

*Food and Drug Administration
Public Workshop*

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*A Matter of Record
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<p>1 FOOD AND DRUG ADMINISTRATION 2 PUBLIC WORKSHOP 3 4 5 MECHANISTIC ORAL ABSORPTION MODELING AND 6 SIMULATION FOR FORMULATION DEVELOPMENT AND 7 BIOEQUIVALENCE EVALUATION 8 9 10 Thursday, May 19, 2016 11 8:31 a.m. to 4:37 p.m. 12 13 14 15 FDA White Oak Campus 16 White Oak Conference Center 17 Building 31, The Great Room 18 Silver Spring, Maryland 19 20 21 22</p>	<p>1 Jasmina Novakovic 2 Apotex 3 4 Kathleen Uhl 5 Food and Drug Administration 6 7 Xinyuan Zhang 8 Food and Drug Administration 9 10 Liang Zhao 11 Food and Drug Administration 12 13 14 15 16 17 18 19 20 21 22</p>
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<p>1 Meeting Roster 2 George Amidon 3 University of Michigan 4 5 John Duan 6 Food and Drug Administration 7 8 Thomas Eissing 9 Bayer Technology 10 11 Masoud Jamei 12 Simcyp 13 14 Filippou Kesisoglou 15 Merck 16 17 Robert Lionberger 18 Food and Drug Administration 19 20 Viera Lukacova 21 SimulationsPlus 22</p>	<p>1 C O N T E N T S 2 AGENDA ITEM PAGE 3 Welcome and Logistics 4 Liang Zhao, PhD 7 5 Opening Remarks 6 Kathleen Uhl, MD 10 7 Introduction and Objectives of the 8 Workshop 9 Liang Zhao, PhD 18 10 The Application of Mechanistic Oral 11 Absorption Model in Biopharmaceutics Review 12 John Duan, PhD 25 13 OGD Experience and Efforts on Oral Absorption 14 Modeling and Simulation 15 Xinyuan Zhang, PhD 45 16 Oral Absorption Modeling and Simulation for 17 Formulation Development and Bioequivalence 18 Evaluation: An Industry Perspective 19 Filippou Kesisoglou, PhD 65 20 21 22</p>

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1 Modeling and Simulations for Development and		1	PROCEEDINGS
2 Bioequivalence Evaluation of a		2	(8:31 a.m.)
3 Generic Drug Product		3	Welcome and Logistics
4 Jasmina Novakovic, PhD	85	4	DR. L. ZHAO: Good morning. Welcome,
5 Mechanistic Oral Absorption Modeling and		5	everyone. My name is ZHAO, and I'm the division
6 Simulation for Formulation Development and		6	director for Division of Quantitative Methods and
7 Bioequivalence (BE) Evaluation		7	Modeling, Office of Research and Standards, OGD. I
8 Gordon Amidon, PhD	100	8	will be the meeting chair for today, and I would
9 Mechanistic Modeling and Simulation of		9	like to welcome everyone to the workshop.
10 Oral Drug Absorption: Opportunities and		10	Thank you to all the speakers, panel
11 Challenges		11	members, and everyone in the audience to make time
12 Masoud Jamei, PhD	117	12	and effort to come to the FDA White Oak campus,
13 Incorporating Mechanistic Modeling and		13	and, also, thank you to those folks on the line to
14 Simulation to Assist with Formulation		14	participate in the meeting.
15 Development		15	I will call the meeting to order, and I
16 Viera Lukacova, PhD	138	16	would like to go around the table for a quick
17 PK-Sim for Mechanistic Oral Absorption		17	introduction. I'll start with Dr. Duan. Just with
18 Modeling and Simulation and More		18	your name, affiliation.
19 Thomas Eissing, PhD	156	19	DR. DUAN: John Duan, biopharmaceutics
20 OrBiTo: Innovative Tools for Oral		20	division, the FDA.
21 Biopharmaceutics		21	DR. ZHANG: Xinyuan Zhang, the Office of
22 Filippou Kesisoglou, PhD	169	22	Generic Drugs, the Office of Research and
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1 Panel Discussion	188	1	Standards, Division of Quantitative Methods and
2 Questions and Comments from the Audience for		2	Modeling.
3 Panel Discussion	254	3	DR. KESISOGLOU: Filippou Kesisoglou, Merck
4 Closing Remarks		4	Research Laboratories, West Point, Pennsylvania.
5 Robert Lionberger, PhD	280	5	DR. NOVAKOVIC: Jasmina Novakovic, Apotex,
6		6	director of pharmaceutical generic components.
7		7	DR. AMIDON: Gordon Amidon, the University
8		8	of Michigan, working in the biopharmaceutic area
9		9	for many years.
10		10	DR. LIONBERGER: Rob Lionberger, director of
11		11	OGD's Office of Research and Standards.
12		12	DR. CONNOR: Dale Connor, Office of
13		13	Bioequivalence in the Office of Generic Drugs, FDA.
14		14	DR. JAMEI: Masoud Jamei from Simcyp.
15		15	DR. LUKACOVA: Viera Lukacova,
16		16	SimulationsPlus.
17		17	DR. EISSING: Thomas Eissing from Bayer,
18		18	representing PK-Sim.
19		19	DR. MEHTA: Mehul Mehta, Office of Clinical
20		20	Pharmacology.
21		21	DR. SAO: Paul Sao, Division of
22		22	Biopharmaceutics, Office of New Drug Products.

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1 DR. P. ZHAO: Ping Zhao, Office of Clinical
2 Pharmacology, Division of Pharmacometrics, FDA.
3 DR. L. ZHAO: Thank you, everyone. We have
4 a very excellent panel to cover all the topics for
5 today. A couple of housekeeping issues for
6 everyone here, so please silence your electronic
7 device that ring, sing or chirp.
8 For all the speakers, we will have to keep
9 time in check. We have a warning light. The light
10 will turn yellow when there is only five minutes
11 left for your allotted time.
12 So for all the panel members, I would
13 respectfully ask you to refrain from using
14 BlackBerry and checking your email. We have two
15 breaks and one lunch period for you to be able to
16 do that. Having said that, for everyone here, we
17 have 20 minutes break, two of them, and one lunch
18 break. So I would like you to check your time and
19 make it to your seat in time.
20 Now, I would like to welcome Dr. Kathleen
21 Uhl -- we call her Cook -- a very important figure
22 in our field, to the podium to do the opening

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1 remarks.
2 (Applause.)
3 Opening Remarks – Kathleen Uhl
4 DR. UHL: Thank you, Liang.
5 Good morning, everyone, and welcome to this
6 FDA workshop on mechanistic oral absorption
7 modeling and simulation for formulation development
8 and bioequivalence evaluation.
9 That's a tongue twister for this early in
10 the morning, I've got to say, and I'm only one cup
11 of coffee into the day. I think that there will be
12 paybacks into the future to Liang for asking me to
13 do opening comments on this one.
14 So, Liang, I'm looking for chocolate or
15 something afterwards.
16 I am very pleased to be here this morning
17 and to offer a few opening comments. This workshop
18 is an example of the collaborative spirit between
19 FDA, academia and industry, and, in this particular
20 circumstance, to collaborate to advance the science
21 that brings generic drugs to market and the science
22 to do this more efficiently.

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1 It's impressive for me to see the level of
2 interest and the level of engagement in this topic.
3 I spoke with Liang yesterday, who told me that
4 there were about 400 people who signed up for this
5 conference. We don't have the exact number of
6 people who are attending via WebEx, but as of
7 yesterday, it was anticipated there'd be at least
8 200 people. We'll know later in the day, I think,
9 how many. But that tells me that there's
10 remarkable interest in this topic, especially as it
11 relates to the development of oral dosage forms for
12 generic drugs.
13 Before I move on, though, I do want to thank
14 Liang and Susie, especially Susie, for the amount
15 of time, effort, and energy that went into putting
16 this workshop together and having this today.
17 Thank you to you, Susie.
18 One of the things that I've commented upon
19 in numerous public meetings, public presentations,
20 et cetera, is the low first cycle approval rate for
21 generic drugs. Generic drug applications are
22 called abbreviated new drug applications, or ANDAs,

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1 here at FDA.
2 Currently, we are experiencing about a 10 to
3 15 percent first cycle approval rate, and that's a
4 little concerning to me. The generic drug program
5 needs improved efficiencies and accuracies in
6 generic drug product development, which should then
7 translate to reduced regulatory uncertainty and
8 reduced regulatory burden.
9 Some of these improved efficiencies include
10 just what we're here for today, the application of
11 modeling and simulation to oral drug products, and
12 oral drug products are actually the largest number
13 of submissions that we get to the agency.
14 The purpose of today's workshop is to obtain
15 input from various stakeholders on when, where, and
16 how to conduct mechanism-based absorption modeling
17 and simulations in the context of bioequivalent
18 product development and the impact of this on
19 regulatory decision-making specifically related to
20 generic drugs.
21 Here's what will happen today. FDA will
22 share our current experiences on the application of

