward, you don't have to do a thorough QT study at that point. When you give this drug in the clinical trials, you are already monitoring ECGs in all patients for safety and understanding what the

proarrhythmic risk is.

So we don't see huge QT prolongers coming through a thorough QT study, and most of the ECGs from those would come from the clinical trials.

DR. WALDMAN: Yes, please.

DR. AU: Jessie Au. I have a question for Dr. Li. I really don't work in this area, and I don't even recognize any of your abbreviations, what they mean.

(Laughter.)

DR. AU: I'm looking at it as a modeler. Your 4 says basically when you account for the temperature-dependent binding, then you improve your fitting a lot, I mean 20 percent at the last data point.

I made an assumption that -- you said this is an in vitro assay. You put a drug, you bind something. You get some binding constant, and you're now corrected for that. Is that a correct assumption?

DR. Z. LI: It's not only a binding. You have to measure the effect of the binding, which is

blocked current through the channel. So it's not just simply binding.

DR. AU: Okay. You measure another endpoint. Then the question is, if you want to use CiPA to help you to screen false-negative, false-positive, doesn't that then require you to know what drug you're looking at.

I mean you're at moiety. When you do in vitro, you're stuck with moiety. So if you have a metabolite, you're not going to find it with this assay, are you?

DR. STRAUSS: David Strauss. Yes, a metabolite, we can assess a metabolite just like we assess the parent drug. And with the hERG assay, a major metabolite, if it's above a certain threshold, will also be assessed, and so that can be done.

Then we also still do have assessing ECGs in phase 1. If there was human-specific metabolite that wasn't predicted or anticipated, we would see if it is causing a clinical effect in the phase 1 studies. But we can assess metabolites, in vitro

also.

DR. AU: Follow-up?

DR. WALDMAN: Follow up, please.

DR. AU: Still, as a clarifying question, I thought you want this -- well, maybe you're going to use any time during the whole development path. If you do this before you have clinical data, then you cannot know if your metabolites in animals are going to predict what happens as well.

DR. STRAUSS: Yes. The focus would be on the parent compound. If there was a major metabolite that emerged, and it was suggested that it was having electrophysiological effects, you could go back after you've been in humans and perform any parts of this assay on the metabolite if that was needed.

DR. WALDMAN: Xander, identify yourself.

DR. VINKS: Xander Vinks, University of Cincinnati. We got a very nice overview about an impressive model. What I was missing a little bit is bridging information in terms of how would this really predict in patients, and I think that aligns

with comments before.

I just wanted to ask the presenters whether they could elaborate a little bit more on it. We have two examples. These are a phase 1 study, so this is data from healthy volunteers.

Whether you have done more of concentration effect in this respect and the proarrhythmic effects that would be predictive by the model, first, in the phase 1 data sets that you have access to. But I would assume also, given that you have this large ECG database, that you would have also this exposure-response-type information in real patients, patient population.

Have you done that type of analysis, and if so, are you planning on it? How do you go from phase 1 to a later phase as you ask us, as a committee, to determine whether ECGs are needed to be collected in phase 3?

I was missing a little bit of that bridging information to make a real good, say, decision on how to answer that question.

DR. STRAUSS: David Strauss. I think a key

point is that our gold standard here for proarrhythmia is not a biomarker signal in phase 1 or phase 2 that is an ECG marker. The gold standard for validating this assay is actually seeing Torsade in patients. These 28 drugs are drugs that have -- many of them that have been on the market for years. Some of them were removed from the market like cisapride or terfenadine.

So it's based on clinical experience. That's how we're validating the nonclinical parts of CiPA. We do have a lot of in-house data at FDA. In terms of looking at these new ECG biomarker assessment that could differentiate the ion channel effects, that was really developed from having the ECG warehouse at FDA and being able to go back and reanalyze the digital ECGs.

But that's not the core part of CiPA. The core part is predicting the proarrhythmic risk based on clinical experience in patients over many years.

DR. WALDMAN: Other questions from the panel? Dr. Polli?

DR. POLLI: Dr. Strauss, you actually just partially answered my question that I was thinking about.

Question 2 concerns these 28 drugs. Of the 28 drugs, I think 8 are in the high-risk category. Can you just elaborate more on the suitability of those 28, whether they -- and I was thinking about the false-negative concept.

Can you just elaborate a little bit more on the suitability of those 28 drugs?

DR. STRAUSS: Yes. It's very tricky to come up with a gold standard because every drug is used in a different patient population. Some used are in cardiac patients, and other drugs are used in healthy subjects who have an antihistamine.

In terms of classifying the risk into different categories, in addition to some quantitative numbers in terms of what signals in the FDA -- or what the number of Torsade events is in FAERS and other case reports in the literature, there is some clinical judgment and experience that went in from the group that categorized these

drugs.

So it is a very tricky thing to do, but if we really want to predict the clinical endpoint that's important and cause a sudden death, this is the best method we could come up with. And I think this is a common problem that would extend to other types of drug-induced liver injury. What is the gold standard? It's tricky.

DR. WALDMAN: If I could take the chair's prerogative and move at the moment to the folks on the phone who haven't had a chance to ask any questions.

Folks on the phone, I'm going to go one by one and ask if you have questions.

Dr. Arkus, do you have questions?

DR. ARKUS: No, I don't have questions at this time. Thank you.

DR. WALDMAN: Thank you.

Dr. Cook?

DR. COOK: Yes. Dr. Cook with Pfizer. With respect to the potential CiPA assessment flowchart, which was slide 12 in Dr. Strauss' presentation, I

understand the value of the preclinical in silico assessments to drug development, but the decisions as far as regulatory and monitoring in future studies seem to rely primarily on the phase 1 human study results.

Am I reading that correctly?

DR. STRAUSS: David Strauss. No, it doesn't rely solely on that. We've tried to compress a lot of information into a single slide. But the phase 1 ECG results are at the bottom of the slide, but the way you use the phase 1 ECG differs based on whether you've predicted it's a low risk from the model, based on no ion channel effects, to the balanced ion channel effects, or you predict it's intermediate or high risk. That is having a substantial influence on how we interpret the later assessment in phase 1 ECGs.

DR. WALDMAN: Thank you, David.

Dr. Cook, any other questions?

DR. COOK: Just one other, and that's the -- not in the paradigm of the large animal cardiovascular safety studies that are done. Not

to be provocative, but is there a suggestion that we no longer do those?

DR. STRAUSS: Those generally aren't related to proarrhythmia.

DR. COOK: Okay.

DR. WALDMAN: Thank you.

Dr. Tenjarla? Are you on, and do you have any questions?

DR. TENJARLA: I'm on. I have no questions at this time. Thank you.

DR. WALDMAN: Thank you.

Dr. Waldo, we have your question from earlier today. Actually, it was asked and answered earlier. Dan Roden asked a question, and it was addressed by the agency.

Do you have any other questions?

DR. WALDO: Yes, I do. Actually, I didn't hear that. You know, there was a time when we lost a voice on the phone, so I'm not sure if I heard that answer. It might have been at that time. I share a lot of Dan's concerns, but let me just do a few before I get to my main point.

First, I want to repeat what Dan said. The longest action potential duration is in the peripheral Purkinje system, and I think that's not a minor thing. The fact that you're only using ventricular cells or ventricles in your studies, it ought to be rethought a little bit, at the very least.

The second thing I wanted to ask you was about just the measurements of the QT, just the information. The QT measurements, there are several that are out there, and each of them have their limits. And the best one, I think, is really not used. Most people use the standard one, which is not all that good I think at the fast rates particularly. I'm just curious to know what QT correction you use.

The next thing that I wanted to ask was about -- oh, no. I wrote a few things down -- yes, about heart failure. That comment was very, very important because you could take a drug -- the most recent one that I know about from personal experience is dofetilide. It's a very good drug,

and Pfizer did a very good job, finally, in recognizing how to control problems with prolonged QT and Torsade.

When you get these QT prolonging drugs -- and dofetilide is a good example of this -- a patient with heart failure, it's a whole lot worse. In fact, that was first described with quinidine by a friend of mine, Eric Prystowsky, who showed that quinidine, which is a famous drug with the QT prolongation, but [indiscernible]. That's a third question.

Then the last question I have was to get back to the original question that I asked this morning. Dan called it the short-long-short, and we call it the long-short. But when you look at most initiation of Torsade de pointes in patients, most of the time, the EAD, it comes out of the T waves. The impulse from the EAD compared to T waves. And if you look at the beat before, which is usually a normal beat, preceding that beat, there's a relatively very long interval.

