FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY ADVISORY COMMITTEE MEETING

Wednesday, May 15, 2017

7:45 a.m. to 11:24 a.m.

Morning Session

Omni Shoreham Hotel

2500 Calvert Street, N.W.

Washington, D.C.

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Division of Advisory Committee and Consultant Management

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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

(7:45 a.m.)

**Call to Order**

**Introduction of Committee**

DR. WALDMAN: Good morning. I would like to first remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so.

I'd also like to identify the FDA press contact, Lauren Smith Dyer. If you're present, please stand, Lauren. Thank you.

My name is Scott Waldman. I'm the chairperson for the Pharmaceutical Science and Clinical Pharmacology Advisory Committee. I'll now call this meeting of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee to order. We'll start by going around the table and introducing ourselves. Let's start on the right.

DR. CLOYD: Jim Cloyd, College of Pharmacy, University of Minnesota, director for the Center for Orphan Drug Research.

DR. SUN: Duxin Sun, University of Michigan,

professor in pharmaceutical science and director of Pharmacokinetics Core.

DR. RODEN: Dan Roden, clinical pharmacologist.

DR. POLLI: James Polli, University of Maryland.

DR. VINKS: Xander Vinks, clinical pharmacologist, University of Cincinnati and Cincinnati Children's Hospital Medical Center.

DR. COLLINS: Jerry Collins, from NIH, National Cancer Institute.

DR. AU: I'm Jessie Au. I have three academic appointments in three different universities. I'm also CSO of a clinical stage biotech company.

DR. AWNI: Walid Awni. I run the clinical pharmacology, PKPD, pharmacometrics at AbbVie.

DR. HUANG: Shiew-Mei Huang, deputy director, Office of Clinical Pharmacology, Office of Translational Sciences, CDER FDA.

DR. UHL: Kathleen Uhl. I'm the director of the Office of Generic Drugs at CDER.

DR. L. ZHAO: Liang Zhao, Office of Generic Drugs, FDA CDER.

DR. P. ZHAO: Ping Zhao, Office of Clinical Pharmacology, Division of Pharmacometrics, FDA CDER.

DR. LIONBERGER: Rob Lionberger. I'm the director of the Office of Research and Standards in the Office of Generic Drugs at CDER.

DR. SLATTUM: I'm Patty Slattum. I'm the director of Geriatric Pharmacotherapy Program at Virginia Commonwealth University.

DR. CARRICO: I'm Jeff Carrico. I'm the director of Research for Pharmacy Services and the director of the Investigational Drug Service for the Florida Hospital System in Orlando, Florida.

LCDR SHEPHERD: Jennifer Shepherd, designated federal officer.

DR. WALDMAN: And again, I'm Scott Waldman, pharmacology and experimental therapeutics, Thomas Jefferson University in Philadelphia.

We have a number of folks on the phone, and you're in order, so if could please identify

yourselves.

Dr. Arkus, are you on?

MS. ARKUS: I'm Bonnie Arkus, and I'm the consumer representative. I am executive director of Women's Heart Foundation.

DR. WALDMAN: Thank you.

Dr. Cook, are you on?

DR. COOK: Jack Cook. Yes, I am. Jack Cook, clinical pharmacology, Pfizer Inc. I'm one of the industrial representatives.

DR. WALDMAN: Dr. Tenjarla, are you on?

DR. TENJARLA: Yes, I'm on. Good morning. My name is Srini Tenjarla, head of pharmaceutical sciences, Shire Pharmaceuticals.

DR. WALDMAN: Dr. Venitz, are you on?

(No response.)

Dr. Waldo, are you on?

DR. WALDO: Yes. I'm professor of medicine, a cardiac electrophysiologist at Case Western Reserve University and University Hospitals in Cleveland.

DR. WALDMAN: Terrific. Thanks so much.

Have I missed anybody?

(No response.)

DR. WALDMAN: Okay.

For the 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 of 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. Thanks.

I'm going to pass this now to Lieutenant Commander Jennifer Shepherd who will read the conflict of interest statement.

**Conflict of Interest Statement**

LCDR SHEPHERD: Good morning. 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., Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with 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 discussion 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 model-informed drug development, or MIDD, for new and generic drugs, which has significantly increased over the past several years. This morning's agenda includes the discussion of strategies, approaches, and challenges in MIDD with specific focus on the approaches and evidentiary information needed for applying physiologically-based pharmacokinetic, or PBPK, modeling and simulation throughout a drug's lifecycle.

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.

We would like to note that Dr. Tonglei Li has been recused from participating in this session of the 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.

We would like to remind members and

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

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

DR. WALDMAN: Thanks, Jennifer.

We will start with opening remarks. I believe Dr. Shiew-Mei Huang is going to provide the opening remarks.

**Presentation - Shiew-Mei Huang**

DR. HUANG: Thanks, Scott.

I'm Shiew-Mei Huang from the Office of Clinical Pharmacology. Dr. Zineh is stuck traffic. He will be here later in the morning.

I'd like to introduce the model-informed drug development, both the opportunities and

challenges. But first, I'd like to thank the advisory committee members for making their effort, the speakers, and also especially the FDA advisory and consulting staff has done a wonderful job under the circumstances.

This slide gives the state of pharmaceutical R&D in a nutshell. A major point is that there's a steady increase in the R&D spending, and despite the increase, the success rate remains low, and the development time is long, although the exact cost is always debatable. It's clear that there is a substantial and growing average cost to develop one new drug that is approved that reach the patients.

To address the pipeline problems, the FDA, at least in part, has developed scientific priorities to address collaborative frameworks to enable new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.

The agency has enumerated several scientific priority areas that, if addressed, would catalyze innovation and enhance the drug development and

regulatory evaluation process. Here are the eight priority areas, and you can see that they are underlined, the regulatory science area that have implementation plans and specific model-based strategies.

There is also an increase in the focus in regulatory science as part of PDUFA, the Prescription Drug User Fee Act. This slide shows that the key provisions of PDUFA over the years allow the FDA to collect fees from the drug developers to support the new drug review process.

Though, importantly, if you look at PDUFA V, the regulatory science enhancement has included model-informed drug development, for example, advancing the use of meta-analysis techniques. And in PDUFA VI, grouped in this current form, will also have enhancement in the MIDD, the model-informed drug development.

MIDD has already paid dividends. They have been appropriately and successfully applied. Here, the definition, either model-informed drug development or model-based drug development, is the

development and application of pharmaco-statistical models of drug efficacy and safety from those preclinical and clinical data to improve drug development knowledge management and decision-making.

The table, you may not be able to read, but it's just to show that we have used model-informed drug development to improve the efficiency in either drug development or regulatory approval.

So FDA has identified MIDD as an important pathway for lowering drug attrition and dealing with regulatory uncertainty. This is really why we're here today, to receive input on both the utility and constraints of MIDD in two specific areas: one is on physiological-based pharmacokinetic modeling, both for new drugs, and lifecycle management, and also safety prediction.

The first topic, you will hear from Dr. Ping Zhao and colleagues on the use of physiological-based pharmacokinetic modeling on the effect of intrinsic and extrinsic patient factors, their effect on system component and drug

development component. And you will hear more on defining the use and constraints of these approaches.

Here's to show the PBPK modeling for new drug, current status. The approach is indeed being used in drug development to inform regulatory decision-making. There are several groups across CDER and other centers, and also other regulatory agencies, as we will hear about it this morning. They're using PBPK to inform a variety of product-specific regulatory decision and also overarching regulatory policy.

So there are two main goals. One is to waive the necessary studies and still have label about certain scenarios, and also to fill the knowledge gaps or certain scenarios that are clinically relevant but will never be conducted clinically.

Of course, you can see here the confidence level decrease as we go down to the bottom row, and we're not quite there yet, but we hope we will continue to improve our understanding and improve

the utility.

There is increasing interest in using PBPK models to support regulatory evaluation in the realm of generic drug development, and you will also hear the application in this case.

For the second topic that we will be discussing this afternoon, I'd like to have a couple of slides just to highlight the need for better safety prediction.

This one shows different stages of drug development and regulatory approval. What are the causes for safety-related attrition? If you look at the purple color, you will see that the cardiovascular effect consistently compose more than 20 percent of the attrition, reason for attrition.

This is a slide to show the PMR, the postmarketing requirement, for new drugs that are approved for the last five years. You can see around 80 percent of new drugs, they all have PMRs. This is to indicate that it is not uncommon to still have knowledge gaps before we approve the

drug, and we need to have these issues addressed after approval. The dash line just shows the rate of safety-related PMR.

So we need new ways during and after drug development and regulatory approval to fill these gaps, and mechanistic model-based strategies are a potential way to do that.

Today, we will have Dr. David Strauss and his colleagues discuss comprehensive in vitro proarrhythmia assay, CiPA, as you will hear throughout the day. The goal is to develop a new in vitro paradigm for cardiac safety evaluation of new drugs that provide a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential.

There will be discussion on the four important components, including the high throughput, a study of ionic currents; in silico reconstruction of human ventricular cardiomyocytes, electrophysiology; the in vitro effects on human stem-cell derived ventricular cardiomyocytes; and also the evaluation of anticipated effects in

clinical phase 1 studies.

The model-informed drug development challenges is including to define best practices for determining a model is fit-for-purpose including the discussion on validation, performance/sensitivity metrics, and also, whether they're platform independent; identification and transparent communication of knowledge gaps, critical part; the data/knowledge warehouses; varying degrees of comfort by met end-users; and very importantly, to have clarity on regulatory expectations.

Today, we have for the advisory committee questions related to physiological-based pharmacokinetic modeling. It's two parts: What information should be included in a PBPK submission to the FDA to ensure adequacy of analysis for its intended purpose? So should these be universal, or should they be different recommendations depending on purpose?

Second question is, based on the proposed workflow, which you will hear from various

presentations, discuss what criteria should be used to determine that the model is adequately verified for the intended purpose; and if the model needs modification, what considerations should be given related to the modification of model structure and/or parameter estimates?

Related to CiPA, there are three parts for the advisory committee. For a QT prolonging drug, will this mechanistic, model-based approach be fit for the following two applications; determining whether ECG needs to be collected in phase 3 and whether it will inform proarrhythmic risk language in the drug labeling.

Second question, does the AC 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? If not, what else should be done?

Third, as this new mechanistic, model-based approach is implemented, should the FDA collect the world's experience, that is the digital waveform data from in vitro experiments, to facilitate

future enhancements as was done by the FDA with the ECG warehouse for QT studies?

So in overview of today's presentation, on session 1, we will discuss the role of PBPK in drug development and regulation. So we will have overview of multi-regional regulatory experience and issues; and we also will hear from drug development point of view.

For session 2, on CiPA, we'll discuss the motivation, progress, and outstanding issues with model-informed dysrhythmia assessment. And finally, we will have Dr. Kathleen Uhl, Cook Uhl, director of OGD to close today's session.

DR. WALDMAN: Thanks so much, Shiew-Mei.

We'd now like to move on to our guest speaker [sic] presentations, beginning with Dr. Zhao.

**FDA Presentation - Ping Zhao**

DR. P. ZHAO: Good morning. Can people hear me okay in the back? Good morning.

Thanks, Shiew-Mei, for the introduction. The title of my presentation is Towards Consistent

Regulatory Assessment of PBPK to Support Dosing Recommendations. I'd like to take this opportunity to thank individuals whose works have been cited in my presentation and also my FDA colleagues for the valuable input for the preparation of my talk.

A drug's PK can be affected by multiple intrinsic and/or extrinsic patient factors. Therefore, the drug dose or dosing regimen may need to be changed in a particular patient population.

The problem is during drug development, it is not possible to evaluate individual factors with the conduct of a clinical study, and it's even more challenging when we have multiple factors present.

PBPK is a mathematical model that connects drug information with that of the physiology. Multiple sources of information or knowledge can be integrated into these models, and one can evaluate patient factors in a more explicit way.

PBPK modeling can be done through this predict, learn, and confirm cycle. And for certain questions, simulations can be applied to understand the drug behavior, and in some circumstances,

support dosing recommendation.

The submissions of PBPK analysis to the FDA have been on the rise. Between 2004 and 2014, the Office of Clinical Pharmacology at FDA has handled 96 PBPK-related reviews, and this number has significantly increased between 2014 and 2016. Among all the intended uses, as you can see, the prediction of drug-drug interactions, or DDIs, is among the highest.

Today, we have about 40 cases in which PBPK simulations have been used to support dosing recommendations in U.S. prescribing information or drug labels. Again, among them, three-quarters are related to DDI predictions, suggesting the high confidence of using PBPK in this particular application.

In my presentation today, I will first go over the evidence-based establishment of predictive performance in using PBPK for different applications or intended uses, and this will be followed by a review of regulatory policy development in assessing PBPK submissions.

In order to demonstrate predictive performance of PBPK for intended use, we need to answer a question like this. Can PBPK prospectively predict the effect of CYP modulation? To address this particular intended use, I listed three FDA research publications.

The first one is an in-house modeling analysis evaluating the drug models for drugs that undergo CYP3A metabolism and CYP2D6 metabolism.

The second study specifically evaluated the sponsor submissions in predicting the effect of a CYP inhibition for their substrate drugs. This was achieved through the analysis of an in-house PBPK review knowledge base.

