Food and Drug Administration
Public Workshop

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FOOD AND DRUG ADMINISTRATION

PUBLIC WORKSHOP

MECHANISTIC ORAL ABSORPTION MODELING AND SIMULATION FOR FORMULATION DEVELOPMENT AND BIOEQUIVALENCE EVALUATION

Thursday, May 19, 2016

8:31 a.m. to 4:37 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

Meeting Roster

George Amidon

University of Michigan

John Duan

Food and Drug Administration

Thomas Eissing

Bayer Technology

Masoud Jamei

Simcyp

Filippos Kesisoglou

Merck

Robert Lionberger

Food and Drug Administration

Viera Lukacova

SimulationsPlus

Jasmina Novakovic

Apotex

Kathleen Uhl

Food and Drug Administration

Xinyuan Zhang

Food and Drug Administration

Liang Zhao

Food and Drug Administration

C O N T E N T S

P R O C E E D I N G S

(8:31 a.m.)

Welcome and Logistics

DR. L. ZHAO: Good morning. Welcome, everyone. My name is ZHAO, and I'm the division director for Division of Quantitative Methods and Modeling, Office of Research and Standards, OGD. I will be the meeting chair for today, and I would like to welcome everyone to the workshop.

Thank you to all the speakers, panel members, and everyone in the audience to make time and effort to come to the FDA White Oak campus, and, also, thank you to those folks on the line to participate in the meeting.

I will call the meeting to order, and I would like to go around the table for a quick introduction. I'll start with Dr. Duan. Just with your name, affiliation.

DR. DUAN: John Duan, biopharmaceutics division, the FDA.

DR. ZHANG: Xinyuan Zhang, the Office of Generic Drugs, the Office of Research and

Standards, Division of Quantitative Methods and Modeling.

DR. KESISOGLOU: Filippos Kesisoglou, Merck Research Laboratories, West Point, Pennsylvania.

DR. NOVAKOVIC: Jasmina Novakovic, Apotex, director of pharmaceutical generic components.

DR. AMIDON: Gordon Amidon, the University of Michigan, working in the biopharmaceutic area for many years.

DR. LIONBERGER: Rob Lionberger, director of OGD's Office of Research and Standards.

DR. CONNOR: Dale Connor, Office of Bioequivalence in the Office of Generic Drugs, FDA.

DR. JAMEI: Masoud Jamei from Simcyp.

DR. LUKACOVA: Viera Lukacova, SimulationsPlus.

DR. EISSING: Thomas Eissing from Bayer, representing PK-Sim.

DR. MEHTA: Mehul Mehta, Office of Clinical Pharmacology.

DR. SAO: Paul Sao, Division of Biopharmaceutics, Office of New Drug Products.

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

DR. L. ZHAO: Thank you, everyone. We have a very excellent panel to cover all the topics for today. A couple of housekeeping issues for everyone here, so please silence your electronic device that ring, sing or chirp.

For all the speakers, we will have to keep time in check. We have a warning light. The light will turn yellow when there is only five minutes left for your allotted time.

So for all the panel members, I would respectfully ask you to refrain from using BlackBerry and checking your email. We have two breaks and one lunch period for you to be able to do that. Having said that, for everyone here, we have 20 minutes break, two of them, and one lunch break. So I would like you to check your time and make it to your seat in time.

Now, I would like to welcome Dr. Kathleen Uhl -- we call her Cook -- a very important figure in our field, to the podium to do the opening

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remarks.

(Applause.)

Opening Remarks – Kathleen Uhl

DR. UHL: Thank you, Liang.

Good morning, everyone, and welcome to this FDA workshop on mechanistic oral absorption modeling and simulation for formulation development and bioequivalence evaluation.

That's a tongue twister for this early in the morning, I've got to say, and I'm only one cup of coffee into the day. I think that there will be paybacks into the future to Liang for asking me to do opening comments on this one.

So, Liang, I'm looking for chocolate or something afterwards.

I am very pleased to be here this morning and to offer a few opening comments. This workshop is an example of the collaborative spirit between FDA, academia and industry, and, in this particular circumstance, to collaborate to advance the science that brings generic drugs to market and the science to do this more efficiently.

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It's impressive for me to see the level of interest and the level of engagement in this topic. I spoke with Liang yesterday, who told me that there were about 400 people who signed up for this conference. We don't have the exact number of people who are attending via WebEx, but as of yesterday, it was anticipated there'd be at least 200 people. We'll know later in the day, I think, how many. But that tells me that there's remarkable interest in this topic, especially as it relates to the development of oral dosage forms for generic drugs.

Before I move on, though, I do want to thank Liang and Susie, especially Susie, for the amount of time, effort, and energy that went into putting this workshop together and having this today. Thank you to you, Susie.

One of the things that I've commented upon in numerous public meetings, public presentations, et cetera, is the low first cycle approval rate for generic drugs. Generic drug applications are called abbreviated new drug applications, or ANDAs,

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here at FDA.

Currently, we are experiencing about a 10 to 15 percent first cycle approval rate, and that's a little concerning to me. The generic drug program needs improved efficiencies and accuracies in generic drug product development, which should then translate to reduced regulatory uncertainty and reduced regulatory burden.

Some of these improved efficiencies include just what we're here for today, the application of modeling and simulation to oral drug products, and oral drug products are actually the largest number of submissions that we get to the agency.

The purpose of today's workshop is to obtain input from various stakeholders on when, where, and how to conduct mechanism-based absorption modeling and simulations in the context of bioequivalent product development and the impact of this on regulatory decision-making specifically related to generic drugs.

Here's what will happen today. FDA will share our current experiences on the application of

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this type of modeling and simulation on our regulatory activities. There will be many external experts who will also present and share their experiences with this modeling and simulation, and I'm sure that there will be a very robust panel discussion, seeing not just the number of people here on the panel, but as well the depth and breadth of your experiences.

I'm hopeful that this will lead to very fruitful discussions about the current and future utility of these modeling and simulation techniques in the development of bioequivalent oral drug products and in our regulatory reviews.

Lastly, and I kind of harp on this all the time when we have public meetings, is the fact that we need comments on this topic. There's a docket that's open for this meeting. We really need people to submit your thoughts, your thinking, your ideas on this topic so that we can advance the science in this area, hopefully use the input that we get to either create a white paper on the topic or, as a regulatory agency, that we can put out

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guidance to industry on how best to use these methodologies in the development of generic drug products. So please, if you have ideas, please submit them to the docket. It really will help us.

Some of my thoughts about this workshop that I'd like to see come about as a result is, first of all, this whole concept of innovation and implementing innovation in the context of generic drug development using these tools, simulation, and modeling. Typically, when people hear the word "innovation," what I'm struck with is they usually think about the new drug side. When they say "innovator drugs," they mean the new drug side, right?

It takes incredible innovation to reverse engineer a drug and to create a high quality generic version of that drug and, in this regard, innovation can actually be the cornerstone or the foundation upon modern generic drug development in almost all steps from formulation design and to the assessment of therapeutic performance.

Mechanistic-based modeling and the

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application of such to improve our understanding of drug absorption can be the very first step to modernize the development of solid oral dosage forms for generic drugs. It can do this by integrating the latest knowledge of drug substance properties, formulation characteristics, in vitro release profiles, and physiologic variables.

In addition, because I know there are industry people here, I'd like to see industry realize the numerous benefits from this type of simulation and modeling. I'm happy to see we have some individuals who work on the review side of new drugs, because this is common methodology applied in new drug development.

Some of these benefits include the ability to extrapolate data from healthy volunteers in BE studies to patients, either patients in general or very specific subpopulations of patients; for example, patients that have GI disorders and alterations in their GI pH and such. It's helpful in informing how and what is chosen for the in vitro release testing methods. It's helpful in

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the ability to evaluate the impact of dissolution deviations and failures. It's helpful in the ability to evaluate potential performance differences for modified release formulations with different release mechanisms from the reference-listed drug; for example, if the generic or the RLD is matrix versus an osmotic pump, for example, with certain extended-release products.

It's helpful in defining critical quality attributes and clinically relevant specifications. It's helpful in understanding pharmacokinetic variability, and if you understand pharmacokinetic variability, you can better design BE studies. You can better address the study in advance so that you have success in that study, and it can also be used to reduce the sample size.

It's helpful to evaluate certain product risk factors that can then aid in very targeted post-marketing safety surveillance. And finally, and this is really where the rubber meets the road for industry, it can certainly help get their products improved, because valid modeling

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components in ANDA submissions can reduce regulatory uncertainty and potentially relieve the regulatory burden in order to support product approval.

In closing, I'd just like to say we grow smarter by learning together and, more importantly, by learning from each other. I'm hopeful that today is not just a learning opportunity for the attendees, but also the opportunity to advance the science in this area, so as to advance the science of mechanistic modeling and simulation.

The agency thanks you for your attendance at this workshop. I am hopeful that you have an enjoyable day. It's going to be a long day. I know a lot of you will also be attending the Part 15 public hearing tomorrow, and so I just wish you a good day. I hope that Liang is able to report back to me about lots of really positive input, and we're ready to put pen to paper on some ideas soon after the docket closes.

I thank you for the opportunity to talk, and I wish you good luck today. Thank you.

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DR. L. ZHAO: Thank you, Cook.

(Applause.)

DR. L. ZHAO: Thank you, Cook, for your very insightful remarks. That's what we need. I just want to give you another round of applause for your support and for your guidance for the industry.

(Applause.)

Presentation – Liang Zhao

DR. L. ZHAO: I will go through some of the slides I prepared for the introduction. Modeling and simulation are one of the priorities in GDUFA regulatory science program. The tools are not only for generic drugs, but also for new drugs, for the drug development and the regulatory decision-making.

As Dr. Uhl just mentioned, today we have more than 400 people registered, and I believe there are many people who may participate without registration. The objective for today's meeting is to share current FDA experiences on the application of mechanism-based absorption modeling and simulation in regulatory activities; to discuss

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current and future utility of mechanism-based absorption modeling and simulation in the development of bioequivalent oral drug products and regulatory reviews; to obtain input from the panel, from the audience, from various stakeholders on when and why and how to conduct mechanism-based absorption modeling and simulations in the context of bioequivalent product development; and, request comments on these topics.

Over a year period from April 1st, 2015 to April 1st, 2016, within the Office of Research and Standards, OGD, modeling and simulations have made critical impacts to 20 ANDA reviews, 54 citizen petitions, controlled correspondence, three ANDA meetings, 33 BE guidances, and 37 regulatory research studies.

Some prominent examples include to use PK modeling and simulation for methylphenidate extended-release products and other asthma controllers. Here, I have left out our analysis contribution to 17 ANDA reviews of dabigatran.

Modeling and simulations has benefited the

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development of BE criteria for painkillers, assessment of BE standards for GI locally-acting products, simulation of in vivo alcohol dose dumping studies. Simulations have been used for the development of BE criteria for highly variable drugs and narrow therapeutic index drugs.

PK/PD modeling and simulation have been used to determine the appropriate study design and evaluate the BE between generic anti-epilepsy drugs and immunosuppressant drugs in patients.

This slide shows a brief summary of the areas where PD/PK modeling has made an impact. First, it has been used to identify very relevant individual testing, including dissolution method. It has been used to identify critical attributes to control product quality. It has been used to evaluate the potential of in vivo alcohol dose dumping after a formulation change.

It has been used to evaluate risk associated with mechanism of change, especially for extended-release products, such as from osmotic release control delivery system to controlled release

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metric delivery system. It has been used to assess the extrapolation of BE from healthy volunteers to special populations.

For locally acting drugs, the modeling and simulation has been used to assess the GI local drug concentration and the correlation between local drug supporter and systemic supporter.

The tools have been used for the waiver of in vivo studies, such as waiving lower strengths, sometimes higher strengths of a product, or increase the space of waiver for BCS III class drugs.

The modeling and simulation are also being used to assess the proton pump inhibitor effect after a formulation change. So we conducted a BE study in healthy volunteers, but without a study with proton pump inhibitor. We want to use modeling and simulation to assess the risk if we have a formulation change.

This chart shows an increasing number of compounds assessed using absorption modeling. Fifteen out of 34 of them are IR products,

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immediate-release products. Nineteen of them are modified-release products. The majority of them fall into the BCS Classes II and IV. Of note, we have assessed seven products in a period of five months in the year 2016. Dr. Susie Zhang will give you some details in her presentation.

For new drug development, as contributed by Dr. Ping Zhao in the last ASCPT meeting, the focus of PBPK modelings, many are on drug-drug interactions and to assess PK profile change in specific populations. These are the main areas from the new drug side.

Areas with limited experience, including assessing the factors on PK exposure for pregnancy, ethnicity, geriatrics, obesity, disease states, food effect, formulation change, pH effect, some of these fall into the realm of generics. So you can see from top to bottom, there is a decreasing degree of confidence level and an increasing degree of reliance on systems knowledge, like locally environmental, physically environmental change and product and the GI physiology instruction and so

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forth.

There's also an increasing number of drug labels with dosing recommendations informed by PBPK. The majority of them fall into DDI, only with two exceptions.

Another stakeholder within FDA is our pharmaceutics colleagues in the Division of Biopharm, Office of New Drug Products, OPQ. The biopharmaceutics emphasize linking the product quality to the product clinical performance. In this regard, PBPK is a must-have tool.

Over a period from 2008 to 2016, the biopharm group has received, reviewed 15 biopharmaceutics-related PBPK submissions. These submissions assess the risk of product and studying dissolution method specifications, clinically relevant drug product specifications for critical material attributes and critical process parameters.

I don't want to steal thunder from Dr. John Duan, as he will give you more details in his presentation.

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With a set of presentations for today from the FDA, the new drug industry, generic drug industry, academia, also, software developers, the hardcore modelers, we are going to discuss three questions in the afternoon. The first question: For the available list of areas or subareas, which one do we have the highest confidence in using physiologically-based absorption modeling for oral dosage forms?

Second question: Do we have enough experience and confidence in applying the current PBPK absorption models to support the following regulatory applications? I can read out the list: Support particle size distribution specifications for an immediate-release drug product of a drug with a low solubility; support dissolution specifications for a modified-release drug product; support request to widen the BCS III biowaiver criteria; support in vitro-in vivo correlation of an API with less than three formulations with different release rates; support new proposals to demonstrate the bioequivalence for GI locally-

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acting drug products.
The panel members can help give more addition to the list, and, also, along with your opinions.
The third question: For the area with middle to low confidence, what are the gaps and how to close the gaps through research? That will give us possible benefit to further improve our regulatory science research program.
Without further ado, I will introduce Dr. John Duan. I welcome Dr. John Duan to the podium to give the first presentation in the morning.
Presentation – John Duan
DR. DUAN: Thank you, Dr. Zhao.
Today, my presentation title is "The Application of Mechanistic Oral Absorption Model in Biopharmaceutics Review." In order to do this topic, I would like to talk a little bit about the overview about biopharmaceutics. After setting the stage, I would like to introduce the current status, what we are doing, and what we have done.

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After that, we will figure out what the problem probably is and what the challenges will be. In that regard, finally, I will propose some future steps, future applications.
In all three parts, the theme is patient-centric quality. In order to do the patient-centric quality, I would like to give an overview about biopharmaceutics' role in the drug development in the patient-centric quality control.
Before doing that, I would like to introduce a concept, CRS. To do the patient-centric quality control, we have to set a clinically relevant specification, so we call it a CRS. The concept comes from the general concept of patient-centric quality control.
That's a paradigm shift for the quality control. In traditional quality control, the control is by testing. After the product is ready, we test, do this test and do that test. But the current concept is we would like to introduce the patient-first concept, to do that from the beginning to design a drug, build the quality in

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the design, and go from there. So that's our paradigm shift.
The paradigm shift will allow us to give the patient focus. When we design the compound, when we design the formulation, we consider the patient need, and then we go from there and do the risk assessment, do the design of experiment, and, finally, define a design space. In that case, everything we consider is from the patient perspective. And from there, we implement the patient-centric concept.
So the patient-centric quality control is a framework. In order to implement that framework, the agency implemented organization reframe. We reorganized our quality-related office. Since 2015, the Office of Pharmaceutical Quality has been stood up. The purpose of this office is to coordinate all the quality aspects and get them together and get one voice for the quality and one voice for the drugs, one voice for the industry and, most importantly, one voice for the patient.
So from there, we've seen the

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reorganization. The biopharmaceutics division was created. Here, I give a brief history about the FDA biopharmaceutics group.
Before 2008, the biopharmaceutics was located in the Office of Clinical Pharmacology. Sometime before, the office's name was called Office of Clinical Pharmacology and Biopharmaceutics. Sometime later, the office's name changed to Office of Clinical Pharmacology, so no biopharmaceutics.
Since 2008, biopharmaceutics group was established. At that time, we had about seven, eight people around there. Since then, we have gradually grown, and in 2014, in preparing for the standup of OPQ, we recruited a lot of people in there. In 2015, we keep going with the standup of the Office of Pharmaceutical Quality. And in 2016, we keep growing. From seven people, right now we have 31 people.
I didn't see the trending stopping anywhere soon, and the momentum is still there. So that means the agency sees the opportunities, sees the

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function of patient-centric quality control and quality framework.

So whenever we do something, we start with the concept, and then we have the organization, we have the people. That's currently what we are doing.

We have the patient-centric concept sitting there, and then we have the OPQ standup. The organization is there. And most importantly, the Division of Biopharmaceutics standup last year. In that case, that indicates there's a trend to emphasize biopharmaceutics in the quality control area.

So to emphasize that -- Liang already presented these slides -- I would like to reemphasize the definition of biopharmaceutics. Sometime before, I attended a national meeting. Someone asked me, "Here at the FDA, what do you do?"

I said, "I'm in the Division of Biopharmaceutics."

"Oh," he said, "Okay. Do you do gene

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therapy or do recombinant DNA or -- well, what do you do?"

At that time, I was speechless. I don't know what to say. He doesn't know. From there, I feel sorrow. I feel sorry, because probably we didn't do a good job to let the industry, let the pharmaceutical science field know biopharmaceutics is there. So here, I would like to reemphasize the definition of biopharmaceutics.

Biopharmaceutics is the study of the physical and the chemical properties of a drug and the proper dosage form. That relates to the onset, duration, and the intensity of the drug action. Here, we can see the concentration of biopharmaceutics not only to the in vivo onset and the duration and intensity, but it also relates that back to the physical-chemical properties and the dosage form properties. That is completely related to the drug quality.

From there, I would say biopharmaceutics plays an important role in the drug quality control, especially in the current framework about

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the patient-centric quality control framework. In that sense, biopharmaceutics concentrates and relates the quality to the clinical performance. The concept generally is that the drug company conducts the clinical trial to show that efficacy and safety is there for the drug quality.

Our future quality control task is to match the clinical trial formulation. Every batch, each batch should be more or less similar to the clinical trial batch and show similar efficacy and safety. In that regard, the bioequivalence between the future manufacturing batch and the clinical batch is very important.

However, we cannot control every drug quality, every aspect, to do a bioequivalence study. In that sense, translating the in vitro properties to in vivo performance is very important. That's biopharmaceutics' role playing over there.

In that regard, the mechanism of oral modeling and simulation is very important. That consolidates the physical-chemical properties and

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the physiological properties together, and do a bottom-up, and figure out what the drug performance would be. Then we have some data, and we top-down, bottom-up and top-down, getting together to get the job done.

So that's biopharmaceutics' role in the drug development and drug approval, and oral mechanistic modeling and simulation is a very important tool for biopharmaceutics to do the job.

From here, we can see the agency's goal is very clear, patient-central quality control. The trending is obvious from concept to the organization to a specific biopharmaceutics division, and the effort has been tremendous.

The opportunity is very exciting, but before we get too much excited, we'd like to introduce the current status of the oral mechanistic modeling and simulation in submissions. In current status, as Liang showed the slides, I borrowed a page from Dr. Ping Zhao. He summarized until 2013 all the 84 PBPK-related submissions.

Among them, 60 percent, only 60 percent

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had -- I multiply the 60 percent to the 84, that's about five. So until 2013, only about five absorption-related submissions to the FDA. That means very, very little.

Recently, we conducted a survey, and Liang already showed these slides. We found 15 submissions using PBPK to do the quality-related justification, such as using the PBPK modeling to do the dissolution methodology selection, to do the dissolution specification setting. Others even used the PBPK modeling to do the quality control for setting specifications for critical manufacturing parameters, such as CMA and CPP. That's critical material attributes and critical process parameters.

From there, we can see there's a trending increase. Compared to Ping's summary, there are five until 2013 and until 2016, until now, we have 15. That tripled, but we still have less. We need to do more.

Following, I'm going to give some examples regarding the submissions and some work the FDA

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reviewers have been doing. The Case Example 1 showed the submission using PBPK to set dissolution specifications and to select dissolution methodology. In this example, this is a low solubility drug. The sponsor says we are going to select a clinically relevant dissolution specification, along with a clinically relevant dissolution methodology.

What they did was they showed the dissolution methodology in different media. As shown here, at pH 2, two formulations, one is the reference formulation. Another one is another formulation, but of different quality. This showed these two formulations in pH 2 medium, they separate. But in pH 4.5, not shown here, and pH 6.8, they are not differentiated. As shown here, the pH 6.8, it's extreme, almost overlap.

When they decide the dissolution methodology selection, the first and most important consideration is clinical relevance. If we can show with overlap they are bioequivalent, we have no problem to select pH 6.8, because if they are

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bioequivalent, we don't want to over-discriminate. However, on the other hand, if they are not bioequivalent, we would like to differentiate. We would like to reject the non-bioequivalent batch and accept only the bioequivalent batch. That's the strategy the sponsor is taking.

They showed using PBPK modeling the two batches with current quality and the other parameters, that they could not be bioequivalent. Then they decided, they say, pH 2 is an appropriate medium to select. And when they set that dissolution specification, they say if I set the dissolution specification, that's an immediate-release, single-point dissolution specification. If I set it at 30 minutes, Q equal to 80, the blue one will pass at pH 2 and the red one won't. That's a perfect example to use PBPK to select dissolution methodology and set dissolution specifications.

The second example not only to set the dissolution specifications, but to also set some CPPs, critical process parameters, and critical

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manufacturing parameters. They not only set dissolution specifications, but they also set the particle size specifications.

It's a very thorough, very detailed PBPK modeling. They did a lot of work and excellent job.

Here, I would like to raise the question and raise a discussion point to see the approach. One of the important themes we notice is that when they do the PBPK modeling, when they establish the model and validate the model, they use a unique approach. The unique approach is selected by several options. Option 1 is they are finally selected. Option 2 is they use the dissolution data as an input. When they input the dissolution data, they use the Weibull function of either dissolved or not dissolved. They use a Weibull function.

Option 3 is that when they input the dissolution profile into the PBPK modeling, they use Z-factor. Finally, they didn't select the two and three. They select Option 1. So I focus on option 1.

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Option 1 is a unique approach and made them a success. Here is what they did. They showed a dissolution profile as a template, and then they tried to incorporate the dose, the volume, and the medium composition and the solubility together. And through modeling, not in PBPK software, somewhere else using another tool, to do another kind of modeling, not necessarily as a PBPK modeling, but it's outside of the PBPK software.

That modeling they did using all the input to figure out what the theoretical particle size should be. In that sense, when they input the particle size into PBPK software, the particle size not only represents the particle size itself anymore, it represents the local volume and the medium composition, also the solubility, because in vivo, the solubility as different, pH could be different. So they took that into consideration through their modeling. That's a unique approach.

I'd like to raise that unique situation for discussion. They did that, and they used that model, validated the model, and then using that for

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dissolution profile comparison; therefore, dissolution methodology validation and the specification setting.

Also, they used the same approach using what's called the virtual BE study. They show virtually the two batches are bioequivalent. The specification setting is based on the virtual BE study and the particle size specification. It's also based on the virtual BE study. That means where I set particle size lowly-mid and highly-mid would be bioequivalent to the clinical batch.

That's the situation, the patient-centric framework we would like to hear, because that shows some evidence, at least in silico, to show they are bioequivalent. That's compared to previous specification settings, why you set this particle size, because we used that before.

This doesn't necessarily mean it will be bioequivalent to that. Here, there are some quantitative indications saying that will be possibly, very likely to be bioequivalent. That's a much stronger argument to make for setting the

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specification.

The third example is what the reviewer in FDA did. The third example is in the situation for ANDA review. In order to make sure the ANDA quality will be consistent, we put an effort for the ANDA PBPK modeling. The intention is to see are there any quality problems.

The situation is that we have ANDA block. That so-called block is we have a whole bunch of sponsors submit for the same API, for the same RLD reference-listed drug. They want to develop a generic drug with that same thing.

The concern is do they have the similar quality, although we observe in some of the BE studies, it's lower, almost at the edge of the bioequivalence range; some of them higher, almost at the edge of the bioequivalence range. So are they bioequivalent?

That's a quality control issue. What our reviewer did was to put them together to see when they do the PBPK modeling, are there any special factors we should consider. In PBPK modeling,

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usually we have a lot of assumptions. Usually, with uncertainty, we have to make assumptions.

Sometimes we don't know the real value. We have to optimize it using the software to optimize. The optimization, the assumption sometimes introduces a lot of uncertainties.