So what happens is the beat to be the action

potential duration, as most people I think on the panel would know, is it changes on a beat-to-beat basis. So when you go to a very long interval, but your restoration gets very wide for just one beat, that's all you need to set off a Torsade.

The point being that the variability of studying at constant rates is maybe a problem. Maybe you want to consider setting some of these things that mimic the clinical situation of the long-short, or as Dan calls it, the short-long-short interval. Those are my comments at the moment.

DR. WALDMAN: Thank you, Dr. Waldo.

I have four questions here. I got the first two. I didn't get the third one. I got the fourth one.

The first one referred back to the Purkinje fibers.

DR. STRAUSS: Yes. David Strauss. Go ahead.

DR. Z. LI: If I understand correctly, the first question was the EAD or Torsade, you can

easily see those in other types of tissues. Now, we are using -- just we're relying on ventricular cardiomyocyte model.

Is that the question you were asking?

DR. WALDO: Yes, because -- I mean, first I have to say the presentations, they're really pretty spectacular. I really enjoyed it, and in fact, I learned a lot, too. But I think it is conspicuous to me -- I won't speak for Dan, although he asked the question -- that, really, we think the spontaneous initiation of Torsade comes from the Purkinje fibers, not the ventricles.

It's believed, from my understanding, is that's because the peripheral Purkinje fibers have the longest action potential duration, and it's actual potential duration that's key in generating the EADs.

DR. STRAUSS: David Strauss. A couple quick points related to that. I think it's important to point out, as in Dr. Mirams' presentation, we're not trying to perfectly model reality, but have a useful model that can predict these clinical

events.

The reason it's an endocardial cardiomyocyte model is that it was validated with approximately 140 human hearts making measurements from endocardial cells. The model can be adapted to represent different cell types; epicardial, midmyocardial could be adapted to represent Purkinje. But the core validation was done with endocardial cells.

If I could try and address a couple other of your questions quickly, you talked about heart failure and dofetilide can be more proarrhythmic. Dofetilide would come out as a high-risk drug. It would require ECG monitoring under CiPA, and it's given in high-risk patients. Those are probably going to be monitored -- that's a different situation than the vast majority of drugs.

Then the short-long-short or long-short-long, we have simulated that, and we have found that it was not more predictive than just simulating bradycardia. But we can simulate any rate we want, and we have investigated

different rates.

DR. WALDO: Thank you, Dr. Strauss. I will only emphasize one thing. That is, I only use dofetilide as an example. Of course, it doesn't need that example to show its difficulty. But I wanted to say that there are other drugs that might be fine in the absence of heart failure, and then when you give it to a patient who has heart failure, all of a sudden it gets worse.

I'm not sure we understand why that is, certainly at a cellular or molecular level. Drugs that prolong the QT but don't ordinarily cause Torsade can do that when you get into heart failure.

It turns out that the studies that I've looked at, particularly Prystowsky did a very good job with that, went back and looked at all initial reports on Torsade with quinidine. And virtually, all the patients that had it were being treated for heart failure.

I just thought that that's something to put in the mix, not necessarily stop what you're doing

and change everything. I think that gets to the issue of comorbidities that's been raised by some of my colleagues on the panel. I think comorbidities do play a role, and that's just one example.

DR. WALDMAN: We appreciate that, and it's noted. We've had some good discussion around that, and the agency is taking that into consideration.

I'm going to move on to Dr. Li on the phone.

Dr. Li, are you on?

DR. T. LI: Yes, and I don't have any further questions.

DR. WALDMAN: Can you identify yourself, please?

DR. T. LI: Tonglei Li, from Purdue University.

DR. WALDMAN: Say it again?

DR. T. LI: Tonglei Li, from Purdue University.

DR. WALDMAN: Very good. Thank you very much.

Okay. That concludes clarifying questions

for the moment. Okay. Good, a very robust discussion.

DR. WALDO: This is Al Waldo. Can I ask one other question that hasn't really come up? And I'm not sure how -- it's a minor relevance I think. But there are lots of patients who have pacemakers, for instance, and they're pacing the ventricles.

How do you measure QT in those? Then patients with bundle branch block, the same thing, how do you measure QT in those things, and is that ever an issue?

DR. WALDMAN: I'm going to punt to you.

DR. STRAUSS: That isn't an issue in this paradigm where the ECGs that are being assessed are almost always in healthy volunteers. It's not an issue in the nonclinical parts of CiPA. So I don't think that's a problem with our validation strategy.

Open Public Hearing

DR. WALDMAN: Very good. Thank you for that.

We're going to juggle the agenda just a

little bit, and we're now going to move forward with the open public hearing. We do have one speaker for the open public hearing. So let me take the liberty of reading this preamble before the speaker comes up.

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

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For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, the FDA

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. With that said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Please, speaker number 1 is up at the microphone. Please introduce yourself, state your

name, and any organization you're representing for the record.

DR. POLAK: Good afternoon, everybody. My name is Sebastian Polak. I'm a paid employee of Simcyp, which is part of Certara. Simcyp operates via the consortium of pharmaceutical companies. I'm also a full-time associate professor at Jagiellionian University Medical College, Krakow, Poland. They also claim they pay me, but I can barely see it.

As for the key points of the presentation, because all those comments which I give in the form of the presentation, and then I have a couple of questions which may or may not be answered, is to go very quickly through the problems with the current paradigm, and what can be modified or added to the newly proposed paradigm to make it even more robust. So what are the known issues of the current practice?

I think we can divide them into subparts. At least some of them were discussed during the panel discussion. We've got a problem with

the -- or a general problem with the channels inhibitions, TdP risk classifications, and prediction algorithms. Then of those, which are focused on the drug, like a problem with the prodrugs, for example, or active metabolites. And I'm just going to discuss just a couple of them during the second part of the presentation.

Then we've got problems, which are connected with the physiology or pathophysiology of the patients, like comorbidity, like dietary habits, like lifestyle, or drug-triggered physiology modification like potassium depletion, for example.

Last but not the least, we've got a problem with the exposure because the majority of drugs, the plasma concentration is a relatively good surrogate. I can think about at least a couple of examples where heart concentration could be or is a better surrogate of the active concentration, to give [indiscernible] as the example only.

I'm going to go into the details of some of them, so a closer look of some of those issues and find some patterns.

First of all is a TdP risk classification. I know it was proposed to develop a new classification and divide the compound into three groups: high, mid, and low risk. But the problem is, it's based on 28 drugs only. So how about the remaining 620, which we classified or which we analyzed?

What we did, we compared multiple classifications of the TdP risk. And among the 650 compounds, drugs, which were found, 80 were classified differently. So 12 percent of drugs were in both groups, TdP plus and TdP minus.

It's relatively easy to do it for 28 drugs, but it's a highly theoretical situation. In reality, we've got much more compounds, much more drugs which are on the market, and even more will be introduced during the years.

So there is a need for a new robust and new classification, and there's a need for consensus here.

Just to give you two examples, the first one is risperidone. Risperidone, which was classified

by classification given by Dr. Gary Mirams as safe, by Dr. [indiscernible] as safe. At the same time, it was a TdP plus drug in the Kramer classification. So the question is, where does risperidone lie? Is it a TdP plus or TdP minus drug?

When we went through the literature, we found that there's much more than just a drug, which caused the problem. It can be a CYP2D6 genotype, which can be a risk factor like a female, sex; age; bradycardia; concomitant use of other drugs.

It gives you a bit of flavor that -- TdP does not depend on the drug only. It's a much more complex story of problems. So I think we should look at this wide picture, rather than focus on the drug only.

The other one is one of my favorites, I would say, because verapamil is always given as an example of a safe drug. Here is just the result of the very quick query through the intervision [ph] system, and about 60 or 70 problems as for the TdP

for this verapamil.

It doesn't mean that the verapamil is Torsadogenic because it's not. The problem is it was probably taken by, I don't know, alcoholics with some other drugs and so forth, which again proves that statement, which was given like 400 years ago by Paracelsus that "everything is a poison." It's true here. And I think it's a chance, right now, with this new paradigm to go into the details and to analyze more than just a drug.

Actually, metabolites were discussed, so here's the good example, I think. It's dolasetron and hydrodolasetron. Dolasetron is a prodrug. It's active, but it's metabolized very, very quickly through 10 or 12 minutes, or half an hour. And then the active compound is a hydrodolasetron. Depending on what and how do we analyze that, we've got a completely different decision or result of this analysis.