A natural extension of the second work specifically looked at the prediction of CYP3A induction. We focus on this enzyme because it is widely assessed in modern day drug development in terms of enzyme induction. Again, this was achieved using the in-house PBPK review knowledge base.

To evaluate the predictive performance, we

applied an R value, which equals the predicted exposure ratio divided by the observed exposure ratio. Here, the exposure ratio can be AUC ratio or a Cmax ratio with or without a CYP perpetrator.

As you can see on this table, there are more drugs evaluated for CYP inhibition predictions. And again, for CYP induction, we only focused on 3A. For each work, there were several observed DDI cases that can be used to validate the substrate model externally, which means this information was not used to develop the PBPK model of the substrate.

One important criterion we're looking at, which is in the middle of the table, is the ability of the base PBPK model to describe the baseline PK. It sounds very obvious, but in-house analysis modeling was done by the FDA fellows so we can ensure 100 percent of the cases, this criterion was met. But if you look at sponsor submissions, this was generally achieved.

The last three rows are really talking about the predictive performance of DDI. Across the

board, more than 70 percent of the cases observed the DDI magnitudes can be described by model predictions. This is done within a predefined, narrow predictive boundary of 25 percent. When the boundary is widened to 100 percent, or twofold, all inhibitions were predicted.

We noticed that there were several cases related to CYP3A induction that fell outside the boundary. Through in-depth analysis, we found that these cases were all related to underprediction of CYP3A induction magnitude by the rifampicin model. Many of us know that rifampicin is not a specific inducer of 3A, and it affects multiple other drug metabolizing enzymes and transporters.

Overall, these findings suggest that the predictive performance has been established for this particular intended purpose. This allows us to use PBPK for this application to support dosing recommendations.

In order to do that, one can follow a workflow as shown on this slide by first developing and verifying a substrate model on a left-hand side

and a perpetrator model on the right-hand side. Before the availability of any DDI information clinically, one can use these models to simulate multiple scenarios and use the simulations to prioritize, design, and conduct a critical DDI study.

When information from this critical study becomes available, the information can be used to verify and modify, if necessary, the substrate model with respect to important assumptions. And from this point on, the model is considered ready to be used to support dosing recommendations.

I've just gone through the establishment of predictive performance for one subset of DDI prediction. In fact, the prediction confidence using PBPK varies among different intended uses.

As we can see on this slide, the confidence starts to decline, and the decreased confidence seems to be associated with the reliance of the model on drug independent aspects.

For example, for the prediction of PK in a specific patient population, a reliable prediction

is highly dependent on our confidence in the physiological model.

In 2012, we reviewed the use of PBPK by drug sponsors in predicting drug PK in children. And in the same work, we summarized a workflow, which begins with developing and verifying a drug PBPK model in healthy adult population before the model can be connected to pediatric population.

Such models can be used for multiple purposes. For example, simulations can be used to design and optimize the first in pediatric PK study, or the information can be used to inform the drug independent component of the physiological model of a particular patient population of a given age range.

The one thing that was not discussed back in 2012, and continues to be a problem, was the direct use of PBPK simulation to replace a clinical PK study in children. It's very obvious that such prospective prediction may not be reliable if we don't have high confidence in the physiological model.

The same issue applies for the prediction of PK in other specific populations. The question then becomes whether we should wait until all the drug-independent parameters have been mapped out before we can conclude the establishment of predictive performance for that particular population, or we can just focus on a subset of drug class to begin with. By doing so, we're proposing a revised workflow, and hopefully this workflow will be generalizable for all specific populations.

The workflow begins with developing and verifying drug model in healthy adult populations, and this is something that we have a lot of experience these days.

The key question here is to see whether the model can adequately describe the ADME processes of the test drug. On the right-hand side, we want to see whether there's a physiological model available for use for the target population. Minimally, this model should account for all the ADME changes relevant to the test drug.

As we can see, if the answers to the questions are yes, we should be able to use such model with a certain level of confidence to support the decision-making.

It's time to revisit the advisory committee questions. I'm not going to read the whole thing. But just to highlight that, for today, we'd like to get the advisors' opinion on what information ought to be included in a PBPK submission, and whether FDA's recommendation should be universal recommendation for all applications, or it should be purpose specific. Your input will be highly valuable for the continuing development of the regulatory policy around PBPK.

This is probably a good time to take quick tour of the policy development in this particular research area. Many of us know that PBPK has been around for many years in the field of environmental science long before it took roots in drug development.

In 2010, our toxicology colleagues have published this first regulatory guidance on PBPK,

also known as WHO guidance. This guidance continues to inspire the development of regulatory policy in drug development.

In 2012, an opinion paper was communicated based on then review experience in the Office of Clinical Pharmacology at FDA. The paper also provided some initial thinking on the elements that ought to be included in PBPK submission by the sponsor.

In 2014, both the FDA and the EMA organized a workshop on PBPK, and the information has been published in the publications at the bottom of the slide. In the same year, the EMA rolled out its plan to publish the draft guideline in its concept paper.

Forwarding to 2016, we have seen the publication of EMA guideline in July and the FDA draft guidance in December. Both documents provided recommendations on how a PBPK model analysis should be prepared by a drug sponsor. The EMA also provided its current thinking on model qualification in its draft guideline.

The FDA draft PBPK guidance was developed with the intent to facilitate efficient, timely, and consistent review of applications using PBPK. It does not address methodological considerations and best practice of conduct of PBPK modeling. By January 31st, which is the cutoff of the public comment period, we received 10 comments from individuals and organizations.

In summary, PBPK analysis has been routinely submitted to the FDA. The confidence level varies depending on the intended use. Establishing confidence in physiological or drug independent component of the model is critical for the effective use of PBPK in the near future.

Thank you for your attention.

(Applause.)

DR. WALDMAN: Thank you, Dr. Zhao.

Our next speaker is also Dr. Zhao.

**FDA Presentation - Liang Zhao**

DR. L. ZHAO: Good morning, everyone. The other Dr. Zhao just covered PBPK prospective from new drugs. I'm going to cover PBPK prospective

from generics. I'm Liang Zhao. I'm going to present Absorption PBPK Modeling and Application to Support Formulation and Generic Drug Development.

After the introduction of modeling and simulation activities at OGD, and the absorption model in general, I will go through a case to aid committee discussion. At the end, we'll come back to the AC questions.

Before presenting, I'd also want to do a quick flashback to the questions to be discussed today. Corresponding to the case example, I want to draw your attention to the first bullet point under question 2. What criteria should be used to determine that the model is adequately verified for the intended purpose?

There are similarities and dissimilarities in new and generic drug development. Applications packages for both include the quality element previously known as CMC. In contrast, bioequivalent study in an ANDA package, is the counterpart of preclinical studies, clinical pharmacology, and clinical studies are included in

the NDA package.

One key underlying question that can be addressed by a bioequivalence study is whether the drugs delivered to the action site is the same way for different formulations. If the answer is yes, brand product can be substituted by generics in the medical practice.

Although it has not been relatively appreciated, modeling and simulation has made critical impact on various regulatory activities in the Office of Generic Drugs. Within the calendar year 2016, modeling and simulation has impacted our ANDA reviews, citizen petitions, pre-ANDA interactions, including pre-ANDA meetings on controlled correspondence and product-specific guidance development. Certainly, all these activities are supported by a broad array of internal regulatory scientific researches.

In comparison, the new drug applications bear most of the effort actually from industry. This modeling effort currently resides in the OGD under the support of GDUFA regulatory science

research program.

Overall, OGD uses modeling and simulation to evaluate deviations from guidance or unusual review situations. One key message for the firms developing generics is that they can use model-informed drug development before they propose novel methods in an ANDA to support new BE approaches, just like for new drug development.

One of the intended meeting objectives is to have industry make good model-based submissions. Physiologically-based models generally involve two sets of parameters. One set is drug and product-specific, and the other set is not.

Drug and product-specific parameters include parameters for drug substance, formulation characteristics, and in vitro testing results. The drug and product-nonspecific parameters are ones used to establish the relevant physiological system.

The physiological system can be the GI tract for solid oral dosage form or GI locally-acting products, intranasal system for local or systemic

drug delivery, ophthalmic system for eye ointments, [indiscernible] for metered dose or dry powder inhalers, and skin for patches, ointments, and creams.

Drug absorption in oral bioavailability can be estimated from the fraction drug absorbed into enterocyte, the fraction of a drug that crosses the gut wall into the portal vein, and the fraction of drug that escapes the liver metabolism. In addition to passive diffusion, as you can see from the bottom figure, the whole process is mediated via a set of transporters and metabolic enzymes in the enterocyte.

This diagram illustrates the workflow of oral absorption model. Modeling simulations start from data collection. First, we want to understand the disposition, or ADME, of the drug substance either by using ADME data or by using the fastest dissolving formulation.

The next step is to establish the drug disposition model to optimize parameters for another formulation, which involves the product

information in terms of its featured release, an excipient that could affect absorption.

We fix the parameters with high confidence and fit the parameters with low confidence. These parameters with low confidence can include in vivo solubility, in vivo release profile permeability, et cetera, depending on the intended purpose.

In the third step, we can further validate the model with different PK data set from different dosing regimens, different formulations, and different food conditions, et cetera. A well-qualified model with high confidence can be used to aid regulatory decision-making such as by conducting virtual BE simulations or scenarios that have not been clinically tested.

What is a virtual BE study? A virtual BE study, they use a model to compare a test and reference formulations. The model must have formulation variable that can differentiate the test and the reference products. The model generates a population for BE study, then compares the test reference in that population. A virtual

BE model can be used to simulate many studies to estimate the probability of success or failure.

The impact that a PBPK can make in the realm of generic drugs range from identification of clinically relevant specifications or in vitro tests, such as dissolution. The equivalent assessment for locally-acting drugs, identification of critical quality attribute such as particle size, assessment of -- alcohol dose dumping risks -- risk assessment for new formulation with release mechanism change risks [indiscernible], bioequivalence extrapolation from healthy volunteers to specific populations, waiver of in vitro studies by conducting virtual BE simulations, assessments of a local drug delivery such as predicting GI local drug concentrations, and assessment effect of proton pump inhibitor on drug exposure especially for formulations that are pH-dependent.

There are many other utilities for PBPK model that's not covered here such as directing formulation design, assessing excipient effect,

identification of major source of the inter- and intra- subject variability, et cetera. Overall, there is an increasing trend in using PBPK models to support regulatory decision-making in the realm of generic drug development.

This table gives the highlight of PBPK model contributions in calendar year 2016, including sample drugs under specific contributions the model has made. Of note, the impact on PBPK model on decision-making for generic drug development is at the drug approval level.

With the highlight, I would like to present the oxybutynin case along with this model qualification process. The first intended purpose is to quantitatively describe the delay in oxybutynin absorption when oxybutynin is formulated as an enteric-coated matrix tablet compared to an osmotic-controlled release oral delivery system tablet. The second intended purpose is to assess the risk of waiving BE study for the lower-strength oxybutynin extended release product. In this case, the in vitro dissolution kinetics was estimated by

the model for the intended purpose.

Oxybutynin is a drug of high solubility, high permeability. Hydrochloride salt is water soluble and shows high lipophilicity. It's rapidly absorbed once released from the formulation, and it's limited with a half-life of 2 to 3 hours. Absolute oral bioavailability is around 6 percent. Therefore, the drug is characterized by high intra-subject PK variability.

Oxybutynin is metabolized by CYP3A4 in the gut and in the liver. There are currently two major release mechanisms associated for its extended-release product either based on osmotic pump or enteric-coated matrix. It was used for the relief from urinary and bladder difficulties, including frequent urination and inability to control urination.

Difference in the in vitro oxybutynin profiles of the reference and the test product allows us to view the in vitro and in vivo relationship, which we call IVIVR.

IVIVR was developed with using a two-stage

process. Stage 1 involves the deconvolution of the mean plasma PK profiles to about 10 kinetics of individual drug absorption. Stage 2 refers to the establishment of a correlation between the in vitro drug absorption and the in vitro dissolution profiles of the formulation. In this case, the in vitro dissolution profile is different from that of the in vitro dissolution profile.

The established IVIVR allows the testing of hypothetical scenarios of product dissolution failure via a waiver request from sponsor.

We conducted the simulations based on the established IVIVR from a single ANDA for the 15-milligram oxybutynin strength. The simulated mean and 90 percent confidence interval was overlapped with mean data observed from five other ANDAs. As demonstrated in the figure, the simulated PK curves were able to capture key features of both test and reference products for the test. The simulated curve not only described the delayed release under fed condition, but also described the double peaks under the fasting

condition.

The physiological explanation for the delayed released under fed condition is rather intuitive. First, the test product can only release drug in the intestine after passing through the stomach due to its pH dependency. Second, the fed condition prolongs the residing time of the drug in the stomach. In contrast, the reference product could release drug in the stomach due to its mechanism of release.

In this product, the IVIVR was established using one of the ANDAs whose data was available. To further qualify the model, we retrieved online PK data from the other five ANDAs and estimated the mean and standard deviation of the means of their PK profiles as shown as circles in the graph.

As a result, we got a prediction for the intra (ph) study variability for oxybutynin. Of note, one of the studies had a PK profile significantly higher than the rest, and that's why it appeared there was underprediction.

We do not want to bias the outcome, and so

we included this ANDA in the analysis. This leads to another side question to the committee, how to handle inter-study variability when conducting PBPK model qualifications.