What is the focus for the uncertainties to be paid attention to? Some uncertainties may not be important. The analysis is to put six uncertainties together and do a sensitivity analysis. Currently, based on our knowledge, the PBPK software, although it can do sensitivity analysis, only one or two factors. Six factors put together is what is the reviewer has done here.

They put API particle size and effect of permeability and precipitation time and precipitation radius and plasma protein by the ratio.

The reviewer made an analysis. The analysis is using all the six factors, that's 13,000 combinations, and put them together and put into the PBPK software to see what the Cmax, AUC

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exposure is.

The sensitivity analysis showed it's a very complex figure. The major interest is about the particle size. That's on the X-axis. And the major interest output is about Cmax. With those two major considerations, at the same time, they consider the solubility on top, three groups, and on the right, four groups about the permeability. They use the symbol to differentiate the precipitation time, and they use the color to distinguish the different radius of precipitate.

That shows a lot of interpretation can be made. A major one is that, as we can see in the very left block, the solubility, the measured solubility is 0.011. The relationship between Cmax and the particle size is pretty steep. On the other hand, when the solubility increases on the right panel, the solubility is 0.11, and at that time, it seems like particle size won't play a role as significant as the left one.

That gives us some interpretation of a regulatory step we are going to take. Based on

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that analysis, we send an IR, say you need to provide this one in exact measurement, so in that case.

In summary, the regulatory implication is -- there are a lot of regulatory implications, but I want to emphasize that during the 15 submissions, there are some limitations. A major one is no detailed information provided, and, also, some models established without validation. If without validation, we cannot trust it.

Also, there's no full validation or the detailed file is not provided. When you use a model to justify the application, it's not sometimes reasonable.

Finally, I would like to say for the patient-centric, we have a lot of bridge. So PBPK modeling, mechanistic modeling and simulation is one way. We are facing challenges. As we said, what model should we select and what validation should we do and what software we should use and what software we should develop, that's our challenge.

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In order to fully explore the possibility for patient-centric quality control, we need to do something beyond dissolution, beyond particle size. We need to do some real manufacturing process, manufacturing parameters, such as compression force, hardness, granulation, that kind of stuff. How are we going to use this one to control that? That's our challenge.

Think about it. Here, we should emphasize when we submit the PBPK modeling, that's our current thinking. We should complete and submit the information in order for us to grow together.

One thing I want to emphasize is it seems like currently regulatory -- when we do PBPK modeling, we have a lot of information. But the companies, it seems like the interest at the initial stage, we don't have any information. So we bottom-up and put something together and get some rough idea to develop.

Here, I want to say there's a difference between regulatory and initial development. But there's a common place, because when they do the

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initial development bottom-up, the model you should keep at the later stage for the regulatory submission to make justification, very useful. The example I showed, that's one they did we accepted. That's why I call it the product life cycle measurement using PBPK.

In summary, the quality in vivo performance is a destination and the ultimate goal and the primary consideration for PBPK modeling in the biopharmaceutics area. Mechanistic oral absorption is a powerful tool, and the models support a decision on product quality specification and risk assessment. Model performance and validation is key to get it through.

Finally, I would like to acknowledge my colleagues, Hopi, Fang and Sandra, Meng and Heta, Paul and our office management. Sorry about over time.

Thank you very much.

(Applause.)

DR. L. ZHAO: Thank you, John.

The next speaker, Dr. Susie Zhang from OGD,

Office of Research and Standards.

Presentation – Xinyuan Zhang

DR. ZHANG: Good morning, everyone. Welcome to the workshop. It's my great pleasure to be here today to talk about OGD's experience in research efforts on oral absorption modeling and simulation. I'm so excited today, so if you hear a choppy presentation, it's not because I'm not familiar with this topic, but because I'm so excited.

(Laughter.)

DR. ZHANG: For today's presentation, I will give you an update on oral absorption modeling and simulation in the Office of Generic Drugs, and then I will share a couple of case examples with you, and, finally, talk about GDUFA-funded research efforts to improve oral absorption modeling and simulation.

In 2011, we published this paper, published a review article, where we put an innovative model for future product development. Basically in this diagram, we have industry, and hopefully industry will use this type of tool to help their product

development, conduct pilot BE studies or PK studies and inform model development, and use this tool to reduce the cost and time.

Today, we'll have the opportunity to hear about industry, how industry uses this type of tool to help their product development. In this diagram, we have regulatory agency who will also use this type of tool to help guidance development, to propose innovative bioequivalence approaches for complex drug products, and the agency and the industry will communicate via different venues, such as face-to-face meetings, conferences or workshops like we do here today.

As you just heard in John's presentation, where he gave an excellent example where industry or the firm used a physiologically-based absorption model to propose their particle size distribution, and this is exactly what we proposed here five years ago.

How are we doing today? In 2014, we published a short commentary paper in which we described several case examples of where and what

issues we applied this mechanism-based absorption modeling and simulation to address various regulatory activities. The paper actually was written in 2013.

We described some of the areas where we used, and the majority of the issues are related to dissolution or product quality, and also innovatively use in the other areas. Whenever I look at this figure, I'm always amazed by the potential utility this tool can provide, as well as being amazed by the creativity our scientists have.

Recently, we have a couple of examples asking the question about bioequivalence in proton pump inhibitor subjects, or the PPI related DDI.

You saw this figure that Liang just presented, but what he did not tell you is that we only had a couple of staff members working on this area part-time, hands-on experience. So we have about four to five examples every year before 2014, and we had low productivity in 2014, because we were busy on hiring and also other activities, such

as issuing new GDUFA research studies.

We had new people onboard in 2015 and now we're in 2016, we have more examples here. It's exciting.

Now, this is a simplified absorption process. There's by no means that the figure can capture all the events happening in GI for a drug to be absorbed. But as you can see here, even for a simplified absorption process, it's already very complicated, and for the sake of time, I'm not going to go through the details of this figure. It's been described heavily in the article.

When we do a model, this type of modeling, this is our general practice. We usually collect data from different resources, including literature, our internal data, and then we perform physiologically-based modeling for IV formulation first. If IV is not available, we'll do it for IR solutions, suspensions, tablets, capsules, and then we move forward to the modified-release products.

We'll do model verification or validation, whatever you call it, extensively, as much as we

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can against datasets that we have. And finally, we'll do a simulation.

Now, because I'm in the Office of Generic Drugs, bioequivalence simulation is really important for us. However, it's not that easy, because a lot of times, the intra-subject variabilities are not available.

In 2015, we published a paper describing how we do this, this type of modeling. In this case, we won't run a single bioequivalence trial. Instead, we will run thousands of bioequivalence trials and give you a passing rate of BE studies. It's more like a probability rather than a definitive answer.

Now, I'll share a couple of case examples with you, and the first example is about warfarin sodium tablets, to evaluate the impact of slow dissolution in a specific pH conditions. Specifically, it's pH 4.5.

The second example is to evaluate the proton pump inhibitor impact on bioequivalence, and we have a couple of drug products in that example.

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Warfarin sodium tablets, from a modeling perspective, it's not a complicated product. Warfarin sodium has been reported as a BCS-I substance, and this is an immediate-release formulation. The challenging part to me is how do we communicate the results to scientists who do not do modeling and simulation.

Back in 2014, we actually did the modeling simulation in 2014, among other things. OGD became a super office in 2014. The Office of Research and Standards was born in 2014, and among a lot of other significant events, we did this piece of modeling and simulation work.

The specific aim of this project is to explore the impact of loss of IPA on in vivo performance for warfarin sodium tablets. The background of this project is that scientists observed that for warfarin sodium tablets, if they are put in high temperature and high humid conditions, the IPA will be lost, and then what you observe is slow in vitro dissolution in pH 4.5 condition. Does that impact bioequivalence or

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bioavailability? That was the question asked.

So we did a modeling and simulation. In this case, we had two scientists perform modeling and simulation in two different platforms, and, basically, they reached the same conclusion.

Let's take a look at the warfarin sodium substance properties. It has a PKa around 5. It has low solubility in low pH conditions and high solubility in high pH conditions. And these are the two solubility versus pH profiles input in the different software.

This is a commonly observed scenario, where we observe different numbers reported by different resources. In this table, the dissolution profile A is what was measured, and dissolution profile B, C, D, F are arbitrary dissolution profiles to test solubility versus pH profiles to test the sensitivity of PK on solubility.

Then warfarin has a long half-life, average 40 hours, range 20 to 60 hours. We did the simulation, and what it told us is that the PK profile is not that sensitive to solubility, even

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though you gave extremely low solubility in low pH conditions.

We did sensitivity analysis on particle size, as well as particle density, and they are not that sensitive. They don't impact PK significantly, either.

This is a straightforward figure for a lot of clinical pharmacologists. Because the model is a linear model, there's no nonlinearity component in the model. However, I put it here because it's also a figure related to an important quality attribute, which is the assay or potency. Potentially, this figure can be used to define your assay or potency specification range.

Now, in order to link the in vitro dissolution profile to in vivo performance, we used the so-called Z factor model, where Z is an empiric number here. We fit dissolution profiles in different pH and get the Z number and put it in the model.

We also conducted on several artificial dissolution profiles, basically. We pushed it to

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extreme cases, where you don't have release at all in the different pH conditions, and now what you can see is in this extreme case, where you don't have any dissolution at all in pH 1.2 and pH 4.5 conditions, you keep dissolution pH 6.8 the same. You see the Cmax ratio is above 0.8. Among other sensitivity analysis, what we concluded was that pH 6.8 is the most relevant or in vivo relevant condition.

Now, meanwhile, we also issued a study or awarded a study in 2014 actually, and then we conducted a dissolution study again in 2015. We put warfarin sodium tablets in high humid and high temperature conditions for 24 hours to have a lower, slower dissolution in pH 4.5 conditions. As you can see, these are the dissolutions in pH 4.5 after the tablets were treated.

We compare if you conduct an F2 test comparing the untreated tablets and the treated tablets. The F2 value is actually less than 50.

We also did a two-state dissolution test for the treated and untreated tablets. As you can see,

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the initial dissolution for the treated tablets is slower. However, they catch up at two hours. Again, we did this type of analysis and, also, bioequivalence simulation using the newly available dissolution profile, and what you can see is that the predicted point estimate for Cmax, as well as AUC are close to 1.

Now, we're in 2016. We got in vivo bioequivalence study results finally, and what the results tell us, basically, is consistent with what the simulation told us. If you compare all the pairs of comparisons, the point estimate of Cmax and AUC, they're pretty close to 1, as well, and the confidence intervals are pretty narrow, as well, because this is what's expected, as warfarin is a narrow therapeutic index drug.

We went ahead using this sensitivity analysis technique, tried to map a dissolution space where you can have a safe equivalent product. We used within standard deviation 0.1 and point estimate 95.5, and if you want to have an 80 percent passing grade, you have dissolution in

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pH 4.5 at 30 minutes above 30 percent and dissolution in pH 6.8 at 30 minutes above 80 percent.

This is actually a pretty wide range. When we look back at all the dissolution studies that we have conducted, they all pass this condition.

The conclusion from this study is that solubility in low pH, particle size and particle density do not have a significant impact on bioavailability of warfarin sodium, and the dose or the potency impacted PK proportionally. Dissolution rate at pH 6.8 was the most relevant to bioavailability, and we did an in vivo to confirm the prediction.

The second example is an example where we used this type of tool to evaluate the bioequivalence in stomach pH elevated subjects, and we did it for prasugrel hydrochloride tablets and fingolimod capsules. If we look at the drug substance properties of these two compounds, they have different indications. They have different pKas. But they all have high solubility in low pH

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and low solubility in high pH.

The half-life for prasugrel is about seven hours. However, the half-life for fingolimod is 6 to 9 days. It's pretty long.

The issue for prasugrel hydrochloride tablets is that it is the concern of salt-to-base conversion during manufacturing or storage, different conditions, and because the base has low solubility. Whether the salt-to-base conversion will lead to lower bioavailability, that was the question.

For fingolimod capsules, the question was whether similar dissolution observed in high pH conditions would impact bioequivalence.

Again, we conducted mechanism-based absorption modeling and simulation, and our recommendation based on the simulation is that the salt-to-base conversion for prasugrel hydrochloride tablets should be controlled, and elevated stomach pH is less likely to impact PK significantly for fingolimod capsules.

Prasugrel is a quite complicated drug

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substance. It has two metabolites. The parent compound is below the quantification limit. We had to develop a model with two metabolites. One is inactive, and one is active.

We developed a model, validated a model against two moieties, two metabolites. This figure shows that if we use the observed solubility profile, the model actually under-predicts the Cmax at high dose. Why is that? We can exclude other possible scenarios and conclude that this could be due to the -- this looks like the solubility limit.

We calibrate the in vivo solubility. We actually have had to adjust the in vivo solubility to improve the model prediction at high dose. Then in order to predict or simulate the case where we have half salt and half base, we had to create two records to do the simulation, and we had to assume that the dissolution of the salt and the dissolution of the base don't interfere with each other.

We went ahead and did the simulation. As you can see here, if we had that assumption, the

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simulation does not do a good job in terms of predicting the scenario where we have high percentage salt-to-base conversion, and the dots are already observed and the line here is the simulation. What we did was we just looked into this range for further simulation.

Sensitivity analysis suggested that for prasugrel, the active metabolite Cmax is sensitive to solubility between pH 3 to 7. We also did a bunch of bioequivalence simulations. As you can see here, when the salt-to-base conversion is beyond 20 percent, the passing rate dropped quickly.

Now, we switch gears a little bit to look at fingolimod. Again, here is what we observed, different solubility versus pH profiles from different resources. So we went ahead using different solubility profiles and to do the modeling.

As you can see here, the PK profiles are very close to each other, suggesting that solubility is not a sensitive parameter for this

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compound. This is what is expected, because it has six to nine days' half-life.

We also did multidimensional sensitivity analysis for fingolimod. As you can see here, this figure suggested that the Y-axis is the particle size diameter, and the X-axis is the pH condition. If you have pH around the 4 to 5, this is where the PPI subjects would have stomach pH. If you have particle diameter above 100, you will fall out of the range of 0.8 or 80 percent BE limits.

To conclude, based on these two examples where we have seen that for BCS Class II immediate-release formulations, mechanism-based modeling could be challenging, as in vitro dissolution and in vitro solubility might not be predictive. In that case, we want to have multiple datasets as much as possible for our model calibration.

We talk about in vivo predictive dissolution, solubility all the time, and how do we evaluate in vivo predictivity of the dissolution profile? And to me, it is important that this predictive in vitro dissolution methodology can be

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used in this type of model and improve model predictability.

Based on what we did, not only these two case examples, but also the other examples that I do not have time to show here today, is that we have high confidence in modeling immediate-release long half-life, relatively high solubility and high permeability drug products.

However, we are facing multiple challenges. The first one is dealing with QC dissolution data. Yes, in FDA, we have a lot of dissolution data, but they're all QC method in different pH. We don't have predictive dissolution methods. Firms may do it, but we don't see it.

We are dealing with multiple data sources, not only the quality, but also the PK. If you have 10 ANDAs for the same reference product, you see several folds of differences in PK profiles, and we're dealing with extremely low solubility drug products. That can be challenging.

Some of the immediate-release formulations, such as amorphous form dispersion formulations,

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those can be considered as complex immediate-release formulations. The models need to be improved for colon absorption, because we are doing more and more modified-release drug products, and colon absorption is very important to have a better prediction for those types of products.

In addition to internal hands-on experience in modeling and simulation, we also have a lot of Generic Drug User Fee Amendment or GDUFA-funded research efforts to improve oral absorption modeling and simulation. We have several ongoing studies. We have multiple BE studies in the human, including a lot of drug products, that could potentially be used to verify our model.

We also have a couple of studies ongoing to measure in vitro and, also, in vivo performance of solid dispersion formulations.

We have an ongoing study with the University of Michigan to measure GI physiology to get intra-subject variance. Basically, that measures the same subject twice. Hopefully, they can come back for the second experiment, because this is

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really a tough experiment and the dropout rate is pretty high.

We have innovative sampling methods for a GI concentration study ongoing, and we recently completed a mesalamine study, which measures the local GI concentration. The manuscript is under preparation.

We also have excipients-targets, excipient-transporters interaction studies to better understand excipients' impact, transporters and further absorption.

This year, we have three requests for applications. The first one is related to supersaturation precipitation of the very low drug substance to improve the absorption modeling in that area. The second one is to improve the optimization algorithm for the very large physiologically-based pharmacokinetic oral absorption models.

The third study is to study the fluid amounts taken with oral drug products. Right now, our recommendation is 250 milliliters. So what

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happens in the real world? We'll find out from this study.

Besides the external studies, we also have internal research efforts. We are evaluating the modified-release products, the risks associated with the mechanism change from osmotic pump to metrix, how that is going to impact the BE in different populations. We are doing formulation analysis for BCS III compounds. We are developing a physiologically-based pharmacokinetic database to share these types of models across the agency with different offices, such as Office of Clinical Pharmacology and also Division of Biopharmaceuticals. We're investigating alcohol dose dumping simulations. These are the long-term studies, we're doing here and there when there's no crisis.

To summarize, OGD has routinely applied mechanism-based absorption modeling and simulation to address various issues, risks in regulatory activities. I want to remind you, you still remember the slide that Liang just showed, the

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impact that modeling and simulation has. You see the distributions and the numbers. The least number actually falls into the category of ANDA applications. That means that could potentially be an area to improve.

OGD is actively improving the science of predictions for oral solid dosage forms via external, as well as internal research studies. OGD is willing to collaborate with internal and external stakeholders to advance the application of mechanism-based absorption modeling and simulation in drug product development and regulatory review.

Along the way, there are a lot of people and colleagues who support us here and there from different aspects, and I want to use this opportunity to thank them, as well, and also thank you for your attention.

(Applause.)

DR. L. ZHAO: Thank you, Dr. Susie Zhang.

This will conclude the presentations from the FDA. We will have a break, 20 minutes. You can use the break to stretch and whatever,

socialize. We'll be back before 10:15, followed with three excellent speakers.

(Whereupon, at 9:57 a.m., a recess was taken.)

DR. L. ZHAO: While we are being seated, let me introduce the next session. The next session will be presented by three outstanding experts in the field. The first one is Dr. Filippos Kesisoglou. I can confirm with him that I can pronounce his name in the correct way.

(Laughter.)

DR. L. ZHAO: Following him, there will be Dr. Jasmina Novakovic. Following Dr. Novakovic will be the top expert from academia, Dr. Gordon Amidon.

The first presenter, Dr. Kesisoglou.

Presentation – Filippos Kesisoglou

DR. KESISOGLOU: Thank you for the introduction and the opportunity to speak today at this forum and provide an industry view on how oral absorption modeling and simulation are used for formulation development and bioequivalence

evaluation of new drugs.

My talk will mostly focus on case studies that demonstrate the different applications of the tools. However, at the end I will also provide some thoughts on what I see the field moving forward both in terms of the formulation development application, as well as for regulatory directions.

Before jumping into the case studies, I wanted to set the background under which these case studies were developed and are presented. The use of these tools is part of a broader biopharmaceutics risk assessment effort and a quality-by-design effort with the endpoint, as mentioned earlier today, the patient benefit, as that is defined by the quality target product profile.

In the simplest terms, what we are trying to achieve with these tools can be broken down into two parts. First, we are trying to understand what is the optimal in vivo release or dissolution of the dosage form that provides the intended

therapeutic dose response to the patient. And second, we are trying to link that in vivo response to an in vitro assay, commonly dissolution, that can be used in the future to ensure the future product consistently delivers a therapeutic benefit to the patient.

In addition, it's important to keep in mind that these models are not applied in isolation from other efforts, but are part of a broad lateral confirm effort where data from in vitro, in silico, and in vivo, either pre-clinically or clinically, are integrated both to inform the models and inform forward-looking projections, but also to refine the assays that inform the model.

I know there's a lot of discussion on how we validate the models, and I think it's important to keep in mind that we need to adopt the model to the question at hand, not necessarily looking for broad validation against questions that might not be relevant to the specific project, as well as when models fail, in my experience, it's usually not because the model itself is incorrect, but because

somewhere in this continuum, we have a disconnect in our understanding of where the in vitro or the in vivo data feed into the model.

With that background, I will argue that for new drug development, use of absorption modeling is a commonplace activity that's routinely applied, especially for BCS Class II and IV compounds.

Models that guide first-in-human doses or formulation selections or subsequent formulation modifications, such as API particle size or release rates for modified-release formulations, are routinely applied in early development. Projections of bioequivalence are also relatively common. They are mostly applied for what we call internal biowaivers, so internal decision-making on conducting or not clinical studies, and can be applied for more regulatory applications for more well-behaved compounds, as we heard earlier today.

In the last few years, models around clinical biopharm questions are getting attention. Food effect projections or projections of DDIs with pH altering agents are also showing up in several

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papers in the literature. Again, they are mostly conducted for internal decision-making or to inform formulation decisions.

Typically, the studies are conducted as far as clinical practice goes, but one can see the potential in the future to serve as a surrogate for some of these clinical studies.

Finally, and I will come back to that at the end of my talk, I think the area that's gaining increased attention is linking the dissolution to PK to drive IVIVCs, in vitro-in vivo correlations, and drive what we heard this morning, clinically relevant specifications. And I think that's the area that we could potentially make a significant impact on patient benefit, because it directly ensures product quality.

Jumping into the case studies, the first case study is an early formulation decision example. In early development, the models are primarily used to define the general platform of the formulation we're going to use to ensure adequate exposures in our first-in-human studies.

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This compound is a weak base compound, and in early development, we often do this parameter sensitivity analysis to identify the main factors that can influence a formulation decision.

In this case, the draft shows a parameter sensitivity analysis for this weak base, the fraction absorbed as a function of the stomach pH, and the dose of what we were trying to cover in our first-in-human study. The simulation shows that as long as the stomach pH is in the normal physiological range, which is roughly 1 to 3, we're going to get reasonably good exposures, 80 percent or 90 percent, while if the stomach pH increases significantly, then we will see a reduced exposure.

With this information, we can move to the first-in-human study and defer mitigating with a dose interaction later, as we want to get some assurance on the PK of the compound. In the first in-human study, we did observe good exposures, linear PK through the dose range tested.

Then let's go on to mitigating the pH interaction. On the left-hand side is a single

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dose simulation that's taken out of the parameter sensitivity analysis that I showed before showing the exposure under normal and accelerated conditions simulated by PBPK.

We need to verify our model somehow. As I mentioned, models should not be standing on their own, without any data verification. In that case, we conducted a preclinical study, where we tested animals with pentaglycine that simulates stomach pH and famotidine that suppresses it, and we see a quantitative agreement between the simulations and the preclinical data. So we have some confidence that our model can be used to inform formulation development.

The next step is to project new formulations. So we have to plug in some new information. In this case, we plug in dissolution data generated in media intending to simulate the PPI stomach.

With this data, we can project the PK for the different formulations. Our target exposure level is the dashed line. So we identify a few

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formulations that look promising, and we also compared our modeling and simulation projections against preclinical validation to make sure, again, that the model is behaving as it's supposed to be behaving. Eventually, formulation 4 is identified as a high possibility of success to move forward, and that was verified subsequently in a clinical study.

In this example, I just mentioned incorporation of dissolution data, and incorporating dissolution data is probably the most important aspect of oral absorption modeling. This case study, I really like it. It's from colleagues at Eli Lilly, where they looked at both mechanistic modeling over dissolution linked to a mechanistic model, a PBPK model.

They're dealing with a BCS I compound. One, we think it's easy, but they're using an enteric-coated pill to protect the drug from stomach instability. What the authors did was they modified the standard dissolution operation that's part of every PBPK software to describe the

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dissolution of their enteric-coated system. They got pretty good agreements between the dissolution simulation and the experimental data for two formulations that differ from their drug loading.

The question is, is this difference in dissolution relevant for exposure? On the left-hand side is a simulation of a human clinical study. You can see that the simulation suggests that despite the dissolution differences, the profiles are super-imposable. On the right-hand side is the actual observed clinical data from the clinical study that verified the simulations.

What the authors also did was they conducted a parameter sensitivity analysis to identify the boundaries in which dissolution will fail the bioequivalence, and what they can find is that even with an 80 percent dissolution in two hours, they will still get sufficient exposure, with no impact on AUC and minimal impact on Cmax. This information and exploring these boundaries can really help in the future if there was a clinically relevant specification.

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Moving from a single stage dissolution to a multimedia dissolution question, that often comes up when we're talking about bioequivalence questions. In this case, etoricoxib is a weak base. It's a BCS Class II compound, with very high solubility in the stomach, but relatively low solubility of the intestine. It's not the worst solubility you'll find, but it's enough to make it a BCS Class II compound.

So we were dealing with a site transfer, where we're manufacturing supplies at two different sites, and according to the regulations for the markets we're filing, we had to do a multimedia dissolution comparison for this change. On the top graph, at pH 1.2, we saw no differences between supplies from the new and the old site. But at pH 4.5, at pH 6.8, they're very similar, we see significant differences with new site supplies being faster, where we're clearly failing the F2 similarity criteria.

We were asked, does this translate to a bioequivalence issue. We first developed a model.

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We verified the model against several protocols, what we had clinical data on.

The interesting graph on this slide is not the verification of the model. Everyone shows the graphs that go through the lines. That's pretty common. The graph on the right shows what the PBPK software suggests, that the behavior of the drug is in vivo.