Dolasetron is safe. Hydrodolasetron is safe, but when it's given intravenously in high

dose, as FDA recognized a couple of years ago, it can be a QT prolonging situation or Tdp risk eventually. Why it is like that? Because the concentration of both of these active moieties, for a short period of time, it's high enough to give this kind of situation or this kind of problem in the real-life situation, in the real-life clinical scenario.

So again, when you analyze dolasetron, it's safe. Hydrodolasetron, it's safe. I think it should be analyzed concomitantly because a single drug analysis can be misleading, and multiple drug analysis might be necessary, not only from the PK side but from the PD side, as well.

Metabolites should be analyzed in parallel because the pharmacokinetic fate of these compounds can play significant role. There is a need to assess, at least theoretically, conceivable extremes. And this is something that we can do with the models and with the approaches, which we've, for example, discussed this morning as a PBPK model because there are tools to accommodate

the scenarios. They exist. They can be used, tools or approaches to be more general.

What we can do, we can account not only for the information which are drug-specific, like IC50 volumes for the inhibition of the currents, but also information about the system, something that we do with the special populations in the PBPK world.

What is the tissue volume? What is the cardiac output? But also we can add, on top of it, information about, for example, cardiomyocyte volume to account for hypertrophy of the heart to give the information or the add the information about the plasma concentration, electric capacitance of the cell. All of that information is available.

Here is the question, comments to the purely stochastic approach of building population of models. Mathematically or statistically, it is very interesting and very correct. But as Dr. Mirams said, statisticians sometimes don't understand the mechanism. We do understand, at

least, partially the mechanism. So we know that there are some physiological parameters which play a role.

Therefore, the purely stochastic approach will be probably done in parallel or even replaced by the deterministic approach because this data, this information, or the physiology, which lies behind the electrophysiological activity of the drug, is available.

By combining those altogether, we can have a population of interest, population of virtual individuals. Again, this is something that we're aware, and this is something that we are investigating for the PBPK. And the PBPK, it does work.

So it is quite likely that if the models are properly parametrized, analyzed, and validated, we can use the same approach in the Torsadogenic risk prediction.

What I would like to advocate for is to be somewhere in between the very simplistic models based on the single cell, and electrophysiology of

the single cell, and the 3D models, which are really, really computationally costly. One-dimensional heterogenic models can be good enough to give us information about the population, about the heterogeneity, and intra- and inter-individual variability, which we can expect. At the same time, if we have a powerful laptop, it can be run on a simple laptop easily. It shouldn't be a problem.

Just to conclude, two last slides, this new approach addresses at least some of the problems which are listed. These three are addressed to some degree at least. Some of them are very, very challenging, and I don't see the possibility to do that very easily, at this stage at least, so much more research is needed.

But at least, some of them can be addressed right now with the tools and approaches which we have, like active metabolites, like prodrugs, like the exposure problem, like drugs-triggered physiology modification, like plasma-potassium depletion, for example.

It's just a relatively small step, and we have to add on top of the existing models a little bit, and that's something we can do. Obviously, IVIVE is not a remedy, neither in the PBPK world, nor in the TdP risk-prediction world. But it's a tool which is very useful. It can be used to give us more information and to make proper decisions at least, where, for example, virtual scenarios testing at low cost, those extremes which we're interested in, this is something that can be done even now.

Trust and validation already exists, and it's still growing. Population analysis can be important, and I think this is something, what we can do with the models, which we already possess. Drug-drug interaction, prodrugs, environmental parameters, all those elements can be analyzed even now.

Thank you very much. As for the comments, two questions only. The first one is about EAD-induced -- drugs which induce EAD. The concentration which was tested was up to 25 times

the maximum concentration.

The problem is, with some of those compounds, we observed the TdP in the clinical settings when we do not reach that level. The problem is whether we can predict with the use of this approach. That's the first thing.

The second thing is about the validation of the iPSC cardiomyocytes. As for the PBPK tools, we have to validate or check the performance of the tool which we're using for the PBPK modeling. iPSC cardiomyocytes are models, same as PBPK but softer models, but biological models.

So what would be the tool to validate -- what will be the procedure to validate, for example, cardiomyocytes from different vendors? Thank you very much.

DR. WALDMAN: Thank you very much for your comments, for your thoughtful comments. Those questions will have to remain rhetorical at this time, but thank you for them.

The open public hearing portion of the meeting has concluded, and we're going to take a

five-minute break. Please be back in the room at 2:47. Thank you. Exactly 2:47.

(Whereupon, at 2:43 p.m., a recess was taken.)

Questions to the Committee and Discussion

DR. WALDMAN: Okay. We're trying to be time-sensitive here. All right. We're now going to proceed with the questions to the completed and panel discussions.

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

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record.

Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

Any questions from the panel about the process?

DR. WALDO: I take it we on the phone will not vote?

DR. WALDMAN: The folks on the phone will vote.

DR. WALDO: What button do we press?

(Laughter.)

DR. WALDMAN: I'm looking to my learned colleague on the left her for the answer to that question. You'll be emailing your vote to Yvette Waples.

Is that clear for the phone folks?

UNIDENTIFIED MALE: Yes, it's clear.

DR. WALDO: He will email us an email, and we then vote; is that it?

DR. WALDMAN: You will email your vote on each of the questions to Yvette.

DR. WALDO: I'm not sure I know who Yvette is.

DR. WALDMAN: Yvette, maybe you want to send them an email.

Yes, we're going to take this offline and get you squared away in terms of the -- I can see Yvette moving to the phone lines. She will help you guys on the phone.

DR. WALDO: Thank you.

DR. WALDMAN: All right.

What I'm going to do is what we did earlier today. I'm going to read the introductory paragraph, and then the first question, and then we're going to open it for discussion. Once the discussion is completed -- parsimonious discussion, I might add.

Once the discussion is completed, I'll try and summarize, and then we're going to take the vote. We'll do that for each of the three questions.

Does that make sense to everybody? Okay. Let me read the opening paragraph.

CiPA is a fit-for-purpose assay that will utilize in silico computational model of the human ventricular cardiomyocyte to serve as the primary prediction of proarrhythmic risk with additional preclinical checks to ensure that drug effects on repolarization are not missed.

Electrocardiograms will still be assessed in phase 1 clinical studies with exposure-response modeling to determine if there are unexpected ion channel effects that were not observed in the preclinical assessments.

Question 1, which is up for discussion and then for a vote, for QT prolonging drugs, will this mechanistic model-based approach be fit for the following two applications: first, determining whether ECGs need to be collected in phase 3; and

second, informing proarrhythmic risk language in drug labeling?

This question is open for discussion by the panel. Let me take the chair's prerogative and just pick on people because I know people want to talk. Dan?

DR. RODEN: My job is to try to hone in on some big questions, not get down in the weeds, which we can do offline. I still think the issue of disease is an important one. Al raised it; I raised it. Let me cast it a different way.

If you were to construct a model of a cell or a multicellular syncytium behaving and misbehaving, one of the things that you might include in a model is how activation of intracellular signaling systems or altered channel synthesis or altered channel trafficking would play into that. And the models lend themselves to modeling that if you have that information.

One of the things I haven't said out loud, but I will say now, is that IKr block is one mechanism whereby you can prolong the QT. I think

there's literature -- it comes from our lab and it comes from other labs -- that inhibition of PI 3-kinase signaling in cardiomyocytes is additional and potentially a very important one.

I think it's important because unlike IKr block, which is static, every single heart beat has an IKr, this is an example of something that can and go, make the QT longer, make the QT shorter.

At the very least, I think that needs to be incorporated into CiPA's thinking, and so I have my question. And my question has to do with why the specific drugs that you chose were chosen; they seem to be the easy cases.

Nilotinib is not on the list, and it's a QT prolonging drug that doesn't block IKr, number one. Number two, vanoxerine, which is a drug that is an IKr blocker, was thought to be dangerous; then went through a CiPA-like process, a ChanTest; was then declared multichannel blocker and therefore safe; went into clinical trials, looked okay at the beginning. Those clinical trials have now been stopped because of a very high incidence of Torsade

in patients with atrial fibrillation.

So that drug, at the very least, should be on the list, not drugs like dofetilide. Dofetilide will never get very far because it's a high potency IKr blocker. In every system, it prolongs the QT, and it's like it's anchoring your thinking because it's at one end of the spectrum. Metoprolol is at the other end of the spectrum. It's not really going to do anything to anything.

So having drugs in the middle that have this spectrum of risk will actually perform the process better than a bunch of drugs, which you know. So I think that's my major comment.

DR. WALDMAN: Can we get response from the agency? David, I'm going to pick on you to start.

DR. RODEN: It's sort of a suggestion.