<p style="text-align: right;">Page 13</p> <p>1 this type of modeling and simulation on our 2 regulatory activities. There will be many external 3 experts who will also present and share their 4 experiences with this modeling and simulation, and 5 I'm sure that there will be a very robust panel 6 discussion, seeing not just the number of people 7 here on the panel, but as well the depth and 8 breadth of your experiences. 9 I'm hopeful that this will lead to very 10 fruitful discussions about the current and future 11 utility of these modeling and simulation techniques 12 in the development of bioequivalent oral drug 13 products and in our regulatory reviews. 14 Lastly, and I kind of harp on this all the 15 time when we have public meetings, is the fact that 16 we need comments on this topic. There's a docket 17 that's open for this meeting. We really need 18 people to submit your thoughts, your thinking, your 19 ideas on this topic so that we can advance the 20 science in this area, hopefully use the input that 21 we get to either create a white paper on the topic 22 or, as a regulatory agency, that we can put out</p>	<p style="text-align: right;">Page 15</p> <p>1 application of such to improve our understanding of 2 drug absorption can be the very first step to 3 modernize the development of solid oral dosage 4 forms for generic drugs. It can do this by 5 integrating the latest knowledge of drug substance 6 properties, formulation characteristics, in vitro 7 release profiles, and physiologic variables. 8 In addition, because I know there are 9 industry people here, I'd like to see industry 10 realize the numerous benefits from this type of 11 simulation and modeling. I'm happy to see we have 12 some individuals who work on the review side of new 13 drugs, because this is common methodology applied 14 in new drug development. 15 Some of these benefits include the ability 16 to extrapolate data from healthy volunteers in BE 17 studies to patients, either patients in general or 18 very specific subpopulations of patients; for 19 example, patients that have GI disorders and 20 alterations in their GI pH and such. It's helpful 21 in informing how and what is chosen for the 22 in vitro release testing methods. It's helpful in</p>
<p style="text-align: right;">Page 14</p> <p>1 guidance to industry on how best to use these 2 methodologies in the development of generic drug 3 products. So please, if you have ideas, please 4 submit them to the docket. It really will help us. 5 Some of my thoughts about this workshop that 6 I'd like to see come about as a result is, first of 7 all, this whole concept of innovation and 8 implementing innovation in the context of generic 9 drug development using these tools, simulation, and 10 modeling. Typically, when people hear the word 11 "innovation," what I'm struck with is they usually 12 think about the new drug side. When they say 13 "innovator drugs," they mean the new drug side, 14 right? 15 It takes incredible innovation to reverse 16 engineer a drug and to create a high quality 17 generic version of that drug and, in this regard, 18 innovation can actually be the cornerstone or the 19 foundation upon modern generic drug development in 20 almost all steps from formulation design and to the 21 assessment of therapeutic performance. 22 Mechanistic-based modeling and the</p>	<p style="text-align: right;">Page 16</p> <p>1 the ability to evaluate the impact of dissolution 2 deviations and failures. It's helpful in the 3 ability to evaluate potential performance 4 differences for modified release formulations with 5 different release mechanisms from the reference- 6 listed drug; for example, if the generic or the RLD 7 is matrix versus an osmotic pump, for example, with 8 certain extended-release products. 9 It's helpful in defining critical quality 10 attributes and clinically relevant specifications. 11 It's helpful in understanding pharmacokinetic 12 variability, and if you understand pharmacokinetic 13 variability, you can better design BE studies. You 14 can better address the study in advance so that you 15 have success in that study, and it can also be used 16 to reduce the sample size. 17 It's helpful to evaluate certain product 18 risk factors that can then aid in very targeted 19 post-marketing safety surveillance. And finally, 20 and this is really where the rubber meets the road 21 for industry, it can certainly help get their 22 products improved, because valid modeling</p>

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1 components in ANDA submissions can reduce
2 regulatory uncertainty and potentially relieve the
3 regulatory burden in order to support product
4 approval.
5 In closing, I'd just like to say we grow
6 smarter by learning together and, more importantly,
7 by learning from each other. I'm hopeful that
8 today is not just a learning opportunity for the
9 attendees, but also the opportunity to advance the
10 science in this area, so as to advance the science
11 of mechanistic modeling and simulation.
12 The agency thanks you for your attendance at
13 this workshop. I am hopeful that you have an
14 enjoyable day. It's going to be a long day. I
15 know a lot of you will also be attending the
16 Part 15 public hearing tomorrow, and so I just wish
17 you a good day. I hope that Liang is able to
18 report back to me about lots of really positive
19 input, and we're ready to put pen to paper on some
20 ideas soon after the docket closes.
21 I thank you for the opportunity to talk, and
22 I wish you good luck today. Thank you.

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1 DR. L. ZHAO: Thank you, Cook.
2 (Applause.)
3 DR. L. ZHAO: Thank you, Cook, for your very
4 insightful remarks. That's what we need. I just
5 want to give you another round of applause for your
6 support and for your guidance for the industry.
7 (Applause.)
8 Presentation – Liang Zhao
9 DR. L. ZHAO: I will go through some of the
10 slides I prepared for the introduction. Modeling
11 and simulation are one of the priorities in GDUFA
12 regulatory science program. The tools are not only
13 for generic drugs, but also for new drugs, for the
14 drug development and the regulatory decision-
15 making.
16 As Dr. Uhl just mentioned, today we have
17 more than 400 people registered, and I believe
18 there are many people who may participate without
19 registration. The objective for today's meeting is
20 to share current FDA experiences on the application
21 of mechanism-based absorption modeling and
22 simulation in regulatory activities; to discuss

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1 current and future utility of mechanism-based
2 absorption modeling and simulation in the
3 development of bioequivalent oral drug products and
4 regulatory reviews; to obtain input from the panel,
5 from the audience, from various stakeholders on
6 when and why and how to conduct mechanism-based
7 absorption modeling and simulations in the context
8 of bioequivalent product development; and, request
9 comments on these topics.
10 Over a year period from April 1st, 2015 to
11 April 1st, 2016, within the Office of Research and
12 Standards, OGD, modeling and simulations have made
13 critical impacts to 20 ANDA reviews, 54 citizen
14 petitions, controlled correspondence, three ANDA
15 meetings, 33 BE guidances, and 37 regulatory
16 research studies.
17 Some prominent examples include to use PK
18 modeling and simulation for methylphenidate
19 extended-release products and other asthma
20 controllers. Here, I have left out our analysis
21 contribution to 17 ANDA reviews of dabigatran.
22 Modeling and simulations has benefited the

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1 development of BE criteria for painkillers,
2 assessment of BE standards for GI locally-acting
3 products, simulation of in vivo alcohol dose
4 dumping studies. Simulations have been used for
5 the development of BE criteria for highly variable
6 drugs and narrow therapeutic index drugs.
7 PK/PD modeling and simulation have been used
8 to determine the appropriate study design and
9 evaluate the BE between generic anti-epilepsy drugs
10 and immunosuppressant drugs in patients.
11 This slide shows a brief summary of the
12 areas where PD/PK modeling has made an impact.
13 First, it has been used to identify very relevant
14 individual testing, including dissolution method.
15 It has been used to identify critical attributes to
16 control product quality. It has been used to
17 evaluate the potential of in vivo alcohol dose
18 dumping after a formulation change.
19 It has been used to evaluate risk associated
20 with mechanism of change, especially for extended-
21 release products, such as from osmotic release
22 control delivery system to controlled release

<p style="text-align: right;">Page 21</p> <p>1 metric delivery system. It has been used to assess 2 the extrapolation of BE from healthy volunteers to 3 special populations. 4 For locally acting drugs, the modeling and 5 simulation has been used to assess the GI local 6 drug concentration and the correlation between 7 local drug supporter and systemic supporter. 8 The tools have been used for the waiver of 9 in vivo studies, such as waiving lower strengths, 10 sometimes higher strengths of a product, or 11 increase the space of waiver for BCS III class 12 drugs. 13 The modeling and simulation are also being 14 used to assess the proton pump inhibitor effect 15 after a formulation change. So we conducted a BE 16 study in healthy volunteers, but without a study 17 with proton pump inhibitor. We want to use 18 modeling and simulation to assess the risk if we 19 have a formulation change. 20 This chart shows an increasing number of 21 compounds assessed using absorption modeling. 22 Fifteen out of 34 of them are IR products,</p>	<p style="text-align: right;">Page 23</p> <p>1 forth. 2 There's also an increasing number of drug 3 labels with dosing recommendations informed by 4 PBPK. The majority of them fall into DDI, only 5 with two exceptions. 6 Another stakeholder within FDA is our 7 pharmaceuticals colleagues in the Division of 8 Biopharm, Office of New Drug Products, OPQ. The 9 biopharmaceuticals emphasize linking the product 10 quality to the product clinical performance. In 11 this regard, PBPK is a must-have tool. 12 Over a period from 2008 to 2016, the 13 biopharm group has received, reviewed 15 14 biopharmaceuticals-related PBPK submissions. These 15 submissions assess the risk of product and studying 16 dissolution method specifications, clinically 17 relevant drug product specifications for critical 18 material attributes and critical process 19 parameters. 20 I don't want to steal thunder from Dr. John 21 Duan, as he will give you more details in his 22 presentation.</p>
<p style="text-align: right;">Page 22</p> <p>1 immediate-release products. Nineteen of them are 2 modified-release products. The majority of them 3 fall into the BCS Classes II and IV. Of note, we 4 have assessed seven products in a period of five 5 months in the year 2016. Dr. Susie Zhang will give 6 you some details in her presentation. 7 For new drug development, as contributed by 8 Dr. Ping Zhao in the last ASCPT meeting, the focus 9 of PBPK modelings, many are on drug-drug 10 interactions and to assess PK profile change in 11 specific populations. These are the main areas 12 from the new drug side. 13 Areas with limited experience, including 14 assessing the factors on PK exposure for pregnancy, 15 ethnicity, geriatrics, obesity, disease states, 16 food effect, formulation change, pH effect, some of 17 these fall into the realm of generics. So you can 18 see from top to bottom, there is a decreasing 19 degree of confidence level and an increasing degree 20 of reliance on systems knowledge, like locally 21 environmental, physically environmental change and 22 product and the GI physiology instruction and so</p>	<p style="text-align: right;">Page 24</p> <p>1 With a set of presentations for today from 2 the FDA, the new drug industry, generic drug 3 industry, academia, also, software developers, the 4 hardcore modelers, we are going to discuss three 5 questions in the afternoon. The first question: 6 For the available list of areas or subareas, which 7 one do we have the highest confidence in using 8 physiologically-based absorption modeling for oral 9 dosage forms? 10 Second question: Do we have enough 11 experience and confidence in applying the current 12 PBPK absorption models to support the following 13 regulatory applications? I can read out the list: 14 Support particle size distribution specifications 15 for an immediate-release drug product of a drug 16 with a low solubility; support dissolution 17 specifications for a modified-release drug product; 18 support request to widen the BCS III biowaiver 19 criteria; support in vitro-in vivo correlation of 20 an API with less than three formulations with 21 different release rates; support new proposals to 22 demonstrate the bioequivalence for GI locally-</p>