The drug goes into dissolution to about 80 percent or so in the stomach, where it has high solubility, and then because the solubility of the intestine is actually not that bad, there's relatively little precipitation until it reabsorbs almost completely. While the drug is classified as a BCS Class II compound, in reality, in vivo, it behaves more like a permeability-limited compound.

With that information, one could expect the stomach solubility will be more important. Regardless, we did conduct the simulation assuming any of the dissolution profiles are relevant to the in vivo performance. So we conducted simulations in a virtual trial based on the pH 1.2, 4.5 and 6.8

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profiles.

I'm not showing the 1.2 outcomes, because it's obviously going to show the same effect since they're super-imposable. But basically, the dissolution at 4.5 and 6.8, we were projecting up to 10 or 14 percent differences in AUC and Cmax. They're not large differences.

You can possibly call them still bioequivalent, but we conducted the clinical study. And basically, the result is that everything is identical. The dissolution difference does not translate to the in vivo differences, as suggested by the pH 1.2 dissolution. So in this case, the clinically relevant dissolution is the pH 1.2, and we can use it in the future to understand future product changes.

One more CMC question that often comes up is around API form and changes in API form in the formulation, for example, due to a stomach excipient interaction or instability. This compound is dosed as HCl salt. It's a weak base, BCS Class II, again, high solubility in the

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stomach, low solubility in the intestine.
The question is, what is the effect or risk of bio performance if the drug disproportion adds to the free base. Instead of doing another simulation, what I showed in the previous slides, I'm going to quickly discuss some virtual population simulations.
We simulated 250 subjects for a formulation. We said we'll assume a 20 percent free base content as a potential limit. Let's see what the effect is on performance.
On the top graph, I'm plotting the fraction absorbed. You can plot AUC. For simplicity, I plotted fraction absorbed as a function of pH. And you do not see a very strong correlation. That's because other factors, such as permeability, solubility, and bioavailability in vivo, also result into a change in fraction absorbed.
However, if we look at this on the same individual patient, if we were to normalize the Y-axis to the expected exposure of 100 percent hydrochloride self-regulation, then we see a pretty

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clear plant, with a significant R-squared of the relative bioavailability as a fraction of pH.
This still, if you look at the bioavailability reactions, they're 0.9, 0.95, so the effect is not big. You can argue that 20 percent free base doesn't affect things for this compound. If we go to 50 percent free base, shown on the right-hand side, you see a larger portion of the population starting to show reduced exposures.
The mean is 0.85. On the mean value, it actually doesn't look that bad. The actual clinical impact appears to be decided based on the known PK/PD of the compound and whether there is a steep exposure response. But since I'm doing a population simulation, we asked the patient -- this was in the healthy volunteer populations we typically run on bioequivalence studies -- what if we run a simulation in a population with a larger portion of hype or achlorhydric [indiscernible].
So it ends up on this population that was built in the software, where they have a higher incidence of pHs above 5. We can again see a

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higher percentage of the population failing this relative bioavailability question. At the end, one needs to decide, based on the compound characteristics, whether this is important or not and set the limits. It will appear around 20 percent appears reasonable, for the most part, but again, it has to be decided on a compound basis.
Moving outside formulation questions, the fifth case study is around food effect questions. Food effect is another bioequivalence question relating to how you take your drug. The example comes from colleagues at Novartis. They're looking at the weak base BCS I compound, highly soluble, highly permeable, and small first pass effect. So nothing complicated, no known EMI of this to worry about.
First, describing the fasted-state data is shown on the slides, pretty good description of the fasted-state data. That's not surprising for a BCS I compound. The question is, how is food effect projected.
On the left-hand side, we have a parameter

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sensitivity analysis. It shows the projected AUC ratio as a function of dose, and it's a pretty flat line on one. So the model suggests, regardless of dose, the compound will not lose any exposure or gain exposures as a function of dosing with food.
On the right-hand side is a simulation of the dose that the authors had, clinical data, and it's interesting that not only the average strength is projected pretty well, but the variability around the observed food effect administration is also described pretty well by the model.
So we do believe that for well-behaved BCS I compounds, if one has fasted data to validate the models, they can actually do reasonable predictions and accurate predictions of the fed state and potentially, in the future, use such type of simulations to replace clinical studies.
The final example I'm going to cover briefly is an IVIVC example. This is a BCS Class III compound. The dose is a modified-release formulation. What's interesting, and we're doing the absorption modeling PBPK for this, is that it

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exhibits regional dependent absorption. So it's reduced by variability as the drug is dosed further down the GI tract.

We used data from six formulations, three matrices and three multi-particulates. There were doses in the clinic against the immediate-release dosage form.

The PBPK model allows us to incorporate the regional absorption into the model. These absorption scale factors, which for simplicity you can think of them as a correction factor on the intestinal permeabilities for each of the regions, you can see, were fitted for the data for the modified release. They are decreasing as we go down the GI tract.

They mimic what we know experimentally for the compound, and we get pretty good agreements with the observed simulated data for all six formulations. That allows us to build a PBPK model for the IVIVC question. The performance of this model was very similar to a more classical deconvolution/convolution model we also developed.

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These case studies cover where I think we are today. As I said, I think we're in a pretty good place, and these models are routinely applied.

What do I expect to see moving forward? First, I do expect to see an increased application of these models to understand fundamental biopharm questions and inform clinical study designs the same way DDI models have done over the years. I think our clinical pharmacology colleagues, at least in the industry, are now becoming more familiar with these oral absorption models. They can trust them more for clinical study designs.

I do expect to see an increased utilization of the models in CMC filing sections mostly as supportive arguments for formulation development and partly by design argument. I have to qualify this, and I think it was mentioned in the morning. A lot of the times, some of the models will not make it into the filing because the decisions are made earlier. So the model might not be relevant to the formulation we're trying to commercialize. If the models are relevant to the final

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formulation, I do expect to see an increased appearance of these models.

Finally, the area I think where we'll see more and more application is the use of the absorption modeling for IVIVC and informing clinically relevant specifications. I will admit we are still not there. All of the tools are in place to actually do this.

We typically talk about biorelevant dissolution and quality control of released method dissolution data separately, as two separate entities. However, we have the modeling tools in place that one can start using both of them together to drive a clinically relevant specification.

Specifically, one can use models to essentially deconvolute the in vitro data and get the inherent formulation behavior, which will be dissolution method independent and then use that information in the PBPK modeling or your IVIVC modeling to project clinical performance.

As I showed you in some of the examples, use

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the PBPK modeling to test the boundaries of performance to understand why you're going to see failure of your formulation and then translate that back to a dissolution specification for your final product, much as how it's currently done for traditional IVIVCs for modified-release products.

Finally, I think regulatory guidances can also serve as another catalyst to push use of these models. For example, guidances around modeling acceptance, the qualification criteria for IVIVC, and bioequivalence questions, there is a traditional IVIVC guidance which we'll be following that one.

A regulatory framework around clinically relevant specifications, especially for immediate-release products, I think modified release is a little bit more clear what we should be doing, but immediate-release is a little bit more difficult. Global harmonization might be a concern there.

Finally, as I mentioned, guidances on using some of these models as surrogates of clinical

studies, as currently done for DDIs.

With that, I would like to acknowledge the PQRI Biopharmaceutical Technical Committee and the AAPS Quality by Design and Drug Product Performance Focus Group for some of the concepts that I'm presenting today and colleagues at Merck for help with the slides.

I'm looking forward to the remainder of the workshop. Thank you.

(Applause.)

DR. L. ZHAO: Next speaker, Dr. Novakovic.

Presentation – Jasmina Novakovic

DR. NOVAKOVIC: Good morning, everybody. I am here today on behalf of Generic Pharmaceutical Association, and the title of my presentation is "Modeling and Simulations for Development and Bioequivalence Evaluation of a Generic Drug Product."

So what is Generic Pharmaceutical Association? This is an association that represents the manufacturers and distributors in the area of generic pharmaceutical products,

including suppliers and manufacturers of active materials.

At the beginning, I would like to start with major phases of generic drug product development. It starts with characterization of a referenced drug product followed by design of the generic product and process, and these two stages are so-called early development. Once generic drug product and process are defined, the manufacturing pivotal biobatch, that biobatch is subjected to bioequivalence studies against reference product. And if the outcome is positive, it means if the product shows bioequivalence, then we are moving into commercial manufacturing and product enters its life cycle. These are post-approval stages.

In today's presentation, I would like to talk about roles of physiologically-based pharmacokinetic modeling and simulations at early development stage, as well as throughout life cycle, and quality risk management of a generic drug product.

Where are the opportunities for PBPK

modeling and simulations? First, we have to start with characterization of a reference-listed drug. Definitely, PBPK modeling and simulations has its role. Then when we are developing product and process, we are also using PBPK as a tool to facilitate product development. Eventually, biobatch or bio lot is manufactured and subjected to biostudy.

How do we select bio lot? Among multiple trials, we can select bio lot by using PBPK as a tool. Also, once biobatch is manufactured, stability is starting. At that time, we should already have a specification. Ideally, the specification should reflect bioequivalence or should be clinically relevant. Therefore, PBPK modeling and simulation is also important for us.

Once the product is shown to be bioequivalent and commercial manufacturing is starting, the product is subjected to changes, and life is change, and, therefore, we cannot avoid changes to the product sometimes. And these are minor changes to the composition or changes in the

process.

In order to assess impact of these changes on drug behavior in vivo, we can use PBPK modeling and simulations. These are the opportunities, but what is the real situation? Based on a survey that has been conducted recently on a very limited number of participants, PBPK modeling and simulation is underused in the generic pharmaceutical industry.

About 75 percent of respondents said that they are using it for characterization of reference-listed drug and development of the process. The same percentage approximately is using it to assess product ability to meet bioequivalence versus innovative product, and about 50 percent said that it is used to develop manufacturing process.

On all other areas, it seems to be unused, but as I said, the sample size for the survey was very small. So it is difficult to say that it is a true representation of the situation.

In this presentation, I would like to share

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with you our experience at Apotex at this time about application of physiologically-based modeling and simulation at early development stage, as well as throughout the product life cycle.

Let's start with early development. At early development stage, we would like to characterize the reference-listed drug in terms of the attributes critical for in vivo performance and to define target product profile. Also, we would like to use that information to facilitate formulation design and define development strategy to achieve bioequivalence with reference-listed drug.

So this is an example from our practice. We started with reference-listed drug characterization, and these are the tools and input in that we needed. We used GastroPlus v. 8. We had physiccochemical and PK properties of the active pharmaceutical ingredient. Dosage form and dosage strength were known to us. Route of administration, pH solubility profile of the active ingredient. Plasma concentration versus time data

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or PK profile and in vitro early-release profile, that is optional, but it can be always generated in-house.

More specifically, the drug was a BCS class steroid. It was an immediate-release tablet, 250 milligram dosage strength, molecular formula and molecular weight unknown. Log D, pKa, Caco-2 permeability are known. pH solubility profile for the active ingredient has been developed or generated in-house, and the PK parameters, including the plasma protein binding, were known. Plasma concentration versus time profile was available in the literature. In vitro dissolution profile was generated in-house, but it was used for information purposes only.

So this is pH solubility profile of the active ingredient measured in-house. It is obvious that the compound has very low solubility, especially at pH above 2. We incorporated all the information that I mentioned before into the model, and we got a simulated profile represented by the full line much, much lower than the observed

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profile represented by the active squares.

So we asked ourselves what was the reason, and when trying to find the answer, we approached it taking into account the so-called parsimony principle, which means the simplest possible hypothesis among multiple hypotheses is most likely to be the correct one.

What we did, we modeled solubility. The blue line in the plot is the modeled solubility profile, and the red line is the experimental solubility. We incorporated the model solubility into the model, GastroPlus model. As the result, we got simulated PK profile represented by a full line, which practically overlaps the experimental or the PK profile reported in the literature.

What was the conclusion that we made based on this? We realized that solubility enhancement based on the modeling results is necessary to achieve bioequivalence. So we focused our development strategy around solubility enhancement, and we were fortunate to achieve bioequivalence. Actually, our product achieved bioequivalence

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against the referenced product.

Now, I would like to move to commercial product manufacture and life cycle management and modeling and simulations to ensure quality risk management. In this case, our product was a BCS I drug formulated as extended-release matrix-based formulation in multiple strengths, exhibiting linear pharmacokinetics. Bioequivalence versus reference product was proven for the lowest and highest strengths.

Formulations subjected to biostudies exhibited different release rates in one of the first medium. The question was, is this relevant to the product in vivo performance. We were pretty much sure that it wasn't relevant, because both strengths exhibited bioequivalence, but classical biowaiver justification for the intermediate strengths or different strengths was challenged due to such discrepancy of the solution profiles in one of the test medium.

Our question was, is the science-based approach that employs modeling and simulation

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applicable. What we did, first, we tried to identify bio indicative solution test conditions and to establish clinically relevant specification limits to ensure bioequivalence. Then we designed a biostudy waiver for the intermediate strengths that can be used eventually for SUPAC changes, and it was IVIVC Level A correlation. We used that correlation to establish boundaries for critical material attributes of a rate-controlling polymer to ensure in vitro release within clinically relevant specification limits.

Let's start with bio indicative, the solution test condition, and specification limits that we established to ensure bioequivalence. So the first thing that we did was to reveal regional gastrointestinal absorption profile of our drug. Why it is helpful, it is helpful because it tells us what should be our starting point in terms of designing these solution test conditions. At least we knew the pH of the region our drug -- by knowing the region our drug is absorbed, we know the pH of the media, and that is most likely to be reflective

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of drug in vivo behavior.

What we had, we had three bio lots and corresponding release profiles for the three bio lots. The PK profiles of the three bio lots are presented without dose normalization. So the lowest strength is presented in red squares, and it was bioequivalent to the corresponding strength of the reference-listed product. And the highest strength, in teal, is also bioequivalent with the corresponding strength of the reference-listed product, and the highest strength, presented in green, was bioequivalent, but with borderline confidence.

You can see in the dissolution plot that dissolution or release rates correspond to biostudy results. There is rank order between results of the bioequivalence studies and dissolution or release rates. We used that information to establish in vitro-in vivo correlation, and Level A in vitro-in vivo correlation has been established with a regression coefficient which is above 0.9, which is very good for such situations.

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Now, we know that our dissolution test method is bio indicative or biorelevant or bio discriminatory. Our next task was to establish specification criteria for the bio indicative dissolution test method.

How we did it, we created number of hypothetical batches with different release rates, and we incorporated those release rates into modeling and simulation. Based on the output, we could specify what are upper and lower specification limits for our product that would result in bioequivalence.

So this is the plot representing dissolution profiles and upper and lower specification limits. The limits are presented in red dotted lines. The biobatch, which was so-called borderline biobatch, bioequivalent, but with borderline confidence interval, is presented in blue. That borderline batch is outside the lower specification limits.

We also introduce something that we call gray area, and that gray area is a reflection of prediction error. By having that product which

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meets specification criteria, we assure that that drug product would be bioequivalent to the corresponding reference-listed drug.

At this point, I would like to mention differences between biorelevant and QC dissolution. These two methods may be different methods, and in most of the situations, they are different methods. QC method is used routinely, but it could be overly discriminating or bio irrelevant. Bio irrelevant methods may be complicated and impractical for routine applications, but these two types of methods complement each other well, because impact of change, such as SUPAC changes or impact of out-of-spec results during stability, for example, which, when product is tested by QC method, may be assessed by bio indicative test method.

So most of QC methods nowadays have the OGD-recommended test method, because somehow the agency is in favor of those test methods, but for generic manufacturers, those test methods may not be suitable. So my question is, does one size fit all. No, definitely not.

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In this plot, we have a generic product, represented by a red line, and innovative product, represented by a blue line, tested as per OGD-recommended test method. The generic product has been proven to be bioequivalent versus corresponding reference-listed drug, but as you see, the dissolution profiles are very, very different, with generic drugs showing practically no dissolution.

Another similar situation to bioequivalent products, different release rate, but when tested by FDA OGD dissolution test method.

Now, I would like to talk about biostudy waiver for intermediate strengths. That biostudy waiver has been justified using Level A IVIVC that we developed, as I explained previously.

In vitro release profiles for the intermediate strengths were incorporated into the simulation, and we obtained simulated PK profiles for each intermediate strength. We were able to calculate test reference ratio and predict bioequivalence against our product and against

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reference-listed drug.

Finally, how did we use physiologically-based modeling and simulation to establish boundaries for critical material attributes of release controlling polymer? It is known that a polymer material or attributes of a polymer material may have impact on the release of the active ingredient and, consequently, on bioavailability.

What are the boundaries? Boundaries should be defined to ensure bioequivalence. We are talking about clinically relevant specifications. How would we know what are the boundaries?

Our ultimate goal is bioequivalence or bioavailability of our product, which is formulated as extended-release formulation with release-controlling polymer. We are applying PBPK modeling and simulation to assess which dissolution test method is bio indicative of in vitro release method.

When we have this, we have to know what our boundaries or what our specification limits for

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that bio indicative in vitro test method are. So we are using physiologically-based pharmacokinetic modeling, as I explained previously, to establish a clinically relevant specification. That clinically relevant specification is a power tool to us during the qualitative management to ensure impact of the changes on bioequivalence, bioavailability, and to define boundaries for critical manufacturing attributes of controlled-release polymer.

Boundaries of the polymer are defined by the product's ability to meet clinically relevant specification when tested using bio indicative in vitro release method.

In summary, I would like to say at early product development stage, PBPK modeling is a proven tool to characterize reference-listed drug, facilitate product development, to define formulation strategy, and achieve bioequivalence.

During lifetime cycle management, quality risk management is ensured by implementing adequate control strategies. Adequate control strategies are both test method that is bio indicative and

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specification limits.

Control strategy established to ensure bioequivalence is developed based on PBPK modeling. PBPK modeling and simulation is powerful, but underused, according to our knowledge, a tool to facilitate development and ensure quality risk management for generic drug products.

These are the references that I used in preparation of this presentation and during my work, and thank you very much for your attention.

(Applause.)

DR. L. ZHAO: Thank you.

Next speaker, Dr. Gordon Amidon from Michigan.

Presentation – Gordon Amidon

DR. AMIDON: Thank you. It's a pleasure to be here and to see the increasing interest in mechanistic oral absorption, mass transport absorption, all of the physical chemistry and chemistry underlying oral drug absorption.

I'm going to make a couple of points, and I know I'm standing between you and lunch, so I'm

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going to try to finish on time. One is that we need to start spending more attention on what's been called bio indicative, biorelevant, I'm calling in vivo predictive dissolution, because that's the input to simulations. And without good input, you don't get good output.

That's going to be kind of the bottom line of my talk here, but I'll give you some history. I've been in this field so long that I will have to show some history.

(Laughter.)

DR. AMIDON: The starting point, and this is true for all routes of administration, it's just more complicated than oral, oral is complicated enough, is this, I'd say, is written in a rather simplistic manner, but it's a function of permeability and concentration at the absorbing site. If we have the same absorption -- we have to maybe define that word a little better -- everything else would be the same.

One of the complexities in our field is that new drug development and product development are

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sometimes connected, intimately connected, and we're trying to separate. I view this biopharmaceutics as about the product performance in vivo, and it's the patient, the patient gets a product, not a drug. They get a product.

It's permeability and solubility at the absorption site. Those are complicated factors. When I'm talking about oral products, and this is a conference about oral product simulation and it's, as I said, a real pleasure to see the increasing focus on mechanistic oral absorption.

First, I want to point out this conflation of term goes back more than 100 years. We often use the term "drug" when we're really talking about drug product, and they're different. This meeting is about product.

This confusion goes back all the way to 1906, but for us in the field, when we talk about drug, when we use the term drug, we know from context what you're talking about, but the average public probably doesn't.

The product and the drug are different.

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They get a drug product. We're talking about product science.

One thing I want to point out is fasted and fed state in the gastrointestinal tract are quite different in terms of their motility patterns, transit pattern, luminal environment patterns. So we have to pay attention to that. I'm talking mostly about fasted state, because that's usually the initial BE, bioequivalence, requirement, but they're very different motility patterns. We are in the process of studying those right now at the University of Michigan as part of the research project funded by the FDA.

I have to show some history here going back to some of the '80s, 1980s and '90s work that we did in some of the pharmacometrics, gastric emptying, influence of gastric emptying on plasma levels, just gastric emptying, and I'll show some of that in the presentation here.

Of course, the early 1980s models were kind of thought of in a pharmacokinetic sense, with boxes and arrows and first order rate constants,

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but, of course, we now know it's much more complicated than that. But that's what we did, but we could look at motility and variation in the '80s -- this is 30 years ago now -- and show that the plasma levels varied significantly with just gastric emptying, nothing else, just gastric emptying variation in the fasted state. We're pursuing, and I'll show another slide on that later, the bioequivalence implications.

Showing your typical gastric emptying curve is often not first order. Anywhere between 10 and 30 percent of the gastric emptying curves are not first order. So we have to begin to account for that in the probability distribution, if you will, in some type of a statistical evaluation of gastric emptying and how we actually, I'm going to say, model that, but using modeled in a mechanistic sense, in a real factual way, where we know the rates, the complexity, the probability distributions. We're in the process of trying to figure that out.

Some of the early transport models that we

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started in the mid '90s, working particularly with Lawrence Yu and developed that based on some compartmental analysis that's commonly used today, as you know, we're continuing to extend that, and we looked at a variety of tube models, chemical engineering type, chemical reactor modeling.

Then we used this residence time distribution from work done by S.S. Davis, Bob Davis and Nottingham for the small intestinal transit time, and we could fit that to a multi-compartment model. Then that's the CAT models and subsequent models that have been further developed by the simulation companies that we'll be talking later.

We continue to play around with that, too, because I think I'm a closet mathematician, not a very good one, but I like to play around with it, with continuous models.

I want to point out that the stomach is more complicated than we think and we'd like to think. There's at least four different compartments in the stomach, and our own studies confirm that. The

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stomach is still complicated, and so it's going to take more work to sort out what's going on in the stomach physiologically in terms of gastric emptying, fasted/fed state.

Fed state might be simpler, depending on the product, than the fasted state, but I want to show an example of what we did in the early '90s -- actually, middle '80s, published in 1990, on gastric emptying variation, just purely gastric emptying variation with a marker compound, non-absorbed compound. We measured the gastric emptying, and the curves here on the left show some of the different curves that we saw for gastric emptying and the gastric emptying rates. We quantitated that.

We've carried that through to today. We fast-forward to 2016, where we just published the paper where we included gastric emptying variation and the plasma level implications of that gastric emptying variation for a well-absorbed drug, BCS Class I and III compounds, actually. The work was done by a former graduate student, Arjang Talattof,

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who is here actually working the lights, I guess, now at the FDA, and a programming consultant colleague of mine, Judy Price. We published this a year ago.

I want to show we fit the gastric emptying curves to a 4H series. I'm not going to get into any of the details. It's in the paper. But then when we computed the bioequivalence implications -- and you don't have to look at the details here, but we computed the expected variation, expected when we simulated a bioequivalence trial.

What we did here is we simulated 5,000 or 10,000 -- I don't remember the number -- simulations to get the so-called population average, and then we simulated samples of 26. From that population, we took samples of 26, and what you can see here is the number of potential failures that would occur just due to gastric emptying rate, nothing to do with plasma or absorption, just gastric emptying.

There's significant variation in our in vivo

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bioequivalence studies just because of the variability in the gastrointestinal process. We'll continue to study that and determine how we can come up with better bioequivalent standards, better and, in some cases, simpler which is kind of a regulatory nirvana, cheaper and better.

We know that's true for BCS Class I drugs if they dissolve rapid enough. Now, can we extend that? That's what we're saying. How far can we push that science of in vitro bioequivalence?

What about GI inputs? This is going to be the point, and maybe I'll be interested in how the simulation presentations talk about this. But the key is going to be the input function. What is the concentration profile of drug along the gastrointestinal tract delivered from the product?

Because that absorption profile is what determines absorption, absorption rate and then subsequently, if the absorption rate of two products -- remember, we're talking about products with the same drug. We often forget that. We're not talking about bioavailability. We're talking

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about bioequivalence, and I think we're establishing a new bioequivalence science.

The difference is because we're talking about relative bioavailability, two products, same drug. The pharmacokinetics are the same, with some exceptions, but they're the same. So we're talking about a product effect, not a bioavailability effect. So we've got to talk about the input and look at that more carefully.

I'm going to give one example here that my brother Greg has done as we're working on this contract, and this is the USP dissolution test, on the left of the RLD, the reference-listed drug product. It dissolves at 10 minutes 100 percent. That's the USP method, but when we use a more -- I'm going to say more because this is not fully bio irrelevant, but when we use a bicarbonate buffer, 15 millimolar, we now know the buffer strength is much less. It takes 60 minutes to dissolve in a more biorelevant media.

Now, I'm not saying this is bio predictive yet, but it just shows you the huge difference of

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dissolution rate. I think we also have to develop a better semantics talking about dissolution. We often talk about dissolution, but there's so many variables that affect that. So we need to get more specific when we're talking about dissolution and particularly when we want it to be in vivo predictive of what's happening in vivo. We're making progress on that. I think that's a major step.