Now, we want to use the model to conduct risk assessment for waiving the in vivo studies for lower strength oxybutynin generic products. For a specific ANDA, a 50-milligram PK profile, along with their in vitro dissolution profiles, were used to view the IVIVR.

The IVIVR was subsequently utilized to generate a prediction of the PK profile for the 5 and a 10-milligram dose where only the in vitro dissolution data, but not the PK data, were available.

We tracked model performance. The same routine was performed to predict 5 and 10-milligram PK for other ANDAs where the PK concentrations are available. This is shown in the plot at the bottom.

The dose normalized PK curves were compared against the dose normalized observed concentrations

and the performance seem to be reasonable. Similarly, when a specific question is put forward, for example, how would dissolution failure for the lower strength impact the systemic exposure, the IVIVC, generated based on the higher strength data from the same ANDA, can be used to predict systemics for the corresponding dissolution profile.

Case conclusions. As mentioned earlier, the in vitro dissolution data does not appear to be predictive of the in vivo drug release; they are different for this case. The developed mechanistic absorption PK models described the key features in their PK curves for both the reference and test products, including the delayed release under fed condition and the double peaks under fasting condition for the test product.

The established IVIVR can be utilized for risk assessment for waiving in vivo studies for the lower strengths when bioequivalence has not been established at a lower strength, but at a higher strength.

Before the end, let's revisit the model qualification. First, model start from data collection, which is viewed as available knowledge. Based on the intended purpose, we fit the parameters with high confidence and fit the parameters with low confidence based on the available in vivo data that can lend us more knowledge for the parameters that we are fitting.

The model can be further qualified with more in vivo data that can gain us more confidence. Once the model is qualified, it can be used to simulate PK profiles for other scenarios that have not been clinically tested but within the scope of model qualification. All these simulations can be potentially used to inform regulatory decision-makings.

Before the next presenter, I just want to restate the questions to the committee. First, should model modification/verification be based on the intended purpose?

Second, based on the workflows I've described, what criteria should be used to

determine that a model is adequately verified for the intended purpose?

When the model needs modification, what considerations should be given related to modifications of model structure and/or parameter estimates?

With that, I want to thank all the committee members, and presenters, and audience. I'm looking forward for constructive discussion in the following sessions.

(Applause.)

DR. WALDMAN: Thank you, Dr. Zhao.

We're going to move now from our FDA presentations to our guest presentations. Our next speaker is Anna Nordmark. She's a pharmacokinetic assessor, Medical Products Agency in Sweden, and a member of the Modeling and Simulation Working Group, European Medicines Agency.

She's going to be speaking to us about PBPK submissions and review experience in the European Medicines Agency and EMA draft PBPK guidelines. Thank you.

**Guest Speaker Presentation - Anna Nordmark**

DR. NORDMARK: Good morning, everyone. Thank you, Ping, and other FDA colleagues for inviting me to present aspects regarding EMA and the EMA draft PBPK guideline.

Why a PBPK guideline in Europe then? Our title of our draft guidance is Guideline on the Qualification and Reporting of PBPK Modeling and Simulation. The draft was released in July last year, and the public consultation ended in January.

We, as well, in Europe, see an increase in PBPK submissions. These are central procedures sent to EMA, and you can see a steady increase over the years. This paper ended in 2015. I don't have any data on last year.

The purpose or intended use of these submitted models, you can see here. And there are more here than the actual submissions that you see on the last page. But that's due to -- one model was used for more than one purpose. But as you, as well, can see here that the DDI aspects are the majority of the intended purpose.

You also can say that the submitted models were either directly supplied by the applicant, but also they could be a response to a question from us regulators. The table doesn't say anything about if we approved the model or not. It's just a list of submissions.

But why a PBPK guideline? We see an increase in submissions. We also see that the qualification of the intended use is mostly lacking, or the confidence in the intended use is lacking. I will get back to these questions.

But we also see that the reports of the PBPK simulations do not contain enough details. And in Europe, we don't do any de novo analysis; we only look at the data that we see from the applicant. Therefore, it's important that the reports are good and contain enough details so we can do a secondary assessment.

Mostly, one of the aspects that I think personally is important is there is not enough sensitivity or uncertainty analysis in these models.

But what do we mean by qualification in our EMA draft guidance? The qualification is related to the PBPK platform. There's nothing about the drug model.

The question we will ask is, is there enough scientific support for a certain use for that particular platform? That is the question that we would like the applicant or the vendor to answer to us. And it could be related to DDI. It could be related to mechanistic absorption modeling. It could be extrapolation of PK data into special populations or in younger children, for example.

We think that qualification is important for higher regulatory impact decisions. What do we mean by that? Higher regulatory impact, some examples are all changes to the label. And in Europe, we call the label SmPC, summary product characteristics. It could also be that you waive a study or that you use a PBPK model to non-studied scenarios. You extrapolate outside your studied area.

We also see a lot of PBPK models in Europe

that have medium regulatory impact decisions, and we mostly see them in pediatric investigation plans. Here, you have your pediatric dose setting, which will be confirmed by a clinical study.

Here, at the moment, we are discussing how much qualification of the platform we will have, if it's needed or not. We will see where we end up in the final slide. But for high regulatory impact decisions, the platform needs to be qualified.

Some other aspects on why we want to have qualification in Europe, in EMA, we are 28 countries that do assessments in Europe, so this is a way of harmonizing assessment through the European countries. We also think that presently, in all aspects in the platforms are entirely scientifically justified and not suitable for high regulatory impact decisions. So the confidence is mostly low in many of the intended use. Of course, this will change over time when we will have more data, and also as the science improves, the impact or confidence will increase.

From our view, this is not a restriction or

hinder in this area. It's expected to improve the acceptability of the models in Europe and by European regulators.

We also describe in the guideline various ways of how you can qualify. I will not go into details there because this is a draft guideline. But what is important is that the data set will be similar, and it should also allow us a secondary assessment, submission of the data set for the qualification.

The qualification data set that is used for the intended purpose should be prespecified. It should be the same data set irrespective of the different processes that we suggest. An applicant or a vendor should describe the criteria for the drugs and parameters, therefore these drugs should be described in details. The data set should, if possible, cover a range of PK characteristics that could influence the outcome of the predictions.

I will show you some case examples. This is the case example 1, and here is the intended purpose to predict whether a drug is an in vivo 3A4

inhibitor in adult healthy subjects based on in vitro Ki.

Here, if you should qualify this platform that is used, you should show the capacity to detect the observed in vivo inhibitor effect of different inhibitors of 3A4 on sensitive 3A4 substrates. And the data set should include a large number of inhibitors of different potency, and you should have both in vitro and in vivo data. And it depends on if it should be qualitatively or quantitively predict the DDI. It depends, so you should address also if you have those negatives in your data set.

Another case example is the intended purpose is to use PBPK to predict the PK of a drug in children below 6 years of age, so the clinical PK data is very limited in this age group.

We think here that the qualification of the platform should show the capacity or predict the PK of same enzymes that are involved in drug X, with the PK using external or literature data from children in the same age range.

The data set should be able to predict the PK of compounds metabolized via the same enzymes as drug X in children. It could be other parameters that you also need to take into account. It depends on drug X, the [indiscernible] class or what absorption characteristics it has, and you should do it with adequate performance. It should not be way off.

Some other aspects that we have in our draft guideline is that you should verify your PBPK platform. There are a lot of equations in the models or in the platforms. You should be able to show to us that you don't have any mathematical errors or you should maintain the mass-balance, for instance, within the platform.

As an applicant, you should also do an installation control of your platform, so you should show to us the key functionality of the program should be tested in the computing environment.

If there are supplied files in your PBPK platforms, you should show to us the advocacy of

the PK of that file. If it's an inhibitor or if it's a prodrug, you need to confirm that it actually can predict the PK of that inhibitor or substrate. And if you use some inhibitor file, for instance, you should also show to us that the in vivo effect of the inhibition is well predicted using a number of in vivo studies. Looking at the substrate file, when it comes to DDI, the fraction metabolized should be confirmed.

Some review experience, thoughts from myself, missing from the reports. One aspect is, of course, that the intended use is not always clear, what the applicant will do with the model or the simulation. But when it comes to the drug model, observed versus predicted data should be shown, of course. Often, we see AUC and Cmax predictions, and we see also the plasma concentration time profile, or we have some ratio of AUC/Cmax. It depends if it is an inhibition or something. But we also would like to see the half-life reported.

When it comes to prediction, we also want to

have a discussion of the prediction, if it's adequate or not, and that could be done taking the exposure response and safety data into account and have discussions around that. It's also important to discuss the variability, if you can capture that or not in your model.

One other aspect, as it's close to my heart, is of course that we generally see a lack of investigation of uncertainty in the models, in the drug model. So we do not often see investigation of sensitivity analysis. And if we see that, it's one parameter at a time, and that could work. But we are simulating a body, and we would like to see more assessing of a multiple sensitivity analysis at the same time, assessing parameters at the same time.

It should be performed for all parameters that are likely to influence the outcome, and it should also discuss the impact of any sensitivity analysis or uncertainty analysis. It could also include system parameters that are uncertain, such as kdeg for instance, if you do time-dependent

simulations. But mostly, sensitivity analysis is performed on drug-dependent parameters.

That was all from me. Thank you.

DR. WALDMAN: Thank you.

(Applause.)

DR. WALDMAN: Our last guest speaker is Neil Parrott, distinguished scientist, Roche Pharma Research and Early Development, Roche Innovation Center, Basel, Switzerland, and he's the leader of the Innovation in Quality Consortium Working Group on PBPK guidances. He's going to speak to us about experience, opportunity, and challenges in submitting PBPK analyses to regulators and comments to EMA and FDA draft PBPK guidance documents. Thank you very much.

**Guest Speaker Presentation - Neil Parrott**

DR. PARROTT: Thank you very much for the opportunity to present here. I will present on behalf of the IQ Working Group. And this slide shows you the members of this working group. We have members who represent PBPK specialists within 23 major pharmaceutical companies. This working

group has been together, as you can see, from July of last year when we started our work of reviewing both the EMA and the FDA guidance documents. And we've had regular discussions and have provided our written feedback to both agencies.

In the presentation today, I will share the experience of the industry working group in terms of PBPK for regulatory applications. I will cover the opportunities that we see in the release of these two draft guidance documents. I will cover also the challenges that we think need to be overcome to obtain maximum benefit from PBPK in the future. Then I will respond to the two questions, which have been raised by FDA for this meeting, and finally conclude with some comments to both draft guidance documents.

With this slide, I'm using the figure, which was taken from a white paper, which was published by the IQ Working Group back in 2015. This slide shows how PBPK now is being used right through from early discovery through to late development within the industry.

Indeed, the majority of the applications that have been used now will never be seen by the regulators. They are made for internal decision, support, and not for regulatory interactions. However, the focus of today's discussion is on the late development use and regulatory questions.

So the IQ Working Group is very positive about the release of these two guidance documents, and we are very motivated to work with the regulators to enable a rapid implementation of these guidances.

We are positive that this guidance can be very beneficial in supporting the further expansion of PBPK to new applications by providing a firm basis. Also, importantly, we see now the opportunity to align across the industry and with regulators to perform the qualification of these models that is needed and to share that work across the industry so that the PBPK modeling is optimally leveraged.

An area where we see a major opportunity here is now to align on the areas where there is

high confidence in the application of PBPK modeling. And again, referring to this white paper from 2015, in that paper, we drew up the different types of application. And on this slide, I'm just showing those where, across the industry, we agreed that there is high confidence in applications. And now we see the opportunity to share that confidence with the regulators and achieve alignment on all of these applications.

However, to appreciate the full benefit of PBPK, we need to overcome some challenges. One of the challenges we perceive is that guidance, which is too rigid and too prescriptive would limit the expanding application of PBPK modeling.

So the guidance, we accept that the guidance needs to define acceptable modeling processes and that verification is certainly needed, but this has to be balanced without being too prescriptive so that there is room for growth.

Another challenge we see is associated with the need for the model qualification. And if each company is faced with this large burden of

qualification, then this could be seen as onerous and could limit the usage because if there's too much investment needed in qualification by each company, then the easier path will be to take the traditional approach and perform clinical studies.

So we see it is extremely important to have an efficient collaboration between the industry and the software vendors with the acknowledgement of the regulators in order to support this model qualification.

Another challenge that we perceive is if the expectations vary between the regulatory agencies regarding the qualification and the level of confidence associated with different applications. Of course, the problem here could be that if any one agency still requires clinical data in order to proceed, then the benefit of the PBPK modeling, from the industry perspective, will be greatly reduced because the investment will be, as before, with the need to conduct that clinical study. And of course, if that's the case, this will be ultimately to the detriment of optimal drug

development.

So we think that there's need for a clear consensus on the qualification requirements among the agencies, and that will help to promote the progress in use of PBPK.

Now, I'd like to turn to the questions, which were raised by the FDA for this meeting. I'm not going to read through this question, I think, because we've already covered these and move directly to our response, which is around how do we ensure the adequacy of the modeling submission for the intended purpose?

To answer this question, I'd, again, like to refer to the white paper where we address this and acknowledge that the level of verification that is needed for modeling will depend clearly on the application that is under consideration.