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

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1 After that, we will figure out what the problem
2 probably is and what the challenges will be. In
3 that regard, finally, I will propose some future
4 steps, future applications.
5 In all three parts, the theme is
6 patient-centric quality. In order to do the
7 patient-centric quality, I would like to give an
8 overview about biopharmaceutics' role in the drug
9 development in the patient-centric quality control.
10 Before doing that, I would like to introduce
11 a concept, CRS. To do the patient-centric quality
12 control, we have to set a clinically relevant
13 specification, so we call it a CRS. The concept
14 comes from the general concept of patient-centric
15 quality control.
16 That's a paradigm shift for the quality
17 control. In traditional quality control, the
18 control is by testing. After the product is ready,
19 we test, do this test and do that test. But the
20 current concept is we would like to introduce the
21 patient-first concept, to do that from the
22 beginning to design a drug, build the quality in

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1 the design, and go from there. So that's our
2 paradigm shift.
3 The paradigm shift will allow us to give the
4 patient focus. When we design the compound, when
5 we design the formulation, we consider the patient
6 need, and then we go from there and do the risk
7 assessment, do the design of experiment, and,
8 finally, define a design space. In that case,
9 everything we consider is from the patient
10 perspective. And from there, we implement the
11 patient-centric concept.
12 So the patient-centric quality control is a
13 framework. In order to implement that framework,
14 the agency implemented organization reframe. We
15 reorganized our quality-related office. Since
16 2015, the Office of Pharmaceutical Quality has been
17 stood up. The purpose of this office is to
18 coordinate all the quality aspects and get them
19 together and get one voice for the quality and one
20 voice for the drugs, one voice for the industry
21 and, most importantly, one voice for the patient.
22 So from there, we've seen the

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

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1 function of patient-centric quality control and
2 quality framework.
3 So whenever we do something, we start with
4 the concept, and then we have the organization, we
5 have the people. That's currently what we are
6 doing.
7 We have the patient-centric concept sitting
8 there, and then we have the OPQ standup. The
9 organization is there. And most importantly, the
10 Division of Biopharmaceutics standup last year. In
11 that case, that indicates there's a trend to
12 emphasize biopharmaceutics in the quality control
13 area.
14 So to emphasize that -- Liang already
15 presented these slides -- I would like to
16 reemphasize the definition of biopharmaceutics.
17 Sometime before, I attended a national meeting.
18 Someone asked me, "Here at the FDA, what do you
19 do?"
20 I said, "I'm in the Division of
21 Biopharmaceutics."
22 "Oh," he said, "Okay. Do you do gene

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1 therapy or do recombinant DNA or -- well, what do
2 you do?"
3 At that time, I was speechless. I don't
4 know what to say. He doesn't know. From there, I
5 feel sorrow. I feel sorry, because probably we
6 didn't do a good job to let the industry, let the
7 pharmaceutical science field know biopharmaceutics
8 is there. So here, I would like to reemphasize the
9 definition of biopharmaceutics.
10 Biopharmaceutics is the study of the
11 physical and the chemical properties of a drug and
12 the proper dosage form. That relates to the onset,
13 duration, and the intensity of the drug action.
14 Here, we can see the concentration of
15 biopharmaceutics not only to the in vivo onset and
16 the duration and intensity, but it also relates
17 that back to the physical-chemical properties and
18 the dosage form properties. That is completely
19 related to the drug quality.
20 From there, I would say biopharmaceutics
21 plays an important role in the drug quality
22 control, especially in the current framework about

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1 the patient-centric quality control framework. In
2 that sense, biopharmaceutics concentrates and
3 relates the quality to the clinical performance.
4 The concept generally is that the drug company
5 conducts the clinical trial to show that efficacy
6 and safety is there for the drug quality.
7 Our future quality control task is to match
8 the clinical trial formulation. Every batch, each
9 batch should be more or less similar to the
10 clinical trial batch and show similar efficacy and
11 safety. In that regard, the bioequivalence between
12 the future manufacturing batch and the clinical
13 batch is very important.
14 However, we cannot control every drug
15 quality, every aspect, to do a bioequivalence
16 study. In that sense, translating the in vitro
17 properties to in vivo performance is very
18 important. That's biopharmaceutics' role playing
19 over there.
20 In that regard, the mechanism of oral
21 modeling and simulation is very important. That
22 consolidates the physical-chemical properties and

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1 the physiological properties together, and do a
2 bottom-up, and figure out what the drug performance
3 would be. Then we have some data, and we top-down,
4 bottom-up and top-down, getting together to get the
5 job done.
6 So that's biopharmaceutics' role in the drug
7 development and drug approval, and oral mechanistic
8 modeling and simulation is a very important tool
9 for biopharmaceutics to do the job.
10 From here, we can see the agency's goal is
11 very clear, patient-central quality control. The
12 trending is obvious from concept to the
13 organization to a specific biopharmaceutics
14 division, and the effort has been tremendous.
15 The opportunity is very exciting, but before
16 we get too much excited, we'd like to introduce the
17 current status of the oral mechanistic modeling and
18 simulation in submissions. In current status, as
19 Liang showed the slides, I borrowed a page from
20 Dr. Ping Zhao. He summarized until 2013 all the 84
21 PBPK-related submissions.
22 Among them, 60 percent, only 60 percent

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

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

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

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

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

9 What they did was they showed the
10 dissolution methodology in different media. As
11 shown here, at pH 2, two formulations, one is the
12 reference formulation. Another one is another
13 formulation, but of different quality. This showed
14 these two formulations in pH 2 medium, they
15 separate. But in pH 4.5, not shown here, and pH
16 6.8, they are not differentiated. As shown here,
17 the pH 6.8, it's extreme, almost overlap.

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

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

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

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

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

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

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

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

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1 Option 1 is a unique approach and made them
2 a success. Here is what they did. They showed a
3 dissolution profile as a template, and then they
4 tried to incorporate the dose, the volume, and the
5 medium composition and the solubility together.
6 And through modeling, not in PBPK software,
7 somewhere else using another tool, to do another
8 kind of modeling, not necessarily as a PBPK
9 modeling, but it's outside of the PBPK software.
10 That modeling they did using all the input
11 to figure out what the theoretical particle size
12 should be. In that sense, when they input the
13 particle size into PBPK software, the particle size
14 not only represents the particle size itself
15 anymore, it represents the local volume and the
16 medium composition, also the solubility, because in
17 vivo, the solubility as different, pH could be
18 different. So they took that into consideration
19 through their modeling. That's a unique approach.
20 I'd like to raise that unique situation for
21 discussion. They did that, and they used that
22 model, validated the model, and then using that for

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1 dissolution profile comparison; therefore,
2 dissolution methodology validation and the
3 specification setting.
4 Also, they used the same approach using
5 what's called the virtual BE study. They show
6 virtually the two batches are bioequivalent. The
7 specification setting is based on the virtual BE
8 study and the particle size specification. It's
9 also based on the virtual BE study. That means
10 where I set particle size lowly-mid and highly-mid
11 would be bioequivalent to the clinical batch.
12 That's the situation, the patient-centric
13 framework we would like to hear, because that shows
14 some evidence, at least in silico, to show they are
15 bioequivalent. That's compared to previous
16 specification settings, why you set this particle
17 size, because we used that before.
18 This doesn't necessarily mean it will be
19 bioequivalent to that. Here, there are some
20 quantitative indications saying that will be
21 possibly, very likely to be bioequivalent. That's
22 a much stronger argument to make for setting the

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1 specification.
2 The third example is what the reviewer in
3 FDA did. The third example is in the situation for
4 ANDA review. In order to make sure the ANDA
5 quality will be consistent, we put an effort for
6 the ANDA PBPK modeling. The intention is to see
7 are there any quality problems.
8 The situation is that we have ANDA block.
9 That so-called block is we have a whole bunch of
10 sponsors submit for the same API, for the same RLD
11 reference-listed drug. They want to develop a
12 generic drug with that same thing.
13 The concern is do they have the similar
14 quality, although we observe in some of the BE
15 studies, it's lower, almost at the edge of the
16 bioequivalence range; some of them higher, almost
17 at the edge of the bioequivalence range. So are
18 they bioequivalent?
19 That's a quality control issue. What our
20 reviewer did was to put them together to see when
21 they do the PBPK modeling, are there any special
22 factors we should consider. In PBPK modeling,

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1 usually we have a lot of assumptions. Usually,
2 with uncertainty, we have to make assumptions.
3 Sometimes we don't know the real value. We
4 have to optimize it using the software to optimize.
5 The optimization, the assumption sometimes
6 introduces a lot of uncertainties.
7 What is the focus for the uncertainties to
8 be paid attention to? Some uncertainties may not
9 be important. The analysis is to put six
10 uncertainties together and do a sensitivity
11 analysis. Currently, based on our knowledge, the
12 PBPK software, although it can do sensitivity
13 analysis, only one or two factors. Six factors put
14 together is what the reviewer has done here.
15 They put API particle size and effect of
16 permeability and precipitation time and
17 precipitation radius and plasma protein by the
18 ratio.
19 The reviewer made an analysis. The analysis
20 is using all the six factors, that's 13,000
21 combinations, and put them together and put into
22 the PBPK software to see what the Cmax, AUC