DR. STRAUSS: David Strauss.

Dr. Roden, yes, we agree that there could be additional drugs to assess beyond these 28 drugs, and it will not stop after 28 drugs, but we wanted to start with a core group of drugs that a group of experts could come to consensus on their

categorization. You brought up a couple of important drugs. Nilotinib, but it's not on the official CiPA list. We have studied it some in these assays already, both ion channels and cardiomyocytes. Vanoxerine, we're aware of that one, and recently went through clinical trials, and it could be a drug that could be added.

DR. RODEN: The business of the PI 3-kinase signaling, CaM-kinase signaling, PKA signaling, PKC signaling, all those things affect some of the currents that you're studying. The models are static until those elements are incorporated.

I'm not sure how to -- maybe the guy from Oxford or Manchester. How do you think about that?

DR. MIRAMS: Gary Mirams, University of Nottingham. I'd agree that we want to end up in a place where we're including PI 3-kinase, the different disease states, and doing predictions for those different things.

The only thing that's stopping us doing that, I suppose, is having models that we trust for each of those aspects. If I had to put a timeframe

on it, I'd say 10 years whereas there is a realistic possibility of getting a model we trust for healthy myocyte in one year's time.

DR. WALDMAN: If I could focus the discussion just a little bit, I'm going to reread number 1 because I want to make sure we're specifically addressing the question that's being asked of us.

This question says: For a QT prolonging drug -- so presumably, the drug is going to show up as a -- it's a true positive in CiPA. I mean that's what I read in this first clause.

DR. STRAUSS: Can I clarify?

DR. WALDMAN: Yes.

DR. STRAUSS: It's positive in that it prolongs QT, but that CiPA could say it is a low-risk drug, or it could say it causes Torsade, and so -- yes.

DR. WALDMAN: Okay. With that caveat, that clarification of this question, for a QT prolonging drug, will this mechanistic model be fit for determining whether ECGs need to be collected in

phase 3 and for, informing proarrhythmic risk language in labeling?

That's the question for discussion right now.

DR. RODEN: Mean by a QT prolonging drug?

DR. STRAUSS: Well, we haven't specified that specifically here. As Dr. Garnett presented, the thinking can differ based on the amount of QT prolongation. But we're not asking for an -- it's always going to result -- if there's this amount of QT prolongation and this output in the proarrhythmic risk score, this will always happen in terms of what you'll put in labeling. But we want to know if this is going to inform labeling, especially for the drugs at the margin.

DR. WALDMAN: Xander, and then Dr. Cloyd.

DR. VINKS: I just have a technical question. Do we have one answer or are we going A and B?

DR. CLOYD: The way this question is phrased, you have the word "will." I'm guessing what FDA wants to know, is it ready today? If

that's not the case, can you clarify what your intent is with this question?

DR. STRAUSS: No, we're not asking if it's ready today. There are a series of -- I mean there are a series of validation -- today, as in March 15th, there are a series of validation studies that will be completed in this calendar year, over the next year, and there will be further discussion with the ICH group.

Assuming that the validation studies come out positive, supporting that you can differentiate risk, would this, at a high level, be fit for informing detailed ECG collection in phase 3 and informing the proarrhythmic risk language in drug labeling?

DR. WALDMAN: To echo check what I just heard, if everything works out in the future with the other studies that they're doing, and it all works out well, does this question get a yes vote or no vote? That's what I'm hearing.

DR. CLOYD: I'm willing to attempt to answer this, but you understand it's conditional. And if

you had us to come back in, what was it, 18 months, you present the new data, it could well be that the answer changes.

Just be clear that you may have something that looks promising, and on that basis, I might say, yes, it could be. But it's different than saying, it's ready for prime time.

DR. STRAUSS: Yes, we understand that.

DR. WALDMAN: Other questions from our panelists? Dan? Other folks here? Yes, Dr. Sun?

DR. SUN: What does "informing" mean? Is that a requirement to put it on the label?

DR. GARNETT: Right now, if the drug prolongs QT above this 10-millisecond threshold, that therapeutic exposure, it pretty much results in the drug having some type of warnings and precautions on the label.

The question is, for this QT prolonging drug, could we modify that language to say, do we need warnings and precautions for every QT prolonging drug, or can we use this proarrhythmic assay to be able to differentiate between those

which we believe will be Torsadogenic versus those, like ranolazine, that we believe do not cause arrhythmias?

DR. WALDMAN: Thank you. Can I ask anybody on the phone if they have clarifying discussion, comments to make at this point? I'm going to go down the list as we do just to make sure that everybody is included.

Dr. Arkus, any comments?

MS. ARKUS: Yes. Ms. Arkus. I have a question about whether or not perhaps a monitor could be used on high-risk patients in case this does receive approval from the panel.

DR. WALDMAN: Can you repeat the question? It's hard to hear you.

MS. ARKUS: I'll take it off the speaker. I was inquiring about whether extra monitoring could be incorporated during this phase of study, and this mechanistic model going into place because there are some high-risk patients, as Dr. Waldo pointed out; perhaps inserting a link, maybe a monitor, something like that, a protocol.

DR. STRAUSS: Yes, monitoring can always be implemented in a high-risk patient population, and decisions are made on a specific drug basis.

DR. WALDMAN: Thank you. Dr. Cook, any questions?

DR. COOK: No questions.

DR. WALDMAN: Thank you. Dr. Tenjarla, questions?

DR. TENJARLA: No questions. Thank you.

DR. WALDMAN: Thank you. Dr. Waldo, questions?

DR. WALDO: Yes, just a quickie, actually that Dan Roden talked about. That's another issue that we touched on only briefly, I think.

The reason that that drug -- there were three cases of Torsade, but each of them was very crazy. One of them had a potassium level that was very, very low. I'm trying to remember what it was, but I don't. I know that it had a magnesium level that was 0.9 or something. The third one had a similar sort of thing.

Oh, yes, the third one that was

taking -- was given another QT prolonging drug that wasn't an antiarrhythmic drug. I mean, how you judge some of these things is really an issue, and what to put on the list. I mean if you're going to give drugs that prolong the QT and don't pay attention to -- I mean, those patients all were contraindicated to answer the study. It was done in Hungary, and that was a major problem.

I'm not sure where that fits in what we're discussing now, except Dan's comments were important. But I think basically that actually got in trouble undeservedly because of violations of protocol and giving a QT prolonging drug in the face of blatant problems, for what that's worth.

DR. STRAUSS: Just to summarize, you're saying that the Torsade cases with vanoxerine may have been due to concomitant factors, and it's hard to attribute it to the drug. Whether that's true or not, I think, is not critical for this specific question. But there's very often concomitant factors with all Torsade cases.

DR. WALDO: Well, I tell you, I know that

drug very well because we studied it in my lab in animal models, and I followed that all the way, on the steering committee. And it was very disappointing what happened. I think it was a small drug company, a start-up company that was doing the study.

Anyway, we don't have to discuss that here. I think it's an issue, though, if a drug is eliminated [indiscernible] because of grossly inappropriate use, I don't know. It seems to me that that shouldn't be a black mark.

DR. WALDMAN: Christine, do you have --

DR. GARNETT: I just wanted to clarify what, at least, my interpretation of A is. Right now, if a drug prolongs the QT greater than 10 milliseconds at therapeutic exposures, it requires additional expanded ECGs in phase 3 to understand the proarrhythmic risk.

What we're asking is, can this proarrhythmic CiPA assay modify that recommendation where we feel comfortable not doing that expanded or some type of less-than-extensive in patients? Maybe targeted

patients may be okay, but we're looking at would those recommendations change?

DR. WALDMAN: Very good. Dr. Li, do you have any questions, on the phone?

DR. T. LI: No. No, I don't have any questions.

DR. WALDMAN: Thank you very much.

Panelists, any other clarifying questions? Yes, Dr. Awni?

DR. AWNI: I was going to ask Christine -- this is Walid Awni -- are you assuming that you're going to get some data from the patient, target patient population in phase 2A/2B before you go to phase 3, with regard to the QTc?

DR. GARNETT: Well, right now, if we apply the paradigm as is, we're getting the ECGs in healthy volunteers in phase 1 for the thorough QT study. So that's going to trigger, if it's a QT prolonging drug, whether you need to expand your ECG collection in patients. So that would include the phase 2 and the phase 3.

DR. WALDMAN: Other questions?

(No response.)

DR. WALDMAN: To briefly summarize the discussion, I think what we're hearing is a theme of the CiPA paradigm has utility. It is utility that is limited only in that it currently doesn't consider the other attributes of patient pathophysiology, intrinsic and extrinsic factors, comorbidities, concomitant medications, et cetera, things that we discussed before.