So clearly, if the modeling is being used to waive a clinical study, then the burden of a qualification will be higher than for an application, which will subsequently be confirmed by clinical data.

The principles, which we identified as key in terms of the qualification and the adequacy of qualification, of course, all of the modeling should be done in the context of the exposure response for the drug and the safety in terms of the patient population. That has to be utmost in the considerations.

We also recognize that in certain areas, the science is less mature, and there is need for adequate qualification for certain types of processes where science is less mature.

The submission should make very clear the assumptions in the modeling, and those assumptions should be physiologically plausible, and sound, and supported by in vivo data.

We recognize the need for sensitivity analyses to be performed on all those model parameters where there is uncertainty, and we also recognize that all of the components supporting the modeling which are submitted, be it associated compound models or special population models, must be defended by the supplied documentation, and

ideally by peer-reviewed publications.

Moving to the second question from the FDA, and this question refers to two separate figures which describe workflows, and we'd like to address those separately.

The first figure shows the workflow for a drug-drug interaction related to metabolism. Concerning this, validation of the CYP3A modulation has been most extensively performed, and this has been carried out with large data sets, including a large number of substrates and inhibitors for the CYP3A enzyme.

We consider that this is really a particularly challenging example because of the fact that the CYP3A enzyme is expressed highly variably, both in the liver and in the gut. So we think it would be going too far to require the same level of validation and large data set to support additional CYPs. Indeed, that would simply not be possible because the amount of clinical data that is available to support that level of qualification is not there.

So we recognize the need to build sufficient confidence for other CYPs, but we have to do that also recognizing the available data sets. We put together proposals for how that might be done for additional enzymes, and we used the CYP2C9 as an example.

So we think that the first step should be having a model for a validated substrate, which is largely cleared by the enzyme, in this case 2C9, and that has to be well-characterized. And then the qualification has to be performed with a number of inhibitors of that enzyme with predictions in agreement with clinical data.

The level of agreement is, of course, as referred to in question 1, dependent upon the application, but often, within twofold, is considered.

Then for high-impact applications, as shown in the figure 2, we recognize that there will be a need to perform a single clinical study with a well-characterized substrate in order to verify the model prediction before making use of the modeling

to waive any clinical studies.

In this slide, we describe similar steps for a 2C9 victim, which I will not go through in detail here because of the interest of time. But rather, moving on to the figure 3, which describes the different application area, this one referring to mechanistic absorption, we consider this as a nice illustration of the application of mechanistic absorption modeling or a formulation-related application where a lot of clinical data would be available for different formulations.

However, we'd like to note that within the industry, within companies, a lot of the absorption modeling that is done is at an earlier stage of the development process and is for applications, which would not be covered by this particular example.

So from the white paper, we had a number of examples where absorption modeling was used, and we'd like to consider that those applications could also be qualified and become more widely used in terms of regulatory applications.

However, there's need for the qualification

in order to do that. As an illustrative example here, we've considered the use of absorption modeling to predict the effect of food on the drug's exposure. This is something which is quite frequently done within the industry, and there are many examples that, some of which we collected in the white paper.

When we look at this in terms of all drugs, it might seem a rather daunting prospect, so we think that it needs to be broken down in terms of the types of molecule, which could be qualified. And whereas in the CYPs, we break it down by CYP, in the case of the food effect, we think that the BCS classification could be one way to break down the qualification into subsets, which could be associated with more or less confidence.

So for example, for BCS 1 and 2 molecules, we think there could be more confidence in this type of predictive modeling. Of course, we'd need to qualify it with some well-defined reference drugs, and we accept also for the later use where we are waiving studies, there could also be the

need to perform a single clinical study to verify the model predictions before going on to apply the modeling to additional clinical scenarios.

With that, I come to the last slide in my presentation, and with this, I'd like to thank both of the agencies for the production of these helpful guidance documents.

As I said at the beginning, we see this very positively, and also, we see these workshops and meetings -- this workshop today, but also the EMA workshop, which took place last year in November, these are very important opportunities to increase the discussion. And from the IQ side, we would welcome further discussion with the agency to address some of the open questions and come to a consensus around these applications. Thank you very much.

(Applause.)

**Clarifying Questions**

DR. WALDMAN: Thank you very much.

So are there any clarifying questions for the FDA or guest speakers from the panel? Please

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

DR. POLLI: James Polli. I have a question about the last question, which starts when the model needs modification. I just want to understand what that means, and it sort of implies that sometimes models don't need modification, given the context of new drug development where the chemical is new, the model may not be modified.

I guess my question is for Dr. Zhao.

(Laughter.)

I'm sorry. Ping Zhao. Sorry. Your slide number 10 where you have a workflow, it seems to imply there are things that change. So is it possible to not have any modifications to the model even though you have a new chemical entity?

DR. P. ZHAO: Yes, as I presented in my second slide, where I sort of laid out the general use of PBPK and I emphasized that this approach particularly is really scrutinized in an iterative way -- so it's predict and confirmed, I think as a

modeler or a person who is preparing this modeling workflow for intended purpose, he or she can choose to modify or not modify. That really depends on whether the new information that's being generated can help us to refine the model.

Though I see it is a necessary step. In some circumstances, you don't have that information probably or just stay with what you have. And then the question becomes, at that particular point, whether we have confidence. Then from the regulatory review standpoint, the reviewer may not be convinced by the current model, and then it will raise additional questions.

So it's a common kind of a platform to allow this kind of a more in-depth discussion to happen. For example, if we don't have a confidence of a submission, which was purely based on phase 1, single-dose PK data -- you did model building, and then you have the single-dose PK data -- without knowing there might be some kind of absorption-related nonlinearity or enzyme saturation-related nonlinearity in the absence of available multiple

dose data or dose escalating data, then it can be questioned about at that point, you don't have the model, you don't have the data.

But once you're in now phase 1B or early phase 2A, when you have that information, you say, hey, I have this additional information. Allow me to understand the observed nonlinearity. Therefore, we went on and did the modification, and here's the updated model.

I think this is where we're kind of trying to get the opinion from the advisors. This is done in a way that is not very common, the "conventional modeling" where it's mainly data-driven. So you do the fitting, you get parameters, and you conclude there whether you have the model can be used.

But PBPK is really through the entire continuum of drug development. One model could be very different at end of phase 1 versus phase 3. Then the question is what level of scrutiny we should put on top of the assessment of such model when we see the modification, whether we should be panicked or whether we should be more receptive.

DR. WALDMAN: Yes, please. Dr. Au?

DR. AU: Jessie Au. I have a question for both Dr. Zhaos. The first Dr. Zhao, in your slide 8 -- and they're related. Your slide number 8 and Liang Zhao's number 4, here you talk about tissue concentration and drug delivery to target sites.

Then to the other Dr. Zhao, you talk about bioequivalence, and you mentioned whether they -- how do you say it -- is the drug delivered to the action site in the same way for different formulations.

So we dig back into the mathematical underpinning of PBPK when it was developed in the late '70s. It's primarily for small molecules. And I think the last speaker also referred to it that it works well for small molecules that use small diffusion transport.

However, today we're dealing with molecules that are every different now. I mean, antibody is one because that's found very heavily. But we're dealing also with nanotechnology, which is no

longer a diffusion-base transport. And I'm talking about interstitial transporter; I'm not talking about membrane transporter.

So in talking about interstitial transport, you can have a nanotechnology like Abraxane versus paclitaxel, which is [indiscernible], an entirely different distribution because the nanotechnology, they move mainly by convective transport and not by the diffusion.

If I look at your PBPK and the question you asked us for advice, the one thing came to mind is it's very difficult to have very rigid guidelines when you're dealing with very different drug entities that, by nature of the physical properties, are transported interstitially very differently.

So that's number 1. And my second question is, PBPK doesn't allow you to look at an organ in a spatial-dependent manner. It allows you to look at time-dependent manner. If you take an organ that, for example -- cancer is a great example. Every part of the cancer is different. That's totally

not in the PBPK.

So in that context, I wonder if you can share with us what you have for experience with -- I'm sorry. Is my question okay still?

All right. With different drug entities, number one, that have different transport, interstitial transport mechanism; and number two, how do you deal with spatial-dependent effect? So within an organ, the left side of the organ, the right side of the organ, how do deal with that?

DR. P. ZHAO: I'll go first, and then I'll defer to Dr. Liang Zhao. Thank you for the question.

This is a very important point that you've made. And as you correctly captured on this slide, this is at the bottom of the table where, back in 2014, we felt that, number one, the biggest utility of PBPK -- kind of a no-brainer that it is for the area that we cannot measure, for example, tissue penetration.

But based on the assessment back then, we felt that we should categorize within that into the

lower confidence area for the moment because, number one, to sort of to answer one of your questions, we don't have much experience seeing submissions dealing with tissue penetration. There are emerging data like a liver safety prediction using some platform, but we hope we could see more coming in.

Your other question regarding the spatial distribution, I think that's probably something that I will not be able to answer from an academic scientific standpoint. But I can observe the emerging trend of the so-called traditional PBPK modeling to system pharmacology, that is quite hot, quite hot in these days.

I think scientifically, it will not be long before we can venture into the spatial question.

DR. L. ZHAO: I can add on Dr. Ping Zhao's comment. I think Dr. Au's question is intertwined with the first question. What we observed is only plasma PK for small molecules. With the observed plasma PK, you see bioequivalence, but are you sure that the drug is being delivered to the action site

with the equal amount or equal time concentration profile? That's always a challenge.

I think if you -- for model modification, so if you see a pattern that cannot be described by the current way of understanding, there are multiple ways to see the pattern. Based on the approach you choose, then the local concentration that has been informed could be different, but it's only with the systemic PK nicely from [indiscernible].

I think depending on the understanding of the formulation, also the physiology, again we come to the bottom line of PBPK model. For nanoparticles, you need to understand that the idea behind the nanoparticle under current treatment could be the blood vessel is leakier for cancer, and you design the right site for the nanoparticle pass-through to the cancer site but not to the normal tissue site.

That needs to be verified by in vitro experiments. Once we have the in vitro experiment, knowledge can form in vitro study, we can

incorporate that knowledge into the model, building model modification. I think model modification cannot live without solid data support.

Regarding the second question, regarding the spatial distribution, this is just my personal opinion, the current PBPK model, even systems pharmacology, do not take the engineer part into account.

We do need some engineering knowledge to be integrated with PBPK modeling technique. That should be the next step, and that should be addressed. Cancer is a complex entity. It has different -- it's not a homogeneous matter. It has angiogenesis and has different pressure, and that all needs to be addressed not only by pharmacometricians but should engage engineers in this regard.

DR. WALDMAN: Thank you.

Dr. Sun, then you. Dan. Sorry. Dan.

DR. RODEN: This is maybe sort of a question that betrays my naïveté about modeling or my fixed ideas about modeling, and I'll try to keep it

short.

One, I understand the virtues of modeling in terms of understanding bioequivalence of a generic issue, but it seems to me that if you take one step back, one of the goals of modeling is to look at special populations and try to predict effects.

What's missing in all these models is the PD part of it because there's variability in the PD piece after the PK piece is considered. And then just to add icing to the cake, the other piece that's missing is the PG piece, which is the prediction -- you had an outlier in your time -- I'm think I'm talking to Dr. Ping Zhao -- you had an outlier in the talk, and the outlier -- and the question is whether you can include the outlier or not. But the history of clinical pharmacology in general and pharmacogenetics is littered with the idea that we have to include the outliers because they may be important and informative in pharmacogenetic.

So I guess my question is, to what extent should the modeling go beyond pharmacokinetics and

include a predicted drug response? For example, the bioequivalence stuff, if the concentrations vary twofold -- but it's well within a therapeutic range, I don't care.

If the concentrations vary twofold and it's a very tight therapeutic range, I care deeply. So it seems to be that there has to be a PD as well, and then layered over the whole thing is the -- just comment on that.

DR. WALDMAN: Ping or Liang, you want to comment?

DR. P. ZHAO: Yes. I would just comment on the PD part. I think, for some reason, when I look at the slide, which is a simplified slide from our communication of the 2014 workshop -- again, the pharmacodynamic is something that's under the radar, but this has also been a low confidence area because we just simply do not have sufficient submissions that we can look at. And we're definitely monitoring the literature in terms of the predictability of pharmacodynamics.

When we get to that area, I think there are

multiple dimensions depending on which target we're looking at and what biomarker.

DR. RODEN: This afternoon, we're going to be talking only about PD. So it's not like it's sort of complicated, but just keep your eye on it. I mean, that's part of the drug response equation.

DR. L. ZHAO: I can add some thought on that. If we talk of PD, how we handle response relationship on new drug and generics are very different. On a new drug, if there's optimized benefit risk profile, the thing's good. For generics, we just want to prove the product identical to the new drug set.

In that regard, we do take PD response or even clinical response into account. We categorize the drug. If there's a steep exposure response curve relationship, then we come -- if the drug also is associated with low within subject variability, we apply a more tighter criteria for the BE assessment. We can classify that drug into the narrow therapeutic index drug list. So that category has a much tighter control, claim of

bioequivalence.

I don't know if that kind of addresses your question.

DR. WALDMAN: Shiew-Mei, do you want to comment?

DR. HUANG: Yes. I agree with Dan that PD is very important, PKPD. So the systemic exposure or tissue exposure versus response relationship is critical in explaining any of the pharmacokinetic changes.