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1 exposure is.
2 The sensitivity analysis showed it's a very
3 complex figure. The major interest is about the
4 particle size. That's on the X-axis. And the
5 major interest output is about Cmax. With those
6 two major considerations, at the same time, they
7 consider the solubility on top, three groups, and
8 on the right, four groups about the permeability.
9 They use the symbol to differentiate the
10 precipitation time, and they use the color to
11 distinguish the different radius of precipitate.
12 That shows a lot of interpretation can be
13 made. A major one is that, as we can see in the
14 very left block, the solubility, the measured
15 solubility is 0.011. The relationship between Cmax
16 and the particle size is pretty steep. On the
17 other hand, when the solubility increases on the
18 right panel, the solubility is 0.11, and at that
19 time, it seems like particle size won't play a role
20 as significant as the left one.
21 That gives us some interpretation of a
22 regulatory step we are going to take. Based on

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1 that analysis, we send an IR, say you need to
2 provide this one in exact measurement, so in that
3 case.
4 In summary, the regulatory implication
5 is -- there are a lot of regulatory implications,
6 but I want to emphasize that during the 15
7 submissions, there are some limitations. A major
8 one is no detailed information provided, and, also,
9 some models established without validation. If
10 without validation, we cannot trust it.
11 Also, there's no full validation or the
12 detailed file is not provided. When you use a
13 model to justify the application, it's not
14 sometimes reasonable.
15 Finally, I would like to say for the
16 patient-centric, we have a lot of bridge. So PBPK
17 modeling, mechanistic modeling and simulation is
18 one way. We are facing challenges. As we said,
19 what model should we select and what validation
20 should we do and what software we should use and
21 what software we should develop, that's our
22 challenge.

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1 In order to fully explore the possibility
2 for patient-centric quality control, we need to do
3 something beyond dissolution, beyond particle size.
4 We need to do some real manufacturing process,
5 manufacturing parameters, such as compression
6 force, hardness, granulation, that kind of stuff.
7 How are we going to use this one to control that?
8 That's our challenge.
9 Think about it. Here, we should emphasize
10 when we submit the PBPK modeling, that's our
11 current thinking. We should complete and submit
12 the information in order for us to grow together.
13 One thing I want to emphasize is it seems
14 like currently regulatory -- when we do PBPK
15 modeling, we have a lot of information. But the
16 companies, it seems like the interest at the
17 initial stage, we don't have any information. So
18 we bottom-up and put something together and get
19 some rough idea to develop.
20 Here, I want to say there's a difference
21 between regulatory and initial development. But
22 there's a common place, because when they do the

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1 initial development bottom-up, the model you should
2 keep at the later stage for the regulatory
3 submission to make justification, very useful. The
4 example I showed, that's one they did we accepted.
5 That's why I call it the product life cycle
6 measurement using PBPK.
7 In summary, the quality in vivo performance
8 is a destination and the ultimate goal and the
9 primary consideration for PBPK modeling in the
10 biopharmaceutics area. Mechanistic oral absorption
11 is a powerful tool, and the models support a
12 decision on product quality specification and risk
13 assessment. Model performance and validation is
14 key to get it through.
15 Finally, I would like to acknowledge my
16 colleagues, Hopi, Fang and Sandra, Meng and Heta,
17 Paul and our office management. Sorry about over
18 time.
19 Thank you very much.
20 (Applause.)
21 DR. L. ZHAO: Thank you, John.
22 The next speaker, Dr. Susie Zhang from OGD,

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1 Office of Research and Standards.
2 Presentation – Xinyuan Zhang
3 DR. ZHANG: Good morning, everyone. Welcome
4 to the workshop. It's my great pleasure to be here
5 today to talk about OGD's experience in research
6 efforts on oral absorption modeling and simulation.
7 I'm so excited today, so if you hear a choppy
8 presentation, it's not because I'm not familiar
9 with this topic, but because I'm so excited.
10 (Laughter.)
11 DR. ZHANG: For today's presentation, I will
12 give you an update on oral absorption modeling and
13 simulation in the Office of Generic Drugs, and then
14 I will share a couple of case examples with you,
15 and, finally, talk about GDUFA-funded research
16 efforts to improve oral absorption modeling and
17 simulation.
18 In 2011, we published this paper, published
19 a review article, where we put an innovative model
20 for future product development. Basically in this
21 diagram, we have industry, and hopefully industry
22 will use this type of tool to help their product

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1 development, conduct pilot BE studies or PK studies
2 and inform model development, and use this tool to
3 reduce the cost and time.
4 Today, we'll have the opportunity to hear
5 about industry, how industry uses this type of tool
6 to help their product development. In this
7 diagram, we have regulatory agency who will also
8 use this type of tool to help guidance development,
9 to propose innovative bioequivalence approaches for
10 complex drug products, and the agency and the
11 industry will communicate via different venues,
12 such as face-to-face meetings, conferences or
13 workshops like we do here today.
14 As you just heard in John's presentation,
15 where he gave an excellent example where industry
16 or the firm used a physiologically-based absorption
17 model to propose their particle size distribution,
18 and this is exactly what we proposed here five
19 years ago.
20 How are we doing today? In 2014, we
21 published a short commentary paper in which we
22 described several case examples of where and what

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1 issues we applied this mechanism-based absorption
2 modeling and simulation to address various
3 regulatory activities. The paper actually was
4 written in 2013.
5 We described some of the areas where we
6 used, and the majority of the issues are related to
7 dissolution or product quality, and also
8 innovatively use in the other areas. Whenever I
9 look at this figure, I'm always amazed by the
10 potential utility this tool can provide, as well as
11 being amazed by the creativity our scientists have.
12 Recently, we have a couple of examples
13 asking the question about bioequivalence in
14 proton pump inhibitor subjects, or the PPI related
15 DDI.
16 You saw this figure that Liang just
17 presented, but what he did not tell you is that we
18 only had a couple of staff members working on this
19 area part-time, hands-on experience. So we have
20 about four to five examples every year before 2014,
21 and we had low productivity in 2014, because we
22 were busy on hiring and also other activities, such

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1 as issuing new GDUFA research studies.
2 We had new people onboard in 2015 and now
3 we're in 2016, we have more examples here. It's
4 exciting.
5 Now, this is a simplified absorption
6 process. There's by no means that the figure can
7 capture all the events happening in GI for a drug
8 to be absorbed. But as you can see here, even for
9 a simplified absorption process, it's already very
10 complicated, and for the sake of time, I'm not
11 going to go through the details of this figure.
12 It's been described heavily in the article.
13 When we do a model, this type of modeling,
14 this is our general practice. We usually collect
15 data from different resources, including
16 literature, our internal data, and then we perform
17 physiologically-based modeling for IV formulation
18 first. If IV is not available, we'll do it for IR
19 solutions, suspensions, tablets, capsules, and then
20 we move forward to the modified-release products.
21 We'll do model verification or validation,
22 whatever you call it, extensively, as much as we

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1 can against datasets that we have. And finally,
2 we'll do a simulation.
3 Now, because I'm in the Office of Generic
4 Drugs, bioequivalence simulation is really
5 important for us. However, it's not that easy,
6 because a lot of times, the intra-subject
7 variabilities are not available.
8 In 2015, we published a paper describing how
9 we do this, this type of modeling. In this case,
10 we won't run a single bioequivalence trial.
11 Instead, we will run thousands of bioequivalence
12 trials and give you a passing rate of BE studies.
13 It's more like a probability rather than a
14 definitive answer.
15 Now, I'll share a couple of case examples
16 with you, and the first example is about warfarin
17 sodium tablets, to evaluate the impact of slow
18 dissolution in a specific pH conditions.
19 Specifically, it's pH 4.5.
20 The second example is to evaluate the proton
21 pump inhibitor impact on bioequivalence, and we
22 have a couple of drug products in that example.

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1 Warfarin sodium tablets, from a modeling
2 perspective, it's not a complicated product.
3 Warfarin sodium has been reported as a BCS-I
4 substance, and this is an immediate-release
5 formulation. The challenging part to me is how do
6 we communicate the results to scientists who do not
7 do modeling and simulation.
8 Back in 2014, we actually did the modeling
9 simulation in 2014, among other things. OGD became
10 a super office in 2014. The Office of Research and
11 Standards was born in 2014, and among a lot of
12 other significant events, we did this piece of
13 modeling and simulation work.
14 The specific aim of this project is to
15 explore the impact of loss of IPA on in vivo
16 performance for warfarin sodium tablets. The
17 background of this project is that scientists
18 observed that for warfarin sodium tablets, if they
19 are put in high temperature and high humid
20 conditions, the IPA will be lost, and then what you
21 observe is slow in vitro dissolution in pH 4.5
22 condition. Does that impact bioequivalence or

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1 bioavailability? That was the question asked.
2 So we did a modeling and simulation. In
3 this case, we had two scientists perform modeling
4 and simulation in two different platforms, and,
5 basically, they reached the same conclusion.
6 Let's take a look at the warfarin sodium
7 substance properties. It has a PKa around 5. It
8 has low solubility in low pH conditions and high
9 solubility in high pH conditions. And these are
10 the two solubility versus pH profiles input in the
11 different software.
12 This is a commonly observed scenario, where
13 we observe different numbers reported by different
14 resources. In this table, the dissolution
15 profile A is what was measured, and dissolution
16 profile B, C, D, F are arbitrary dissolution
17 profiles to test solubility versus pH profiles to
18 test the sensitivity of PK on solubility.
19 Then warfarin has a long half-life, average
20 40 hours, range 20 to 60 hours. We did the
21 simulation, and what it told us is that the PK
22 profile is not that sensitive to solubility, even