On the left, we have a USP dissolution apparatus. On the right, we have what we're calling an in vivo predictive dissolution apparatus, which was developed by a generic company, by one of my former students, because they did a BE study and failed. They wanted to know why. I mean, they should determine that before they do the study, right? So that's what we're trying to do.

Now, this is in no way going to be a quality control device, but it can help you set your quality control specifications. It can be used for product development and for understanding how your

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product and the critical product and manufacturing variables.

So think this what I'm calling IPD in vivo predicted dissolution method, which we're extending basically from the ASD that has been developed and published in the literature and we basically added another beaker to their device and call it GIS, gastrointestinal simulator. That's one of the projects we're working on, because we want to develop -- you need an experimental input function for your simulation. We need something that we think is relevant in vivo. We need the evidence to show that, and that's what we're doing now.

Some ways where we can extend biowaivers based on IPD and subsequent quality control specification, can we slow dissolution for BCS Class I, even Class III? I saw that question earlier today. Likewise, the quantitative versus qualitative differences that we can allow for BCS Class III and, of course, BCS Class II and IV and I'll talk about them more in a minute, but I'm going to propose subclasses, acid, base, neutral,

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because we know that makes all the difference in the world to product performance, the in vivo product performance.

I'm proposing that we at least start talking now not only about BCS class, but BCS subclass. Principally, I propose for II and IV, but it could also be relevant for I and III, particularly III where permeability and solubility, particularly permeability, can vary along the intestine because the pKa if it's in the physiologic range. We need a subclassification at least as the next step in talking about in setting dissolution standards, even IPD, but also quality control standards.

I'm proposing that we use acid, base, neutral, because if you're a development scientist, you not only want to know that, you want to know everything else related to your product, but that's one of the things you want to know.

This is just a very preliminary step. Actually, when we first tried to publish this paper, which was published about a year ago, it was rejected, and I'm the editor of the journal. But

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it's because dissolution specifications are so darn hard. Dissolution specifications, you've got to think, it's almost product dependent. Certainly, it's subclass dependent, but we're making progress at some general recommendations about dissolution methodology that would be predictive for subclasses. We're still working on that, and I'm working closely with Greg Amidon to do that and develop that as part of this FDA research grant effort.

I'm going to conclude with my key point. The key to predicting in vivo is predicting the input concentration profile of the drug at the absorbing site in the GI tract. It's also true in other routes, too, but it's more complicated because of local effects there. But at least for the gastrointestinal tract, we want to develop a methodology that we think will reflect the in vivo dissolution conditions and the variable conditions of the gastrointestinal tract.

That's where I think we're going to go today. That's what we're trying to develop today,

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and I think this conference -- and I think one of the things that the mechanistic simulation approaches that we're talking about here are really bringing those fundamental mechanistic questions to the forefront. We're beginning to ask what those questions are and determine methods for determining what are the key crucial variable controlling product performance for clinical performance to the patients.

Finally, I just want to say, of course, this is a picture from my colleague, Gus Rasagna, on my real BCS, you're either in heaven or purgatory, depending on what you have for BCS class and, I would say, now subclass. But I think that what this initiative which was actually started in the early '90s, 20 years ago, by FDA-funded research at Michigan and at the University of Uppsala to develop the permeability database that subsequently became used for the biowaiver BCS guidance, which has evolved today.

I think there's a draft guidance, now nearly in final form, revising the guidance, which is very

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satisfying to me to see the scientific -- seeing the uptake of the scientific approach by the FDA, and then, of course, there's many considerations around that, especially at the FDA where you've got public policy, as well as science considerations that impact how the agency has to operate.

It's been a real pleasure. I think I actually finished ahead of time, because I think I talked faster than I usually do.

(Laughter.)

DR. AMIDON: I want to thank you again for the opportunity to present here. Thank you.

(Applause.)

DR. L. ZHAO: Thank you, Dr. Amidon.

With this, I want to thank again all the speakers in the morning. Thank you to download your thoughts, your guiding principles in the PBPK field, and to make the meeting exciting and valuable.

So we are looking forward for this afternoon, and we have another three presentations, followed by a panel discussion.

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Thank you, Dr. Amidon, for giving us extra time.

I think everybody, in BE terms, are in the fasting condition. So we'll have a one-hour break, and please be mindful about the time, to be coming back in time. We will reconvene at 12:30. Thank you. See you soon.

(Whereupon, at 11:22 a.m., a luncheon recess was taken.)

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A F T E R N O O N S E S S I O N
(12:30 p.m.)
DR. L. ZHAO: Hello, everyone. I think the majority of people probably -- the key people are here. More people may come in once the meeting is in session.
I will introduce the next speaker, Dr. Masoud Jamei, a vice president from R&D, Simcyp, the first presenter from software developers.
Presentation – Masoud Jamei
DR. JAMEI: Thank you very much for the introduction and, of course, for the opportunity to be here.
I have considered three main topics for our discussions in terms of the opportunity and the challenges. The first one is the IVIVE-linked PBPK absorption modeling. The second one is physiologically-based or mechanistic IVIVC, and then bioequivalence and PBPK modeling.
I'm trying to do some parallels between the success that we have in the PBPK in other areas and

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see what we can do to speed up the success or the development of PBPK in the absorption side.
From Simcyp, in 2012, we put this paper in NCPT in why PBPK has been successful and so rapidly had developed over the last 10 or 15 years. And we believe that the main reason is the connection between in vitro and in vivo extrapolation. That has been the missing link that PBPK modeling over the last 70 years hasn't been picked up. But when the link between in vitro and in vivo is established, then the development becomes much faster.
We believe that without IVIVE, the PBPK, the ability to be able to predict or extrapolate will become very limited. I'll show you why. What is the reasoning behind that one? One element of PBPK is that always the data in the model, they have been combined, and if you put PBPK in this system in a pharmacology context and we separate the parameters, we get lots of benefits out of it.
You will see, we have done it this one, for other areas, and we would like to do the same for

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the absorption side. So we divide the data in three different categories: what we call the system data or the species that you're -- the drug or drug product. There are some physiological, anatomical, or biological information, but they are nothing to do with the drug. They are specific to individuals, or even if you are giving that to rat or monkey or dog, they are specific to that species.
Some other parameters are intrinsic to the drug. Intrinsic solubility, it has nothing to do with the varieties. Intrinsic solubility is the same, or intrinsic permeability, if we can get that number, or some of these problems, they are specific to the drug itself. Then we have a clinical trial, how many people you are putting in, what is the age and all the rest of the thing.
If we can combine these using IVIVE and PBPK, then we can look at the variability. You can look at the prediction and lots of other things. What is the advantage is the advantages we will be able to develop a generic model that then you can

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change only the system parameter and then you can extrapolate from healthy volunteers to different population. A cirrhotic patient, if you know what is changing in terms of physiology, that is relevant to absorption, then we will be able to predict in cirrhotic patient; so beginning one drug and then we saw the changes from one population to another population.
We can give rosuvastatin to obese people or we can give it to Chinese or Japanese or elderly people. So you can see you are changing one part of the system so the other part will stay the same. And the same with the pediatric. Hopefully, you will be able to do the same with drug product, as well. We have done it so far for drug. Now, we want to do it and be able to do it for drug products.
It is a big challenge, and you need to mechanistically understand many different things. So one of the models that can be used is the other model that we have, and there are various processes that happen, and we have to account for those. If

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you look at the color, the purple color is the density changing, and in this case, it shows the distribution of three or four in the GI tract. We have to have this type of information to be able to provide in the model.

One thing that is very important when we are building individual, because we are dealing with virtual individuals, we can do one-color sampling, which is very common. If you open any paper, they say, "Oh, we'll be using one-color sampling."

If you want to create a subject using one-color sampling, this may happen. You are putting different size of individual, so the individual will not be a proper individual. But you have to do correlated sampling.

If you do correlated, then you keep the correlation between the different physiological or anatomical or even biological aspects. It is the same if you change the subject and then you can do that, but moving from the left to the right is a huge amount of work.

I think in the morning we got a good mention

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that gastric emptying by its own can affect the plasma concentration. When we were developing this seven years ago, we had that question. If the pH in the stomach in some subject is 2, is the duodenum pH going to be affected or not? If somebody's stomach pH is 5, is it going to affect the duodenum pH or not? I understand for motility.

At the time and still, we haven't found the evidence, which is fine, so we can independently generate this, but if there is any evidence that they are correlated, then we have to incorporate those.

So we have to do this. Another question when we're developing the pediatric absorption model was that is gastric emptying related to the age. Is it changing by age? So we had the post doc. She collected six months or nine months of -- to collect all the data, and the data didn't show any relationship between gastric emptying and age. But there was a good correlation between the type of food and gastric emptying.

This type of information is very important

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if you want to generate realistic mechanistic modeling, but they are taking time. Another thing which is very important is the amount and the way that the fluid dynamic is changing in the GI tract, because everything, as we know, is going to be affected as part of that one.

If you look at the MRI data, these data are coming from Werner Weitschies in Germany using MRI. He generated the data, and if you look after one hour, they gave the individual 150 milliliters of water, after one hour, on median, you have 85 milliliters of water, which is very low, very low compared to what sometimes we are using.

We were a bit skeptical, and then you see the data that is coming out of, again, Gordon Amidon's group and Marciani's collaboration, you see that the variability is very high. So we will see that the variability is there.

Another thing is that after one hour, the mean value is almost the same. This is the reality that we have, and you don't have the static fluid; it is changing by time. So it goes up and comes

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down, and if we ignore this, you will not know how many of the parameters can be affected.

We know, in reality, there is a fluid dynamic that happens, and considering that one allows us to consider many other factors, like variability, how much of the water they have taken, the dynamic of the dilution and viscosity, because we want to know what is the viscosity and how it is changing to be able to look at the effect of formulation, if you are adding any specific excipient, how are you going to be affected. Precipitation and supersaturation, they are going to be affected by the level of fluid. These are very important for us to know.

These two slides are from Professor Yamashita from Japan. He presented these last year. They are very interesting. He did a survey of 500 people and how much water they are drinking with a tablet. If you see, the mean value is 80, and we are doing most of the control study by 250 milliliters. This is the reality, and you see there can be some disconnect between what we do in

clinic and what people are doing at home.

There are direct effects. Again, he checked for three different drugs, and he saw the impact. The Cmax is different, the AUC is different, as well as the Tmax, they are changing.

It is not only dissolution. Permeability has almost the same story. These are the data that I think Gordon mentioned the lucky gut at experiments. You see that there are good level of variability from 10-fold, 11-fold, fivefold and fourfold, that they are happening for permeability of different drugs.

There are models that we can get some idea from as to some of the drug. If you look at the metoprolol, we are able to come up with some idea of the prediction mechanistically to be able to get some idea of the variability of dose.

Another aspect, as I said, is that IVIVE side. One thing that we are doing at the moment, not everybody, but the most common practice is that we do some experiment in a different shape, so different pH, different RPM, and then we get those

data and we directly plug them into a PBPK model.

This is good, but it's not good enough. We see what we are missing from that one. If, rather than doing that one, we put many of these data together and we model them, mechanistically we model them, then we can separate whatever is related to the in vitro and what is related to the API or even formulation.

The next step would be formulation. We are separating the system data from drug data, and then we can put them back. If we don't have to put them back, then they allow us to extrapolate. You don't need to do so many different experiments to be able to get to the point that you want. If you extract the in vitro intrinsic parameter, you will be able to do it.

We have been doing this one for metabolism, for transfer, for induction, for inhibition. We know how to do those, and now our idea is to bring it and do it for the absorption side. Is it working or not? As part of the OrBiTo that Filippos is going to explain, we have been working

with different groups. So there are some data. We are running different experiments, and then we combine all those data and together, we fit them and then we input them into the PBPK model.

Then when you combine these, there are some data that Christos Reppas from Athens University, they have measured the duodenal concentration, and then when you put it in the model, you see that it is possible -- at least in this case, we were lucky for ketoconazole to get a close prediction or simulation of what is happening. It is a close relationship between what is observed and what is predicted.

Moving to the IVIVE side, again, what we are doing, usually, we go from plasma concentration. We directly go from the deconvoluted, but we can deconvolute only the absorption profile or most of the time absorption profile. If you have the first-pass effect or you have got a different location for the permeability, when you want to link in vitro and in vivo, then you will come up with some complex IVIVC, because we are linking the

dissolution with absorption or absorption with absorption. That is complex.

If you use the PBPK model that we have, then we can separate each of these processes, because we have information for those. We can separate first-pass effect. Metabolism, we can remove it. We can remove the permeability side, and we get only the dissolution part and then make the connection.

In many cases, it comes up with the simpler IVIVC that allows us to extrapolate and change the formulation, which is an advantage. This is one case that we have been working on this one. In this case, we are using metoprolol data, and this specific graph, we use the PBPK. You see that for three different formulations, we managed to get a solid line for IVIVC, but any other method that we try to get, it was always biased. It was always biased.

The method that was published in 2002, in 1998, and, again, we repeated, the bias is there, which is obvious, because the absorption is not

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necessarily the same as dissolution. But if you use PBPK, it allows us to go back and get the dissolution profile.

This is very good work that Marilyn and Bipin did to do PBPK IVIVC and look at various scenarios, what happens. So it's a huge amount of work even to this one, and it should come out very soon. They use a PBPK model for IVIVC, the same metoprolol data, but we had individual data. That was the good thing. The individual data was available.

Then they tried various scenarios to look at the consequence of choosing different options on the outcome. Like if you use a waiver function, how you choose the alpha and beta and which you fit, it has some consequences for you. If you are using different fitting module or if they are using different rating algorithm, then it's going to have a different impact. If you are looking considering fitting gastric emptying or if you are not considering that, again, it can have some impact as with the importance of the population variability

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and how you incorporate the dose.

At the end, the good thing is when you are using PBPK IVIVC, then you can extrapolate. So in this case, we are looking at metoprolol, and most of the individuals in the study, they were extensive metabolizers of 2D6. Then you can change it to a poor metabolizer and see if the formulation is changed, how it's going to affect other population that they haven't been in your study.

Moving to the bioequivalence work, some have a similar approach. They're first starting to develop a good model for the drug without going to any complexities, and using the clinical observations to assess the performance. So whatever, again, we learn from the PBPK in other areas, that's when we develop a model, we have to qualify it. We have to see if it can predict the cases that it hasn't been used to fit the model or to improve the model.

When you do, then you can start to develop a physiologically-based IVIVC module. The next step is that we have to have some idea about inter-

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location variability, and this is one of the challenges that we don't have much of a grip on this type of information.

Assuming we have those, then we can conduct the bioequivalent, and we can determine the solution limited specification or safest space design. All of these can come out of this approach.

This is what my colleague, Shriram, did for tramadol. He went through systematic work, and then what you see on the left, he did lots of different simulations based on the Weibull function that he fitted for in vivo dissolution. Then he came up with a range that's in vitro dissolution is acceptable, and it's keeping the IVIVC valid.

One thing that we have to always remember is that there are -- we have to be realistic. There are things that we don't know what is happening. There are some data that we don't know them, so we have to fit some parts, but when we are doing a bottoms-up approach, if it's not working and if you are using the clinical studies, then we have to be

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careful when we go for the next step forward extrapolation.

When we are fitting or we are assuming parameter, those assumptions and those fitted parameters we are using, we have to declare them, because sometimes we may make four or five or six different assumptions, but we forget to declare them. It can cause confusion.

Sometimes we are going beyond the range that the model can predict, and you get disappointing results. And then you blame the model. However, the model, I think Filippos in the morning said, modeling is not wrong. The assumptions that they use and then afterward we try to extrapolate, they may not be correct.

Of course, sensitivity analysis, so in the morning, I think John showed the value of sensitivity analysis. As I said, we agree that there are parameters that they are not certain. So we can do sensitivity analysis.

Sensitivity analysis is a very good tool to assess the impact of these uncertainties or the

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fitted parameters or unknown even type of phenomenon to see what is the range, what is the scope of under-prediction or over-prediction. Sensitivity analysis is a very important factor.

This is the work, the joint work with Nikunjkumar and Jennifer Dressman from University of Goethe and Cristofoletti from a Brazilian agency that they are in the process of submitting this one. They tried posaconazole and ketoconazle, and they wanted to see bioequivalence assessment. They want to see what situation is the most striking or differentiated between the two cases.

So they run various simulations. If you look at the top, you have ketoconazle with the fasted considering only bulk pH for the dissolution or the next to that one, they're using more common multi-climate pH that improved the predictions. Then you go for fasted and fed for the posaconazole or if you come down, for ketoconazole, if you have PPI, what happens? If you have fed for ketoconazle or PPI on posaconazole, what happens?

They investigated various scenarios all in

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the population and considering the variabilities. This is, I think, a good outcome out of that study there.

Now, you want to see when you are doing this virtual bioequivalence which conditions are going to be the most reflective of each scenario or which one is the worst case scenario that you want to do. So at the top, you have ketoconazle, you have fed, fasted-plus soft drinks and you have fasted-plus water or achlorhydria.

We have those information, so we can model them. You see that in the fasted state for ketoconazle plus water, it was almost borderline, but for achlorhydria, it was very different. You see for posaconazole, in the case of achlorhydria, again, it was different. So these two cases for both drugs are very different, but for posaconazole, the fed state was the worst part.

You expect them, because they are very similar, to be the same, but even small changes in the properties can have an impact on which bioequivalence is going to be most differentiated,

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why the -- I think for the test, as well as the reference data, there were two different particle sizes.

This is another study from the same group. This one is putting the question of bioequivalence a bit higher, because most of the time, we are looking at the PK side. In this case, they said, "Okay, let me get the PD side, what happens," because the ultimate aim is that you want to get an effect.

For the case of ibuprofen immediate release, at the top, it is for pediatric, and at the bottom, the graph is for adults. If you look at the left side, you see almost linearity for the two cases, but if you look at the left, for one endpoint, which is the pain relief, you get almost, again, bioequivalence, if you want to call it that. But if you go to the temperature reduction, you see that there is a significant difference.

While in PK we may get bioequivalence, in PD, we may not or we may. Dependent on what you are looking at, there can be a difference between

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those.

Looking at the extrapolation, because at the very beginning, I said that if we go for the system separations of the data and drug, we will be able to extrapolate. These are some cases. Again, the first one coming from Cristofoletti, they looked at many from the simulation side at what are the impacts going to be in the children.

In the second one, coming from Roche colleague, that they investigated the PBPK and the impact on pediatric. And the bottom one is, Trevor [ph], my colleague with AstraZeneca, they did. They developed an IVIVC model in adults, and they use it for extended-release module for pediatric.

When we say pediatric, they are adolescents. They're not really 4 years old or 3 or 2 years old. So they are from 10 or 11 years up to 15 years, but it works.

The same for the food effect, so food effect, this morning it was mentioned. They are cases that we have been able to predict. Even if

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you look at the middle one that, again, Nikunj did for nifedipine, even formulation, when we manage bottom-up to predict the food effect, which was very encouraging. Maybe it was lucky that in nifedipine it worked for that case or dose formulation, it was a good prediction.

Overall, there are lots of opportunities to use PBPK and for mechanistic absorption, but at the same time, there are lots of challenges and maybe we should be aware of the challenges.

Extrapolation to population, we are using it for other cases, it will be great if we can do it in the absorption side. Better understanding of formulation performance in vivo. Determining the product clinical qualities. Prediction of food effect, of course, is very desirable. PBPK IVIVC that potentially can expand the application of the IVIVC and virtual bioequivalence, as well.

There are lots of gaps in our knowledge about digestive systems, different parameters, and, hopefully, the work that Gordon is doing and FDA support will allow to fill in some of the gaps.

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It is very important that we spend time on the education side. This is a new area, so everybody will have to learn how to deal with those, and, of course, colonic absorption.

I would like to thank all the people who contributed to the work from Simcyp's side, as well as many of the regulatory, as well as the academic colleagues that provided those data. I would like to thank them and, of course, the OrBiTo that is providing a forum for advancing the absorption. Thank you.

(Applause.)

DR. L. ZHAO: Thank you, Dr. Jamei.

The next speaker to have us fight against a food coma probably is Dr. Viera Lukacova from SimulationsPlus.

Presentation – Viera Lukacova

DR. LUKACOVA: Thank you, Liang.

As you might have noticed, my slide deck had quite a few slides in there, but fortunately, all the speakers ahead of me already described half of those slides, so we'll be moving through quite

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quickly.

I won't be spending too much time on this initial slide. Jasmina did a very nice job describing the opportunities for including the modeling and simulation in the generic drug development starting from identifying your products, identifying the initial formulation all the way up to use of modeling and simulation during the scale-up process.

What I will be focusing a little bit on is some outlines of where modeling and simulation again can help in the formulation design, describe a little bit more details on the mechanistic simulation models and some of the case examples on IVIVC's equivalence trials, food effects, and also describe an example of a biowaiver study that we were involved in.

Again, I think it was the first presentation by John Duan, who already highlighted some of these utilities of simulation in the formulation development, starting from helping with the development of the dissolution method to help you

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get a method, which is more biorelevant, which is better discriminative, which gives you better information about the possible in vivo performance of your formulation through the design of the formulation; evaluating what are the possibilities or what you need to have, what kind of release profile you need to achieve bioequivalence, as well as establish the dissolution specifications, evaluate what deviations from the brand product you can afford to still have a bioequivalent product.

This article I'm pointing out was coming out from the OGD group back in 2011, where they nicely highlighted the process of the mechanistic absorption model development to be used in the formulation design, starting from collecting the information about your compound, collecting information about the drug and formulation through finding information about the PK of the compound to build the mechanistic absorption and pharmacokinetic model.

This model needs to be validated, of course, before you use it for your formulation development.

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So we would be using additional datasets to validate the model and make sure that it's capturing the assumptions that are relevant for your formulation. And finally, the validated model can be used to do the sensitivity analysis, to do deconvolution, to figure out your target profile for your formulation, to simulate different dosing regimens, to finally conducting the virtual bioequivalence studies to evaluate the probability of success when you go with your formulation into the clinic.

GastroPlus helps you to follow that type of paradigm, where, just like with the other mechanistic absorption and PBPK models, you are linking the physicochemical properties and formulation properties of your product and your drug with the physiology itself. Starting with the information about your compound-specific physical properties and information about the formulation about the drug product, you can start predicting your regional absorption, where the drug actually may be getting absorbed in the different regions of

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the intestine.

Filling in additional information on the pharmacokinetic description, which is very important since your evaluation is based on plasma concentration, so having correct PK description is important in having an accurate evaluation of your formulation performance. So once you get your PK filled in, you can start using this model to create deconvolution to come up with your desired in vivo dissolution profile in order to match the formulation performance.

This would help you to get your first formulation, and once you get the first formulation, the initial pilot study, you can use the data from the initial pilot study to possibly create an IVIVC, maybe come up with a better in vitro dissolution test, which gives you better correlation, and, finally, evaluate the bioequivalence trials or possibility of bioequivalence for your final formulations.

Within GastroPlus, we are using the ACAT model, which is the next generation of the CAT,

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compartmental absorption transit, model. It's split into nine different compartments. The intestine is split into nine different compartments, each of them defined by its own properties, by its own pH, volume of fluid, transit times and so on, which allow us to describe the ever-changing environment in the intestine going from stomach, through the stomach, intestine, all the way down to colon.

The drug and all of these arrows that you are seeing through the figure are representing different processes that are happening in the intestine, and I'll be describing those arrows in the next slide. But once the drug makes it through the enterocytes and gets collected by the portal vein, the portal vein carries it through the liver into systemic circulation. Here, you have options to describe the disposition via the simpler compartmental model or a full PBPK model.

To look a little bit more closely on what all of these individual little arrows mean, the processes that we are accounting for are, of

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course, transit through the intestine. This could be transit of the drug from the previous regions of the intestine or the dose if we are talking about the stomach. As the drug is moving into a specific region of the intestine with its own local pH, specific concentration of the bile salts, the actual amount of fluid that's available for dissolution at a given place and time, the drug can undergo dissolution.

In many cases, especially as we are talking about basic compounds, you might see a significant precipitation. You might have chemical degradation. We all know about compounds, which are not stable except in pHs; again, something that needs to be accounted for.

The dissolved drug can get absorbed, and again, here, you might need to account for different processes for the absorption, passive diffusion, transporter effects, uptakes, efflux transporters and so on.

In the enterocytes, you may have metabolism, and, finally, the drug may be getting into portal

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vein through, again, passive or carrier-mediated processes. The rest of the compound is moving to the next region of the intestine, and the success of how much drug actually makes it into systemic circulation is really just a matter of different rates of these processes and how these processes are competing for the drug and which of these processes is most favorable.

Even if you are dealing with the generic product development, you make assumptions that the rates of the processes affecting your API will stay constant, but, of course, the rate for your dissolution will have to compete with these rates. You still need to make sure that you are properly accounting for what is happening with the API so that any small differences in that input function, in how quickly your drug is dissolving, can be properly accommodated and predicted by the model.

One of the topics that actually wasn't covered much yet were the saturable processes happening in the enterocytes, and this is, again, something that may be very important, especially if

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you are trying to describe or look at the bioequivalence across different doses or in case of transporters if you are dealing with a narrow absorption window and so on.

These are just some of examples showing nonlinearity in these processes. This is the classic example of midazolam, which undergoes saturable intestinal metabolism. And as you are going from doses from 7.5 up to 30 milligrams, the model is able to account for the saturation of the metabolism and increased bioavailability due to increased fraction escaping the intestinal metabolism.