I think Ping, when he mentioned the drug-drug interaction prediction using PBPK, it's important to see which direction we're looking at it. If we're looking at modulator effect, then we're interested in the extent of change that's to define the modulator effect. So you wouldn't need to think about exposure response. We have certain definition. How do you affect this enzyme activity, whether it's strong, moderate, or weak inhibitors?

But on the other hand, if we're looking at a drug as a substrate, then the effect, whether you

have twofold changes, threefold changes, then we really need the PKPD relationship. That's a very a key point.

DR. WALDMAN: Thank you.

Dr. Awni?

DR. AWNI: I was going to ask Dr. Ping Zhao, philosophically, when you look at the clinical data, when one looks at the briefing document and some of the statement made with regard to the value of the clinical data, do you look at the clinical data as just nice to have or a must have?

Because when one looks at the drug development process, the only time you really don't have any clinical data on new drug molecule is just before you go to the first in-human; the first few subjects, and the first in-human teach us quite about the behavior in a human.

So philosophically, is it just to verify is the clinical data there to verify the in vitro parameter we had thought we should be using in the -- or really is to optimize and is central. It must depend on the in vitro and in vivo data to get

some valuable prediction.

DR. P. ZHAO: Thank you. That's very a good point. Basically, in any of our workflow, it starts with these terms of building and verifying. So verifying, what we meant was a verification based on the clinical data.

Personally -- and I think this probably will be agreed by the PBPK modelers from industry who are preparing these things these days. I'm talking about 10, 15 years back, about PBPK as a purely bottom-up approach. Nowadays, it's essential to look at the model, whether it has been considering the available clinical data. It's a must to me.

DR. WALDMAN: Very good. Xander, then Dr. Polli, then Dr. Sun.

DR. VINKS: This is a question for Dr. Liang Zhao about -- one of the things that was complicated is having your model really predict the data that is being showed in your oxybutynin example, where you state the model reasonably well predicted the data.

That's always a problem. So could you

elaborate a little bit more, do you see this as reasonably well predicted, and how that then is being integrated into your assessment and how you get to the [inaudible]?

For an experimentalist, this may not be the best model fit, if you will, but still there is very important information there. And I'd like to hear from you what steps and the thought processes are.

DR. L. ZHAO: That's a very good question. Regarding with oxybutynin model qualification, that's the nice thing to work with Office of Generic Drugs. There, we can take advantage of lots of in vivo PK data available.

So for a certain ANDA, if it only has like the higher strength drug PK, what will make us comfortable to extrapolate the PK to the lower strengths dosage form, we can take other ANDAs, which has the PK from the lower dosage form.

Then we use the same routine to derive in vitro/in vivo relationship between the in vitro dissolution profile and the in vivo dissolution

profile. Because we are not sure of the ANDA in question to down extrapolate the PK profile to the lower strengths, we do that for other ANDAs, observe concentration for the lower strengths.

If for those ANDAs, we are not fitting the PK for the lower strengths, we just extrapolate from a higher strength to a lower strength based on their dissolution profile.

If all those practices work and we see a match, they can really predict a PK profile from lower strengths and we are using the same routine for this ANDA, that will gain us very high confidence, okay, if there's a difference in dissolution release, then we can use the model, apply the same routine to extrapolate to the lower strengths performance. That's kind of how we validated the model.

I'm not sure if I'm clear in addressing your question.

DR. WALDMAN: Xander, did that answer your question?

(Dr. Viniks nods in the affirmative.)

DR. WALDMAN: Okay. Dr. Polli?

DR. POLLI: I think I have an easy question, and it has to do with the word "verification." Dr. Nordmark used the word "qualification" typically. Are they pretty much the same concept?

DR. WALDMAN: That was a no.

(Laughter.)

DR. WALDMAN: Can you expand on that?

DR. P. ZHAO: Based on our communication with the EMA colleagues, in the period preparing the document, the guidance separately, I think "verification," we use "verification" mainly for the development of a specific drug model. And once you have clinical data, phase 1, phase 2, to qualify the drug, you verify the drug model for the next step used.

When the DDI information becomes available, that particular DDI data can be used to, again, verify the assumption. So it's only a subset of the model component that can be verified.

The DDI data, for example, you see ketoconazole increasing the exposure of the

substrate drug by twofold, then you can go back and see the initial assumption that I made for the fractional metabolism of that pathway is reasonable.

I guess, going back to Dr. Vinks' question about reasonable or how do you quantify that, that's a separate issue. But that's what we meant by verification. And I think extending this verification term, you can also apply to a general verification of an intended use.

Again, my opinion here is, for example, if you have sufficient data for the ontogeny of a particular enzyme, your goal is try to predict drug PK in pediatrics, and that was the only enzyme that you're interested in. If you have external data that goes through the model, and also you have the observed data, that kind of a comparison will help to verify the further use of this model. So that could be a drug independent aspect.

Keep going. Back to the qualification question, I think what Anna specified very clearly in her slide is really just the qualification of

the platform. There's a whole package of PBPK being submitted. And that could be maybe 10 percent or even less that are related to drug of interest. But the majority remaining are coming from the developer of a software platform.

I think that's what they meant for the qualification, but Anna can correct me.

DR. WALDMAN: Dr. Nordmark?

DR. NORDMARK: Yes. Dr. Nordmark. From the EMA perspective, qualification is to support the intended use for that particular platform. It has nothing to do with the drug model and how well it predicts. So it's intended scientific use of the platform, is supported.

DR. WALDMAN: Thank you. Not such a little question.

Dr. Sun?

DR. SUN: Thank you. A quick clarification. When we talk about the presentation today and the guidance, it seems a lot of examples are focused on oral products, both in new drug and the generic side, all the examples.

To follow up on Dr. Au's question also, is it the agency's intention to also include the complex injection, which perhaps the criteria all the morning will be very different? So is this also into this discussion?

DR. L. ZHAO: I cannot address that from OGD perspective. I'm pretty sure Dr. Uhl or Dr. Lionberger will have more later on.

So complex products is -- or locally-acting products is one of the key area in the Office of Generic Drugs. They bear high stakes for the public health.

So while there are many scientific challenges, before we can comfortably approve same safe, effective generic version of product, that engages a very thorough understanding of the critical quality attribute and of the local drug delivery. And all those can be aided by PBPK model for a clearer understanding.

We have many ongoing research grants or contracts in this area, almost from every locally-acting or complex product. I showed a

graph for ophthalmic, for inhalation, for transdermal, and for a locally-acting product. We have a full array of research in this area.

We hope we can generate more meaningful results that can help with decision-making in the near future. We kind of also need help from the all the stakeholders, including industry and academia in this regard.

DR. WALDMAN: Cook?

DR. UHL: Can I just add? In answer to your question, the bottom line is yes. I think the furthest advanced understanding is obviously with the orally-administered products. Is the science kind of mature enough, ripe enough so to speak, to translate that into other types of products or other delivery forms, et cetera? I think we welcome your input if you see any particular challenges in that or not. Okay. Thank you.

DR. WALDMAN: Thank you. Yes, Dr. Awni?

DR. AWNI: For Dr. Liang Zhao, you have absorption models for the formulation. You have the drug substance, the drug product, and also

there is quite a bit related to the manufacturing parameters, lot size, where you make it.

How do you incorporate that knowledge into how you're trying to actually do it?

DR. L. ZHAO: That's a very tough question to me. So the model always involves the substance and the product. I think the most important part resides in the product, how the drug is released if we are talking about oral dosage forms.

Would the manufacturing process affect the quality of the product, that's a very good question. We need to expand our capability for the PBPK model to address those issues. But currently, from our side, we more focus on regulating the product quality perspective.

We have Office of Pharmaceutical Quality, like many initiative in this regard that can integrate with the modeling process, and we need to expand our collaboration.

DR. HUANG: So there's some basic understanding of what are the regulatory parameters for a generic drug. Those are well-written in

statute and in regulation.

Although we're focusing on bioequivalence, bioequivalence is essentially irrelevant if there's not pharmaceutical equivalence, and that includes the same active ingredient, the dose, delivery, et cetera, along those lines.

So demonstrating bioequivalence with some fancy modeling and simulation, and PBPK, and other stuff is not going to subsume the lack of pharmaceutical equivalence. That needs to be first -- you know, that's kind of the foundation. If the applicant can't demonstrate that, demonstrating bioequivalence isn't going to get them out of a regulatory hurdle.

DR. WALDMAN: Thank you. Dr. Cloyd?

DR. CLOYD: Jim Cloyd, University of Minnesota. This question is directed to Dr. Parrott. And as a disclaimer, this is not my area of expertise, so the answer to my question might be evident, self-evident.

But it refers to slide 13. I want to make sure I understand the nature of this proposal. In

the case of a putative 2C9 inhibitor that's under development, you would look at its predicted inhibition of a well-characterized substrate and compare that to other inhibitors.

If the range is acceptable within twofold, you would then propose to carry out a clinical study with the putative inhibitor and the well-characterized substrate. If that, again, falls within what I presume to be the acceptable limit, do I understand then that you could then extrapolate that result to other 2C9 substrates, put that in the label?

DR. PARROTT: That is the proposal, yes.

DR. CLOYD: And this is going back to Dr. Roden's point. When you have a wide therapeutic range, if you can alter the concentration of the affected drug, the substrate, by twofold, that may be irrelevant. But if the predicted result with the one substrate is not consistent across other substrates, it may be substantially affecting the ultimate exposure of the affected drug.

Can you comment on the risk of that?

DR. PARROTT: I'm not sure I've really understood the point. I'm sorry.

DR. CLOYD: Well let me try again. What I understand you to say is that if your one clinical study with the drug under development in a particular 2C9 substrate falls within acceptable range, you could then extrapolate that finding to other drugs that are substrates that were not tested --

DR. PARROTT: Yes.

DR. CLOYD: -- and propose some similar dosing adjustment. So I guess the question is how consistent can you be across multiple substrates when you have a similar inhibitor?

DR. PARROTT: I think I take your point now. So that relies on the other substrates having well-verified models because the prediction is obviously intrinsically dependent upon those models. I think that comes back to the overall qualification of the platform.

So for those predictions to other

substrates, those models would have to be part of the qualified platform as has been described by Anna in her presentation.

It's not just the inhibitor model but also when using it to predict the impact on other substrates, those substrates models would have to be adequately verified.

DR. WALDMAN: Can I give a friendly amendment to your question? A friendly amendment to that question.

The issue is can you extrapolate a drug that has a broad therapeutic dose response versus a drug that has a substrate that has a very narrow and tight --

DR. PARROTT: Yes. Obviously, that would depend on the individual waiver of that particular study. And if the drug which is being considered has a very narrow therapeutic range, then obviously, the twofold criteria would not be appropriate.

DR. WALDMAN: Right.

DR. PARROTT: That is yes, accepted, yes.

DR. WALDMAN: That makes sense.

DR. PARROTT: The twofold here is put in brackets because it has to be considered in the context of the exposure/safety relationship for each drug, yes. Sorry, I didn't understand.

DR. WALDMAN: Good. Thank you very much.

Other questions from panelists that are in the room?

(No response.)

DR. WALDMAN: How about panelists that are on the phone? Do we have questions from folks on the phone?

UNIDENTIFIED MALE: Yes.

DR. WALDMAN: Was that a yes?

UNIDENTIFIED MALE: Yes.

DR. WALDMAN: Number 1, do you have a question?

UNIDENTIFIED MALE: Okay. There we go.

DR. WALDMAN: Please say your name, and then ask your question.

Did you lose the phone? Can you please unmute your phone?

DR. COOK: This is number 2, Jack Cook, Pfizer.

DR. WALDMAN: Thank you.

DR. COOK: I do have a question. Can you hear me?

DR. WALDMAN: Yes.

DR. COOK: All right. So I have two questions for Dr. Nordmark. The first will concern the platform validation, and the second would be more along an individual drug.

I was impressed with the thinking around the platform, and I wondered if any thought has been given around the type of data used for input for individual drugs and whether there should be criteria or requirements for them.

Specifically, one could envision that permeability needs to be an input parameter, and there are lots of different ways to obtain permeability. How do we ensure that the acceptable methods have been used?

Second question surrounds an individual drug approach. Currently, the EMA thinking seems to be

around the platform qualification. Another approach might be if I predict an individual drug well enough across the variety of, let's say, subpopulations and drug interactions, could I then be allowed to extrapolate to another population?

So for instance, if I predict drug interactions, well, hepatic and renal impairment, could one then use the model to extrapolate into a pediatric population, given the others as the validation for an individual drug? Thank you.

DR. WALDMAN: Anna?

DR. NORDMARK: Yes. This is Dr. Nordmark. When it comes to qualification and the platform, we have not discussed all details, so we are not ready to answer all detailed questions. But of course, permeability, as one expects it, could be of importance. It depends on the intended purpose or use of your platform and what data that are needed to show that the intended purpose is working. So yes, permeability could, of course, be of importance.

Then to question number 2, when it comes to

individual drug models, of course, it's difficult if you have a drug model that is validated or predict well in a healthy adult population to go into children and predict that as well. And from our point of view, it depends on if the platform has been qualified in the pediatric population; for instance, if that is what you want to go for your drug.

So it's not enough to just rely on one single drug application for a qualification in our view.

DR. WALDMAN: Very good. Thank you.

Okay. Are there any other phone callers who have questions?