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1 though you gave extremely low solubility in low pH
2 conditions.
3 We did sensitivity analysis on particle
4 size, as well as particle density, and they are not
5 that sensitive. They don't impact PK
6 significantly, either.
7 This is a straightforward figure for a lot
8 of clinical pharmacologists. Because the model is
9 a linear model, there's no nonlinearity component
10 in the model. However, I put it here because it's
11 also a figure related to an important quality
12 attribute, which is the assay or potency.
13 Potentially, this figure can be used to define your
14 assay or potency specification range.
15 Now, in order to link the in vitro
16 dissolution profile to in vivo performance, we used
17 the so-called Z factor model, where Z is an empiric
18 number here. We fit dissolution profiles in
19 different pH and get the Z number and put it in the
20 model.
21 We also conducted on several artificial
22 dissolution profiles, basically. We pushed it to

<p style="text-align: right;">Page 53</p> <p>1 extreme cases, where you don't have release at all 2 in the different pH conditions, and now what you 3 can see is in this extreme case, where you don't 4 have any dissolution at all in pH 1.2 and pH 4.5 5 conditions, you keep dissolution pH 6.8 the same. 6 You see the Cmax ratio is above 0.8. Among other 7 sensitivity analysis, what we concluded was that pH 8 6.8 is the most relevant or in vivo relevant 9 condition. 10 Now, meanwhile, we also issued a study or 11 awarded a study in 2014 actually, and then we 12 conducted a dissolution study again in 2015. We 13 put warfarin sodium tablets in high humid and high 14 temperature conditions for 24 hours to have a 15 lower, slower dissolution in pH 4.5 conditions. As 16 you can see, these are the dissolutions in pH 4.5 17 after the tablets were treated. 18 We compare if you conduct an F2 test 19 comparing the untreated tablets and the treated 20 tablets. The F2 value is actually less than 50. 21 We also did a two-state dissolution test for 22 the treated and untreated tablets. As you can see,</p>	<p style="text-align: right;">Page 55</p> <p>1 pH 4.5 at 30 minutes above 30 percent and 2 dissolution in pH 6.8 at 30 minutes above 80 3 percent. 4 This is actually a pretty wide range. When 5 we look back at all the dissolution studies that we 6 have conducted, they all pass this condition. 7 The conclusion from this study is that 8 solubility in low pH, particle size and particle 9 density do not have a significant impact on 10 bioavailability of warfarin sodium, and the dose or 11 the potency impacted PK proportionally. 12 Dissolution rate at pH 6.8 was the most relevant to 13 bioavailability, and we did an in vivo to confirm 14 the prediction. 15 The second example is an example where we 16 used this type of tool to evaluate the 17 bioequivalence in stomach pH elevated subjects, and 18 we did it for prasugrel hydrochloride tablets and 19 fingolimod capsules. If we look at the drug 20 substance properties of these two compounds, they 21 have different indications. They have different 22 pKas. But they all have high solubility in low pH</p>
<p style="text-align: right;">Page 54</p> <p>1 the initial dissolution for the treated tablets is 2 slower. However, they catch up at two hours. 3 Again, we did this type of analysis and, also, 4 bioequivalence simulation using the newly available 5 dissolution profile, and what you can see is that 6 the predicted point estimate for Cmax, as well as 7 AUC are close to 1. 8 Now, we're in 2016. We got in vivo 9 bioequivalence study results finally, and what the 10 results tell us, basically, is consistent with what 11 the simulation told us. If you compare all the 12 pairs of comparisons, the point estimate of Cmax 13 and AUC, they're pretty close to 1, as well, and 14 the confidence intervals are pretty narrow, as 15 well, because this is what's expected, as warfarin 16 is a narrow therapeutic index drug. 17 We went ahead using this sensitivity 18 analysis technique, tried to map a dissolution 19 space where you can have a safe equivalent product. 20 We used within standard deviation 0.1 and point 21 estimate 95.5, and if you want to have an 22 80 percent passing grade, you have dissolution in</p>	<p style="text-align: right;">Page 56</p> <p>1 and low solubility in high pH. 2 The half-life for prasugrel is about seven 3 hours. However, the half-life for fingolimod is 6 4 to 9 days. It's pretty long. 5 The issue for prasugrel hydrochloride 6 tablets is that it is the concern of salt-to-base 7 conversion during manufacturing or storage, 8 different conditions, and because the base has low 9 solubility. Whether the salt-to-base conversion 10 will lead to lower bioavailability, that was the 11 question. 12 For fingolimod capsules, the question was 13 whether similar dissolution observed in high pH 14 conditions would impact bioequivalence. 15 Again, we conducted mechanism-based 16 absorption modeling and simulation, and our 17 recommendation based on the simulation is that the 18 salt-to-base conversion for prasugrel hydrochloride 19 tablets should be controlled, and elevated stomach 20 pH is less likely to impact PK significantly for 21 fingolimod capsules. 22 Prasugrel is a quite complicated drug</p>

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

5 We developed a model, validated a model
6 against two moieties, two metabolites. This figure
7 shows that if we use the observed solubility
8 profile, the model actually under-predicts the C_{max}
9 at high dose. Why is that? We can exclude other
10 possible scenarios and conclude that this could be
11 due to the -- this looks like the solubility limit.

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

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

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

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

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

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

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

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

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

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

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1 used in this type of model and improve model
2 predictability.

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

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

15 We are dealing with multiple data sources,
16 not only the quality, but also the PK. If you have
17 10 ANDAs for the same reference product, you see
18 several folds of differences in PK profiles, and
19 we're dealing with extremely low solubility drug
20 products. That can be challenging.

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

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1 those can be considered as complex
2 immediate-release formulations. The models need to
3 be improved for colon absorption, because we are
4 doing more and more modified-release drug products,
5 and colon absorption is very important to have a
6 better prediction for those types of products.
7 In addition to internal hands-on experience
8 in modeling and simulation, we also have a lot of
9 Generic Drug User Fee Amendment or GDUFA-funded
10 research efforts to improve oral absorption
11 modeling and simulation. We have several ongoing
12 studies. We have multiple BE studies in the human,
13 including a lot of drug products, that could
14 potentially be used to verify our model.
15 We also have a couple of studies ongoing to
16 measure in vitro and, also, in vivo performance of
17 solid dispersion formulations.
18 We have an ongoing study with the University
19 of Michigan to measure GI physiology to get
20 intra-subject variance. Basically, that measures
21 the same subject twice. Hopefully, they can come
22 back for the second experiment, because this is

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1 really a tough experiment and the dropout rate is
2 pretty high.
3 We have innovative sampling methods for a GI
4 concentration study ongoing, and we recently
5 completed a mesalamine study, which measures the
6 local GI concentration. The manuscript is under
7 preparation.
8 We also have excipients-targets,
9 excipient-transporters interaction studies to
10 better understand excipients' impact, transporters
11 and further absorption.
12 This year, we have three requests for
13 applications. The first one is related to
14 supersaturation precipitation of the very low drug
15 substance to improve the absorption modeling in
16 that area. The second one is to improve the
17 optimization algorithm for the very large
18 physiologically-based pharmacokinetic oral
19 absorption models.
20 The third study is to study the fluid
21 amounts taken with oral drug products. Right now,
22 our recommendation is 250 milliliters. So what

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1 happens in the real world? We'll find out from
2 this study.
3 Besides the external studies, we also have
4 internal research efforts. We are evaluating the
5 modified-release products, the risks associated
6 with the mechanism change from osmotic pump to
7 metrix, how that is going to impact the BE in
8 different populations. We are doing formulation
9 analysis for BCS III compounds. We are developing
10 a physiologically-based pharmacokinetic database to
11 share these types of models across the agency with
12 different offices, such as Office of Clinical
13 Pharmacology and also Division of
14 Biopharmaceuticals. We're investigating alcohol
15 dose dumping simulations. These are the long-term
16 studies, we're doing here and there when there's no
17 crisis.
18 To summarize, OGD has routinely applied
19 mechanism-based absorption modeling and simulation
20 to address various issues, risks in regulatory
21 activities. I want to remind you, you still
22 remember the slide that Liang just showed, the

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1 impact that modeling and simulation has. You see
2 the distributions and the numbers. The least
3 number actually falls into the category of ANDA
4 applications. That means that could potentially be
5 an area to improve.
6 OGD is actively improving the science of
7 predictions for oral solid dosage forms via
8 external, as well as internal research studies.
9 OGD is willing to collaborate with internal and
10 external stakeholders to advance the application of
11 mechanism-based absorption modeling and simulation
12 in drug product development and regulatory review.
13 Along the way, there are a lot of people and
14 colleagues who support us here and there from
15 different aspects, and I want to use this
16 opportunity to thank them, as well, and also thank
17 you for your attention.
18 (Applause.)
19 DR. L. ZHAO: Thank you, Dr. Susie Zhang.
20 This will conclude the presentations from
21 the FDA. We will have a break, 20 minutes. You
22 can use the break to stretch and whatever,

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1 socialize. We'll be back before 10:15, followed
2 with three excellent speakers.
3 (Whereupon, at 9:57 a.m., a recess was
4 taken.)
5 DR. L. ZHAO: While we are being seated, let
6 me introduce the next session. The next session
7 will be presented by three outstanding experts in
8 the field. The first one is Dr. Filippou
9 Kesisoglou. I can confirm with him that I can
10 pronounce his name in the correct way.
11 (Laughter.)
12 DR. L. ZHAO: Following him, there will be
13 Dr. Jasmina Novakovic. Following Dr. Novakovic
14 will be the top expert from academia, Dr. Gordon
15 Amidon.
16 The first presenter, Dr. Kesisoglou.
17 Presentation – Filippou Kesisoglou
18 DR. KESISOGLOU: Thank you for the
19 introduction and the opportunity to speak today at
20 this forum and provide an industry view on how oral
21 absorption modeling and simulation are used for
22 formulation development and bioequivalence