Many of the panelists, in their own way, raised these individual issues. They've been addressed by the FDA in the current thinking about these models.

I think at the end of the day, to summarize the discussion, I think Dr. Cloyd's comment of the vote that we take on this question is going to be a conditional vote, at the end of the day, with the caveats that there's a lot of work that still needs to be done in order to make this ready for prime time, to coin the phrase.

Did I capture --

DR. CLOYD: Yes, sir.

DR. WALDMAN: Okay. With that summary, we're going to vote. I think we're going to vote on both A and B individually, so individually, and the voting is in front of you, on your microphones. We're all familiar with how this works? A yes is a yes, a no is a no, and an abstain is an abstain.

Okay, just making sure.

DR. RODEN: Mine says, plus, zero, and minus.

DR. WALDMAN: Say it again?

DR. RODEN: Mine says, plus, zero, and minus. Is that yes, no, and maybe?

DR. WALDMAN: It's yes, no, and -- not maybe. Abstain.

DR. RODEN: I was only looking at the flashing lights. I was looking at the --

DR. WALDMAN: Yes, look above them, to the writing.

DR. RODEN: Everybody, look above the lights.

DR. WALDMAN: Okay. Ignore the flashing lights.

All right. Let me read the question, and we will take a vote. Are we ready? Yes? Okay.

For a QT prolonging drug, will this mechanistic model-based approach be fit for the following two applications: A) -- and we're going to vote -- determining whether ECGs need to be collected in phase 3. Please vote yes, no, or abstain.

(Pause.)

DR. WALDMAN: My colleague tells me we're hanging. We're waiting for the phone people to complete their voting.

(Vote taken.)

DR. SHEPHERD: For the record, the vote is 11 yes, 2 no, zero abstain, zero no voting.

DR. WALDMAN: So we're going to now go around the table and read it into the record with our names. Does that make sense to everybody? I'll start. Yes, we have to do it in the auditory record. Yes, we actually have to read it.

Scott Waldman. I voted yes.

DR. CLOYD: You're asking, what?

DR. WALDMAN: State your name and what you voted.

DR. CLOYD: Jim Cloyd. I voted no, and it's a conditional no. The evolution of this model could well result in me changing that vote sometime in the future.

DR. SUN: Duxin Sun, voted for yes.

DR. RODEN: Dan Roden. Mine was a conditional yes to balance Jim's conditional no, for exactly the same reasons.

DR. POLLI: James Polli. I voted yes.

DR. VINKS: Xander Vinks. I voted yes.

DR. COLLINS: Jerry Collins. I voted no. If we had the data that's going to be available next month or next year for the two studies ongoing, we could look at it. I can't conditionally say what would be compelling and what wouldn't be without seeing the data.

DR. AU: Jessie Au. I voted yes because the background, it's not a whole lot different from what you're doing now. It's a supplementary test, so I thought no harm done.

DR. AWNI: I didn't vote (off mic).

DR. SLATTUM: This is Patricia Slattum. I voted yes with the conditions we've already discussed.

DR. CARRICO: I'm Jeff Carrico. I voted yes.

DR. WALDMAN: Okay. We're going to ask the folks on the telephone what they voted.

Dr. Arkus, what did you vote?

MS. ARKUS: Ms. Arkus votes yes.

DR. WALDMAN: Thank you. Dr. Cook?

DR. COOK: Not a voting member, not allowed to vote. Jack Cook.

DR. WALDMAN: Okay. Dr. Waldo?

DR. WALDO: I voted yes.

DR. WALDMAN: Dr. Li?

DR. T. LI: Yes, I voted yes.

DR. WALDMAN: Terrific. I think we've got everybody. Thank you for that very efficient process. Let's do it again.

(Laughter.)

DR. WALDMAN: I'm not going to read that

question again.

(Laughter.)

DR. WALDMAN: Fit for the following two applications, we already did A; let's do B. Informing proarrhythmic risk language in drug labeling, please vote yes, no, abstain, or no voting on your microphone. And the lights are flashing so you can vote.

(Vote taken.)

DR. WALDMAN: All right. Surprise.

(Laughter.)

DR. SHEPHERD: For the record, the vote is 11 yes, 2 no, zero abstain, zero no voting.

DR. WALDMAN: All right. And we're going to read that now into the record. So this is Scott Walden, and I voted yes.

DR. CLOYD: This is Jim Cloyd. I voted yes. And I voted yes here because you're able to combine the model with clinical data that's been collected on these already approved drugs.

DR. SUN: Duxin Sun. Yes.

DR. RODEN: Dan Roden. Yes.

DR. POLLI: Jim Polli. No, in part because I took a sunny view for the last question. This one, I took a less sunny view. And for the same reason that Jim said, I said, well, you don't necessarily need it, so why include it?

DR. VINKS: Xander Vinks. I voted yes.

DR. COLLINS: Jerry Collins. Voted no. I thought it was consistent with my first vote.

DR. AU: Jessie Au. I voted yes, same reason, A.

DR. AWNI: Walid Awni. I didn't vote, consistent with my first vote.

(Laughter.)

DR. WALDMAN: Very consistent.

DR. SLATTUM: Patricia Slattum, voted yes.

DR. CARRICO: Jeff Carrico, yes.

DR. WALDMAN: Okay. On the phone, Dr. Arkus, your vote?

MS. ARKUS: I voted yes.

DR. WALDMAN: Thank you. Dr. Cook?

DR. COOK: Again, I can't vote.

DR. WALDMAN: Okay. Got it.

Dr. Waldo?

DR. WALDO: I voted yes.

DR. WALDMAN: Good. Dr. Li?

DR. T. LI: I voted yes.

DR. WALDMAN: Terrific. Okay. I think that's everybody.

All right. We're going to now move to the next question. The question -- and this will entail some discussion, and then we'll move to a vote -- does the committee agree with the proposed approach for validating the new paradigm that involves assessing 28 drugs classified into low, intermediate, and high risk by an expert panel?

I'm going to turn to my learned colleague on the right, Dan, because you raised this in the last piece of the discussion.

DR. RODEN: If I had to vote -- well, I'm not going to say what I would vote. I think there are other drugs that need to be included, and there are other pieces of modeling that need to be included. I already talked about that.

The other issue that we haven't talked about

much is the iPS cells themselves. I recognize, we all recognize, that this is rapidly-evolving technology. Incredibly, just to back up for one second, those of us who have studied things like the congenital long QT syndrome have wanted to get myocytes from patients for years. So this is a fun, fun time to be a biologist in this area.

That said, two of the channels that you want us -- two of the currents you want to study, the IKs and IK1, almost absent from the current myocytes that we study. So they're very immature. They're not really human adult myocytes yet; they will be. Somebody will figure out how to do that.

I'm a little nervous about the primacy of the iPS cells in this paradigm, and I'm nervous about the choice of the drugs, because I think a wider choice of drugs with a wider spectrum -- and we're learning about other mechanisms that need to be included. Those are my comments, I think.

DR. WALDMAN: I have a clarifying question for the agency about this question. It says 28 drugs, but it doesn't actually say which drugs. It

doesn't say it has to be the 28 drugs that we saw in the slides; it just says 28 drugs. And it's 28 drugs that are picked by an expert panel.

So the question, does it have to be 28 drugs, or can it be something else? Does it have to be the drugs on that panel, or can it be other drugs that the expert panel selects?

DR. STRAUSS: David Strauss. That is referring to the 28 drugs that have already been classified. Am I able to make a comment in response to Dr. Roden's -- yes, so regarding the iPS myocytes, we agree and know that they don't have this IK1 and IKs currents currently, and they're still maturing. That's the reason that they're not the primary proarrhythmic risk prediction here, and we're using the in silico model as the proarrhythmic risk prediction. If the myocytes were perfect, we could probably just use them, but that's why we don't that currently.

DR. RODEN: If you could drive them into the Purkinje lineage, it would be even better. I just have to say this, don't say "IKs current." The "I"

in "IKs" stands for current.

DR. WALDMAN: Duly noted.

DR. RODEN: Data R.

DR. WALDMAN: Other questions, discussion from the committee? Duxin?

DR. SUN: I actually have a question to follow up with Dan. You raised a good point that the drug is not on the list. Based on your experience, the data changes to low, intermediate, high-risk category?

DR. RODEN: I think the drugs that they've chosen are in the -- they're in the right categories. I just think that there are other drugs that have emerging mechanisms, and emerging clinical contradictions that would be really good to put into this model.