DR. WALDO: Yes. This is Al Waldo. Can you hear me?

DR. WALDMAN: Can you identify yourself?

DR. WALDO: Yes. I'm Dr. Albert Waldo, W-A-L-D-O. I have a question that I'm not sure is the right time to ask, but I'm not sure when there will be the right time to ask.

One of the things with all this modeling

that I haven't seen to take any effect is the effect of heart rate on all these parameters. In terms of we were all worried about Torsade de pointes with the low QT here.

It's really striking as a clinician -- and in fact, we actually described this some time ago -- that Torsade de pointes almost always starts at what we call a long-short. In other words, what happens is a premature beat occurs, and then because of that, there's a compensatory pause. That compensatory pause before the next beat comes can be quite remarkably long.

But what happens is that the refractory period of the heart tissue is regulated, and it changes on a beat-by-beat basis. So when you have a very long -- then what happens is next beat -- it's so long that the next beat has the initiation of a Torsade. We see the EAD occurring early, after the polarization, occurring in the middle of the T-wave, and that's the first beat of the Torsade.

So in thinking about it clinically, one of

the ways we meet [indiscernible] cases that come in with Torsade doing that is to pace the heart fast at a regular rate so these premature beats don't recur until we can change the other circumstances related.

I don't know when to ask the question and how. But in modeling, I never saw any consideration of heart rate in this -- and particularly in this so-called long-short -- or actually, it's short-long-short beat because what happens is there's the normal beat, then there's a premature beat. That's short.

That premature beat makes a compensatory pause. That's long. And then the next beat, that long beat has a very long duration for which we get early after the polarization, and then you get the first beat of the tachycardia. So it'll be a short-long-short sequence.

I never see this taken into account in any of models. I'm not sure if that's even critical for the models. The models don't talk about that at all, and I didn't know when to bring it up, and

I think this is a good time as any probably.

DR. WALDMAN: Dr. Waldo, it was really hard to hear you through the telephone line, and I apologize for that because your question is an important question.

What we're going to do is we're going to ask you to write the question out in email and send it to us, and we'll consider it after the break.

Is that okay?

DR. WALDO: Yes. Well, can you hear me now?

DR. WALDMAN: No.

DR. WALDO: Can you hear me now?

(Laughter.)

DR. WALDMAN: Well, the reason I'm saying that is I was on speakerphone.

DR. WALDMAN: It got worse.

DR. WALDO: It's just not any better.

DR. WALDMAN: Sorry about that. So email the question, and we'll get it out to the panel after the break.

Are there any other questions from the folks in the room?

(No response.)

DR. WALDMAN: Okay. If there are no other questions, we're going to take a ten-minute break. We'd like to be back in the room at 10:10.

Please let me remind you, to the panelists specifically, not to discuss the issues at hand amongst yourselves during the break, And I'll see you all back here at 10:10. Thank you very much.

(Whereupon, at 9:59 a.m., a recess was taken.)

DR. WALDMAN: Ladies and gentlemen, please take your seats. We're going to resume. Thank you very much.

I'd like to start by giving Dr. Zineh an opportunity to just introduce himself very briefly.

DR. ZINEH: Sure. Thank you. Issam Zineh. I'm the director of the Office of Clinical Pharmacology. And I just wanted to echo Dr. Huang's earlier comments welcoming everybody and thanking the AC staff, the committee members, and the speakers for making it here despite the logistical challenges.

**Open Public Hearing**

DR. WALDMAN: Okay. We've reached the part of the meeting that concerns the open public hearing. We have two registrants for the open session. Let me read a preamble.

Both 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's important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

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

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

One of our goals 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.

Will speaker number 1 step up to the podium

and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ROMERO: Klaus Romero, with Critical Path Institute. Thanks again for the opportunity. This is great.

Now that Issam is in the room, I'd like to reiterate the importance of something that was brought up in the morning session about the notion of clearly defining the intended use or context of use for the PBPK model platforms because that leads to then, an informed discussion about what are the requirements in terms of data, external validation exercises, sensitivity analyses, depending on the application.

It's not the same to say that you're going to use a PBPK platform to inform the design of first in-human studies, then to say that you're going to use or propose a use of PBPK platform to replace actual DDI studies, and then to say that you're going to also include pharmacodynamics components into those platforms.

So I wonder if OCP folks could comment on that notion and how that links to the opportunity of potentially submitting PBPK platforms for review and potential endorsement through the fit-for-purpose initiative similar to what EMA has put forth in their guidance or the opportunity to submit those models through the novel methodology and drug development pathway. Thank you.

DR. WALDMAN: So I'm going to remind the folks for the open public hearing session that the FDA and the panelists are not required to respond to queries provided by the speakers at the open public hearing. Sorry about that.

Can speaker number 2 approach the microphone and identify themselves?

DR. ROSTAMI: Hello. My name is Amin Rostami. I'm professor of systems pharmacology at the University of Manchester, but at the same time, I am chief scientific officer for Certara, who is the provider of one of the platforms used for the PBPK. And by virtue of the consortium that they arranged, I have got connections with the majority

of the pharmaceutical companies.

I have got actually one comment and one question. The question that I was going to ask is just to get clarification or declaration from both the OCP, as well as OGD, that all the requirements that they are having under PBPK is platform-agnostic, because in the set of slides that Dr. Liang Zhao showed today, in slide number 9, there's a referral to a particular, let's say, model, which I am guessing by mistake it has been put there. Otherwise, the general, I will say, intent was all the compartmental models for the absorption.

So that is one comment. Whether they want to respond or not, I can move on.

DR. WALDMAN: There's not going to be a response. I'm sorry about that.

DR. ROSTAMI: Okay. All right. So that's one. The second part was related actually to the issue of the validation; qualification, verification, and validation.

This is just a comment to, I think, bring

up. If for every single case of the modeling and simulation we would like to do validation, then what is the purpose of actually modeling and simulation?

We would like to predict all cases, scenarios that we are not going to do in many of these cases. If for every single situation we need also to provide the validation, that actually defeats the purpose of the prediction. Thank you.

**Questions to the Committee and Discussion**

DR. WALDMAN: Thank you very much. I want to thank both speakers in the open session for their comments.

Let me read a statement.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with panel discussion and questions to the committee.

This is the part of the meeting where the committee deliberates and discusses the questions. Is it fair to read the questions that are going to be -- okay. And can we maybe put them up on the slide?

So I'm going to read, and they're going to up on the slide. The first question for discussion this morning, what information should be included in the physiologically-based pharmacokinetic, PBPK, submission to the FDA to ensure adequacy of an analysis for its intended purpose?

Should these recommendations be universal or should there be different recommendations depending on the purpose for which the PBPK submission will be used; for example, to inform clinical study planning versus labeling or regulatory decision-making. What are the principles or criteria that should be considered?

This question is now open for discussion by panelists, and I would invite panelists to have a vigorous and robust discussion for the benefit of the agency.

So who wants to be first? Dr. Awni?

DR. AWNI: I was going to just make a comment at the beginning, which is basically, what we have is like four components for really building this model as they progress. There is the platform or the software itself. And the companies that have done this commercially have done a great job actually in improving, and continue to improve.

Then there is the in vitro data and in vivo data, which is the clinical data. And as the drug move through the cycle of drug product development, that data increases with the quantity but also with the quality because some of the experiments you do to estimate your parameter early on are maybe just quick and easy things to get you to the next stage.

Finally, the last one is really the people who actually do the modeling, the training of the individual.

So when one looks at it as the product moves through development, those elements increase as you progress. You also need increases, and therefore your requirement must increase. At the beginning,

you're trying to design phase 2. We don't want to hurt anybody in any clinical trial, so we tend to be much more diligent in saying, okay, let's avoid using this based on the model. As the thing progress at the end, the criteria becomes much more rigorous and must be rigorous.

So should it be by the intended use? Absolutely, because the intended use is very broad when you list these things. And as you progress, what is the question, the most important thing? What is the price? What is the knowledge? How do I optimize it?

I also think there this modification of the model, I don't believe the clinical data is there just to verify the nonclinical data. The clinical data is there because it's essential to our confidence in what we are developing. And if you come to it from the bottom-up or top-down, ultimately, you meet somewhere in the middle and trying to actually declare your assumption.

So the criteria must be much more rigorous, for example, for labeling recommendation or

compared to early on with very little knowledge, but it is also very rigorous.

So I think the question, as stated, it clearly will have to be dependent on the application, but it's also at what stages and what information. And even the verification, the qualification, you sometimes don't have enough information, again, early on, but you say, what do I want to use the model for?

So as you progress, that information must be actually documented, both in vitro and in vivo data, and how you did the model, and what you want to come out of that model.

DR. WALDMAN: So to echo back to you what I'm hearing, in part, I'm hearing that what's important is not only the -- so intended use is very important. But the other piece of that, the other piece of equation is the impactfulness of whatever the decision-making process is going to be. If it's going to be, for example, to define the next clinical trial, that may be different than, for example, the impactfulness of a labeling

indication, for example. So impactfulness is important.

DR. AWNI: Its impactfulness, absolutely critical and what the -- in addition, I really want to focus on also the quality and the quantity because sometimes the quality is actually increasing as you increase through the drug development process.

The only time you don't have any clinical data is before you give it to the first few humans. After that, you have a clinical data on the PK of the drug, and you must use it because that's what you're trying to do.

It's very difficult to actually think -- none of us, for example, will say, we do phase 2 trial to confirm our EC50 in vitro on animal. We don't. Actually, both are very important. It's for translation, backward translation. It's very important.

DR. UHL: Can I just ask a clarifying question?

DR. WALDMAN: Yes.

DR. UHL: To your aspect of impactfulness -- I just want some clarity -- are you saying that any type of PBPK submission to the agency should also include in it the impact or the impactfulness of such data modeling, et cetera?

DR. AWNI: I'm going to use the submission. The submission clearly by the end. But if we are submitting a phase 2 protocol and saying we are giving this recommendation not to co-administer for this drug, you should actually justify it. If it really has -- to the earlier discussion about the safety impact, because you should not harm anybody who participates in our trial. That's the most important thing.

But, ultimately, if I am asking you to approve a drug, a label indication, I must also give you all the information to allow you to say, yes, I feel comfortable to do that, which is all the pieces: the in vitro, the in vivo, how we did it, the confidence around what we did.

Because we also don't -- since I represent the industry, we don't want to mess up

[indiscernible] at that stage either because that goes to a broader use of the drug in society.

DR. WALDMAN: Other comments? Please.

DR. CARRICO: I'd like to add to what I believe you were both saying. I had made some notes to talk a little bit about how I feel, that the submission should include almost a timeline of the model so that -- as you were saying in the beginning, when, really, there's a model that's being used that does not have any clinical data backing it up -- so that when you receive this model, you can see, well, it used to be this, and then it became this when we got this data.

So I think that also plays into the idea that there should be different requirements based on what the model is being purported to be used for. So with that timeline, I think you can determine somewhat what the strength of the model is and therefore what can be taken from the data from the model.

DR. WALDMAN: Yes, Dr. Au? Then Dr. Polli.

DR. AU: Jessie Au. I think it has to

depend on the intended use. They're very different. So that part, I think, is quite [inaudible - mic fade].

Now, thinking about how to you use it, for example, how to design a clinical study which is a first in-human study, for example. Just like any publication that we write in modeling paper, there has to be some way to extrapolate because the whole purpose is for facilitating translation of laboratory findings to humans. So there has to be components that tell you how you take in vitro to in vivo translation, how do you scale up, and then from animals to humans.

I mean, it's well-known, right? Cancer drug is really great in animals. It doesn't kill tumors in humans. So what are the assumptions that you're using to extrapolate to humans? Nanotechnology, beautiful in the lab; fail miserably in humans. So why?

Those are the issues. I think it will be helpful if the document provides some assumptions, so when a reviewer looks at it, at least you can

follow the logic. It's reasonable.

So I think those two are useful for the translation side and also for the model assumption side.

Also, it helps when you're dealing with science that's not mature enough. We talk about spatial problems. If the science is not there, then what assumption are you making? And what variations would you accept? Because it all depends on the assumption you use when you go into the model.

So those are the aspects. I think it's reasonable details to ask for. It's not rigid. It's really a way for a reviewer to follow the logic of how the model is built. So if you can check whether the model is reasonable or not when the first in-human data comes in, you can go back and say, this assumption is entirely wrong, so now we can modify it.

DR. WALDMAN: Thank you. Dr. Polli?

DR. POLLI: James Polli. I mean I think modelers can be tough on other modelers.

(Laughter.)

DR. POLLI: But I think giving context about impact -- and I like the idea of timing, very helpful. Dr. Nordmark, she made something that really resonated with me. I kind of interpreted it as she didn't want to scare people away.

What I'm reminded of is quite some time ago, I think there was an example about IVIVC modeling, and there's a guidance on IVIVC modeling which is 10 [indiscernible] years old now. And many times, I've heard people say, oh, we're not going to do that because we don't want to fail.

Admittedly, I think that guidance is a pretty tough to thread. So I think quite often, there's a psychology where, well, we just don't want to do that science; we don't want to contribute to it because we actually may fail. And I think that would be good to avoid.

DR. WALDMAN: Yes, Dr. Cloyd.