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1 evaluation of new drugs.
2 My talk will mostly focus on case studies
3 that demonstrate the different applications of the
4 tools. However, at the end I will also provide
5 some thoughts on what I see the field moving
6 forward both in terms of the formulation
7 development application, as well as for regulatory
8 directions.
9 Before jumping into the case studies, I
10 wanted to set the background under which these case
11 studies were developed and are presented. The use
12 of these tools is part of a broader
13 biopharmaceutics risk assessment effort and a
14 quality-by-design effort with the endpoint, as
15 mentioned earlier today, the patient benefit, as
16 that is defined by the quality target product
17 profile.
18 In the simplest terms, what we are trying to
19 achieve with these tools can be broken down into
20 two parts. First, we are trying to understand what
21 is the optimal in vivo release or dissolution of
22 the dosage form that provides the intended

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1 therapeutic dose response to the patient. And
2 second, we are trying to link that in vivo response
3 to an in vitro assay, commonly dissolution, that
4 can be used in the future to ensure the future
5 product consistently delivers a therapeutic benefit
6 to the patient.
7 In addition, it's important to keep in mind
8 that these models are not applied in isolation from
9 other efforts, but are part of a broad lateral
10 confirm effort where data from in vitro, in silico,
11 and in vivo, either pre-clinically or clinically,
12 are integrated both to inform the models and inform
13 forward-looking projections, but also to refine the
14 assays that inform the model.
15 I know there's a lot of discussion on how we
16 validate the models, and I think it's important to
17 keep in mind that we need to adopt the model to the
18 question at hand, not necessarily looking for broad
19 validation against questions that might not be
20 relevant to the specific project, as well as when
21 models fail, in my experience, it's usually not
22 because the model itself is incorrect, but because

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1 somewhere in this continuum, we have a disconnect
2 in our understanding of where the in vitro or the
3 in vivo data feed into the model.
4 With that background, I will argue that for
5 new drug development, use of absorption modeling is
6 a commonplace activity that's routinely applied,
7 especially for BCS Class II and IV compounds.
8 Models that guide first-in-human doses or
9 formulation selections or subsequent formulation
10 modifications, such as API particle size or release
11 rates for modified-release formulations, are
12 routinely applied in early development.
13 Projections of bioequivalence are also relatively
14 common. They are mostly applied for what we call
15 internal biowaivers, so internal decision-making on
16 conducting or not clinical studies, and can be
17 applied for more regulatory applications for more
18 well-behaved compounds, as we heard earlier today.
19 In the last few years, models around
20 clinical biopharm questions are getting attention.
21 Food effect projections or projections of DDIs with
22 pH altering agents are also showing up in several

<p style="text-align: right;">Page 69</p> <p>1 papers in the literature. Again, they are mostly 2 conducted for internal decision-making or to inform 3 formulation decisions. 4 Typically, the studies are conducted as far 5 as clinical practice goes, but one can see the 6 potential in the future to serve as a surrogate for 7 some of these clinical studies. 8 Finally, and I will come back to that at the 9 end of my talk, I think the area that's gaining 10 increased attention is linking the dissolution to 11 PK to drive IVIVCs, in vitro-in vivo correlations, 12 and drive what we heard this morning, clinically 13 relevant specifications. And I think that's the 14 area that we could potentially make a significant 15 impact on patient benefit, because it directly 16 ensures product quality. 17 Jumping into the case studies, the first 18 case study is an early formulation decision 19 example. In early development, the models are 20 primarily used to define the general platform of 21 the formulation we're going to use to ensure 22 adequate exposures in our first-in-human studies.</p>	<p style="text-align: right;">Page 71</p> <p>1 dose simulation that's taken out of the parameter 2 sensitivity analysis that I showed before showing 3 the exposure under normal and accelerated 4 conditions simulated by PBPK. 5 We need to verify our model somehow. As I 6 mentioned, models should not be standing on their 7 own, without any data verification. In that case, 8 we conducted a preclinical study, where we tested 9 animals with pentaglycine that simulates stomach pH 10 and famotidine that suppresses it, and we see a 11 quantitative agreement between the simulations and 12 the preclinical data. So we have some confidence 13 that our model can be used to inform formulation 14 development. 15 The next step is to project new 16 formulations. So we have to plug in some new 17 information. In this case, we plug in dissolution 18 data generated in media intending to simulate the 19 PPI stomach. 20 With this data, we can project the PK for 21 the different formulations. Our target exposure 22 level is the dashed line. So we identify a few</p>
<p style="text-align: right;">Page 70</p> <p>1 This compound is a weak base compound, and in early 2 development, we often do this parameter sensitivity 3 analysis to identify the main factors that can 4 influence a formulation decision. 5 In this case, the draft shows a parameter 6 sensitivity analysis for this weak base, the 7 fraction absorbed as a function of the stomach pH, 8 and the dose of what we were trying to cover in our 9 first-in-human study. The simulation shows that as 10 long as the stomach pH is in the normal 11 physiological range, which is roughly 1 to 3, we're 12 going to get reasonably good exposures, 80 percent 13 or 90 percent, while if the stomach pH increases 14 significantly, then we will see a reduced exposure. 15 With this information, we can move to the 16 first-in-human study and defer mitigating with a 17 dose interaction later, as we want to get some 18 assurance on the PK of the compound. In the first 19 in-human study, we did observe good exposures, 20 linear PK through the dose range tested. 21 Then let's go on to mitigating the pH 22 interaction. On the left-hand side is a single</p>	<p style="text-align: right;">Page 72</p> <p>1 formulations that look promising, and we also 2 compared our modeling and simulation projections 3 against preclinical validation to make sure, again, 4 that the model is behaving as it's supposed to be 5 behaving. Eventually, formulation 4 is identified 6 as a high possibility of success to move forward, 7 and that was verified subsequently in a clinical 8 study. 9 In this example, I just mentioned 10 incorporation of dissolution data, and 11 incorporating dissolution data is probably the most 12 important aspect of oral absorption modeling. This 13 case study, I really like it. It's from colleagues 14 at Eli Lilly, where they looked at both mechanistic 15 modeling over dissolution linked to a mechanistic 16 model, a PBPK model. 17 They're dealing with a BCS I compound. One, 18 we think it's easy, but they're using an enteric- 19 coated pill to protect the drug from stomach 20 instability. What the authors did was they 21 modified the standard dissolution operation that's 22 part of every PBPK software to describe the</p>

<p style="text-align: right;">Page 73</p> <p>1 dissolution of their enteric-coated system. They 2 got pretty good agreements between the dissolution 3 simulation and the experimental data for two 4 formulations that differ from their drug loading. 5 The question is, is this difference in 6 dissolution relevant for exposure? On the 7 left-hand side is a simulation of a human clinical 8 study. You can see that the simulation suggests 9 that despite the dissolution differences, the 10 profiles are super-imposable. On the right-hand 11 side is the actual observed clinical data from the 12 clinical study that verified the simulations. 13 What the authors also did was they conducted 14 a parameter sensitivity analysis to identify the 15 boundaries in which dissolution will fail the 16 bioequivalence, and what they can find is that even 17 with an 80 percent dissolution in two hours, they 18 will still get sufficient exposure, with no impact 19 on AUC and minimal impact on Cmax. This 20 information and exploring these boundaries can 21 really help in the future if there was a clinically 22 relevant specification.</p>	<p style="text-align: right;">Page 75</p> <p>1 We verified the model against several protocols, 2 what we had clinical data on. 3 The interesting graph on this slide is not 4 the verification of the model. Everyone shows the 5 graphs that go through the lines. That's pretty 6 common. The graph on the right shows what the PBPK 7 software suggests, that the behavior of the drug is 8 in vivo. 9 The drug goes into dissolution to about 80 10 percent or so in the stomach, where it has high 11 solubility, and then because the solubility of the 12 intestine is actually not that bad, there's 13 relatively little precipitation until it reabsorbs 14 almost completely. While the drug is classified as 15 a BCS Class II compound, in reality, in vivo, it 16 behaves more like a permeability-limited compound. 17 With that information, one could expect the 18 stomach solubility will be more important. 19 Regardless, we did conduct the simulation assuming 20 any of the dissolution profiles are relevant to the 21 in vivo performance. So we conducted simulations 22 in a virtual trial based on the pH 1.2, 4.5 and 6.8</p>
<p style="text-align: right;">Page 74</p> <p>1 Moving from a single stage dissolution to a 2 multimedia dissolution question, that often comes 3 up when we're talking about bioequivalence 4 questions. In this case, etoricoxib is a weak 5 base. It's a BCS Class II compound, with very high 6 solubility in the stomach, but relatively low 7 solubility of the intestine. It's not the worst 8 solubility you'll find, but it's enough to make it 9 a BCS Class II compound. 10 So we were dealing with a site transfer, 11 where we're manufacturing supplies at two different 12 sites, and according to the regulations for the 13 markets we're filing, we had to do a multimedia 14 dissolution comparison for this change. On the top 15 graph, at pH 1.2, we saw no differences between 16 supplies from the new and the old site. But at pH 17 4.5, at pH 6.8, they're very similar, we see 18 significant differences with new site supplies 19 being faster, where we're clearly failing the F2 20 similarity criteria. 21 We were asked, does this translate to a 22 bioequivalence issue. We first developed a model.</p>	<p style="text-align: right;">Page 76</p> <p>1 profiles. 2 I'm not showing the 1.2 outcomes, because 3 it's obviously going to show the same effect since 4 they're super-imposable. But basically, the 5 dissolution at 4.5 and 6.8, we were projecting up 6 to 10 or 14 percent differences in AUC and Cmax. 7 They're not large differences. 8 You can possibly call them still 9 bioequivalent, but we conducted the clinical study. 10 And basically, the result is that everything is 11 identical. The dissolution difference does not 12 translate to the in vivo differences, as suggested 13 by the pH 1.2 dissolution. So in this case, the 14 clinically relevant dissolution is the pH 1.2, and 15 we can use it in the future to understand future 16 product changes. 17 One more CMC question that often comes up is 18 around API form and changes in API form in the 19 formulation, for example, due to a stomach 20 excipient interaction or instability. This 21 compound is dosed as HCl salt. It's a weak base, 22 BCS Class II, again, high solubility in the</p>

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

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

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

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

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1 exhibits regional dependent absorption. So it's
2 reduced by variability as the drug is dosed further
3 down the GI tract.
4 We used data from six formulations, three
5 matrices and three multi-particulates. There were
6 doses in the clinic against the immediate-release
7 dosage form.
8 The PBPK model allows us to incorporate the
9 regional absorption into the model. These
10 absorption scale factors, which for simplicity you
11 can think of them as a correction factor on the
12 intestinal permeabilities for each of the regions,
13 you can see, were fitted for the data for the
14 modified release. They are decreasing as we go
15 down the GI tract.
16 They mimic what we know experimentally for
17 the compound, and we get pretty good agreements
18 with the observed simulated data for all six
19 formulations. That allows us to build a PBPK model
20 for the IVIVC question. The performance of this
21 model was very similar to a more classical
22 deconvolution/convolution model we also developed.