Similarly, for the transporters, you may need to account for these effects. These examples showing experimental data published for valacyclovir for different dose levels showing nonlinearity in the overall absorption and, again, the mechanistic model utilizing the in vitro Km values for the interaction with the transporters was able to account for the nonlinearity in the absorption.

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When it comes to mechanistic absorption and mechanistic models, it's a possibility to expand these to other administration routes, as long as we can describe the other route of administration by similar models as we were working with the intestine. It really comes down to knowing the physiology.

Right now, the models are probably more in the stages of helping us figure out what we don't know about these routes yet, but as we go, hopefully, they'll make it to the process with a similar predictability with the oral absorption routes.

One of the applications for the mechanistic absorption models, of course, is doing the in vitro-in vivo correlations, where, again, with the mechanistic models, what we are trying to do is to deconvolute the in vivo dissolution. Masoud already did a very nice job describing this, so this is just a different version of the point that he was trying to get across, that as the drug is being dissolved, there are other processes that

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govern the absorption of the compound.

In the passive diffusion transporter effects, you can have metabolism in the intestine, the rest of the drug hitting portal vein. The portal vein will carry it through the liver, where you can have additional metabolism, and, finally, getting the drug into systemic circulation.

The advantage of the mechanistic absorption models in this deconvolution is that it's really trying to deconvolute the dissolution in the intestine. All of the other processes are handled by the model parameters themselves. It's just for a very quick comparison of what you are deconvoluting with the more traditional methods, where everything is lumped into one rate of appearing in systemic circulation.

This is one example of publication from 2012 where the authors were evaluating the more traditional method with the mechanistic IVIVC, with the mechanistic deconvolution, and their conclusions were with the internal validation, the models did perform in a similar way. But when it

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comes to external validation, the GastroPlus model had a greater prediction accuracy and will be wider applicability domain.

Another article published for Class II compounds, again, utilizing GastroPlus model, where, again, for risperidone, they were able to build a nice mechanistic IVIVC properly predicting the Cmax, as well as AUC for the test formulation.

For virtual bioequivalence trials, again, it's very nice to show your mean simulation, how they are matching between the test and the referenced product, but eventually, it comes down to running a trial in the clinic.

The virtual bioequivalence trials are a nice tool to help you evaluate or predict the probability of success, help you predict how close you might be when you account not only for differences between formulations, but account also for variability in the subjects, inter-subject variability, as well as possible variability in the formulation itself, how close you might be with the bioequivalence there.

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Again, it is also a good tool to help you with your dissolution specifications so you can evaluate your range of dissolution profiles within the bioequivalence trial accounting for the population, as well.

It's, again, just an example of looking not only at mean profiles and comparing the average CP time profiles, but accounting for the variability in the predicted CP time profiles.

Food effect is one of the very big aspects for mechanistic simulations and, to a degree, you can actually anticipate an expected food effect just based on the BCS classification. But running the full simulations for mechanistic absorption models could help you take this predictability a little bit further.

With the domain changes that you are looking at, the standard ones, of course, come down to the stomach volume, stomach pH between fasted/fed state, concentrations of the bile salt in the intestine as the gallbladder empties in response to the meal and so on.

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There are also differences that you may need to account for not only between fasted and fed state, but also for different types of meals. The high calorie meals versus low fat meals versus high fat meal versus standard meal may also have different parameters. Some of those expected ones would be gastric emptying, stomach volumes. Possibly with high fat meals, you may need to account for additional aid in the dissolution of your compound, in addition to the bile salt concentrations.

This is, again, one of the examples from the literature where the authors used, again, GastroPlus to do the food effect, where they actually tried to use the simulation to design out a food effect, but they built a model that was able to account for the food effect for their formulations. They started using this model once it was validated to explore whether there is a range of formulation parameters that would help them to overcome the observed food effect.

They've done a sensitivity analysis on the

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dose and particle radius. It was immediate-release formulation, so particle size was the driving force for the dissolution rate, and came out with a conclusion that a particle size reduction might help them to mitigate the food effect, even though as you look at food particle size, they would have to have -- I think they came down to about 50 nanometers maximum, so probably not a very practical solution. But it did show a possible sort of a blueprint for utilizing the simulations for these kinds of purposes.

There are a variety of other publications looking at other applications of mechanistic simulations of GastroPlus model within the pharmaceutical development either from industry or even from the FDA scientists.

Finally, one case study for the successful biowaiver case study where the virtual bioequivalence was done. This was actually a case where the sponsor -- and actually, since this was done, it was actually presented by J&J also at the AAPS last year, where they went through a

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manufacturing change which resulted in different particle size distributions for the new lot.

They wanted to look at the mechanistic simulation to see if they can avoid having to do a bridging study by assessing the effects of particle size on the in vivo and show that the difference was not significant enough to actually cause any difference in the exposure.

Of course, the modeling went through the standard phases of creating the absorption and PBPK model that would be accounting for the clinical data available already and was validated and then used the sensitivity analysis and virtual trial simulations to evaluate the sensitivity to particle size and predict the bioequivalence probability.

This is showing the particle sizes for the original formulations in the table on the left versus the new formulations in the new table on the right. As you will see, the d50 values were actually very similar. The main change was in narrower and better controlled formulation with the new engineered particles.

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So the first part was, of course, the model development and model validation, and here it's showing how the model was able to nicely account for different doses spanning the entire range of their clinical doses from 50 to 300 milligrams. These were all done with actually different lots of the initial non-engineered particles, and when the simulation used the particle size for the specific lot that was used in each of these doses, it was nicely accounting for pharmacokinetics.

The sensitivity analysis showed that the particle size starts affecting the fraction absorbed once the diameter changes or increases above, I think, about 30 or 50 microns. The Cmax, as well, would start getting affected, as well as the Tmax.

Finally, the virtual bioequivalence simulations were performed with several different lots of the original non-engineered particles and compared to the new lot of the particles with the new particle size distribution. Again, the mean radius was well in line with many of the previous

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ones. It shows the distribution was a bit narrower.

The bioequivalence trial shows that for -- this is a summary for 250 virtual subjects, and it is showing a big higher Cmax when the new formulation was compared to one of the original lots, but it was well bioequivalent with all of the other original lots of the formulation of the API.

In summary, this simulation was not standing on its own. It was part of the full submission package. There was other supporting material, as well, but it did help to make the point that the new formulation or the new manufacturing process did not create enough difference to affect the PK. The sponsor's biowaiver application was approved.

To sum this up, the modeling and simulation can help you gain insights into absorption of your compound or of the drug that you are trying to model; can help you guide formulation, design; can help you to evaluate probability of success once you go into the clinic by running the virtual bioequivalence trials, hopefully speeding up the

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drug development process so you have fewer failed trials before you find the one that's actually working on. I think that's all.

(Applause.)

DR. L. ZHAO: Thank you, Dr. Lukacova, for your excellent talk.

Next speaker, Dr. Thomas Eissing from Bayer Technology.

Presentation – Thomas Eissing

DR. EISSING: Thanks a lot. First of all, I would like to thank the organizers for inviting me to this interesting workshop. It's a pleasure to, last but not least, talk as a PBPK software provider.

I will keep the introduction on PBPK modeling short. I think Masoud and Viera already introduced the general concepts also on oral absorption and dissolution modeling. I will then provide examples and, hopefully, at the end, also provide a glimpse of how that looks like.

One point, in PK-Sim, similar to GastroPlus and Simcyp, we also have a large database of

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relevant physiological information in order to parameterize physiologically-based models that describe the distribution, metabolization and elimination, and, of course, also the absorption, which we'll focus on later.

At one point, I again would like to pick up -- I think Masoud already focused on that -- that in PBPK, you have a clear distinction between properties which characterize the organism and properties that characterize the drug, and I think, therefore, PBPK provides the ideal framework in order to bring these things together and deconvolute information.

Of course, this framework also allows you to learn from one drug about, for example, physiology or pathophysiology how certain enzyme expressions or other parameters are changed and translate that use of knowledge you gained for one drug for another drug, which is the basis, for example, to extrapolate to specific populations or, of course, also in a similar conceptual framework, to novel formulations.

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PK-Sim is embedded into a platform. It's fully compatible with our second software, MoBi, which allows you to really add and change the models we provide as like a standup model. It provides a very flexible environment, and we also have interfaces to both MATLAB and R so you can do a customized coding around there.

Yes, all this should add to points we consider for our daily work are very important, and that is flexibility and reproducibility, transparency. I hope I will be able to focus on that during my talk in the following.

Pur PBPK modeling can, of course, be used to address many questions during preclinical and clinical development. From my perspective, the most important is probably to really challenge and test our understanding of a drug or drug product and also to evaluate the consistency of the different data that is out there. Of course, if you have an incomplete understanding, it's not always a problem, per se, but at least it's always good to be at least aware of that.

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Regarding oral absorption and dissolution modeling, we have a compartmental approach to this. So this is kind of very closely related to the ACAT model which Viera just introduced. The GI tract is basically divided into different subcompartments both in the lumen and on the mucosal side, and there you describe how the drug is released or dissolved and from there, systemic circulation.

General features, there is a separation between liberation, transit and absorption. You can account for food effects, including caloric content, and enterohepatic cycling you can consider. Through the mucosal blood flow, you have a physiological way of absorbing your drug into the systemic circulation. Of course, you can include transporters and GI metabolism, as well as hepatic first-pass.

Regarding dissolution, we offer a predefined thing so as to find out are there viable first order. Also, just a table reading or particle dissolution, so all, again, very similar to what was already presented.

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In our software, it's also rather easy to implement your own equations or at least you are very flexible in doing that to any kind of complexity.

Regarding passive absorption, we validated our absorption model or we developed it based on a collection of a 111 passively absorbed drugs, and we could get a nice correlation between the intestinal permeability based on molecular weight and a measure of lipophilicity, an affinity in our lower case.

Coming to examples, if we integrate dissolution data, basically, here, we show eight different examples, where, on the left hand, we have the dissolution data where we used the Weibull function to fit that and then predicted in vivo PK. That worked overall pretty well.

Two exceptions can be understood from taking a closer look. One was diclofenac, and here, we do an individual fit and really consider the variability in the gastric emptying time, so 0.1 already that is highly variable. If you really

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take a look using such a model, you can understand that inter-individual differences can provide different Tmax, which then, on the population level, also lead to a decreased Cmax, where you basically get a broader shoulder. Also, a nice example for how in a PBPK setting, you can understand observations which might otherwise be more difficult to understand.

Similar for furosemide, we used just one Weibull function, and I didn't consider for pH differences in the stomach and the intestine in the first chart. If we basically take that into account, we can also get a good description or reasonable prediction of the data.

What we also looked at was cilostazol kinetics. This was done in dogs. Here, there was basically a published case where people published in vitro dissolution data and also in vivo-absorption data. And they concluded, yes, there's relation between particle size, but we can't really quantitatively relate that based on the data alone.

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If we fit the particle size distribution, which they published in the data, just with simple distribution functions and input that into our software and anchor that for one particle size distribution, we basically can describe all three in a very reasonable way.

So, yes, the rate and extent of absorption based on particle size is well predicted here and can be nicely described and understood. This is really where mechanistic modeling helps you to get an IVIVC, which can also increase your understanding of what's going on.

Another drug, just as a quick example what you can all do, here we looked at different doses, and our model can nicely describe that with increasing doses, our fraction absorbed decreases. We have a solubility limitation here. We looked at food effects, fasted/fed conditions. Different doses can be nicely described with one consistent model. I guess that's an important point about PBPK, that you want to get to a consistent description and, from one setting to another, just want to change

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those parameters which are also changed in the experimental setting.

For this substance, that results in an absorption site study done with [indiscernible]. So really the drug is in the GI tract released at the different sites, which can trigger externally. Also, there, you can see that regional absorption can be nicely described and understood in a PBPK setting.

For this drug, we also looked at the GITS formulation, so where you basically have this tablet with a defined pore, which releases substance, in this case, particles at a basically zero rate for a longer time. We could combine the zero order rate release from the GITS formulation with the particle dissolution function and, again, nicely describe here, show population simulations where we had inter-individual variability contained in our database.

Again, you can nicely describe that, and if you have done all this for one drug, you, of course, have quite high confidence that you have really understood how you can model that drug in the physiological, in the in vivo setting. That, of

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course, allows you to explore the design space if you go for extended-release formulations, if you go for different particle size. All kinds of questions can be addressed from there on.

Another example is looking at food, at drug interactions. Here, my colleague, Christian Wagner from the University of Frankfurt, back then looked at nifedipine dissolution and, also, the influence of grapefruit juice, which always prolongs gastric emptying, as well as reduces GI CYP3A4 activity. That could also be nicely described by the model, as you can see on the right-hand side, where the comparison with and without grapefruit juice inclusion is shown.

This study looked at different in vitro tests, and there, again, a very important point is that at least we in our model always assumed that the dissolution function we get represents kind of the in vivo setting. For that, of course, at least biorelevant media should be used, and if you have that, of course, you can also use such a setting to really explore the design space.

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Another example which our colleagues in Florida did from Stephan Schmidt's group, they looked at the oral absorption in pre-term neonates. We had a pre-term neonate model for the distribution of drugs, and because the physiological changes going on in pre-terms are very complex and not enough data out there, it's difficult to inform that really mechanistically.

They chose a simplified approach to just develop equations, which describe that, and then of course, in principle, you are free to combine this kind of equation, which was with a mechanistic PBPK type distribution model. This is just an example meant to show you what is technically possible. Of course, here, this example, because of the challenging data situation, there's still a fair bit of uncertainty left. Still, I think it's interesting to explore with this technology what is possible.

Another example where we really stretch what is possible is population PBPK modeling is where we really try to merge the concepts of PBPK modeling

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with traditional pop PBPK approaches. So we are working on hierarchical Bayesian statistical models to be combined with our PBPK model, which really allows us then to, for example, assemble from the knowledge databases you have included in the PBPK software and then use, for example, Markov Chain Monte Carlo methods to really both fit individuals, as well as population data at the same time and thereby really derive and further develop your knowledge.

You go from a prior distribution based on additional PK data. You get additional information out of that. You really deconvolute your data in a clear and clean setting. This is definitely still challenging. Also, on the conceptual side, still needs to be somewhat done, and also on the implementation side, of course, PBPK models are numerically more demanding than if you have a two- or three-compartmental model. But yes, this looks really promising, and our first example here is where we applied this method to a crossover study so where both IV and PO data were available and

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where then you can really deconvolute parameters based on the PK data, so absorption parameters based on the PK data.

This concept, again, because we have separation between the properties of the organism and the drug and formulation, we can really learn in a systematic and more or less unbiased way mathematically and further develop our knowledge base.

I mentioned our focus is on flexibility. Most of the examples I showed were, when we did them, not yet easily possible in PK-Sim. Of course, as we do new things, we also try to provide them in a user friendly, but the first things we usually do in the first versions, we also develop in MoBi ourselves. Yes, this really is a very flexible way of proceeding.

This is a screenshot from PK-Sim. You can see you have full access to all the parameters. You see the different building blocks, how it's separated. We have a history. Every modeling step you do, every parameter change is really locked.

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You can roll back, but, of course, it also helps you to really go back, what did I do, to be transparent. You can compare different things. We have a working journal integrated so you can do additional documentation, comments on your own.

You can then send models you built in PK-Sim over to MoBi and then customize them. There's a button there. You can just press it, and then you get -- although the software is the same look and feel, you still have a different view.

In MoBi, you take more the modeling view. You really see how the different things are interlinked and work together. You have access to -- so here, you basically have an overview on the whole body scale, how the different organs are connected. You can zoom into the substructure of the organs, and if you look, for example, into the duodenal mucosa in the intercellular space -- in this case in this example, we have a metabolization process entered, and you see the formula, how this is done.

You can not only change the values, but also

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the formula at additional reactions, whatever you want. In fact, we also use this environment to really bottom-up, build up, for example, our systems pharmacology, mechanistic PD models which you can link or not to PBPK models.

In summary, I showed examples how to model different formulations and the oral absorption in our software environment in order to better understand the PK. Yes, in conclusion, I believe that our software environment has a focus on both flexibility and transparency, especially together with MoBi, and leaves a lot of room to explore new ideas one may have. That's it. Thanks.

(Applause.)

DR. L. ZHAO: Thank you, Dr. Eissing.

The last presenter is supposed to be an OrBiTo representative, Dr. Xavier Pepin. He cannot be available, so Dr. Filippos Kesisoglou will present instead.

Presentation – Filippos Kesisoglou

DR. KESISOGLOU: Thank you.

It's my pleasure to present on behalf of the

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OrBiTo team. Unfortunately, Xavier couldn't make it. I cannot take credit for all of the slides. He made a lot of them.

Throughout the day, we discussed the models and their application, as well as we heard the need for fundamental research to improve some of the input. OrBiTo has intended to do exactly that.

OrBiTo stands for oral biopharmaceutics tools. I will spend most of my talk giving you some background of the project, how it's organized and what is the research that is taking place and how that feeds into some of the topics we're discussing today. At the end, I will cover a little bit more specifically the integration of dissolution in PBPK models, which is directly related to what we discussed this morning and earlier this afternoon.

The OrBiTo vision statement is a single sentence shown on the slide: To transform our ability to accurately predict the in vivo performance of oral drug products across all stages of drug development. That's a pretty lofty goal,

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and throughout the day, based on the discussions, I think it's becoming apparent that's a multidisciplinary question. It's not easy for a single person or a single scientific principle to provide an answer to this.

So given the multidisciplinary nature, the partnership, collaboration and data sharing is the first part that's highlighted in the OrBiTo mission statement. Through this data sharing that involves both from academia and industry, OrBiTo intends to develop both fundamental knowledge, which is important in our developing these models, but also deliver on the practical aspects, deliver innovative tools that can be used to accurately predict product performance. That includes both the in vitro, as well as the in silico approaches that can be integrated with the endpoint, improving how we do drug development.

One step further, meeting of the objectives, a lot of that is reflective of the mission statement. First, the idea is to define the critical physicochemical formulations and

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physiological factors that determine drug product performance, then develop the experimental and theoretical models that we can use to predict in vivo performance, and then, finally, again, bridging the multidisciplinary and collaborative effort, to leverage industrial knowledge and academic knowledge to bring our experience together to validate these models and be in a better position to inform future drug development.

How is exactly the program structured? The program started in 2012, in October of 2012. It's a five-year program, so we're about a year and a half from completion. It's funded by the European Innovative Medicine Initiative.

The consortium comprises 13 pharmaceutical companies, listed on the slides, and 14 academic centers, universities throughout Europe or subject matter expert companies, such as some of the software companies that are represented here today.

How is the whole program structured? I will go from the bottom to the top of the slide. There are four work packages that are looking at these

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major categories of tools and fundamental knowledge being developed: physicochemical tools, in vitro tools, in vivo tools, and in silico models.

For each work package, there's a co-lead from the industry and a co-lead from the academia. These work packages do the scientific work, the data generation for the project.

There are a couple of governance committees. The executive committee comprises the work package leads, as well as key contributors from academic institutions or industry. It's responsible for the project leadership on an operational level, and the steering committee where all the consortium participants have a member there is responsible for the annual reviews and also facilitating resource management.

You can see throughout these different levels of governance, collaboration between academia and the industry is a key component to driving success of this project.

In addition, all of the fundamental goals of OrBiTo is the science of doing drug development.

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It's not disconnected from the regulatory environment.

There is a regulatory stakeholder board where there are representatives from all the major regulatory agencies, from several representatives from the EMA, from the U.S. FDA and from the NIHS in Japan that we will occasionally, periodically, provide an update to them to make sure that what we do in OrBiTo remains connected to the regulatory environment, because at the end, we need the drug approved. In order to influence drug approvals, we need to see how what we developed during the project can be leveraged also in the regulatory space.

I will move now into describing the different work packages. Again, I want to emphasize although there are four work packages and they are called in vitro, in silico, in vivo, and physicochemical tools, in reality, there is significant crosstalk between these work packages, and there is data information flowing from one to the other to really enable an integrated

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development of these tools.

Work Package 1, physicochemical tools, in vitro tools, in vivo tools, and in silico models, there is a flow of information both into informing the in silico models, as well as informing the tools to eventually allow us to develop what we call predictive models and predictive experimental methods.

Starting with Work Package 1, Work Package 1 is the first building block in understanding the drug product. It deals with understanding the active pharmaceutical ingredient. The objective of the Work Package 1 is to provide a range of in vitro physicochemical tools or in silico models that can be used to assess the key API properties and how those may impact in vivo performance. That may include excipient interactions.

In early drug development, especially before we get into the humans, a lot of times, the API supply is limited. We need to deal with all the drug product, and we need to deal with small-scale experiments. What Work Package 1 is trying to

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deliver is tools that at those early stages can be used to develop early drug development decision trees, expanding on the drug classification or the drug developability classification system to facilitate those early decisions before we start going into more classical drug product development.

Then again, obviously, API is important for the models. It informs both in vitro tools. We need to understand the API first before we start adding dissolution of the drug product, as well as key physicochemical parameters for the PBPK modeling that were mentioned throughout the talks today.

The second work package deals with in vitro tools, mostly dissolution systems. There are a lot of dissolution systems. Everyone probably in each company has their favorite tool to use for drug product performance, but we heard from Dr. Amidon that in vitro, the predictive dissolution system, there are transfer systems, systems with an absorptive compartment like this cell monolayer, biphasic systems or even much more public systems.

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This is the TNO system that's intended to mimic the entire gastrointestinal tract.

How do we go about using them in drug development? Which one is the best to use for its purpose? The intent is not to declare the best system, but basically to declare -- to understand what information we get out of each one of them. Again, eventually everything feeds to building predictive models.

The goal of Work Package 2 is to optimize these tools to have maximum predictability for oral absorption. Ideally, develop a decision tree to select the most appropriate in vitro tools and provide the data for the PBPK modeling. I'll come back to the dissolution incorporation in a few slides.

Each work package has published in the last one to two years a review of the current status of the science in the field. I just happened to highlight here the one from the Work Package 2 that summarizes the current state of the art on in vitro tools for prediction of in vivo performance, but if

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you go to the European Journal of Pharmaceutical Sciences, you'll find similar review articles for all the other work packages.

Work Package 3 deals with the in vivo tools. You can think of Work Package 3 as the one that generates most of the fundamental knowledge on the system that we're trying to model. The idea is by understanding the in vivo system and the physiology, we can then start improving our tools. We can start better understanding the in vivo to in vivo animal to human translation or in vitro-in vivo correlations.

Going into a little bit more detail, the gastrointestinal system, we already heard today from Dr. Amidon about motility and fluid volumes. That's also studied under the OrBiTo. Intestinal fluids and composition, how can those translate to dissolution media? Clearly, there is a lot of variability in each one subject of the intestinal composition, and OrBiTo is intending to characterize the variability and help us develop better predictive dissolution media.

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Finally, a lot of the stuff we discussed today and most of the examples we showed were around predicting PK out of a dissolution input or a particle size input. However, what we are really trying to predict as far as the dosage form goes is how does that behave in the gastrointestinal tract.

However, it's not an easy measurement to measure what actually happens to a tablet or a capsule upon ingestion. We rely on PK because it is something we can measure, but in reality, direct behavior of a dosage form is what you see in the gastrointestinal lumen.

In OrBiTo, there are specific studies being conducted where upon dosing of different dosage forms, there is some link of the gastrointestinal fluids to better understand how in vivo dissolution is actually taking place. Hopefully, by having this data, we can then drive even better predictive models on the in vivo dissolution part.

Finally, Work Package 4 is the in silico tools, is the integration of all the knowledge and all the data to drive a predictive mathematical

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model. Several efforts have been started earlier on with a database creation. As I mentioned, an important part of this exercise was data sharing and knowledge sharing across the partners of the consortium. It did take a significant amount of work out of the Work Package 4 team to put all this data together in a database to be able to be used for those projections.

I know it's hard even within a single company to get information together to drive decisions. You can imagine how difficult it is to do this against 13 pharmaceutical companies and 14 universities to gather all the information.

Based on these databases, the next step was an initial gap analysis. You can think about this as a blinded bottom-up PK projection analysis. What can we basically see if people are giving given datasets, how can they actually drive PK models.

This effort has been completed, and now the team is in the steps of evaluating the needs for improvements into the models and identifying the

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gaps in our knowledge of the model that we should be implementing moving forward.

Some brief highlights of progress to date, I mentioned the reviews already. I will encourage everyone who's interested, these are summaries of the state-of-the-art in each of these topics.

The database, so you can see this is top of the database, 90 compounds, almost 600 formulations, 500 studies, 25,000 data points. It's a lot of information that we can tap in to understand better how we're doing drug development and how we're developing these models.

For the in vivo studies, again, these are not trivial to develop, but standardized protocols have been developed for sampling of gastrointestinal fluids. Many of the studies have been completed, and some of them are already published. Compositions of human intestinal fluids was also recently published, and some of the studies on the in vivo characterization, such as non-absorbable markers to define the transit time, novel MRI methods to measure the water content,

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have been completed and also recently published.

I will move to my last part of the presentation, which is the integration of dissolution profiles in the PBPK models. The challenge is that this beaker appears a little bit simpler than the gastrointestinal tract. We need to be able to translate dissolution data that we generate in vitro to the in vivo situation.