I have confidence that you guys follow the literature better than I do, and know about those things, and will incorporate those. That's why I don't like this 28 drugs -- I'd prefer if you chose a little more expansive in the choice of drugs.

DR. WALDMAN: Yes, but we have the question

that's in front of us, and that's the issue.

DR. SUN: You have concern for 28 drugs, but you don't have a concern for the three categories?

DR. WALDMAN: Let me fine-tune that question. Do you have concerns for those 28 drugs? What I'm hearing is, the categorization is good. The three categories is good. The 28 drugs are all good. We just want more drugs on there that represent new, and evolving, and emerging paradigms.

I'm just trying to fine-tune this discussion.

DR. RODEN: You say "we," I say "me," I say "I."

DR. CARRICO: Jeff Carrico. The way that I'm interpreting this -- and I'd love to hear your answer -- is that these 28 drugs are to validate this, and then you will move on to other medications as you see fit.

So the question we're being asked is, are we okay with this way of validating CiPA? Is that a fair summary?

DR. STRAUSS: Yes, I think so.

DR. CLOYD: That's not what I heard. I heard this way is the 28 listed drugs.

DR. WALDMAN: You heard right.

DR. CLOYD: Okay.

DR. WALDMAN: The consensus -- I'm going to summarize early.

(Laughter.)

DR. WALDMAN: The consensus around the table, so far, the three categories is good. The 28 drugs is good. What's not exactly here yet are additional drugs that are emerging with new molecular paradigms that could even fine-tune this further.

I'm actually not trying to steer the committee. I'm just trying to fine-tune how we're thinking about the specific question being asked. the three categories are good; the drugs that are on the list are good. The list will benefit, in the future, from additional drugs. That's what we're hearing.

Does that make sense? Anybody want -- yes,

please, Jerry and then Jessie.

DR. COLLINS: At the of the day, the purpose of this committee is to provide advice to the FDA. I think they've had plenty of time to hear our advice.

DR. WALDMAN: Jessie, you want to come up behind that comment?

DR. AU: No, not that one. I think Dan's point is, to me, a very serious one because if you have well-known drugs that you should challenge your model against and you haven't done it, being a scientist, meaning I've very negative to begin with, I want to see that, why don't you do it? It's so obvious. You nodded your head when Dan mentioned those two drugs, so you knew they were there.

Sitting here today, my answer to that is, it's not how you say it's better to have more drugs. I am saying I'm actually not optimistic at this moment. I wouldn't go that far and say more drugs are good. I'm saying you know those drugs are there; they are problems. Why are you not

attacking them with your models and see if your model start to fall apart? This is what I'm worrying about.

DR. WALDMAN: Do you want to respond to that, or should I just move on?

DR. STRAUSS: There was a committee that came up with these drugs a couple of years ago, and they selected drugs that they could come to consensus on, and there are some additional drugs out there that would be very interesting to study.

We're not going to study every drug that's ever come into humans. So I think the question is, is 28 drugs a reasonable number to rack it into general high, low, and intermediate risk categories?

DR. WALDMAN: Okay. Let me move to the telephone folks and find out if they have any comments.

Dr. Arkus, any questions?

MS. ARKUS: Well, I'm wondering -- there is a 28-drug list. Are these also referring back to question 1B about those particular drugs being

labeled as proarrhythmic risk?

DR. WALDMAN: It's a little difficult to hear your question, but I'm going to suggest that the 28-drugs on the list are to validate the CiPA model, if that answers your question.

MS. ARKUS: Is that going backwards to the other question, 1B, does that mean that those 28 drugs are the ones that will be labeled as risk drugs, as the proarrhythmic risk drugs, those 28?

DR. WALDMAN: Did you hear her question, David?

DR. GARNETT: I understood the question that the high and intermediate -- I haven't gone through to look at all of them, but those would likely be labeled, whereas the low risk would not be labeled, if I just remembered --

DR. WALDMAN: Generally, the answer to her question is yes.

MS. ARKUS: My concern is that there's just going to be a measure of comfort by consumers that those drugs are to be avoided, but others are okay. That's my comment. I'm thinking we might be giving

the wrong message to consumers that something else is safe when it's not.

DR. WALDMAN: I'm actually going to --

DR. STOCKBRIDGE: Norman Stockbridge, FDA. The 28 that we're trying to validate with are 28 where we had confidence. We knew what the proarrhythmic risk was. So there's no concept here of running them through CiPA and then relabeling them. Okay?

There are some others that are labeled that maybe are ripe to get an analysis done that will relabel them. But the 28 that are on the table, we understand their true proarrhythmic risk.

DR. WALDMAN: Essentially, that risk is a list of true positives and true negatives.

DR. STOCKBRIDGE: Correct.

MS. ARKUS: Okay. When you get a label on a drug that says this drug is a proarrhythmic risk of a certain number, 1, 2, 3, does that take into account the comorbid conditions of that particular patient? Is it more specific to the patient?

DR. STOCKBRIDGE: I can answer that, too.

We strove to find a list of drugs whose proarrhythmic risk was not tainted by the risk of the underlying population.

This whole exercise is about trying to identify properties of a drug. And it is certainly true that if you take a drug of some proarrhythmic potential and put it in a vulnerable population, you're going to see Torsade cases. And if you put it in patients who are at low risk, you won't see anything at all, no matter how proarrhythmic it is.

So this is really about trying to identify fundamental properties of the drug.

DR. WALDMAN: Thank you.

MS. ARKUS: Understood. All right. Thank you.

DR. WALDMAN: You're welcome.

Dr. Waldo?

DR. WALDO: I vote yes.

(Laughter.)

DR. WALDMAN: What did he say?

DR. WALDO: I have no further questions. I vote --

DR. WALDMAN: Dr. Cook?

DR. COOK: I have one comment, one question. The comment is that when evaluating the drugs, in addition to having the three different categories, you may want to also have maybe -- I guess you'd call it in a clinical study a key secondary parameter. It's something done on a continuous scale, only because a drug that's very high in class 2 may have a similar potential with something that's very low in class 3, class 3 being the greatest risk.

The other question I actually have is not directed to -- it's directed to one of the panelists on a presentation he made a few years ago, Dr. Roden. And it concerns a study in the European Heart Journal done with sotalol, where they took two groups, one that had actually suffered Torsade and a control group.

What I remember from that particular talk is how the two responses were intrinsically different. And I wonder if there is a chance that we need to collect more data to understand the

electrophysiology in the Torsades group better.

DR. WALDMAN: Dan, you want --

DR. RODEN: I will echo what Dr. Stockbridge said, that I think the intent here is to identify drug entities that might impose a risk and not to figure out whether a patient who is sitting in front of us or in the CCU is at low, medium, or high risk. It's to find drugs that are at risk.

So sotalol is a drug that's at risk in that study, which I may have shown a slide of, but I certainly was not involved in and would never get by an IRB on this continent because it involves re-challenging people who have had this reaction with the drug again. Anyway, it's a long story.

So I think that we knew sotalol was at risk, and sotalol would come out as a high-risk drug, is a high-risk drug in this paradigm.

So the whole discussion of which patients are at high-high risk is a separate one. I've raised it because of this signaling business and atrial fibrillation and all that because I think that gives you some insights into mechanisms that

might then define what drugs are at risk.

DR. COOK: What I wondered was if one of the pathways was altered or different in individuals that develop Torsades as opposed to those that don't.

DR. RODEN: Yes, no. There is a possibility that there are other mechanisms besides IKr block, which is the focus here. And that's one of the things that -- I think this paradigm has the advantage that it can incorporate new models and new mechanisms.

DR. WALDMAN: Very good.

Dr. Tenjarla, questions?

DR. TENJARLA: No questions from me. Thank you.

DR. WALDMAN: Thank you.

Dr. Li, any questions?

DR. T. LI: No questions. Thanks.

DR. WALDMAN: Okay. Any more discussion or questions from the assembled?

DR. AU: Sorry. No discussion. I just want to point out that it's not 28 drugs that were

validated. Twelve of those were used for training data sets, so we only validated 16.

DR. WALDMAN: So the validation --

DR. AU: It's only 16 drugs.

DR. WALDMAN: Point of information, it's 28 drugs on the list, 12 were used for training, and then 16 will be used for validation. Yes. Yes. Okay.

So we're up to the voting stage. Telephone guys, we're going to vote. I'm going to read, and then we're going to vote.

Does the committee agree with the proposed approach for validating the new paradigm that involves assessing 28 drugs classified into low, intermediate, and high risk by an expert panel? The vote is yes, no, abstain.