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1 These case studies cover where I think we
2 are today. As I said, I think we're in a pretty
3 good place, and these models are routinely applied.
4 What do I expect to see moving forward?
5 First, I do expect to see an increased application
6 of these models to understand fundamental biopharm
7 questions and inform clinical study designs the
8 same way DDI models have done over the years. I
9 think our clinical pharmacology colleagues, at
10 least in the industry, are now becoming more
11 familiar with these oral absorption models. They
12 can trust them more for clinical study designs.
13 I do expect to see an increased utilization
14 of the models in CMC filing sections mostly as
15 supportive arguments for formulation development
16 and partly by design argument. I have to qualify
17 this, and I think it was mentioned in the morning.
18 A lot of the times, some of the models will not
19 make it into the filing because the decisions are
20 made earlier. So the model might not be relevant
21 to the formulation we're trying to commercialize.
22 If the models are relevant to the final

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1 formulation, I do expect to see an increased
2 appearance of these models.
3 Finally, the area I think where we'll see
4 more and more application is the use of the
5 absorption modeling for IVIVC and informing
6 clinically relevant specifications. I will admit
7 we are still not there. All of the tools are in
8 place to actually do this.
9 We typically talk about biorelevant
10 dissolution and quality control of released method
11 dissolution data separately, as two separate
12 entities. However, we have the modeling tools in
13 place that one can start using both of them
14 together to drive a clinically relevant
15 specification.
16 Specifically, one can use models to
17 essentially deconvolute the in vitro data and get
18 the inherent formulation behavior, which will be
19 dissolution method independent and then use that
20 information in the PBPK modeling or your IVIVC
21 modeling to project clinical performance.
22 As I showed you in some of the examples, use

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1 the PBPK modeling to test the boundaries of
2 performance to understand why you're going to see
3 failure of your formulation and then translate that
4 back to a dissolution specification for your final
5 product, much as how it's currently done for
6 traditional IVIVCs for modified-release products.
7 Finally, I think regulatory guidances can
8 also serve as another catalyst to push use of these
9 models. For example, guidances around modeling
10 acceptance, the qualification criteria for IVIVC,
11 and bioequivalence questions, there is a
12 traditional IVIVC guidance which we'll be following
13 that one.
14 A regulatory framework around clinically
15 relevant specifications, especially for
16 immediate-release products, I think
17 modified release is a little bit more clear what we
18 should be doing, but immediate-release is a little
19 bit more difficult. Global harmonization might be
20 a concern there.
21 Finally, as I mentioned, guidances on using
22 some of these models as surrogates of clinical

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1 studies, as currently done for DDIs.
2 With that, I would like to acknowledge the
3 PQRI Biopharmaceutical Technical Committee and the
4 AAPS Quality by Design and Drug Product Performance
5 Focus Group for some of the concepts that I'm
6 presenting today and colleagues at Merck for help
7 with the slides.
8 I'm looking forward to the remainder of the
9 workshop. Thank you.
10 (Applause.)
11 DR. L. ZHAO: Next speaker, Dr. Novakovic.
12 Presentation – Jasmina Novakovic
13 DR. NOVAKOVIC: Good morning, everybody. I
14 am here today on behalf of Generic Pharmaceutical
15 Association, and the title of my presentation is
16 "Modeling and Simulations for Development and
17 Bioequivalence Evaluation of a Generic Drug
18 Product."
19 So what is Generic Pharmaceutical
20 Association? This is an association that
21 represents the manufacturers and distributors in
22 the area of generic pharmaceutical products,

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1 including suppliers and manufacturers of active
2 materials.
3 At the beginning, I would like to start with
4 major phases of generic drug product development.
5 It starts with characterization of a referenced
6 drug product followed by design of the generic
7 product and process, and these two stages are
8 so-called early development. Once generic drug
9 product and process are defined, the manufacturing
10 pivotal biobatch, that biobatch is subjected to
11 bioequivalence studies against reference product.
12 And if the outcome is positive, it means if the
13 product shows bioequivalence, then we are moving
14 into commercial manufacturing and product enters
15 its life cycle. These are post-approval stages.
16 In today's presentation, I would like to
17 talk about roles of physiologically-based
18 pharmacokinetic modeling and simulations at early
19 development stage, as well as throughout life
20 cycle, and quality risk management of a generic
21 drug product.
22 Where are the opportunities for PBPK

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1 modeling and simulations? First, we have to start
2 with characterization of a reference-listed drug.
3 Definitely, PBPK modeling and simulations has its
4 role. Then when we are developing product and
5 process, we are also using PBPK as a tool to
6 facilitate product development. Eventually,
7 biobatch or bio lot is manufactured and subjected
8 to biostudy.
9 How do we select bio lot? Among multiple
10 trials, we can select bio lot by using PBPK as a
11 tool. Also, once biobatch is manufactured,
12 stability is starting. At that time, we should
13 already have a specification. Ideally, the
14 specification should reflect bioequivalence or
15 should be clinically relevant. Therefore, PBPK
16 modeling and simulation is also important for us.
17 Once the product is shown to be
18 bioequivalent and commercial manufacturing is
19 starting, the product is subjected to changes, and
20 life is change, and, therefore, we cannot avoid
21 changes to the product sometimes. And these are
22 minor changes to the composition or changes in the

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1 process.
2 In order to assess impact of these changes
3 on drug behavior in vivo, we can use PBPK modeling
4 and simulations. These are the opportunities, but
5 what is the real situation? Based on a survey that
6 has been conducted recently on a very limited
7 number of participants, PBPK modeling and
8 simulation is underused in the generic
9 pharmaceutical industry.
10 About 75 percent of respondents said that
11 they are using it for characterization of
12 reference-listed drug and development of the
13 process. The same percentage approximately is
14 using it to assess product ability to meet
15 bioequivalence versus innovative product, and about
16 50 percent said that it is used to develop
17 manufacturing process.
18 On all other areas, it seems to be unused,
19 but as I said, the sample size for the survey was
20 very small. So it is difficult to say that it is a
21 true representation of the situation.
22 In this presentation, I would like to share

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1 with you our experience at Apotex at this time
2 about application of physiologically-based modeling
3 and simulation at early development stage, as well
4 as throughout the product life cycle.
5 Let's start with early development. At
6 early development stage, we would like to
7 characterize the reference-listed drug in terms of
8 the attributes critical for in vivo performance and
9 to define target product profile. Also, we would
10 like to use that information to facilitate
11 formulation design and define development strategy
12 to achieve bioequivalence with reference-listed
13 drug.
14 So this is an example from our practice. We
15 started with reference-listed drug
16 characterization, and these are the tools and input
17 in that we needed. We used GastroPlus v. 8. We
18 had physicochemical and PK properties of the
19 active pharmaceutical ingredient. Dosage form and
20 dosage strength were known to us. Route of
21 administration, pH solubility profile of the active
22 ingredient. Plasma concentration versus time data

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1 or PK profile and in vitro early-release profile,
2 that is optional, but it can be always generated
3 in-house.
4 More specifically, the drug was a BCS class
5 steroid. It was an immediate-release tablet, 250
6 milligram dosage strength, molecular formula and
7 molecular weight unknown. Log D, pKa, Caco-2
8 permeability are known. pH solubility profile for
9 the active ingredient has been developed or
10 generated in-house, and the PK parameters,
11 including the plasma protein binding, were known.
12 Plasma concentration versus time profile was
13 available in the literature. In vitro dissolution
14 profile was generated in-house, but it was used for
15 information purposes only.
16 So this is pH solubility profile of the
17 active ingredient measured in-house. It is obvious
18 that the compound has very low solubility,
19 especially at pH above 2. We incorporated all the
20 information that I mentioned before into the model,
21 and we got a simulated profile represented by the
22 full line much, much lower than the observed

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1 profile represented by the active squares.
2 So we asked ourselves what was the reason,
3 and when trying to find the answer, we approached
4 it taking into account the so-called parsimony
5 principle, which means the simplest possible
6 hypothesis among multiple hypotheses is most likely
7 to be the correct one.
8 What we did, we modeled solubility. The
9 blue line in the plot is the modeled solubility
10 profile, and the red line is the experimental
11 solubility. We incorporated the model solubility
12 into the model, GastroPlus model. As the result,
13 we got simulated PK profile represented by a full
14 line, which practically overlaps the experimental
15 or the PK profile reported in the literature.
16 What was the conclusion that we made based
17 on this? We realized that solubility enhancement
18 based on the modeling results is necessary to
19 achieve bioequivalence. So we focused our
20 development strategy around solubility enhancement,
21 and we were fortunate to achieve bioequivalence.
22 Actually, our product achieved bioequivalence