As I mentioned, in vivo dissolution is very challenging to determine. We infer what it looks like based on some mathematical models, but we actually almost never measure the in vivo dissolution.

Why are we doing that? First of all, for the majority of the formulated projects, when we are not dosing API partner solution, which we typically don't do other than some early clinical studies, the dissolution modeling based on the API properties doesn't agree with the observed dissolution data. We need to figure one way to incorporate formulation information into the model.

Second, as I mentioned, there are a lot of

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different dissolution methods, a lot of different media. We need to be able to use the data regardless of the source to drive a model. Can we use modeling to eliminate some of these system parameters for the dissolution interest? Finally, I think we discussed it already quite well, the facilitation of development of bio predictive dissolution methods.

Again, multiple dissolution systems, this is not even half of what's being probably used in practice. How does each one of these data points go into informing a model?

I think I stole this slide from Masoud. Here, you saw it already. The idea here is, again, we typically talk about deconvolution when we do IVIVCs, and we're trying to deconvolute the oral profile against the IV profile. In this case, we're talking about the deconvolution of the in vitro data where we separate the system data, meaning the dissolution apparatus, the media, the rotational speeds from the API and the formulation.

Once we have that, we convolute that back

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into the in vivo system for a PBPK projection. So why that might be important, let me go through a case study, and through this case study, we'll also highlight some of the questions that I asked earlier in the morning model selection and how do we validate models.

This is a compound. It's neutral, for the most part, of the physiological pH range. So the media is -- it's a simple system where with the factor here that's being used. There are different API lots with different particle sizes from this API.

Using the standard Noyes-Whitney equation that's, again, available in all of the commercially available software, we can simulate the dissolution profiles based on the API particle size distribution. We can compare, at least for some of them -- I'm not showing all of them here -- the dissolution simulation, which is on the left-hand side, against the experimental data, on the right-hand side, and we see that that model works which is expected. These models were published, I think,

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more than 100 years ago, and for the most part, they work as intended for API powder. So this looks pretty good.

If you look at most of the papers in the literature in the PBPK modeling, they use the particle size distribution-based model to do a projection. This was done here for the case of this exercise. We take the different particle size dissolution as projected from the model. You plug them in your favorite PBPK software, and you get a projection of the different sizes.

Although all the projections are clearly so small an impact on what the dissolution shows, which is not unusual, but you start seeing some differences. As you move to the animal API, Cmax is delayed for a few hours. It's down by 20, 30 percent. One could say that maybe these are milled material, and I might have an issue with PK.

If someone didn't do anything else and they used the API PSD model, they might conclude, well, I need to mill my compound to I get PK exposure.

Let's look now at how the dissolution of the

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compound looks once it's formulated in the final product. So what we see when you finally formulate the compound is that smaller particles actually dissolve relatively fast as formulated product. It's slightly slower than what the API particle size model suggests, but because you make granule, it does take a little bit longer for it to dissolve compared to the net API of a couple of microns.

What we also see is that the larger particles actually, once you put in the formulation, either break down due to the compression or if you are doing a well regulated product, part of it might dissolve, in which case you would get faster dissolution profile from the product than what your API model suggests.

If someone was to do a projection based on this -- and I'm not showing this since everything is on top of each other -- they would see no PK impact, and then from a practical standpoint, this means one can actually have more relaxed API requirements as far as the particle size control goes.

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I think that also talks to about understanding what model we should use for one question. If someone were to use the API particle size model without generating the dissolution data and they ran a PK study, they might conclude that the model was wrong, because you would have projected differences while there is no difference in vivo. But in reality, you need to generate all these data points and the dissolution to really understand what the true impact of particle size on the PK response.

I showed this slide, so I'm not going to go through this in detail again. What I'm really thinking is that incorporation of dissolution into PBPK models can really drive what I term bio predictive methods that will really ensure future product quality.

With that, I will acknowledge Xavier, Mark and Masoud for their help with the slides and the many, many OrBiTo contributors that have generated a lot of data. I think in the next year and a half, you're going to see even more of the data

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coming out in publications that will really help with driving this field moving forward.

Thank you for your attention.

(Applause.)

DR. L. ZHAO: Thank you again to all the speakers, and I congratulate everyone that we still have full stroke after lunch.

After another break for 20 minutes, we will start at 2:30 sharp. We will start another exciting session. Especially for the panel members, we like challenging, controversial questions, so we are looking forward to the discussion.

(Whereupon, at 2:06 p.m., a recess was taken.)

Panel Discussion

DR. L. ZHAO: We're going to shoot up the first question, and once you're being seated, you can start to think about it, especially for the panel members.

At 4:00, we have a half-hour session opening to the floor to all the audience. If you have

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comments or questions, feel free to participate in that session. Given the time is very short, we probably can only accommodate three, four questions.

Then for the panel members, first of all, I want to thank again all the speakers to deliver such an outstanding talk, in my opinion. We've already received several comments from the audience and they're highly positive. They like the talk, the content, the technical side of the presentations.

It's also a very rare and valuable event for FDA OGD to have all the top experts in the field to get together to brainstorm, to share ideas.

Dr. Robert Lionberger also mentioned earlier that, hey, we'd like to see the panel discussion to be controversial, challenging. So we are not here just trying to be friends, even though we are in the same field being colleagues, but for the impact, we need to be critical.

We'll go with the first question. For the available list of areas, sub-areas, which ones do

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we have the highest confidence in using physiologically-based absorption modeling for oral dosage forms?

We do not have a list. It's kind of a super long list, but I trust your knowledge, your expertise, and your brain. You probably have an even longer list.

With that, I will open the floor to the panel members. Since the talk of the meeting is transcribed, so I would like to ask you to identify yourself one more time when you start having your input. Thank you.

DR. LIONBERGER: I'll start. This is Rob Lionberger. One thing I saw from the presentations, just to encourage people to start talking about this, is that there are a bunch of examples that looked at particle size and dissolution specifications for basically immediate-release dosage forms. That seemed to me an area where there were actual case examples, and, hopefully, someone will agree with me.

DR. AMIDON: The only comment I would make

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there, Rob, is that the particle size you put it, or is it the particle size that comes out and is wetted in the intestine?

DR. LIONBERGER: I would suspect and I would appreciate, industry colleagues, that probably you're putting in your drug substance particle size into these models in most cases; is that correct?

DR. KESISOGLOU: I think it depends on the dosage form. This is Filippos Kesisoglou from Merck.

If we have dissolution data that suggests that the dosage form behaves like particle size, then I think we can put it directly in the model. If our dissolution data suggests that we need additional processes, I think it's important for us to also model that.

Overall, I would agree that the models for particle size are appropriate for use.

I guess just back to the original question, in my view, I would classify some areas that we have more or less confidence as a blanket statement. In my experience, it comes down to the

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specific compound and formulation. If you understand how the drug product is behaving, can you build a reasonable model with reasonable assumptions and reasonable input to describe the behavior?

In my view, if you can achieve that, I would consider that model having confidence in doing a projection. So that would be my view to the original question.

DR. ZHANG: This is Xinyuan Zhang from DQMM. I think we use particle size all the time, because it's an available input parameter in the model, and oftentimes when we see the prediction is off, we would rather adjust solubility than particle size, because we consider particle sizes that are reported are relatively reliable. We have more rationale to adjust solubility especially for low solubility drug products where we thought the in vitro measurement might not be in vivo relevant. That was my experience.

DR. LIONBERGER: One thing I noticed, and I think we've seen this and Susie's mentioned we've

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seen this, is that sometimes there's ambiguity about the solubility as an input parameter into these models, where sometimes we see experimental reported data that varies and sometimes we are uncertain about what the real in vivo solubility is.

I appreciate maybe comments from some of the software companies here, what do you people think in terms of the solubility inputs, since that especially for some of these, say, immediate-release particle size applications, the solubility input that you assume might be a driver of some of the results that you would see.

DR. EISSING: Yes. I would agree that it's often difficult to one-to-one, it takes a solubility. We at least rarely do total ab initio predictions. So usually, we start modeling when we have some in vivo data available in order to anchor that, and, of course, obviously, if you start, for example, with the water solubility, that may be really way off and you can't describe your PK data with that. If you go to more biorelevant media, in

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my situation, that gets better, but still I would always allow to fine tune that parameter based on PK data.

Once you have anchored that for a substance, of course, you would expect that it's then a measure of solubility is the same as if you change particle size, for example, if the other ingredients are the same.

DR. LUKACOVA: Viera Lukacova. Solubility is a simple word, but a very complex environment in the intestine, right? So it comes down to either having in vitro data or a model that can translate across dose environments. You need to have well characterized both the effect of pH on your solubility, as well as the effect of bile salt on the solubility so the models can properly translate into how the changing bile salt concentrations, as well as how the changing pH would be affecting or would be changing the solubility in different regions of the intestine.

DR. DUAN: Based on our limited experience, as I showed in the presentation, the in vivo

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exposures do have -- it's affected by the particle size, but the solubility plays a role over there.

As I showed in the slides, the reviewer did a sensitivity analysis. The sensitivity analysis showed at the lower solubility the relationship between the particle size and the Cmax is very sensitive. When the particle size becomes larger, the Cmax becomes smaller, but when the solubility becomes high, the sensitivity is not critical.

That's the interpretation of that data that shows that's correlated, particle size and the solubility effect is correlated. I didn't explain that figure in detail. If you look at the figure, very bottom right, the particle size of the radius of precipitate, that's differentiated by the shape of the symbol and do affect the relationship between the particle size and the Cmax in the condition of high solubility and the lower permeability, at that corner. That's the relationship.

That probably tells us the relationship is interplay. Something gets together might be

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different from one by one, just examining that way.

Thank you.

DR. LIONBERGER: I want to raise the point that in a lot of the biopharmaceutic modeling that we're doing related to product development, we often have some human data available. Earlier in drug discovery, you may be trying to predict what's going to happen in a first-in-human study, but by the time you get to biopharmaceutic questions, even the one that John answers for new drugs or certainly for generic drugs, like generic drugs, there's always human data available for us to get our model into the right ballpark.

As we're talking about biopharmaceutics, I would want people to be thinking that that's the assumption, that you're working on a case where you have some human data on some formulation. You may be looking at asking a question about a different formulation or a different patient population, but you have some human data that you can check your assumptions about your model against at the time.

In that context, I think one of the -- and I

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would like some comment on this in terms of the particle size question. When you do a parameter sensitivity analysis and you find out particle size isn't important, that can be potentially very helpful to our regulatory review to say, no, your particle size specification is acceptable. This is not so that I have to predict what the boundary of success or failure is, but that I found that the space is flat.

I would like some comment on thinking about that and how that's something that you would say, "Well, I have high confidence." So I propose that as a case where I have very high confidence, that if I've seen the simulation model generally predict some human data and then a parameter sensitivity analysis showing me that particle size is not sensitive around that space, that that would be an area where I would say I have high confidence that I would even -- that it would be input into some sort of a regulatory decision about a particle size specification.

DR. CONNOR: One of the things that

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impresses me about virtually everything that we're talking about, but particle size is a good example, is that even the questions that first came up when Rob brought this up is we say particle size. Those who aren't true experts in the area just think it's very simple. You measure it, you measure it at the right time, but it can change throughout the life of the product and even within the patient, which is a point that was brought up before.

Even the things that we think are very, very simple and can be simply plugged into an appropriate model actually have unexpected complexities. The question that I think is true with all modeling is how far do you have to drill down into the details to make your model work effectively, because I think modeling in general is -- or one impression of modeling is to make things complicated and then weed them out when they don't have sensitivity or when it isn't necessary to know that, well, occasionally, this forms an agglomerate, but maybe agglomerates don't matter, or it changes in the patient, but still that maybe

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doesn't matter very much either for this particular drug.

Everything on this list and that we can think of is much more complicated than it seems at first glance, but how complex do we need to make it for modeling purposes and for predictability? And it changes. John's example of, well, we have particle size and we have solubility and they have this relationship, they're not independent, and perhaps if the solubility went up, maybe your cutoff for particle size where it really matters also changes in relationship.

It's not like just one A to B relationship. It's in flux and correlated. Bringing those, is it necessary to bring that into your model or not? One of the things that is one of the questions for modeling is general is how deep do we need to go into the details to really make the thing work.

DR. AMIDON: I want to comment on Dale. I think one thing you forget also is what I call a dose number, because we have a common dose, and as we change particle size, we're changing particle

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size density, which can affect wetting and agglomeration and even the solid properties. I do think you're right. You have to be careful, and it has to be consistent with other measurements and particularly, your dissolution, I think good dissolution.

I agree, and we are looking at that. I think that's an unappreciated dose number and particle density needs some investigation. But I think if we have a good in vitro predictive dissolution methodology, predicting in vivo, that would answer the question, right? But we're still getting there.

DR. L. ZHAO: I just want to follow up the in vitro biorelevance prediction method. I think it's kind of a -- for most of the products still kind of a dream. So we need the panel or the scientists in the field to further contribute, aside from particle size distribution.

Based on my understanding, also, I kind of consulted with several experts in the field. The areas we are comfortable using PBPK, include

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drug-drug interaction, drug as enzyme substrate, drug as enzyme protease inhibitor, transporter-based absorption.

Then the confidence level may decrease a little bit with you predict PK for specific populations, then followed by effective factors like pregnancy. I think that's the tough one. Then obesity, also a tough one. Disease states is a tough one, but it's very relevant to the field.

Then food effect, I don't know if this is really beneficial, if the panel members can make your comment, when would you trust the predictions for food effect, under what scenarios you would trust the predictions for food effect.

The other is pH effect, local, like we've irreverently changed theological parameters such as pH, that would lead change to solubility. It sounds like solubility is the key parameter to consider. Those are the comments, I think, given the limit of time, so if the experts here can make some input to us, really, please.

DR. AMIDON: I'll comment on one. The first

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is pH. It's not just pH. It's actually buffer capacity. Buffer capacity in vivo was very low. Our intestine is mostly CO2, and the bicarbonate buffer capacity is measured in Leuven about average to millimole per liter per pH unit.

We measured actually lower than that, but we don't have enough data. It's very low USP, is 50 millimole and nothing to do with in vivo. They call it simulated intestinal fluid. Why do we let them get away with that? But anyway. So, yes, that's just one factor, I would say. One factor is something like buffer capacity, as well as pH.

DR. NOVAKOVIC: Hi. Jasmina speaking. I am from generic pharmaceutical company, and talking about pH, I was thinking about pH from a different angle. I was thinking about changes of the stomach environmental pH, and I find predictions pretty reliable in terms of being to identify biostudies outliers based on the changes in the stomach pH, as well as drug-drug interactions, because those changes might be due to drug-drug interactions.

In my experience, it is reliable in the case

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that the drug is low soluble in acidic environment, and, therefore, due to lack of the solubility, because of the changes of the pH due to, for example, administration of some PPI inhibitor of any other drug that might modify environmental pH. Bioequivalence for that particular patient or volunteer is questioned, and bimodally, we were able to provide that it was due to the change of the pH in the gastric environment.

DR. SAO: I just have a quick comment, too, and I know Rob and Liang, you guys want some controversy. So I'm going to give you a noncontroversial response.

I guess what we have -- I don't want to say we have the highest confidence in a particular approach when it comes to the modeling aspect, but what I can say at least from the biopharm discipline, what we've seen so far is out of the 15 and a subset of those are the ones that we found successful, so to speak, a good portion of them, the ask starts out with particle size, right?

So naturally, I think -- and the way the

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conversations are going here, again, I don't know. I don't want to call the highest confidence, but I think our experience is growing when it comes to particle size and PBPK modeling. I just wanted to put that out there to digest on.

DR. P. ZHAO: This is Ping Zhao from pharmacometrics, Office of Clinical Pharmacology, FDA. Responding to the question on the screen and, also, I will try to allude to the points raised by Liang regarding the food effect prediction, as well as pH modulating prediction.

I'm looking at the agenda. I would say when we talk about confidence, we have to further define it into one I call a prediction confidence, meaning that whether we are able to predict in the absence of a study.

In another sense, whether this can lead into high impact decision, for example, biowaiver. The other one, which has, I'm told, a confidence, rather, the entire day that all these applicable sub-bullets, I would say, in terms of exploration, explaining the mechanisms, PBPK modeling definitely

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has its role and is an indispensable role other approaches cannot replace just because of the ability to integrate all kinds of information.

Going back to the other aspect of the confidence, which we, at clinical pharmacology, define as predictive performance, as Liang mentioned in his introduction slide, where we have highest confidence with DDI, lower confidence with special population, and even lower with other application, I think the angle we're looking at is using mechanistic model, at what stage you can say this study definitely, I can just do a prediction. I don't need to do an in vivo clinical pharmacology study or maybe a BE study to confirm the knowledge and give us some regulatory decision-making power.

I think looking through all the bullet points, especially focusing on this food effect prediction, at least throughout the discussion today, I am not fully convinced that we're there. I think there is still quite some mileage in the coming years with the help of all the stakeholders to move the field forward.

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Being negative, but I think to give it another level of negativity is a challenge toward a conclusion from two talks, one from the Merck colleague and one from Susie with respect to our confidence in predicting oral drug absorption for BCSI.

Playing the devil's advocate, for the Merck example, are we able to just use BCS to just make the decision for that food effect example? Because you have a very good solubility, you're going to have a -- the model just isn't sensitive to respond to any critical changes.

But having said all that, I really enjoyed the whole session and I learned a lot, and special applause to Susie and John for the nice update on FDA examples.

DR. SAO: I guess I had an add-on comment to that, as well. It's a good point that Ping made that at least from a regulatory perspective, we talk a lot about clinical relevance and clinical relevant specs, but in a lot of cases, an approach such as PBPK modeling, it's very intensive and

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resource oriented. It may not be necessary for every product, right? Only high-risk products we're talking about.

In the sense if it's a BCS Class I, Class III, arguably, this approach may not be necessary, right? BCS in itself is clinically relevant, so to speak. I just wanted to add on to that. I think it's a very valid point.

DR. AMIDON: Can I comment again?

DR. L. ZHAO: Please.

DR. AMIDON: I would say that the particle size importance will depend on BCS subclass whether it's an acid, a base, depending on the pKa, as well, and whether it's non-ionizable in the physiologic arena. So the data has to be a package.

DR. KESISOGLOU: I guess to the original question, some of the areas you mentioned, if you look at literature, there are published examples of successful applications for both food effect, PPIs, or specific compound. So we cannot discount. These examples are out there and are at least past

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the peer review process. People were convinced that the models were valid.

I will agree that at the end, it comes down to the totality of your data, does your in vitro data, your modeling and your clinical data support what question you're trying to answer. Even from a simple question as a particle size, the model will always tell you the smaller the particle size, the better for dissolution, but I've worked on products where actually the smaller the particle size, the slower the dissolution, because it gradually became more dense. You have to have your in vitro and your model together to drive a decision.

I also agree we shouldn't be doing the modeling for the sake of doing modeling. BCSI, I agree fully that the modeling is insensitive to solubility. I guess all the model is testing is gastric emptying time, for the most part. That is definitely the PK profile. If it was a BCS Class II compound, I think the question becomes a little bit more complicated.

Sometimes the model just helps with

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communication of data. Even if it's an obvious answer, just having the model to explain to the formulation group, explain to my clinical colleagues some of these concepts, I think it helps with just that sometimes, and I think we just need to keep in mind that utility of the model, too.

DR. P. ZHAO: Just to add on to that, don't get me wrong, that's proposing something that I have been defending for the past eight years at FDA. I'm a big fan of PBPK. I'm just saying like for this particular question relevant to oral absorption, if you ask me whether I would be convinced that we are ready to predict food effect based on at least my reading of the literature and our limited experience of clin-pharm review of maybe two or three submissions in NDA, just because of the number of parameters that may impact the final prediction, I just feel for other BCS class compounds right now, there is still some ways to go.

DR. EISSING: I would believe an example like food effect for most examples, I would believe

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for PBPK model is able to predict it if you account for the changes in the relevant parameters, but there might be additional effects which none of the PBPK models, I guess, consider so far.

For example, if, in rare cases, a drug would bind to the food or something like that, I don't see an easy way how you can predict that beforehand. I guess at least for the time being, I kind of also see that you at least need to confirm what you predict to a certain extent. Overall, I think, food effect based on the examples I know of, usually you predict it well, but how can you exclude that it's not doing something additional which you don't consider in your model and which is rare which you can't really predict? I guess that's the challenge.

DR. AMIDON: Can I comment again? I think we should be careful about whether we're talking about bioavailability or bioequivalence. I think they're separate questions. Bioavailability is more complicated because it's got metabolism consideration. It's elimination, the BDDCS

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considerations.

Bioequivalence, we're talking about the same drug, different product, and so I think the importance of particle size is potentially important depending on whether it's physical properties, but for both. But I do think the questions are somewhat different, and we need to define the bioequivalence science questions more carefully to not confuse them with the bioavailability questions, which are systemic availability, which is our goal.

No one doubts that that's our goal, but it's a little bit different between bioequivalence and bioavailability.

DR. L. ZHAO: Given the time, we are not leaving question number 1 yet, but if we proceed to question number 2, it's kind of intertwined. Number 2, I'll read out.

Do we have enough experience to confidently apply the current PBPK absorption models to support the following regulatory applications?

So we don't have to really go through the

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list, but in your opinion. I think this is a very relevant question to industry, to FDA. It's kind of a key component of this workshop. From this regard, we really want to listen to the experts' view, which area is kind of mature enough for either generic drugs or new drugs, we can apply PBPK absorption model to sometimes waive the study or sometimes to shorten the product development timeline, sometimes to just increase FDA reviewers' confidence to trust in the result.

DR. MEHTA: Just to add to everybody else's questions, on the list here, one thing I didn't see being addressed by any of the presenters and I'm very much interested in knowing more about it is this proposition that widening the BCS III bio criteria, proposing longer dissolution times and/or different excipients. If we have good data to shed light on that, I'd be very much interested in knowing.

DR. AMIDON: I didn't quite understand the question.

DR. MEHTA: One of the bullet points is that

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PBPK can be used to support a request to widen BCS Class III biowaiver criteria, meaning recommending longer dissolution time than what we are asking for right now, very rapid dissolution instead of that longer dissolution, and, even more important, excipient aspects, different excipients.

DR. AMIDON: Well, I'll comment. I think it depends on -- you probably have to look at A, B, C, acid, base or neutral. I don't think you could -- I think we need to define the BCS classes into subclasses and look at the effect of an acid or a base, because I think of the pH dependence, the low permeability, the permeation variability along the intestine, the pH variability. I don't think we can really answer that today.

I don't think we have enough case honestly to say we can relax the dissolution specification, but I think we should investigate it. Maybe we do for a II-C compound or something, but we need to -- you, of course, the FDA, has presumably bioequivalence data.

I think, theoretically, it could be relaxed,

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but I'm not sure we have a good basis for saying it could be relaxed today.

DR. MEHTA: I just wanted to hear that, and that question being posed that I thought there was information to that effect, and if there was, then that's what I wanted to know. So I appreciate your clarification.

DR. ZHANG: I want to respond to that question. Internally, we have a couple of research studies ongoing. We want to evaluate all the formulation factors for all the BCS III drug products and see how different they are.

Externally, we have a couple of ongoing studies to study excipients' impact on transporters and to what level, and we also internally conducted simulation studies to study hypothetically if we vary the transporters' activity, but the abundance, those type of parameters, how that is going to impact drug absorption for specific BCS III compound.

So I think all these components should come together. We combine all the knowledge from

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different aspects and combine them together. So maybe at the end, we can make a list of the excipients that we don't have to worry about, a list of drug products that have high risks.

I agree that we are not there yet, but there is some room that we can improve.

DR. MEHTA. Sure we can.

DR. LIONBERGER: Like all the BCS guidance, especially when you get to Class III, it can cover a drug that's 84 percent absorbed or a drug that's 1 percent absorbed. I probably think that there's completely different risk profiles in those two different situations for some of the factors.

If you're going to set general criteria that applies to all of them, you have to be very conservative, but as you get into specific cases, then I think there may be some aspects where modeling and simulation can help understand what the risks are, map out what the risks are at least for a developer to say I want to pursue this or just to understand the studies that you've done.

DR. MEHTA: I agree with you on that, sure.

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DR. AMIDON: I want to comment, Rob. Absolutely, when we drafted the first BCS guidance in the mid '90s, 20 years ago, it was purposefully discussed and debated to be very conservative, to be safe. Yes, I think the BCS Class III, I agree with you completely, between 1 percent absorbed and 90 -- it's 85 or 80 percent, 84, there's a huge difference, yes, huge range.

One thing I wanted to comment about, to Susie's comment, is that I think the question for bioavailability versus the question for bioequivalence is a little bit different with regard to what's happening in the transporters' pH, whatever the conditions in the GI tract, because if it's a bioequivalence question, then if the dissolution in vivo is the same, it will be the same.

Bioavailability is a little more complicated because of metabolism, the transporter effects, distribution, but even there, if the dissolution in vivo is the same, they'll be the same.