(Vote taken.)

DR. SHEPHERD: For the record, the vote is 10 yes, 3 no, zero abstain, zero no voting.

DR. WALDMAN: Okay. We're going to individually read this into the record. So Scott Waldman voted yes.

DR. CLOYD: I voted no, and I was persuaded by Dr. Roden's eloquent comments about the addition of selected additional drugs.

DR. SUN: Duxin Sun. Yes.

DR. RODEN: Dan Roden. No. And again, I emphasize that I like the paradigm. I just think that there need to be other drugs because there are these emerging mechanisms.

DR. POLLI: Jim Polli. Yes.

DR. VINKS: Xander Vinks voted yes, and I appreciate the additional clarification that was given, 28 drugs were selected and [inaudible - mic fades].

DR. COLLINS: Jerry Collins voted yes. It's a good set of 28 drugs, and the agency has heard a lot of comments about the value of additional drugs.

DR. AU: Jessie Au. I voted no.

DR. AWNI: Walid Awni. I did not vote.

DR. WALDMAN: Dr. Arkus -- oh, I'm sorry. Patty? Sorry.

DR. SLATTUM: Patty Slattum. I voted yes.

DR. CARRICO: Jeff Carrico. I voted yes because I'm focusing on the word "validation."

DR. WALDMAN: Now, Dr. Arkus, what did you vote?

MS. ARKUS: Yes, with previously spoken reservations.

DR. WALDMAN: Okay. Reservations duly noted.

Dr. Waldo?

DR. WALDO: I voted yes.

DR. WALDMAN: Very good. Dr. Li?

DR. T. LI: I voted yes.

DR. WALDMAN: Thank you very much.

All right. We're in the homestretch. We're on to the third question. Let me read it, and then we'll have discussion and then vote.

As this new mechanistic model-based approach is implemented, should FDA collect the world's experience, that is digital waveform data from in vitro experiments, to facilitate future enhancements as was done by the FDA with the ECG warehouse for QT studies?

Can we have some discussion?

DR. AWNI: Walid Awni. I was going to ask at the beginning, do you expect that these will be in similar format. I know with the ECGs, consistent machine, different machine that you collected. But will there be quite a bit of variability across labs? This is from everybody, basically.

The other thing is what do you expect to do with the data? Because there's 9.7 million ECGs, for example, from 500 studies, thorough QTc studies, so now what to do with it? Because it's actually quite a bit of cost in providing you with it.

It's not difficult, but it just takes resources to actually do it, and should this be more targeted toward a certain set of drugs or a certain set of information to make it easy for you and the other company?

DR. STRAUSS: David Strauss. There's already a working group that includes industry members and device manufacturers of these assay

systems to standardize the output so we can have one format.

Your second question, what would we do with this data, we want to continue to learn and improve methods going forward. The community was able to do that with thorough QT studies, and so we envision something similar.

DR. AWNI: Thank you.

DR. WALDMAN: Jerry?

DR. COLLINS: I just had the same question so I got my answer.

DR. WALDMAN: Very good.

Dan, questions?

(No response.)

DR. WALDMAN: Any other questions from the panelists?

DR. RODEN: It's hard to argue with more data. And it's a matter of the format, and what you're going to do what it, and how you're going to store it, and how accessible. It's impossible to say it's a bad thing, I think.

DR. WALDMAN: I agree. Any other discussion

by the panel here?

(No response.)

DR. WALDMAN: Let me go to the phone folks.

Dr. Arkus, any comments about this?

MS. ARKUS: No comments.

DR. WALDMAN: Good.

Dr. Cook?

DR. COOK: A clarifying question, the extra resources. Will there be any requirements as far as conducting the data that go into the thought along the GLP, or will just a statement of the current state of the data suffice?

DR. STRAUSS: This is David Strauss. I think there was a question about whether it'd be required to be GLP, and that has not been determined at this point.

DR. WALDMAN: Terrific.

Dr. Tenjarla, questions?

DR. TENJARLA: No questions. Thank you.

DR. WALDMAN: Dr. Waldo, questions?

DR. WALDO: None, thank you.

DR. WALDMAN: Dr. Li?

DR. T. LI: No questions, thank you.

DR. WALDMAN: Very good. To summarize, it sounds like a slam-dunk to me.

(Laughter.)

DR. WALDMAN: Okay. Is that going to go into the record?

(Laughter.)

DR. WALDMAN: All right. We're ready to vote. Let me read it again, and then we will vote up or down.

As this new mechanistic model-based approach is implemented, should FDA collect the world's experience to facilitate future enhancements as was done by the FDA with the ECG warehouse for QT studies? Please vote yes, no, or abstain on your microphones. Telephone people, please email your votes in to Yvette. We will vote.

(Vote taken.)

DR. SHEPHERD: For the record, 13 voted yes, zero no, zero abstain, zero no voting.

DR. WALDMAN: I think that's a clear mandate. All right. This is Scott Waldman,

reading into the record, I voted yes.

DR. CLOYD: Jim Cloyd. Yes.

DR. SUN: Duxin Sun. Yes.

DR. RODEN: Dan Roden. Yes.

DR. POLLI: James Polli. Yes.

DR. VINKS: Xander Vinks. Yes.

DR. COLLINS: Jerry Collins. Yes.

DR. AU: Jessie Au. Yes.

DR. AWNI: Walid Awni, did not vote.

DR. SLATTUM: Patricia Slattum. Yes.

DR. CARRICO: Jeff Carrico. Yes.

DR. WALDMAN: Dr. Arkus?

MS. ARKUS: Bonnie Arkus. Yes.

DR. WALDMAN: Dr. Waldo?

DR. WALDO: Al Waldo. Yes. Yes.

DR. WALDMAN: Dr. Li?

DR. T. LI: Tonglei Li, voted yes.

DR. WALDMAN: Terrific. Thank you very much. Thank you for that very efficient process. I appreciate it.

Dr. Kathleen Uhl will now present her concluding remarks.

Concluding Remarks - Kathleen Uhl

DR. UHL: It's pretty hard to be the last person on a very long day that started quite early, and also recognizing that I am what stands between you and either your commute home or you and the ASCPT opening ceremony, as well as an adult beverage. So that said, let's just get through this here.

First of all, I just want to thank everyone for being here today. You've heard, from the very beginning, Shiew-Mei, who talked for Isaam, made a nice acknowledgement to everyone for your time here.

In addition to the participants, and the committee members, and presenters and such, I want to also thank ASCPT for agreeing to do this advisory committee here and co-located with the ASCPT annual meeting.

I also want to thank Scott for chairing this. There was an email flurry over the last couple of days because of the weather. I just want to acknowledge Scott for being so flexible to

figure out how to do this, especially with people on the phone and such.

(Applause.)

DR. UHL: For the record, I'd say Scott is blushing.

We've talked a bit about the value proposition here of model-informed drug development. We got way down in the weeds today as we talked about this. But I want to back us up a bit and be a little bit higher-level here. There are absolutely some incredible opportunities at play here for both new and generic drug development, and, as well, regulatory decision-making by using model-informed drug development.

Here are just a couple that we even talked about today, the ability to streamline and optimize drug development. There are absolute implications across the entire drug life cycle. There's an impact on study design, and not just when to do it, how to do it, and certainly an impact on regulatory decision-making, which can improve accuracy, efficiency so that we can make better and faster

ddecisions.

Usually, we're criticized about that here at the agency, so it'd be nice if we can use this to do that, and thus, also, for industry, decrease the regulatory burden.

Although we talked about PBPK in the context of certain utility in new drug development and also in the cardiovascular safety assessment, I think it's pretty obvious that there's the ability to have much broader expansion of this modeling across a variety of different drugs and drug products.

The morning, Shiew-Mei's comments or introduction, was really more new drug-focused. So since I live in the world of generic drugs and I have the microphone, I want to selfishly spend a little bit of time just talking about generic drugs. And I want to do that because, one, most advisory committees focus exclusively on new drugs; two, this is the ASCPT meeting which almost always is excessively new drugs. So I want to broaden your horizons a little bit, so bear with me. I appreciate your patience here.

We did talk about this a tiny bit already in the context of today, and I appreciate several of the advisory committee members actually bringing this up, the difference between a new drug, or an innovator drug, and a generic drug; and also, in the context of clinical pharmacology, whether we're talking about drug substance or drug product.

I say that because having been clinical pharmacology-trained, when we say "drug," we usually mean drug substance. We don't mean drug product.