DR. CLOYD: Our center focuses on translational and clinical research on drugs used for rare medical disorders and particularly rare

pediatric neurological disorders. So the development of these model-based schemes to accelerate the introduction of drugs is vitality important to people, and particularly so for children.

I would just make a comment here that where extrapolation from adult PK down to children becomes problematic, not only is under the age of 2, but we have found that children with chronic CNS disorders, usually comorbid disorders such as epilepsy and cerebral palsy, have a very different pharmacokinetic profile, and it's not easily extrapolatable.

So the challenge to everyone is finding a way to obtain efficiently and safely minimum PK data in children and marry that to a model so that we can then go on to further develop these drugs.

I would also further say that this is vital for the industry. But having good guidances could also be useful for others, such as those in academe who are interested in drug development, which may not necessarily end up with a change in label.

DR. WALDMAN: So let me throw a question out -- I'm sorry -- the chair's prerogative. Let me throw a question out.

So Dr. Nordmark got up and presented extremely concrete criteria, data, that they like to see at the EMA to qualify -- I hope I'm using that terminology correctly -- to qualify and/or validate the PBPK models that they're using. And she went through with the qualification, the confidence in the model, very concrete stuff.

I guess a question that I would ask the panel is, should the FDA be requiring those kinds of data in that level of information to support submissions that are dependent on PBPK modeling? Very concrete questions.

Because I think one of the things that the agency is looking for is our guidance in what should a sponsor include in their submission to support the submission and the PBPK modeling that's being submitted and the goodness of that modeling? Very concrete questions.

So what does the panel think about? Xander,

identify yourself.

DR. VINKS: Xander Vinks, Cincinnati. So when I was looking at the question, it's a very broad question that we're trying to answer here, and so your point is well-taken. I mean, it would be great if we could be very concrete.

Now, having said that -- and I think some of the members have addressed this too -- you don't want to overly be concrete because that would basically have people not be creative. And I think transparency, and providing data, and having the model timeline tell a story that really that can be followed by the reviewers but also has data that when it comes in, during this process, be available for potential updating of those models, I think that type of flexibility is very important.

The other thing is that if you are too concrete, you may defeat the purpose, as Dr. Rostami brought up. I think modeling and simulation is to predict and to verify, to learn, confirm, and apply as we now say. But those things are very important. So it has to be placed in

context. It's very important, I think, that it's fit for purpose, so that it needs to be very clear as part of the submission.

It needs to be, again, part of the all the other data and information that is being submitted, and again, needs to tell its own story. And as you say, models are very critical, but models are also talking different language.

So it's very important that this type of information is clearly conveyed and has that, that it doesn't become rigid. Concrete, yes. And it would be great if we get some alignment between what our colleagues do in Europe, as opposed to what we do here in the U.S. because that would only, let's say, facilitate our drug development processes on both sides of the ocean.

DR. WALDMAN: Because I cut Jerry off a minute ago, let me ask him to speak, and then Patty after Jerry.

DR. UHL: Can I just ask a clarifying question?

DR. WALDMAN: Yes.

DR. UHL: To your point then, the current guidance that exists about PBPK modeling and such, is it flexible enough? Or is it as you -- is it too concrete or too rigid? Or you have no opinion?

DR. VINKS: I think it's flexible enough because it doesn't have those concrete elements that Dr. Nordmark mentioned. But it might be something to consider to talk about. That's one of the questions that we were asked. That might be for the agency to consider.

DR. WALDMAN: So I have Jerry, Patty, Dan, Duxin, in that order. Jerry?

DR. COLLINS: Jerry Collins. Modeling can be done for many reasons as we've already discussed. The best reason is when you can't do the experiment for some reason, usually ethically, so rely on simulation. Other times, it's just nobody wants to do a lot of studies on kids, so you try to extrapolate as much as possible.

I just wanted to put in a plug for special populations because I think for both the very young and those of us who are getting toward the very

old, simply simulating plasma concentrations is not going to be enough.

I understand that the topic of PD that Dan Roden tried to bring up is too big to fit into this tent that we have this morning, but we do need to think that the reason we call them special populations, they have some fraction that's related to drug disposition and can be simulated by PBPK. But more likely, there are data that say that at equal concentrations, kids and/or the elderly are more fragile, more sensitive, and have different PD.

So just a pitch for understanding the limits and the very populations you want to get at, but they're also the toughest to interpret.

DR. WALDMAN: Thanks, Jerry. Patty?

DR. SLATTUM: So I actually want to echo what you just said -- interesting -- is that when we think about these PBPK modeling approaches and how, I guess, specified we should be about what would need to be produced to say that they're adequate or fit for their purpose, it has the

potential, if it's too rigid, to impair the very things you're talking about in development for the populations where we really need to be able to predict when we can't study.

Here, we've talked about pediatrics, but I also think about the frail elderly, which we're not likely to do in large clinical trials. So I think rigidity could get in the way of making progress in those areas.

I think if we clearly articulate the purpose, we follow it over time, we are clear about what the stakes are for patients and their outcomes, which -- and that has to do with how narrow the therapeutic range is and how much we think the risks are, actually, of what we're attempting to do.

Can we communicate clearly in labeling if we're predicting something in lieu of a study that practitioners are actually going to be able to understand, and buy, and use? Those are the kinds of questions that would need to be addressed. And because it's so specific to the purpose, I don't

think you can leave it so rigid in the specifications.

DR. WALDMAN: Very good. Thank you. Dan?

DR. RODEN: Let me just preface my question or comment by saying I'm a big fan - I'm an defrock [ph - ??] math geek, and I'm a big, big fan of modeling. I want to echo what Jerry said, that you have to ask yourself why you're modeling. And I think the compelling reason is to do an experiment, a thought experiment that is otherwise difficult or impossible to do in the very frail elderly or very, very young.

Dr. Cloyd alluded to the idea that disease itself can modify either PK or PD. As well, there are examples. The psychotic drugs and the difficulties in evaluating their effect on QT, we'll talk about that.

So one of the things that I want to echo is the idea that modeling will not become fossilizing. It has to be viewed as sort of a dynamic tool.

I think to myself what a model would've looked like ten years ago to try to construct it to

actually [inaudible - mic fade] profile. And there are many elements that you might not have included, some of the details of transporters.

I wonder, for example, what models will look like in ten years when somebody understands the microbiome and where does that fit in to all this. So you really have to sort of keep an open mind of what the model is doing.

One of the outputs is that the model needs to reproduce what is seen in an actual experiment. So here I echo the comment from Dr. Nordstrom, and that is this sensitivity analysis.

So there's a lot of components that go into what the model produces, which is, one, PK and with confidence intervals around it. And there are many ways in which perturbing that system could produce smaller or bigger changes.

So I think a really important component to assessing a model is to figure out what components are there in the model that are particularly sensitive to having changes. That's a piece that I would like to sort of see.

But it would be a big mistake to sort of not consider modeling somewhere in the drug development process. There are experiments that you just can't do, or if you want to do hundreds of experiments, modeling is probably the only way to do that.

DR. WALDMAN: Thank you. Duxin?

DR. SUN: Duxin Sun, University of Michigan. I try to answer this three-part question in a reverse order. What are the criteria we should consider?

My thought would be for the new drugs side, the generic drug side, and injection complex, the criteria would be surely different. You cannot generalize because -- let's come to the new drug side, and of course, you can generalize the AUC versus clinical outcome, toxicity and efficacy, or Cmax, or plasma concentration with that. That you can generalize.

But the proposal by the gentleman, which is the DDI, then they have a different, very concrete criteria, which is very solid already, then that proposal develops very well.

For generic side, you want to consider AUC/Cmax off of the reference versus the generic product. Then the 90 percent confidence interval has to be in there within the range by the computation model.

So I have two parameters, but the generics, perhaps is even much more complex in the GI tract because you compare two subtle differences of two formulation, that's different from your new drug side, which is really considered one drug, whereas the exposure was clinical outcome.

When it comes to generic side, it's pretty subtle. Then can you use model to capture the subtle difference in two different drug products? You have the same clinical outcome. So a lot of parameters in GI tract is unknown. So really, that has to capture it.

Then what do we need to require to submit it, I think along the last 10, 20 years, there's some data available which provide the experiment data for the parameter. I think we should require them to submit that. Then some other parameter

which is unknown, then they have to use a simulation and computation model to simulate that. They have to divide which is known already, which is verified by experiment. And which is unknown, you have to use a computation to simulate.

So then you come to the injection complex, that PBPK part is even more critical because the AUC/Cmax perhaps will not capture the difference in terms of tissue concentration because the distribution, early part, the subtle difference will reflect the tissue distribution dramatically, but you have no way to know.

So therefore, only for Cmax and AUC will not be adequate. You have to define other things. So that's the third part of the question.

Then go back to the second part of the question, should it be universal or should it be specific? I think the two guidelines, the FDA current guidelines and the EMA current guidelines is universal enough to just lay out a foundation. However, each application is so different. The DDI, pediatric, generic, injection; everything is

different. I don't think that you can use universal to capture everything.

So the idea would be you have a general outline of the guiding principle. My hope is maybe we can form -- or you guys can form a working group for each application. You have a generalized, not too rigid, because I agree, if it's too rigid, then you limit the scientific development. But each direction, I think the agency already laid out the different aspects of the application. Then we should also use a generalized aspect for each application, have some sort of guideline. Otherwise, people don't know what to do.

Then for the reviewer then, the format would be really different. It's very hard for a reviewer to handle. So each application, each area should have some sort of a generalized format as guidance.

Then go back to what information should be submitted, I think in terms of model, you can always fit the data if you add one more parameter; you can always do that. The question is, is that valid? Is that verified? Who knows?

Then the sensitivity, I think we have to minimize the additional parameter. So you have to critically validate if you add one more part [indiscernible] to fit your model, is this critical parameter important? That's number 1.

Number 2, again, as I said earlier, you have to define very clearly what is known, what is simulated, then very clearly ask the submission to very clearly define. That's easier for a reviewer to handle. So that's a very crude thought I had.

DR. WALDMAN: Thank you for that. Other comments from the group? Yes, Dr. Awni?

DR. AWNI: Very quickly to your question about should the FDA focus on the qualification of the software? I honestly think it will be chasing -- as the software is developed, as you go move forward -- so the focus ought to be on the output, on the outcome, what are we trying to answer and what is this model trying to do, and what we're trying to predict.

So from a clinical relevance -- and therefore, what tool do I use? Sometimes you don't

need PBPK even to do a model to actually address the question.

So chasing what the software should be or not is actually, I think, directing the resources to the side and just focus on what is the output from this model.

DR. ZINEH: Can I follow up on this question?

DR. WALDMAN: Yes.

DR. ZINEH: Thanks for bringing that up. As you know, the end users of these models are not modelers, and the folks who aren't familiar with the science or skeptical of it, it's very easy to point that skepticism to the platform largely because some of these platforms are opaque.

So are you saying then that we should accept that the platforms are well-developed and sort of move on to the decision quality now?

DR. AWNI: I actually agree with your statement at the beginning because even internally, I could have a junior scientist who uses this or that software, and come up with an answer. And I

have a more experienced scientist within the group who will come with completely different answer because the junior scientist had missed all the inherent and sometimes assumption that they need to interrogate.

I'm not saying that. I'm actually saying what you need to focus is what you're trying to accomplish, what is the decision you are trying to make, and was the software or the interrogation of the sensitivity analysis, the data was used to generate all that information, did they actually do -- was there some assumption that completely makes no sense? And sometimes it does, the size of the GI or the water level. I mean, there's a fudge factor or scaling factor.

So I think the focus ought to be on the outcome and how you do it, not on the software. I'm just saying the software itself is going to continue to develop, and I think they are in decent shape, but they're going to continue to do that. So just focus on the outcome.

DR. WALDMAN: So let --

DR. ZINEH: Yes. Can I throw a question out there that's a follow-up? And then Dr. Waldman, you can decide if you want to take it.

So this is, again, with expectation. So all the speakers were talking about different applications and really talking about whether it's drug interactions or bioequivalence. These are scientific applications, scientific context.

But there's another way to think of applications, and that was the one that was raised earlier. And that is review of a new drug application, which is very data-rich, in order to inform labeling and other regulatory decisions. And then the question of drug development, engagement during the drug development process, the IND process, which are very tight in terms of time. There's a lot happening and development programs are moving fast.

So can the committee opine on expectations of the regulatory scientists, in terms of level of intensity of our own effort in those two junctures? I just wonder do we need to approach those

particular points of interaction differently, the conceptual side versus the data-driven side.

DR. WALDMAN: Dr. Au?

DR. AU: It would seem -- I mean from your side as a reviewer, because modeling can go so many different ways because it's highly flexible, how many parameters. It seems from a reviewer standpoint, you have to give some objective measurement, like you call workflow chart.

When you do accept it? You do sensitivity analysis, so you identify the most critical parameters that will alter your outcome. So what is the range of acceptance? I think it will be helpful for a reviewer if it was defined up front, so that when you exceed that by X percent, then you know you got to go back and redo the model.

So as a modeler, that's what you're thinking, when do you accept a model and when do you say this model is so flawed? So you need an objective measure to help you decide that.

DR. WALDMAN: For what it's worth, I would echo that. And not only is it going to be helpful

for the reviewers, but it's going to be helpful for the sponsors to know what the targets are that they're supposed to be hitting.

Xander?