DR. LIONBERGER: Generic products, solid

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oral products, often have different excipients.
DR. AMIDON: Yes.
DR. LIONBERGER: Right, and so we think that modeling and simulation can predict excipient effects, excipient differences that may come from different formulations? Maybe some comments from industry in terms of excipient selection.
Do you think it's a problem? Do you never worry about it? If you never worry about what excipients are in your products because you don't think they interact with transporters or the drug substance, I think that's useful to know or it is something you consider. Is it something that we should be able to predict?
DR. AMIDON: I would say, Rob, it might depend on the excipient. So there may be a class of those where we know they have -- I'm not sure we do, but very little effect and there's others where we have to be more careful. I think we need to be a little more careful and maybe classify our excipients a little more carefully.
DR. L. ZHAO: I agree with -- I'm not an

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agreement person, but I agree with what Dr. Amidon has said. For each category, we need a subclass. I think today we really appreciate if you can give us some input based on your experience under what special occasions you will trust the model to say waive a study for basically based on your experience, you will say my model will predict the human PK kinetics. Under what scenario?
In that case, industry can waive a study or can give FDA some relief. It's kind of a common interest between FDA and industry. We want to make the review to be science-based, less regulations. We have a common goal to have more quicker development timeline and have less burden to the drug developers.
DR. P. ZHAO: This is Ping again. Go ahead, Masoud.
I think this question has a very similar structure as the first one. Again, I would push it to break them into a predicted ability confidence versus a confidence to use that and give us enough room to make either a drug development decision or

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regulatory decision, but not necessarily to the point of a waiver of a study or additional studies.
I like the way the question is structured -- I mean, the bullet points are structured. It says, "Support particle size distribution," so on and so on. Again, similar to what I responded to the first one is that right now the model is very sophisticated. You can literally do anything, anything that you can think of, any mechanism. You can build into it.
Now, when it gets down to another level of confidence, which is around predictability, again, I think you have a long way to go, especially for this particular application, which is actually quite a broad application for generic drug oral absorption.
As many of the speakers alluded to today, the biggest challenge right now is the interaction between what's called the formulation component. Throughout the years, we have been within clin-pharm, we've defined PBPK being a component of -- being the combination of system component and

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the drug component, as Dr. Amidon clearly proposed in the morning.
We need to pay attention to the difference between drug and drug product, and it seems like we know very little about a very different formulation, how that will impact the drug behavior in the GI tract, even though we have the same dissolution in a given dissolution media.
Am I correct? I'd be happy to hear other's comments.
DR. AMIDON: I agree. I think the -- yes, I agree.
DR. DUAN: Just to follow up Ping's comments, right now, that's a very good point, because the formulation effect is very complicated and we know a little about it. That's a problem. But on the other hand, right now, the industry seems like towards that direction.
In the QbD paradigm, they did something to investigate that. One, they said what is optimum process parameter? The designed called the DOE study design of experiment. Different process

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parameter at different level and to detect it.
Formulation, they did the same thing. We saw a lot of that. From that regard, I want to emphasize a point I made previously. At the regulatory decision-making, we have much more data to borrow to be taken into consideration.
Right now, to answer question 2, I think the confidence comes from the validation. Whenever we do something, we look at the model building using what kind of data and using what kind of technology, using what kind of methodology.
Finally, we look at the validation, because as I said, at the regulatory decision-making stage, we have a lot of our in vivo data available, phase 1, phase 2, phase 3. So phase 1, they did a lot of formulation development. At that stage, different formulation, different excipients, different process parameters, different manufacturing technology were used.
At phase 2, phase 3, a lot of in vivo efficacy and side effect, safety information were incorporated. In that case, when we make the model

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evaluation, we concentrate on the model validation.
For example, we give in the presentation an example over there. They did the model using one clinical study, but they used three clinical studies to validate it. You see this clinical study showed that formulation is BE to that, and the model predicts its BE. The second study showed that the clinical studies showed our formulation is not BE to the clinical formulation, and the model predicted it's just not BE. That gave us some confidence.
To answer that question, I think that's case-by-case basis. We need some validation to build up the confidence. In order for us to be confident to make the regulatory decision, we need more validation studies using previous conducted clinical studies, phase 1, phase 2, phase 3. In that case, gradually, the confidence can be built.
Thank you.
DR. JAMEI: I just wanted to follow up what John said. I fully agree. None of these questions, nobody can say 100 percent we can

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support it or 100 percent we can just reject all of them, the method of confidence building.
Going back to what Filippos at the very beginning said, we have to then know what type of information and have that the work has been done. We are not looking at a single parameter. We have to look at the whole package, and we have seen, even the publication, people they are publishing something that they don't know what they have done. If it has happened in the submission, it won't be any difference.
Knowing even the capacity of the models, there are different models available. They have very high level of complexity, and if they use it if they don't know the limitations, this is another danger, that they are going beyond the capacity of the software. Being aware of the limitation of the software, what are the assumptions and writing them down -- you have to ask them to write down all the assumptions that they have made, what parameters they have fitted and why they have fitted. If they can justify what they have done, then you will

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develop the confidence in what has happened.
One more thing is I think I mentioned, and also other people they mentioned, the sensitivity analysis. We have to be a bit careful with the sensitivity analysis, because if you are fitting one or two parameters, already we have to if we are doing sensitivity analysis on one or two parameters, we have to be careful we are looking at the local sensitivity.
If solubility has changed, then the whole impact of the particle size can be different. This is one point.
Another point is that I think one of the points that maybe Susie mentioned, that there are limitations in the number of parameters that you can fit simultaneously. Perhaps this is a good thing because some of these parameters are inter-correlated.
I think David mentioned when the example for the multiple sensitivity analysis was shown that at the same time the particle size as well as the precipitation rate as well as the other parameters,

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they have changed independently. They are not independent. Sometimes there is a dependency between those.

A very simple example is that I have seen the publication, they did the sensitivity analysis on Log P, as the partition coefficient in the tissue. These two are not independent. If the Log P is changing, the KP is changing as well. We can't independently do sensitivity analysis on those two parameters.

DR. L. ZHAO: To be honest, I'm a little bit distressed to see the experts in the field all telling, okay, we need validation, we cannot 100 percent support, even in certain applications, a specific area in regulatory review.

I kind of have some reservations. If we're talking about validations for new drug, yes, we do not need to come up much, but for generics, they already accumulated experience with the compound. There's some compounds do have very thorough studies.

Then for generic drug application, the only

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change most likely is just the formulation. So in that scenario, I think there are already some clinical validations done in the NDA stage. My opinion is we cannot totally rule out the bigger utility of models in the realm of generics.

DR. EISSING: I guess it's also a little bit a question of how you interpret the question. It's like I believe PBPK models. Can I support all of the questions in that sense that it supports understanding? And you said you want to do science-based decisions, and it's like only if you can explain what you observe in a model, you have really understood it. In that term, it can help, but if you can based on the modeling alone really wait for complete clinical study, I think that really needs good case-by-case argumentation, and justification.

DR. L. ZHAO: For new drug applications, there are some packages with good received packages. In those cases, if there is a generic drug application, if there is change in formulation, I think the validation already has

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been nicely done in the new drug application stage in that.

Dr. Lukacova, you're looking to have something to tell in this.

DR. LUKACOVA: Well, just to follow up on that, yes, if we are both talking about generic application, you are really worried only about the input about the dissolution, right? If the dissolution is the same, your exposure will be the same.

The issue is how you're validating that in vivo dissolution is the same, right? You are comparing it to the in vivo exposure. Your in vivo exposure is your target, and I'm not trying to say that the PBPK model should not be used. I'm fully confident that they can help with generic development. But the model still needs to be developed and needs to account for all of the processes in order for you to have a confidence that in vivo dissolution was the same for the generic drug as for the brand product.

Unless Dr. Amidon can say that we solved the

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problems with an in vitro dissolution assay that can predict the in vivo dissolution and we'll all be happy and we can start using them. But I'm not sure we are there yet.

I'm definitely believing the PBPK models can help with the generic drug development, but still needs to be validated to make sure the drug properly accounting for your compound, because CP time profile is what is your target where you are measuring.

DR. CONNOR: I'm not sure that dissolution is the only thing. I go back to Rob's comment. It's not just disintegration plus the drug dissolving. There are excipients in there which are assumed to be inactive. But they aren't necessarily all inactive.

The way we have of evaluating their so-called inactivity is probably old by now and could be improved, because we assume or a company assumes, oh, well, I've used this excipient 10 times in my last 10 products, no problems at all. But there is a theoretical problem.

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I use it in number 11. It gives me a lot less or even a lot greater bioavailability than my target, assuming I'm a generic sponsor, than my target product, very surprisingly, because I assumed it was simple and this was inactive. That doesn't even address the fact that, in theory, although I don't know any cases of this, in theory that two seemingly inactive ingredients combined together in the same product could actually interact and create a surprising result as well.

Just simply getting the drug to dissolve in the body isn't necessarily the whole story. Most of the time it is, but not always.

DR. P. ZHAO: Just responding to Liang's sort of unsatisfied comment, I had to say upfront that my comments around all of these are definitely taking a lot of consideration about new drug development. What you said is valid. There might be situations where this model will be sufficient for you to make a decision in generic drug development, but that has to be, as you strongly believe, a verification or validation of a

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particular application is needed.

This can be easily done, and we have done that with DDI. As you set the conditions, let's take the first bullet, for example, poor particle size distribution specification for IR drug product with a low solubility. Then you say, okay, what does it take for me, you go from bottom to top. What does it take for me to make a biowaiver based on what I know from the NDA experience, right?

You have a generic coming in. What kind of study do I need in the middle in order to say, okay, now I have enough confidence with what I know about this particular API and in this new generic formulation and then in the innovator's different formulations? I know the PK there.

How much does it take for me to feel confident instead of doing a BE study, I can just stop here with an in vitro dissolution with my knowledge about the drug and my knowledge about a PBPK software platform in terms of the capability of handling the interaction between excipients and the physiology condition? It's robust enough.

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You can already imagine this middle level of this workflow, you need some data to support that. Maybe you need to try five different APIs. You have to observe the data. You do a blind prediction. You tell the world that, look, any software can do this or a couple of software. We have experience in-house or in the scientific field that we can do this.

I think that could apply to all of your bullet points, so set the condition.

DR. AMIDON: A different direction, looking at the five sub-points there, the two that I have the most concern about would be supportive dissolution for a modified-release product, because dissolution does not account for gastrointestinal motility and variability effects along the intestine from stomach all the way to the colon. That's where I would have the least confidence in a dissolution spec, at least as we think of USP. That's a whole other thing.

Then the last one with locally acting drugs, one of the questions there is where, what part of

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the intestine. I think both of those are more complicated than maybe the other ones. They're all complicated.

DR. LIONBERGER: I have a related question on here. I think we saw some examples in the presentations today of mechanistic IVIVC which I would contrast with an empirical IVIVC essentially. The mechanistic one, you sort of deconvolute against the physiologically-based model to try to get more factors out of it.

There seems to be evidence in the literature that this is better. I'd like the panel members to comment on that. Do you agree that mechanistic IVIVCs are preferred over empirical IVIVCs, and should then our expectation that is the state of the science that we should really think that if someone presents an empirical IVIVC, they should be doing something more complicated?

Have we reached that state yet where we want to put those on really different -- is there enough scientific evidence to say that those two approaches really are on different levels that we

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want to really endorse strongly the mechanistic IVIVC as the preferred approach to --

DR. AMIDON: Absolutely, Rob. Absolutely, but I'm an academic, so what do I know?

DR. DUAN: I would say depends, because IVIVC, if used in the traditional way, three formulations, slow, fast and medium. That's validated. It's very difficult.

We made a survey. We have a publication probably just for that. It's very difficult. From that perspective, we have to go this way, for the mechanistic-based IVIVC. That might be an alternative.

DR. AMIDON: We should do both, right?

DR. DUAN: Right, yes. If it's the traditional way, it's doing that IVIVC, that probably is pretty solid. When we do the mechanistic-based, that probably will get the same results, but for the traditional way, it's very difficult for the provability. As far as I remember, it's very low. It's about 30, 40 something.

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I couldn't remember exactly the number, but with that, we take another alternative way to get some same interpretation. That will be a good alternative.

DR. JAMEI: I think just to answer your question, yes, the confidence is there. In terms of the performance, they are better than the classical one, but it doesn't mean that the classical ones are useless now. There are many cases, as people have viewed them, that classical are enough. We don't need to force people to different. Now, you have to go and do PBPK.

I think two years ago, we had that discussion with Filippos, when we had that discussion. If you start pushing this one tomorrow, FDA is asking, we have to do everything PBPK IVIVC, it's not necessary for all the cases. There are some cases that they are improving the performance, but those cases are necessary to do it, but not absolutely for everything.

DR. KESISOGLOU: I would say I see them as complementary approaches. I don't think I would

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declare one is always better than the other for each compound. I have compounds that I develop both of them, and they had similar qualification performance. There's clearly, in the past, several classical IVIVCs that have been proven useful, right? So we cannot discount the old methodology.

I do think if we have -- absorption modeling IVIVCs give you another tool to use to develop these correlations, but I wouldn't necessarily throw everything we've done in the past out because it's the old way and we're doing things. I would just use them as complementary, and at the end, you have to use whatever makes sense and gives you the best product, right?

DR. JAMEI: I fully agree.

DR. L. ZHAO: With time, we probably need to proceed to question number 3. Based on the current discussion, I think we need to slightly change question number 3. Initially, it was for the areas with middle to low confidence, what are the gaps and how to close the gaps through research.

I don't think we are differentiating low to

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middle confidence. We are just asking the question what are the gaps and how to close the gaps through research.

I think what I got is that we need some validation for if we are applying PBPK approaches and we need to understand the system's parameters. A mechanistic model is not always better than the empirical model based on our limitation in understanding the details of the theoretical parameters' properties and DDS between property and theoretical environment. That's my take on it so far.

Any corrections? If there's no corrections, please comment on how to close the gap. I think here we are all doing PBPK research. With the experts, hopefully, we can define a direction to go.

DR. LIONBERGER: There are two types of gaps, I think. One is there's a confidence gap in what people believe and what our assessment of the model is, and then there's, two, sort of things about scientific understanding.

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Leave the second one aside, but I think the confidence gap, I really am impressed with what the OrBiTo group really tried to do with, say, let's put out a challenge and say here's some datasets, go have different groups take different tools and say how well you do. I think there's risk in doing that, but that's, I think, one way to really assess how well you're doing.

I think I would say the challenge I would put out would be an easier one that would be a little bit more relevant to generic drug development where you have human data. I think the challenge that the OrBiTo presented was sort of a little bit more first-in-human type study, which I think is even harder, but I would like to see us having some type of other areas, like protein folding and things like that, do yearly competitions on here's a dataset, all of the modelers who are in that area can then put in their prediction and assess both their ability against their peers, but also of the state of the field.

I think that's something that I think would

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help advance the first part of the gap and give a sort of benchmark for where we are. You could formulate the problem in different ways as an IVIVC-type problem or a bioequivalence prediction or biopharmaceutics type. But having a biopharmaceutics-related type challenge with an appropriate here's the blinded dataset and having something that then can be revealed, I think would be very helpful.

DR. DUAN: I think the OrBiTo approach is a good approach. The key point here is validation. So using this methodology, using that software to validate the results from the other things. That's what came from our experience regarding the ANDA block review.

When we set the particle size or other specifications, we put all the ANDAs together and try to get a consistent model. We can imagine if we can build a universal model for this block of 15, 17, whatever number that the ANDA block is, and then the model can apply to each ANDA and predict the BE study. That's where it'll be a beautiful,

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beautiful work, but we have not got there yet.

I think that OrBiTo approach, that's really a good approach. That can give us some confidence for the future study.

DR. SAO: For me, one of the gaps I think that currently exists is the excipient effects. I think they have to be characterized in the model. I know there have been a lot of studies about excipient effects just in permeability and things like that, but specific to a model. Out of the many models that we've seen so far, I think I might be wrong, but very close to 100 percent of the cases, one of the assumptions have been no excipient effect. It's probably something that we want to look into.

DR. KESISOGLOU: I agree with everything said so far. I guess I see this more as a validation of our biopharm knowledge than a validation of the model. I don't think it's the model necessarily itself, the structure of the model. It would be if the model worked for a BCS-I compound, it means the underlying structure of the

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model is reasonable.

Is the input in our biopharm knowledge? If we're failing the model, we're probably failing something in our understanding of the system. Either we are not accounting for something correctly or we're not putting the right parameters.

I think that's what OrBiTo is trying to accomplish, too. It's not just the in silico models themselves. It's generating all the fundamental knowledge, like in vitro-in vivo, that can help us with our understanding.

I think at the end, it's an overall biopharm view everyone's asking, not a model question.

DR. AMIDON: I want to come back. I think dissolution can solve everything. I think we need to separate quality control dissolution from what would be useful in product development. When we try to use quality control methodology which is set up for commercial product and along with other quality control measures, but we need a better dissolution methodology that does reflect in vivo,

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that would become a better validator, if you will.
Looking at question 3, what are the gaps, I think I would say product development dissolution methodology, which is a big gap in our field. Of course, there are many reasons for that, but that's what I would say about number 3.
DR. ZHANG: We hear a lot of validation, verification of the model so to improve our confidence, but I do have a question for the members. This is just a question that is coming up.
To what extent, to what kind of validation we think that will be enough for us to generate the next level of simulation that we are confident with? For example, if we validated the model with two ANDAs, can we extrapolate to the third ANDA the same API, different formulations?
The question is to what extent validation is enough to give us enough confidence since we are talking about validation and verification and we are all quantitative scientists. Let's have some quantitative discussion, as well.

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DR. L. ZHAO: I think dissolution seems to be one of the anchors for PBPK model, but I feel there's no SOP to establish dissolution method yet. If you have any input on that, that will be great.
DR. AMIDON: Yes, that's correct. I think industry has dropped the ball here. I'm sorry. I'm being an academic, but no, I agree.
I don't think a dissolution methodology for product development, in answering the type of questions that we're asking here, I don't think the USP methodology is good enough. We know it's not good enough. We need to evolve that. It's good enough for quality control maybe, at least we like to think it is. But I think we need to separate out a methodology or a method, an SOP. But when I look at the dissolution apparatus that we're developing at Michigan, the SOP would be a nightmare. It's not going to be useful for that, but it's going to be -- we need something, I agree. We need something
DR. NOVAKOVIC: I would like to add I absolutely agree with the statement that

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dissolution is the most critical or one of the most critical points in a physiologically-based pharmacokinetic modeling, but on the other hand, we can do modeling.
Depending what is the purpose of the modeling, we can do modeling without dissolution, and the modeling should be up to come to dissolution profile that has bio indicative or biorelevant potential and then how we are going to achieve in vitro dissolution that would match that profile that we saw by doing modeling and simulation.
That is the major obstacle, because we have so many techniques. We have different pHs. We are using different rotation speeds. We are using pH gradient. We are simulating fasted and fed conditions, but still we have difficulties to obtain dissolution profile in vitro that would be reflection of in vivo dissolution.
But as I said, physiologically-based pharmacokinetic modeling is a tool to come to that solution. It is mutual process. They are

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interacting, and it is interplay between the modeling and the solution.
DR. KESISOGLOU: I guess I have a -- to Dr. Amidon. I'm so sorry. I didn't see you. Go ahead.
I guess to Dr. Amidon's point about the dissolution USP being not useful --
DR. AMIDON: I didn't say that.
DR. KESISOGLOU: -- for development purposes. I don't think the problem is the dissolution apparatus necessarily. I think it's how we've used dissolution data in the past. There are people looking at two curves and trying to make sense of what two curves mean.
I think we have now the tools -- Masoud mentioned, for example, the mechanistic modeling of the dissolution. I think if we go to the next step of getting a closer look at the dissolution data and understanding what they're really telling us, I think there is value even to the simpler systems. I just think we haven't done that as consistently in the past.

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DR. JAMEI: I agree. I think it would be able -- I think, Gordon, you mentioned that the buffer issue, that we cannot. We think it is possible by modeling to be able to account for that one.

If we thought to incorporate the surface pH rather than the bulk pH for the dissolution and then we get some idea and there are some data on what is the buffer capacity in different part of the GI tract and explore those, then by separating the information that we have from in vitro and knowing what were the buffer capacity and translate it to in vivo buffer capacity, there are hopes to be able to predict.

DR. AMIDON: Yes, in some cases, but it does depend on the drug, the PK, its solubility.

DR. JAMEI: Yes, absolutely.

DR. AMIDON: Every drug has to be looked at. When we look at matching bicarbonate with phosphate, it varies with the drug's solubility and pKa, but yes, we can calculate that out. Then we go and do the experiments to see if it worked,

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because there's always assumptions in your transport analysis. But I think, theoretically, yes, but it does vary from drug PK and solubility, yes.

DR. JAMEI: Absolutely true. I think the same approach that we are doing with PBPK, we have to do more of in vitro modeling to get more experience and in which cases, then we don't need to do any extra in vitro experiment. We can model it. There are some cases definitely that we have to do the experiment so we carry on doing that.

One more point is that we are emphasizing too much on the dissolution, but permeability is another problem that we haven't sorted out. So permeability and predicting permeability, regional permeability, colonic permeability, they are another aspect we have to look at as well. This is another gap that we have.

DR. AMIDON: That's a gap. That's true. But I would say that's why we restricted BCS Class I to very high permeability, because once it dissolves in the stomach, it's all gastrointestinal

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variabilities that are affecting it, not the product. For BCS Class I, you're testing gastric emptying doing BE, not product differences. But when you slow down the dissolution rate, it gets more complicated, yes.

DR. P. ZHAO: I fully agree. During the presentations, Dr. Amidon and Masoud both mentioned the quality of input parameter drives good prediction. There's no doubt about it. I think we also have a previous experience in terms of predicting clearance based on in vitro system like human liver microsome hepatocytes, transporter systems.

Back to Liang's question around the confidence that one should have for in vitro solubility, it just seems like you can handle better with solubility than a human liver microsome, to my opinion.

But that said, there is still another direction of complexity that we probably haven't got the chance to talk about is the dissolution in what, a little bit maybe in Filippos' presentation,

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biorelevant solubility. Which one would be my true input parameter?

I think I'm pretty sure the experience we will get accumulated some years down the road, we will be able to say better in terms of looking at the drug characteristic and the accumulated experience for drug or drug product, what should go into the model.

Back to Susie's question, the qualification of validation, I think this is really getting a very general PBPK debatable area. We're developing the guidance right now for clin-pharm submissions. We try to shy away from this, because personally, I really don't think right now there is a good way that we can make some cutoff values up there and if people fail, they have a lousy model, just don't even submit to us. We don't look at that.

I think just based on the DDI prediction, our experience was that, again, you focus on and imagine the workflow. You focus on the end product, which is a biowaiver. For us, there's whether there's a need to do another DDI study, and

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then you trace your flow up and then decide, okay, if I have 10 drugs tested in PBPK and I blind myself from the observed study and this is the outcome, I have maybe one or two that is beyond 1.25. Do I tolerate that?

That's something, also related to what Filippos presented at the end, that might imply some kind of a paradigm change, which I have no authority to comment on that. I'm just proposing my personal opinion or personal sort of thinking around, reflecting what he said.

Think about clinically relevant BE. Then the other advantages for generic drug development, again, you have a lot of the new drug information to power the model. Not like us, we probably will be limited with maybe Phase 1 SAD data, multiple ascending dose data, that's it. We may have nonlinearity and get excited, oh, now I know there's something I can deal with a model.

Then you go beyond that. You still need a ketoconazole study to verify the model, and then you say, okay, I can waive the study. There's

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nothing that we just do bottom-up.

Even for DDI, we say we have high confidence there's a condition. That's why I think for all these applications, we need to set a condition. You identify your end question that you want to address and then try to build yourself up. I think that's when we do narrow the gap.

DR. AMIDON: I'm going to make one comment about it. You have all of that NDA information. The generic company doesn't have that. I think that part of the problem is --

DR. P. ZHAO: Good point. I think I'm assuming the purpose of this meeting is, also, whether from the agency we can do something to facilitate the broader use of the mechanistic modeling. If the generic companies decide to just go ahead and do the BE, I guess end of the question.

But still you're going to run into a scenario where a BE study is conducted and you get puzzled by the outcome and then all this inter-individual inter-variability, the patient versus a

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healthy volunteer, a single dose versus multiple dose, those questions. That's why we're here. That's my impression.

DR. AMIDON: I think that's a good question, but it's getting into the public policy realm, I think. If you can develop some internal understanding from all of the NDA's information and, of course, you can use that internally for your decision-making, but I don't know how that -- I don't know what more could be --

DR. P. ZHAO: That's a fair point.

DR. AMIDON: I think it's more of a public policy issue or there's public policy issues embedded in that.

DR. P. ZHAO: That's why I said personal opinion.

DR. L. ZHAO: I think we almost got the whole stakeholders in the field here. Actually, regarding the information sharing, we are sponsoring building internal PBPK database probably for primary. I'm not sure whether the CRO industry or the software developers have interest. I know

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there are already some working groups existing.

What is the most effective way for knowledge sharing in this regard to keep continuing the communication to build the PBPK future mechanism-based modeling? Maybe in the future, it's not called PBPK anymore once the knowledge is mature enough.

DR. JAMEI: I just thought right now, we had something around maybe 70, 80 compounds that are in the simulator, but many from the metabolism side, they don't have the absorption or the sophisticated models. They need a database. People are publishing, and maybe we have prepared a part of our website that people they can upload there to share between with the people who are using Simcyp.