Duxin, you can take this back because Gordon Amidon at University of Michigan, he has argued this point. And this was one of the most compelling comments he ever made that I heard, was, no patient takes a drug. They take a drug product. And we forget that when we're talking about either drug development, drug regulation, et cetera.

This is just an example of an oral product. The drug substance would just be the active ingredient. All those other items listed here could very well be in one drug product, and there's

the ability for a lot of interactions and such related to the drug product and the therapeutic effect.

We also talked about drug life cycle today, industry concept of life cycle versus the CDER concept of life cycle. The industry concept, you've got this. You start out with the IND. You do your different phase studies. We're well aware of that, phase 1, 2, and 3. You file your NDA. Hopefully, you get approved.

Then there's the postmarket area. In postmarketing, you're looking for particular safety signals that you couldn't identify in a smaller data set in the NDA, or we're also talking about some SUPAC-type things, scaling up, different types of manufacturing, and whatnot.

In CDER, the ultimate life cycle is actually what happens next, which is the introduction of generic drugs on the market and the filing of multiple ANDAs or abbreviated new drug applications.

I think we're well aware of what types of

quantitative methods are used in new drugs. It's well-recognized what these methods are, those on the left-hand side, new drugs; PK-PD modeling, exposure-response, clinical trial simulation, and population PK.

It's also easy, especially for someone who lives in the generic space here though, to correlate those key components of pharmacometrics that are frequently used in new drug review to their generic counterparts.

PK-PD modeling is basically bread and butter bioequivalence in the generic drug review process. This is basically the core and the foundation of a BE assessment. But we also use exposure-response for things like narrow therapeutic index. Liang Zhao actually talked about that this morning.

Clinical trial simulation can be posited in the generic space to do virtual BE studies, again, a topic mentioned this morning. And Pop PK, that same type of methodology can be used for model-based BE assessments for drugs that have sparse PK.

The utility of PBPK actually was talked about or alluded to quite frequently this morning in using this to test or to predict untested clinical scenarios. A lot of the panel members actually talked about this. And you can see here a variety of ways that's used in the new drugs. We know this, drug-drug interactions, labeling recommendations, pediatrics, organ dysfunction, and the like.

It's also very helpful in the generic drug arena, predicting untested situations like what formulation to use, whether there's food effect or the predictions of food effect, which would mean, do you need to do a fed and a fasted BE study, aspects of risk assessment, dissolution specifications, identifying the critical quality attributes, and as well, regulatory standard development.

In that case, what I mean is very different than what is done in the new drug setting. But in the generic drug setting, we have over -- I'm going to get this number wrong -- but over 2,000

product-specific bioequivalence guidances that are published, and we use the results of sophisticated methodologies like modeling and PBPK to help inform some of those product-specific guidances.

This slide you've already seen. I think the most important thing here is just to recognize that in generic drug development, in generic drug regulatory decision-making, there is definitely an increasing trend of using modeling and simulation, including PBPK, to support generic drug product development and to support regulatory decision-making with respect to generic drugs.

I looked at the backgrounder document and was able to use one of the addenda to this, and just put this list together. This is 2009 through 2016, how many times it was acknowledged that PBPK was used for regulatory decision-making for a new drug.

You can obviously see some kind of increasing trend over time. This number doesn't necessarily match perfectly with the presentations earlier this morning, but I think you get the

point. It's being used more, and you can see that as a time trend.

We compare this to generics. It wasn't used in the past, but in one year alone, over 14 times that PBPK, not in modeling and simulation, but just PBPK was used for regulatory decision-making. That said, generics might be late to the party, but we're going to make a lot of noise at the party because -- I'm going to walk you through why.

Essentially, unless you've lived under a rock for the last year or so, you probably know that there's been a lot of noise, a large national debate about healthcare in this country, and access to and affordability of medications. That's a large component of this debate, correct? I hear little chuckles. Thank you.

So that said, right now, generic drugs are more important than they have ever been. To give you a scope of this, 90 percent of the drugs dispensed in the U.S. is a generic drug, and they only represent about 27 percent of the spend for drugs. Generic drugs have saved the U.S.

healthcare system almost $1.5 trillion in the last 10 years, so 1.5 trillion, with a T. That's not an insignificant amount of money.

Additionally, the scope of the generic drug program is very different from the new drug program. We receive, on average, a thousand applications a year, a thousand abbreviated new drug applications. Last year alone, we approved over 800 applications.

There are about 10,000 currently approved generic drugs in this country, and 25 percent of those were approved just since GDUFA, the Generic Drug User Fee Amendments, was implemented four years ago.

On a volume basis, we have the opportunity to really use these models and such to test the system, to think about a high throughput screen and whatever, this is your ability to use a high throughput screen for these methodologies.

GDUFA II, which hopefully will initiate October 1 -- Congress needs to reauthorize it -- there is what was mentioned earlier this

morning pre-ANDA. It's similar to what the IND space would be for new drugs. But the pre-ANDA space is something that I think we're going to see more of the ability to use modeling and simulation, more of this PBPK, and more in the interactions between FDA and industry.

GDUFA II is really intended to decrease the number of review cycles and increase chances for first-cycle ANDA approval. Right now, comparatively, generic drugs are approved on the first cycle less than 10 percent of the time. New drugs are approved on the first cycle more than 90 percent of the time. We have a long way to go to match these two programs together.

GDUFA II also has this -- thanks, Duxin, for bringing this up -- the complex products. There's a particular focus on complex products in this pre-ANDA, the opportunity to get it right the first time, so we decrease the number of cycles.

A comment that was brought to me by Jerry Collins -- and Jerry, I appreciate that because he said why is the modeling that you guys are talking

about in generics a GI model -- gastrointestinal, not military -- is the fact that most of the approved generic drugs, or even most of the applications, are for oral drugs.

That leaves a tremendous amount of opportunity then for these complex products and these complex delivery forms such as dermals, inhalants, ophthalmics, nasal, and transdermal; hence, the reason why the slide from Liang had all those different organ systems, because as we understand the physiology of those systems, we can apply the PBPK to an understanding of these products in that use.

I got this as a shout-out to you here. The March issue of Clinical Pharmacology and Therapeutics, the theme is precision medicine. Probably everyone would see that and say, we're talking about new drugs. Right? Pretty much, so thank you.

I would argue, though, there are two publications in this March issue: The Molecular Basis of Innovation in Drug Excipients and

Between-Batch Pharmacokinetic Variability for conventional BE studies published by card-carrying, certifiable, clinical pharmacologists, Kathy Giacomini and Leslie Benet.

I would argue the case that the DDRU paradigm of CPT, which is -- for those of you who aren't familiar with that, drug discovery, development, regulation, and use -- is just as applicable in the generic drug space as it is in the new drug space.

So there is tremendous opportunity here for both new and generic companies to submit more of these types of data and analyses. There's tremendous opportunities for innovation and modernization, and, as well, a lot of opportunity to improve our reviews, improve our processes, and also opportunities, as was talked earlier this morning, for FDA to highlight what's considered an appropriate submission and what are the submission standards as it relates to PBPK-type submissions.

In the generic drug space, that is absolutely critical. It is critical to get the

right submission, to get a submission that's of high quality. We don't need additional data submitted that is not of high quality, that does not help us have less review cycles or *less chances of approval.

I'm frozen. That must mean that I'm done.

My closing comments here, though, is that the modeling and simulation and PBPK actually is the opportunity to be transformative for the generic drug industry. It can be transformative for drug development, for our regulatory decision-making. We can take this and move way past the oral absorption model and apply this to other types of locally-acting drugs and complex drug products.

So it has transformative potential for GDUFA II, where we have the pre-ANDA and where we have opportunities to discuss alternative BE models that companies might want to use. Using this type of modeling would be very advantageous to inform why you might want to do a different BE approach and aid in the conversation with the agency, should

a company want to do that.

So there are abundant opportunities. There are opportunities for the agency, for ASCPT, for CPT, for industry. There are lots of students and people in training who are at ASCPT. I think you can see there's lots of opportunity out there for modeling in the generic space.

I thank you, and I cede my time back to Scott.

DR. WALDMAN: Thank you very much.

(Applause.)

Adjournment

DR. WALDMAN: A couple of concluding comments, just administrative. As a reminder, a docket is open for this meeting until April 14, 2017. More information on submitting written comments to the docket can be found on the FDA's website.

Then finally, panel members, please take all your personal belongings with you. All materials left on the table will be disposed of. Please also remember to drop off your name badges at the

registration table on your way out so they can be recycled.

We will now adjourn the meeting. Thank you very much for all your participation.

(Applause.)

(Whereupon, at 4:05 p.m., the afternoon session was adjourned.)