DR. VINKS: This is Xander Vinks, Cincinnati. In addition to having these clear criteria, do I understand you correct that you would like to encourage a discussion early on between the developer or the sponsor, and the, say, review group or the pharmacometrician? Because I think that would tremendously help as opposed to having sponsors bring a complete package where then there is this review and there is no discussion.

If you were to have an opportunity to get in touch, have the modelers talk to modelers, and clearly have people understand what the different decisions were at the different points, I think that would tremendously help this whole process move forward.

DR. ZINEH: Yes. To answer that question, it's a balance. On the one hand, that would be very educational. Now, you're taking the sort of

understanding of the model, and it becomes longitudinal so that at the end of the day, when you have your regulatory submission, we don't have to reiterate what's happened with the model and sort of where the holes are.

On the other side of that, though, as the point that was made by Dr. Awni, things are moving along so quickly and iterating during development that is that the best time to have that discussion, at the conceptual stage?

That's challenging. We have that experience with the end of phase 2A where it just became untenable to sit at the end of phase 2, and model, and discuss the models, and replicate the models. But maybe for a subset of applications, it makes sense. This is sort of what we're trying to figure out in the investigational drug side.

DR. WALDMAN: We're going to have two more comments from the live people on the panel, and then we're going to go to the phones.

Cook?

DR. UHL: I just want to --

DR. RODEN: Point of clarification -- I'm sorry.

DR. WALDMAN: Dan barged in.

DR. UHL: All right.

DR. RODEN: Something you just said suggested everybody has to model in an IND process. Is that correct or no?

DR. ZINEH: No. What I mean is there are two places to introduce this. One is when you're in the concept stage of protocol development, and the other is when all is said and done, and a rich data set comes in, and now you have to make a decision about approvability, dosing, and labeling.

So there are tradeoffs in having the discussions early at the conceptual stage versus later. And I'm trying to get a sense for what the sort of utility would be in those two specific points of interaction.

DR. RODEN: But you're not saying they have to --

DR. ZINEH: No. No.

DR. WALDMAN: Okay. Cook, you're up.

DR. UHL: I just want to elaborate on what Issam is saying because what Issam is talking about is pertinent to the new drug space and the IND stage. The conversation has talked a bit about generic drugs here, and thank you for bringing that up, related to complex products -- I guess complex products.

Under GDUFA II, which hopefully will start October 1, there will be something called the pre-ANDA. Although there is that space right now, it is not formalized in the generic user fee amendments, but it will be in GDUFA II.

It relates specifically to complex products, and there's even a definition of complex products. Also, where generic developer may want to differ in their bioequivalence approach, on that pre-ANDA area would be where they can come in with these types of questions. And we would expect that they have done modeling in order to have that meeting and have an informed conversation and discussion.

DR. WALDMAN: Thank you. Jeff?

DR. CARRICO: So your comment added one more

point to my comment. I'm Jeff Carrico from Florida Hospital.

I was just going to say that I am more concerned about modeling when we talk about strictly in the labeling sense, unless modeling was used earlier to determine what was going to happen in the clinical trials, et cetera. And then again, you're using that, but you're not using it solely for labeling.

So that's kind of how I feel in the new drug space. As far as the generic drug space, though, I think it is very reasonable for labeling at that point because, again, there's a background, a history if you will, that you can draw from to use for that generic product.

But just to sum up, strictly for labeling, that's where I get a little uncomfortable, personally. But to determine what's going to happen in the new drug process and for the clinical trials, then that's where I really see that this could be useful.

DR. WALDMAN: Thank you.

Are there folks on the phone with comments?

DR. COOK: Yes, there is.

DR. WALDMAN: Let me do this by the numbers. Dr. Arkus, do you have a comment?

MS. ARKUS: I have no comment.

DR. WALDMAN: Thank you.

Dr. Cook?

DR. COOK: Jack Cook, Pfizer. Several comments, first, criteria and information requirements are desirable to states by regulatory agencies. That's lauded, as it ensures that regulators get what they want and will eliminate, what I'll call, regulatory uncertainty for sponsors.

I believe criteria should vary with the application, so the incidents that you're applying for, not particularly the drug but the application to something, and the risk should guide the requirements and the criteria.

Ideally, the models would not only come with the data and criteria requirements, but they would come with assumptions. And in a particular

application, the data for the compound would also support why those assumptions by the model are considered reasonable.

The systems approach or platforms approach may need a requirement as to how input data are obtained. And this was my comment earlier that if there's more than one way to obtain an estimate, one might want to make sure that the data used to validate a model use the same methodology as would be used for the particular drug.

While the EMA proposal is wonderful and it talks about the type of data, I actually think that it might be good to go down to a more and more explicit criteria but realize that it would be hard to establish and will undergo a lot more debates than we can carry out today.

Finally, I'll note that with special populations, while we want to do no harm, there are actually many special populations where dosing recommendations, they are not explicitly stated in the label.

There was a recent publication by myself and

others that looked at drug approvals from the FDA in 2013 and 2014, and that it is noted that even in well-studied areas such as renal impairment, for severe renal impairment, 40 percent of the labels lack explicit dosing recommendation. Thinking on to an area that's not as well-studied, explicit dosing recommendations were not available for 100 percent of the approvals with respect to pregnancy. This is important because when no information is provided, prescribers have to guess. So they assume that because nothing is written in the labels that the same doses are appropriate.

So while we want make sure our models are adequate and we don't do harm, by the same token that there are special populations out there that are in the need of such information. And one might want to consider that for those populations in terms of requirements of what might be needed; a best guess may be better than no guess. Thank you.

DR. WALDMAN: Thank you, Dr. Cook.

Dr. Tenjarla?

DR. TENJARLA: Yes. Good morning. I think

most of my comments have already been addressed by some of the other members, but I'll just highlight a couple of main ones.

I think the clarity on the guidance is very, very important because then we look at it, we need to make a call on what is exactly we will be doing or we have to do in terms of validating the model.

So some level of clarity in requirements in the model in the guidance will be very helpful. At the same time, I think it cannot be too rigid because these are evolving things, and then things change as they progress.

DR. WALDMAN: Very good. Thank you.

Dr. Waldo, any final comments?

DR. WALDO: Yes, I don't know -- can you hear me this time?

DR. WALDMAN: Yes.

DR. WALDO: I think everyone's comments -- the broad feel of this -- I really have nothing to add. I think everything I could've thought of has been brought up very well. Thank you.

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

So just to wrap up this part of the discussion, I think that there was a recognition of the importance of modeling for drug development and regulatory sciences.

I think for the first part of this question, I think there was enthusiasm to keep it less proscriptive and more flexible in terms of the data sets that are provided to the agency in terms of support for sponsor applications, particularly with a focus on maybe presenting the data in a timeline as it evolved to tell the story with appropriate annotations, detailed data-driven annotations, to support the modeling and the conclusions from the modeling.

In terms of the second and third parts of the question, should the requirements be universal or less one-size-fits-all and more tailored to the applications, and what should the guiding principles be.

I think we heard a lot of discussion about

the various special cases, the unique cases that will be/could be considered in terms of modeling: special populations, pediatrics, the elderly, people with various organ dysfunction, et cetera, and that the guiding principles should be -- essentially, that the interpretation of the applications and the modeling should be in the context of the populations that are being considered the intended use of the modeling and the impactfulness of decisions based on the modeling, significant health-related impact versus drug development, moving from phase 1 to phase 2, for example.

I'm going to stop there for the first question in this discussion, and I'm going to ask us to move to the second piece of the discussion, and I'm going to read that.

Based on the proposed workflows as examples, please discuss briefly what criteria should be used to determine that the model is adequately verified for the intended purpose? And when the model needs modification, what consideration should be given

related to modifications of model structure and/or parameter estimates?

Are there points that the panel want to raise in addition to what we already discussed in terms of these additional questions? Yes, please.

DR. SUN: For the second, for the B, I wonder because if you give the question to a different modeler, they can come up with different structures, and they both may have very good result. The question is, which structure is correct?

So I wonder is it possible to require the sponsor to say, if you want to submit something, you need to give me a different model to say why you chose this one versus another one. Otherwise, you don't know which is correct. I don't know if it's feasible or not. That's number 1.

Number 2 -- I had another question here. It slipped my mind. Also, the equation. So when you give the modeler not only the structure difference, let's say generic, for the dissolution part, they may use totally different equation. The different

people are familiar with one side of the equation versus another one. Each equation requires different parameters to define that. So it's very difficult to validate or verify which one is correct. So again, then maybe require maybe a different model to test.

When you do a sensitivity analysis, at least on a different model to see why you chose each one, it's better than the other one, and which is the final model you should choose.

So that's B. I actually don't know how to answer A.

DR. WALDMAN: Yes, please, Dr. Awni.

DR. AWNI: I think with regard to 1, clearly, the intended purpose is the driver for your comfort level. And what you come out of it, as you stated, Dr. Waldman, is what the final thing.

If there is a safety issue that you're trying to address, then the criteria and what is adequate is going to be dependent on how much you pay for a cost for the model not predicting what

happened. So it's all driven by the intended purpose and your comfort level on that.

I think what is important in these modeling exercises is the sensitivity around not only, honestly, kind of like pretend sensitivity, but true sensitivity around the parameter, and what information you have, and what you do.

Sometimes even internally, we ask two different scientists to actually use the same data to come up with a model, and then have talk to each other to see what assumption they made in that, because declaring the assumption is very important.

So to me, that second one would say, how was the sensitivity analysis done, what is the scope, are there any parameters that were assumed that make no physiological sense)?

Sometimes you need to actually use some factor that's unknown to actually get the model to work, but you should declare it and see what you should get out of it. So I think the intended purpose is the most important out of all of that.

DR. WALDMAN: So the discussion is very much

following along the same lines as the first part of the earlier discussion.

Dr. Au, did you have something to say?

DR. AU: Only in the sense that there has to be some way to know where you are in the loop because the whole thing is model-informed. The model, I look back in my own work, I mean there's never the first model that worked right away.

So there has to be a decision point. But then you're asking us the question, can we now tell you ahead of time how to do it? And I don't think that's something one can think of sitting here today.

But we cover that with flexibility, and we cover that in saying there are some minimum things that they have to give, what are your specification for the model assumption.

Maybe what may be useful is use a sensitivity analysis to find the most sensitive parameter, so that could be a warning sign. If your model is failing, then you see there's -- assembling compartment where you can

actually get data. Then you say at what time am I seeing deviation? For example, this morning, someone showed the double peak. If you're missing the double peak, then you know something is wrong. Maybe there has to be some objective way to complete this because it is a loop.

DR. WALDMAN: Point well taken.

Jim, you had something to say?

DR. POLLI: James Polli. I just want to say transparency. Transparency is very important in driving a model, both structure of the model, as well as the parameters, so you can do parameters sensitivity analysis.

What's the origin of the model? Maybe you're only considering one model because you've been working on this for 20 years and have thousands of man-hours, years built into the model. Or is it a scenario where you've considered more than one model?

How did you go about choosing one model over the other? I think there's a lot of developed methodologies to choose one model over the other.

And as far as model selection, arguably, you've identified your criteria for model selection a priori.

DR. WALDMAN: Other points? Xander, you're looking at me? Because I'm good-looking?

(Laughter.)

DR. VINKS: Xander Vinks, Cincinnati.

Actually, I was just thinking things like flexibility and putting some parameters around this maybe and aligning this with what's already out there as guidelines across the ocean probably is a good thing.

Again, as the panel and other people have said, there are so many scenarios, so many models, so many parameters and variables that cannot be defined all in one guidance. So I think that, for me, would be a very important, and the transparency.

DR. WALDMAN: Other comments?

(No response.)

Anybody on the phone have further comments? Let me ask Dr. Arkus, more comments?

MS. ARKUS: No comment at this time. Thank you.

DR. WALDMAN: Thank you. Dr. Cook?

DR. COOK: Jack Cook, Pfizer. No comments.

DR. WALDMAN: Thank you. Dr. Tenjarla?

DR. TENJARLA: Srini Tenjarla. No comments. Thank you.

DR. WALDMAN: Thank you. Dr. Waldo?

DR. WALDO: Not at this time. Thank you.

DR. WALDMAN: Okay. Let me summarize the second part of the discussion very quickly because it followed close on to the first part of the discussion.

The theme here is that since the science is so new and we are evolving, it's hard to anticipate what we're going to need to provide in the future as these models and the technology evolve. So it's very hard to specify today what we're going to need tomorrow since we don't have all the information at this point.

The other theme that arose was in the absence of understanding exactly what we're going

to need to do, that presenting the thought process logic and the rationale for the information that we provide, that sponsors provide in their submissions and in the development of their agents in collaboration with the agency, is actually the watchword of the day, keeping it more flexible instead of more proscriptive, with the caveat that it will be useful as we move forward to harmonize with other places in the world, with other regulatory bodies in the world, in terms of what our expectations are, so that it can be a uniform playing field as close to worldwide as possible.

Close enough summary? Okay.

**Adjournment**

DR. WALDMAN: All right. So that has concluded this part of the meeting, the morning session of the meeting. We'll now adjourn and break for lunch. We will reconvene in this room in 50 minutes, at 12:15 p.m., at which time we will begin the afternoon session.

I want to thank the panelists for their time and the audience's attention. Thank you very much.

(Whereupon, at 11:24 a.m., the morning session was adjourned.)