It is very good to generate it, but I understand from innovative company side, that they expend huge amount of effort to create those ones. Even if they don't want to share it, I won't be able to force them. This is another thing that unless they want to share it -- because understandably, they have spent lots of effort,

data, individual man months. They are going through these.

We are publishing and we are publishing ourselves. One of the needs the consortium has asked us over the last two, three years, that we curate all so they will be available.

Now, we have started to put all the data, validation, they're all for the consortium members, they are available.

DR. P. ZHAO: I think just to speak to that, within clin-pharm, we're trying to set up a repository for the submissions right now, because the task will be so daunting. We haven't got to the stage to put in the specific software, specific model into this database, although we can trace where they are.

In the public domain, I know several journals nowadays are requesting the authors to supply software-specific model files. Hopefully, that will be another mechanism for us to tap into the resource down the road for a specific API where the model has been published.

Questions and Comments

DR. L. ZHAO: Okay. We are almost two minutes to 4:00 o'clock. We do want to give the audience a chance, if you hear something which is obviously wrong or you have a driving desire to voice your opinion, here is your moment.

Unfortunately, for the people online, we haven't set up the connection. We are not going to address questions from online. It's more like benefit to the people here in this room. Now is the time if you have any comments. It's good to stand up and approach the microphone. We appreciate any kind of inputs.

DR. SUN: Duxin Sun from University of Michigan, [inaudible - off mic]. As George Box said, "All models are wrong, but some are useful." I do agree the PBPK model is very, very useful to do the prediction, especially I do agree use PPBK model to set the boundary condition. I don't think it's real you can actually predict the spectrum to see if it makes accurate prediction, but the boundary condition is very useful to do the BE

study. That's one comment.

I think I can address the number 3, where is the low confidence. Because in the model we use a lot of in vitro data, then we have a plasma profile. The big gap in between is the black box, what is happening in vivo GI tract. But we have to use the in vitro data to somewhat predict in vivo what is happening, then use that data to predict plasma profile.

When we talk about validation, what we validate is use in vitro number versus PK profile, plasma. We don't have data to validate what is really happening in GI tract. Based on the data we already have worked with the FDA -- we work with, of course, Dr. Amidon, together work with the GI drug concentration. We measure local concentration of mesalamine. We measure the ibuprofen local dissolution.

The data that comes out is very surprising, very, very different than we thought. To give you one quick example, in the stomach, the concentration of both drugs, they stay in the

stomach over seven hours, for very long, for very high concentration. We would never predict that. We never assumed that.

What does that mean? The in vivo real data, very different from our assumption, very different from our prediction. Yet, we still can't use the model to predict from in vitro to in vivo PK. What does that mean? Does that mean in vivo does not matter or does that mean is the model perhaps wrong in some way?

Really, I feel number 3 will be we really need the in vivo data to validate. Once you get that data -- right now we have a local-acting drug. We complete that study. We're doing immediate-release

drug. We're going to finish within this year or next year. I think we need another modified-release formulation for GI.

So once we get the GI dissolution data, then we can really use that to validate the in vitro dissolution condition, also validate the model. So I feel that's fundamental. Without that data, we can do all different validations, but it's very

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hard to know whether it's true or not.
DR. MARROUM: I think that we have --
DR. L. ZHAO: Can you please identify yourself?
DR. MARROUM: My name is Patrick Marroum. I work for AbbVie Pharmaceuticals.
I think that we're discussing a lot in PBPK modeling, but I don't think we have an agreement on how we define a good model. At least with the classical IVIVC when the guidance was developed, there was a lot of discussion and a lot of work to come up with an acceptance criteria. I've seen many, many PBPK models that are developed and are so-called good models that have very different prediction errors that deviate quite a bit from the observed in vivo data. And yet they call them good models.
As long as we do not agree on what's a good model, I don't think how are we going to be able to use it from an application point of view? We have to first agree on what is a good PBPK model, and I don't think in this discussion anybody addressed

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that issue really.
DR. JAMEI: Can we answer or we wait?
DR. L. ZHAO: Please go ahead.
DR. JAMEI: I think, Patrick, that the question is maybe you're comparing two different things. When you say for IVIVC we know what is the criteria for success, I think you are considering that look if IVIVC are in the 85 percent to 125 percent, then it's acceptable. If it is not, then it's not acceptable. But this is not telling you about the performance of the model. You are accepting or rejecting is IVIVC -- you're not saying anything about the model itself.
Exactly the same thing if you are using physiologically-based IVIVC, exactly the same criteria is applicable there. There are no changes. If you get 85 percent, that's done. If not, then it's not acceptable.
DR. MARROUM: Most of the models don't achieve that level of criteria. Unless I'm mistaken, the vast majority of PBPK models that I've seen so far in that area for DDIs, for

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example, they say, oh, if you're within twofold, you're okay.
But if you want to use it for bioequivalence or waiving studies, either we change our definition of bioequivalence or we define our models to meet the relative definition of bioequivalence and be able to waive it.
DR. JAMEI: I see this one, two different things. You can say, okay, when a prediction is from PBPK model, it is acceptable. This is one question, which is valid and lots of discussion has gone everywhere and there is some commentary on that one, as well.
But comparing that against IVIVC acceptance or rejection is not correct, from my view, because they are two different things. We are not saying the performance of the model is acceptable. We say the formulation and everything, that way that it's working is these two are bioequivalent or not. We are not saying anything with the model.
In the PBPK, you're right. There are different people that are coming with different

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things, and this is a good thing. I don't see this one as a bad thing. The data commentary on pH in clinical pharmacology and therapeutics or pharmacometrics and system pharmacology, that one is comparing the PK top approach against PBPK oral quantititative systems pharmacology approach.
The purpose for them is not to match the observed data. The observed data, the source of the observed data we have, A, a clinical study with six people or 10 people, and we say these are the observed data. If you run the same study again with the same people, you are not going to get the same answer. Why do we expect PBPK to always match 10 people? So this expectation may be not right.
DR. MARROUM: But that's the definition of bioequivalence. You're implying that we need to change our definition of bioequivalence? We're stuck with it. There's nothing we can do. We have certain predefined criteria that we need to be able to pass, and our model should be good enough to give us enough certainty to determine whether we pass that criteria or not.

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This is exactly the same problem we had 20 years ago when we developed the critical IVIVC guidance. This is no different whatsoever.

DR. JAMEI: I fully agree, and I don't see any reason to change that criteria. If you are using numerical method or any other method you are using or if you are using a PBPK model, the criteria is exactly the same. There is no need to change it. The same acceptance or rejection can be applicable to PBPK. Because this is another model, they try to match two different in vitro and in vivo dissolution. The same criteria is applicable to both of them.

DR. MARROUM: Yes. And one more comment that I wanted to make is I would have a very great difficulty in accepting the concept that if you develop a classical IVIVC that met the stringent criteria of predictability that you need to force the sponsor to go back and do a mechanistic PBPK model.

You don't need to really understand sometimes what's going on. Probably sometimes you

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can never understand what's going on, but at least if you have enough certainty and confidence in your model to make a decision and relieve the burden on the company, that's good enough.

A lot of, for example, the exposure response relationship, we don't understand the initial relationship, but we still use it to select the dose or do something. So it is somewhat very difficult to say, oh, you always have to do PBPK model and it has to be mechanistic. If you have an empirical model or a statistical model that is predictive and robust, it's good enough.

DR. L. ZHAO: Thank you for that comment. If there's no clear benefit to do a mechanistic IVIVC or PBPK model, I don't think we would be forcing that.

DR. MARROUM: I heard someone commenting that we should go that way, I think.

DR. MEHTA: I thought I heard they were complementary. That's what I heard.

DR. MARROUM: Okay.

DR. GOOD: Good afternoon. David Good from

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Bristol-Myers Squibb. Thank you for the very nice panel discussion.

I think that we've talked a little bit about the confidence levels, so just have one question to supplement that. That's related to, I guess, what we've been talking about and what was shown about the wider adoption, the only 6 percent adoption for absorption of PBPK versus things like DDI where there's maybe more penetration currently. I think the comments that were made about confidence in vitro microsomal or hepatocyte data are very poignant.

I think that one of the things that we have in absorption that gives us this confidence and has been pointed throughout multiple presentations is the combination of these models with the in vitro data but also the in vivo data. And it's not just the validation against multiple formulations that contain different excipients throughout all of the clinical studies that were conducted, but it's the ability to have confidence in future predictions, too, by being able to leverage across species.

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That's something where the fundamentals of absorption that we're talking about dissolution rate, solubility, permeability would still apply, and our PBPK models are often constructed such that we can bridge across species and also be able to probe new formulations and leverage that in a way that for things like DDIs we can't, because the mechanisms of clearance can be quite different across species.

I guess my question is in the absorption space for PBPK modeling. Does the panel feel like we have additional tools to validate and to demonstrate our confidence in predictability for new formulations?

DR. AMIDON: I think it depends on BCS class and subclass, so some yes, some no today.

DR. KESISOGLOU: I guess in the development space, we often use animal data to validate whether the model is directionally at least or qualitatively giving us the right answer. Whether it would be quantitative or not in the animal model, it's a little bit more difficult question,

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because we typically don't measure animal-specific parameters. We have the human solubility estimate, but we don't have a dog solubility estimate necessarily.

I think that you can use the data supplementary in the development space. I do not have an experience in regulatory application to validate something against an animal model myself. I cannot comment on that, but I think in the development space, the totality of the data serving supplementary to inform the models.

DR. P. ZHAO: Just responding to your last question, based on experience, I'd feel cautious in terms of answering absolute yes even though I'm pretty optimistic. The reason I'm cautious is because for the lower confidence applications that Liang presented in the introduction on behalf of clin pharm, we are still struggling. For example, we have data around the multiple compounds with regard to their PK in hepatic impairment, and this is a high impact regulatory issue that we try to get a good hold around it.

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But at the moment, the published software characteristics around that already alluded to the bigger problem around some physiological impact on drug ADME that are not well characterized. Are we at that end? I don't think so because I think maybe we can further subset the question. Maybe in hepatic impairment of what kind of compound, and when you have what information, maybe you can use PBPK.

We're moving towards that end, but a global validation of a particular application I'd like to see maybe five years down the road whether we can say in confidence that, yes, we can do that. Mathematically, I'm optimistic that it's just a matter of getting the information.

You also alluded very correctly around the utilization of in vivo data. I think on the one hand, we need to be very critical about the input in order to drive a better prediction, but also once the in vivo data becomes available, this PBPK, the whole point we do that is it follows this predict-learn-confirm cycle. You really keep

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learning the system and improve the modeling.

Just one example, 2014, the ontogeny of CYP3A4 in pediatrics had been updated. That doesn't mean that the model was completely wrong in 2006 by different groups, but it's at least saying that with updated knowledge, we know better. The predictions should be narrowing us down within a narrower space to give a better prediction.

DR. L. ZHAO: I want to add something to Ping's comment. I think one thing, the technology is the responsibility of both sides, both from FDA's scientists and from industry. I think most of the innovation should be from industry. You're more than welcome to thrust new ideas or new data to support the validity of model, always submit to FDA or discuss with us at other venues, platforms. It's kind of we together need to advance the field.

As we have heard from today, there are many challenges, barriers. The field is still young, still in infancy, so we need lots of investment.

DR. CHIEN: Hello. My name is Caly Chien from Janssen R&D or Johnson & Johnson. I heard a

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comment from Ping about the prediction of food effect using PBPK may be at this moment, the level of confidence seems to be insufficient to give us the comfort level.

Can you also comment on your comfort level about the prediction of drug-drug interactions with acid-modifying agents, like PPI or X2 antagonists? I think throughout today we have listened to the presenters that there are successful cases, but there are also some cases that are not so predictive. I would like to hear your opinion on that.

DR. P. ZHAO: I'll try to make it quick because this is a generic drug workshop.

(Laughter.)

DR. P. ZHAO: Quick answer, again, as I mentioned while responding to the first question, in terms of predictability, all of the bullet points, we will need some more work in order to say in the absence of an in vivo study, we're good. Basically, I'm not convinced that if you just do a software prediction in the absence of the pH

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modulating agent prediction, a DDI study, that you can get away with it.

Again, conditional, there are certain compounds, these behave very well in the Phase 1 study. We have one oncology drug that we sort of gave a waiver, but it was very cautiously mentioned in the label, which is panobinostat. The sponsor submitted one prediction using one software. We sort of retested with another software.

Again, that's a case where probably just based on the pH and the solubility, it was sort of mediocre, but it was not too bad and also has very good permeability. We agreed that there's no need to do a pH-dependent DDI study, but other conditions, probably we wouldn't feel comfortable just by accepting the model prediction.

DR. CHIEN: Thanks.

If I can, I would like to ask a second question. I would like to continue to expand on Susie's questions about the model validation questions. I think a practical concern that I have when doing this hands-on is about the prediction

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error of the model, comparing the predictive versus the observed data, because if I'm trying to -- if the application is to assess bioequivalence, perhaps we would like the model to be as accurate as possible.

At what point do I have to stop and say that the model is good enough, that it can be used for simulation? Can I say that a percent error, 20 percent is good enough, or do I have to go continue until I have 10 percent? Because to go from 20 to 10 percent, maybe I have to spend another month to build a model or maybe do a lot more experiments to get to that level.

I would like to ask the panel members to share your experience. That would be great.

DR. NOVAKOVIC: I can answer this question because I have that experience with my case. It was in the percent prediction error criteria for percent prediction error exactly the same as for classical IVIVC Level A which means mean prediction error less than 10 percent for each parameter, AUC and Cmax and individual percent prediction error

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may be up to 15 percent. This is exactly the same as for classical IVIVC Level A.

DR. LIONBERGER: I think it depends what you're trying to predict. If you're trying to do I'm going to predict the --

DR. NOVAKOVIC: Biowaiver.

DR. LIONBERGER: Yes, but for example, if I'm going to try to predict what the result of giving this drug product to a particular human being is, right, you're never going to get the right answer from a model given the variability of what the inter-subject and inter-occasion variability of that person is. You're going to get some statistical answer.

You have to be careful about what your expectation is about trying to predict. Maybe in a bioequivalence context is you want to have confidence in your test to reference ratio that you're trying to predict. If you define it that way, some of the common errors may drop out, and it may be much easier to achieve a 10 percent prediction error on a test to reference ratio. But

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you're not going to be able to see a 10 percent on predicting the raw, what the distribution of all of the test values in your subjects are across the whole population.

It also depends in what sense you're averaging the data. Do you average it down to just the mean data or the whole study, or are you making a prediction about including some variation in the population? I don't know that a plus or minus 10 percent prediction error is always right. I think it's reasonable for IVIVC, but in a traditional IVIVC, you have some type of sort of also model normalization and correction between them at least going on implicitly so it looks sort of like this test to reference ratio thing that some of your errors that you're fitting can cut off.

If you're looking for the difference between the fast, slow, and the medium in your fitting process, the sort of overall shifts of your errors can get canceled out, too. I think you have to be careful of how you define the error that you expect in that way and what specifically you're trying to

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predict, whether it's individual subject or mean data, as well.

DR. L. ZHAO: Yes, I think I fully agree with Rob. I think there's no difference between the validation of PBPK model if we are only talking about data or population PK or exploratory response model from pharmacometrics. I think the guiding principle is the feed for purpose, depending on the purpose.

Then if you want to do a trial simulation later on, then you probably need to check all the quantiles, the predicted quantiles, develop the quantiles. You need not only describe the median, the mean, but also the uncertainty. That's what I'm thinking. I don't see any big difference between PBPK model or other models.

DR. FANG: Lucy Fang from Division of Quantitative Methods and Modeling. I want to make a comment on the data available to FDA. People always tell me FDA has the largest database, but what people don't know is from generic perspective, all the data we have actually is drug products, are

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so-called ideal drug products. That means they all pass the bioequivalence studies.

This means the drug are full on one side, on both sides. When we use those data to build the model, then this could limit our ability to explain the conclusion on those models.

As a modeler, I would like to see that more data submission for the drugs on both sides. I want the GPHA to take that into consideration.

DR. L. ZHAO: Lucy's from the FDA, so we are not addressing that comment unless the panel wants to comment.

DR. SUAREZ: This is Sandra Suarez from the FDA. Just coming back to the question previously raised about criteria for validation, we have had already two or three questions about that, and I was just going to somehow echo on to what Rob said. That's based on my experience on my involvement of several PBPK models submitted to new drugs.

For those limited experiences that we have had, the applicants have used a criteria very similar to what IVIVC guidance reflects, right?

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But I want to tell you, again, I don't know if it's clear. I said that the applicants have used the same criteria used for IVIVC, meaning 10 percent or 15 percent, depending on its internal predictability or external predictability.

It's pretty similar to what the IVIVC guidance specifies, but my opinion is that -- of course, I agree with that, because it's a conservative approach. But my opinion is that we need to gather experience in terms of the use of the models to really determine if 10 percent or 15 percent predictability is right not, and it will depend on the quality of the data that's going to be submitted into the NDA.

Again, the bottom line for me to determine the right criteria for model predictability is going to be based on experience and is based on what kind of data the FDA gets. Just like John was saying, we have data showing -- for extended predictability, let's say they use bioequivalence studies that fail and pass, and the model is able to predict that or not. Then we will build

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experience to really say 10 percent is sufficient or 15 percent is sufficient or not or to expand those goal posts for predictability, and that's what I wanted to convey to the audience here.

DR. WANG: Hello, everyone. I'm Meng Wang. I'm from the Division of Biopharmaceutics, and John Duan in the center is my mentor.

I want to express some of my rough ideas about IVIVC. Just so we are comparing a traditional IVIVC and empirical IVIVC, I just thought in the last whole year, I think the applications, there are only 12. The number is actually very, very few.

I just always think about why this number is very, very few. I guess maybe very, very small. I guess maybe it's because there are some people from company -- this is just my guess. I guess it's because the success rate is very small, and another reason is because I think the time is maybe more precious than the money.

So I just wonder maybe if the IVIVC success rate is very small, maybe we can use the PBPK model

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to do risk assessment, say, if it is feasible to do IVIVC. This PBPK model may be not very, very good, but maybe we can use it for the risk assessment, so maybe we can shorten the time. We can increase the success rate and also shorten the time to make this decision. That's all.

Thank you.

DR. CHOW: Hi, I'm Edwin Chow from Division of Quantitative Methods and Modeling. I want to make a comment about the PBPK modeling.

I think it's useful in a way that it really does address mechanistically how the drug is absorbed. Even though for BCS Class I drug you're looking for a modified-release drug, even though the generic company might match Cmax and AUC, the Tmax might shift. And how does that really reflect therapeutically what happens?

NTF, an epileptic drug where the PD response is really seizure risk, you can really use partial AUC to identify that. If you have a generic submission showing bioequivalence in terms of Cmax and AUC, but you definitely see a shift in the Tmax

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or any shape of the response, how would that affect the PD during multiple dosing? It will be in question.

I think it's really good to use a PBPK model to explain those kinds of situation. Thank you.

DR. PATEL: Nikunj from Simcyp. I think when the panelists were getting started, I had about eight points to discuss, but most of them are already done.

So just following up on the [indiscernible], it probably it looks to me that the highest confidence application area looks like it will be physiologically-based IVIVC, and there was some discussion on what should be the qualification criteria, whether it should be the same as conventional. As Sandra mentioned, that it is the same and also Masoud pointed out, I think we use the same criteria.

There was a good point from Rob about how to assess the prediction performance, and he actually brought up a nice idea of having a challenge, a competition, a blind competition. If that is the

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case, I think the physiologically-based IVIVC database as a prediction challenge would be probably a first good set to put, that you give that IV data, oral solution data and control all this data and see how well different people can predict using different platforms, numerical, physiologically-based, whatever. Then you can assess.

That would give you confidence that it is totally blind as well as it would give you an unbiased comparison of numerical versus physiologically based or whatever different approach people used.

DR. L. ZHAO: Thank you, everyone. Thank you for all these comments.

Again, I really want to show my thanks to all the speakers, the panel members, also for people who traveled. I see your luggage there, have been sitting here listening. I hope you enjoyed it.

At the end, I would like to turn it over to Dr. Robert Lionberger, office director of research

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and standards, OGD, to give the closing remarks.

Closing Remarks

DR. LIONBERGER: Thank you, Liang.

Again, I'd like to thank the organizers of this, especially you and Susie, for the work in setting up this very interesting meeting and really getting a diverse panel of lots of different perspectives here to talk about this and advance the field of modeling and simulation of biopharmaceutics going forward.

To me, this is an essential core technology area and knowledge gap for the Office of Generic Drugs. Still, almost all of our products are solid oral dosage forms, and the more we know about what they do, the more the companies that develop them can predict them, the better off the American public will be.

Certainly, this also affects new drug development, development of new formulations, post-approval changes to those, as well. There's broad CDER and FDA interest in advancing this type of tool set. I think it's really important to keep

this in mind, that we need to be continually advancing these tools.

When we think about where we should be, where we should be in the future is less uncertainty, more predictability about what happens to drug product factors. That should be the specific focus of, I think, this audience here. There are other people in FDA who have a lot more interest in first-in-human questions about drug absorption that are important, as well, but the focus here and the challenge is to really advance, as Gordon says, the product science aspects of this, because as we see here, there's a lot of uncertainty about that in the dissolution, the interaction of the physiological environment. But there's a huge upside to having a much better understanding of it for both FDA's regulators and for industry as product developers.

I think with that in mind of where we want to get, you should be thinking about as we go forward to the next workshops, what we'd like to see in this future state. I think people from

industry can speak more to this, there's things you do that you don't submit in the applications to FDA, just to help you develop it. If a tool is useful, you're going to use it. You're not going to leave things that save you effort off the table.

The next step beyond that is when and how do these things begin to show up in your interactions with FDA, and that is something that as we go forward, we can begin to figure out and say, well, if you describe a model, here's how we'd like you to describe it.

We often for these model cases and I think our experience for IVIVCs over the past is, yes, we want to replicate. We want to say, well, do we get the same answer when we run the model. We can do a sensitivity analysis of our own to say does this model look robust.

That can be an important part of that, but we want to think about and have discussion about what pieces that we want to see if you say, well, I used a model to support my argument, it doesn't have to be a waiver of a study. It could just be

supporting some aspect of your application, a specification, some type of argument. But you include a model to support that. What types of information should you include about that model is an important part of the future state of discussion, to have more clarity on that.

That will help FDA focus. We look at this model. You've basically met the sort of basic standards for what we expect to see in a model, and that gives us the -- and then we can sort of evaluate it in a more consistent manner.

I think that's where we want to be, and as we close the workshop, I want to think about what some of the next steps should be. I think the key ones to me are as we go forward with this, really getting the agreement on the science in the public literature. What can these tools do through these public competitions, tests of the models?

Getting agreement on where they work in cases that are publicly made available through the literature that people can really see, criticize, analyze, that sort of scientific foundation is

essential for moving acceptance of modeling and simulation forward.

I think another thing to think about as we go into the next steps is to communicate the impact beyond the modeling and simulation community. The importance of modeling and simulation, to try to say it helps make decisions. If modeling and simulation is useful, it helps people make decisions, that you, as industry, developing products, you have to decide what formulations should I choose, what bioequivalence studies should I do. Those are all decisions.

For us, as regulators, we also have to make decisions. Is this specification acceptable or not? Is this bioequivalence study acceptable or not? Is this new bioequivalence approach going to be valid or not? All of these are decisions.

Then we want to use the best tools available to make those decisions. As we think about modeling and simulation, we have to recognize that the audience that we're trying to reach is the people who are in the end making those decisions

and we want to think about how we present the models to those people in terms of their accuracy, reliability, what they've been able to do in the past, and, also, how they're just based on fundamental understanding of physiology and physics and mass transport and things like that.

No one's going to argue or people shouldn't argue with things like the second and first laws of thermodynamics. There's a fundamental basis for the models in physics and chemistry that should be solid. There's also understanding of the physiology, as well, that need to be integrated.

We need to be thinking about how we explain what the models are including as we go forward. And to echo sort of the last question here, what are the gaps that we need to close, so tomorrow we're having a Part 15 hearing for our GDUFA regulatory science program. This is an opportunity where you can specifically tell us what you want FDA to do.

To me, the thing that we really need to focus on as we look at gaps, where are the

new -- where are the publicly available in vivo datasets that we need to move the area forward? I think there's significant efforts in that in Europe in the OrBiTo consortium and FDA through things that we can fund through the generic drug regulatory science program to generate new in vivo datasets that answer and help advance the modeling and simulation tools.

Then I think Duxin and some of the comments gave about measuring the direct GI concentrations, that's something that's not often available. The more data you have there really helps build this bridge up between the in vitro dissolution and the in vivo product performance.

Please come tomorrow or make comments to the docket about those in vivo pieces of data that would be really helpful to have in the public domain to advance the entire field.

I just want to again close by thanking everyone for their time here, especially the panel for your expertise and thoughtfulness about this, and I hope that we will be continuing this type of

discussion in many different forms going forward and seeing much broader use of modeling and simulation in the sort of development of generic products and also the review and evaluation of those application.

Again, thanks very much to everyone.

(Applause.)

(Whereupon, at 4:37 p.m., the meeting was adjourned.)

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