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1 against the referenced product.
2 Now, I would like to move to commercial
3 product manufacture and life cycle management and
4 modeling and simulations to ensure quality risk
5 management. In this case, our product was a BCS I
6 drug formulated as extended-release matrix-based
7 formulation in multiple strengths, exhibiting
8 linear pharmacokinetics. Bioequivalence versus
9 reference product was proven for the lowest and
10 highest strengths.
11 Formulations subjected to biostudies
12 exhibited different release rates in one of the
13 first medium. The question was, is this relevant
14 to the product in vivo performance. We were pretty
15 much sure that it wasn't relevant, because both
16 strengths exhibited bioequivalence, but classical
17 biowaiver justification for the intermediate
18 strengths or different strengths was challenged due
19 to such discrepancy of the solution profiles in one
20 of the test medium.
21 Our question was, is the science-based
22 approach that employs modeling and simulation

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1 applicable. What we did, first, we tried to
2 identify bio indicative solution test conditions
3 and to establish clinically relevant specification
4 limits to ensure bioequivalence. Then we designed
5 a biostudy waiver for the intermediate strengths
6 that can be used eventually for SUPAC changes, and
7 it was IVIVC Level A correlation. We used that
8 correlation to establish boundaries for critical
9 material attributes of a rate-controlling polymer
10 to ensure in vitro release within clinically
11 relevant specification limits.
12 Let's start with bio indicative, the
13 solution test condition, and specification limits
14 that we established to ensure bioequivalence. So
15 the first thing that we did was to reveal regional
16 gastrointestinal absorption profile of our drug.
17 Why it is helpful, it is helpful because it tells
18 us what should be our starting point in terms of
19 designing these solution test conditions. At least
20 we knew the pH of the region our drug -- by knowing
21 the region our drug is absorbed, we know the pH of
22 the media, and that is most likely to be reflective

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1 of drug in vivo behavior.
2 What we had, we had three bio lots and
3 corresponding release profiles for the three
4 bio lots. The PK profiles of the three bio lots
5 are presented without dose normalization. So the
6 lowest strength is presented in red squares, and it
7 was bioequivalent to the corresponding strength of
8 the reference-listed product. And the highest
9 strength, in teal, is also bioequivalent with the
10 corresponding strength of the reference-listed
11 product, and the highest strength, presented in
12 green, was bioequivalent, but with borderline
13 confidence.
14 You can see in the dissolution plot that
15 dissolution or release rates correspond to biostudy
16 results. There is rank order between results of
17 the bioequivalence studies and dissolution or
18 release rates. We used that information to
19 establish in vitro-in vivo correlation, and Level A
20 in vitro-in vivo correlation has been established
21 with a regression coefficient which is above 0.9,
22 which is very good for such situations.

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1 Now, we know that our dissolution test
2 method is bio indicative or biorelevant or
3 bio discriminatory. Our next task was to establish
4 specification criteria for the bio indicative
5 dissolution test method.
6 How we did it, we created number of
7 hypothetical batches with different release rates,
8 and we incorporated those release rates into
9 modeling and simulation. Based on the output, we
10 could specify what are upper and lower
11 specification limits for our product that would
12 result in bioequivalence.
13 So this is the plot representing dissolution
14 profiles and upper and lower specification limits.
15 The limits are presented in red dotted lines. The
16 biobatch, which was so-called borderline biobatch,
17 bioequivalent, but with borderline confidence
18 interval, is presented in blue. That borderline
19 batch is outside the lower specification limits.
20 We also introduce something that we call
21 gray area, and that gray area is a reflection of
22 prediction error. By having that product which

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1 meets specification criteria, we assure that that
2 drug product would be bioequivalent to the
3 corresponding reference-listed drug.
4 At this point, I would like to mention
5 differences between biorelevant and QC dissolution.
6 These two methods may be different methods, and in
7 most of the situations, they are different methods.
8 QC method is used routinely, but it could be overly
9 discriminating or bio irrelevant. Bio irrelevant
10 methods may be complicated and impractical for
11 routine applications, but these two types of
12 methods complement each other well, because impact
13 of change, such as SUPAC changes or impact of out-
14 of-spec results during stability, for example,
15 which, when product is tested by QC method, may be
16 assessed by bio indicative test method.
17 So most of QC methods nowadays have the
18 OGD-recommended test method, because somehow the
19 agency is in favor of those test methods, but for
20 generic manufacturers, those test methods may not
21 be suitable. So my question is, does one size fit
22 all. No, definitely not.

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

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

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

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

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

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

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

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

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1 reference-listed drug.

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

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

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

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

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1 specification limits.

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

8 These are the references that I used in
9 preparation of this presentation and during my
10 work, and thank you very much for your attention.
11 (Applause.)

12 DR. L. ZHAO: Thank you.

13 Next speaker, Dr. Gordon Amidon from
14 Michigan.

15 Presentation – Gordon Amidon

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

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

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1 going to try to finish on time. One is that we
2 need to start spending more attention on what's
3 been called bio indicative, biorelevant, I'm
4 calling in vivo predictive dissolution, because
5 that's the input to simulations. And without good
6 input, you don't get good output.
7 That's going to be kind of the bottom line
8 of my talk here, but I'll give you some history.
9 I've been in this field so long that I will have to
10 show some history.
11 (Laughter.)
12 DR. AMIDON: The starting point, and this is
13 true for all routes of administration, it's just
14 more complicated than oral, oral is complicated
15 enough, is this, I'd say, is written in a rather
16 simplistic manner, but it's a function of
17 permeability and concentration at the absorbing
18 site. If we have the same absorption -- we have to
19 maybe define that word a little
20 better -- everything else would be the same.
21 One of the complexities in our field is that
22 new drug development and product development are

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1 sometimes connected, intimately connected, and
2 we're trying to separate. I view this
3 biopharmaceutics as about the product performance
4 in vivo, and it's the patient, the patient gets a
5 product, not a drug. They get a product.
6 It's permeability and solubility at the
7 absorption site. Those are complicated factors.
8 When I'm talking about oral products, and this is a
9 conference about oral product simulation and it's,
10 as I said, a real pleasure to see the increasing
11 focus on mechanistic oral absorption.
12 First, I want to point out this conflation
13 of term goes back more than 100 years. We often
14 use the term "drug" when we're really talking about
15 drug product, and they're different. This meeting
16 is about product.
17 This confusion goes back all the way to
18 1906, but for us in the field, when we talk about
19 drug, when we use the term drug, we know from
20 context what you're talking about, but the average
21 public probably doesn't.
22 The product and the drug are different.

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1 They get a drug product. We're talking about
2 product science.
3 One thing I want to point out is fasted and
4 fed state in the gastrointestinal tract are quite
5 different in terms of their motility patterns,
6 transit pattern, luminal environment patterns. So
7 we have to pay attention to that. I'm talking
8 mostly about fasted state, because that's usually
9 the initial BE, bioequivalence, requirement, but
10 they're very different motility patterns. We are
11 in the process of studying those right now at the
12 University of Michigan as part of the research
13 project funded by the FDA.
14 I have to show some history here going back
15 to some of the '80s, 1980s and '90s work that we
16 did in some of the pharmacometrics, gastric
17 emptying, influence of gastric emptying on plasma
18 levels, just gastric emptying, and I'll show some
19 of that in the presentation here.
20 Of course, the early 1980s models were kind
21 of thought of in a pharmacokinetic sense, with
22 boxes and arrows and first order rate constants,

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1 but, of course, we now know it's much more
2 complicated than that. But that's what we did, but
3 we could look at motility and variation in the
4 '80s -- this is 30 years ago now -- and show that
5 the plasma levels varied significantly with just
6 gastric emptying, nothing else, just gastric
7 emptying variation in the fasted state. We're
8 pursuing, and I'll show another slide on that
9 later, the bioequivalence implications.
10 Showing your typical gastric emptying curve
11 is often not first order. Anywhere between 10 and
12 30 percent of the gastric emptying curves are not
13 first order. So we have to begin to account for
14 that in the probability distribution, if you will,
15 in some type of a statistical evaluation of gastric
16 emptying and how we actually, I'm going to say,
17 model that, but using modeled in a mechanistic
18 sense, in a real factual way, where we know the
19 rates, the complexity, the probability
20 distributions. We're in the process of trying to
21 figure that out.
22 Some of the early transport models that we

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1 started in the mid '90s, working particularly with
2 Lawrence Yu and developed that based on some
3 compartmental analysis that's commonly used today,
4 as you know, we're continuing to extend that, and
5 we looked at a variety of tube models, chemical
6 engineering type, chemical reactor modeling.
7 Then we used this residence time
8 distribution from work done by S.S. Davis, Bob
9 Davis and Nottingham for the small intestinal
10 transit time, and we could fit that to a multi-
11 compartment model. Then that's the CAT models and
12 subsequent models that have been further developed
13 by the simulation companies that we'll be talking
14 later.
15 We continue to play around with that, too,
16 because I think I'm a closet mathematician, not a
17 very good one, but I like to play around with it,
18 with continuous models.
19 I want to point out that the stomach is more
20 complicated than we think and we'd like to think.
21 There's at least four different compartments in the
22 stomach, and our own studies confirm that. The

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1 stomach is still complicated, and so it's going to
2 take more work to sort out what's going on in the
3 stomach physiologically in terms of gastric
4 emptying, fasted/fed state.
5 Fed state might be simpler, depending on the
6 product, than the fasted state, but I want to show
7 an example of what we did in the early
8 '90s -- actually, middle '80s, published in 1990,
9 on gastric emptying variation, just purely gastric
10 emptying variation with a marker compound, non-
11 absorbed compound. We measured the gastric
12 emptying, and the curves here on the left show some
13 of the different curves that we saw for gastric
14 emptying and the gastric emptying rates. We
15 quantitated that.
16 We've carried that through to today. We
17 fast-forward to 2016, where we just published the
18 paper where we included gastric emptying variation
19 and the plasma level implications of that gastric
20 emptying variation for a well-absorbed drug, BCS
21 Class I and III compounds, actually. The work was
22 done by a former graduate student, Arjang Talattof,

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1 who is here actually working the lights, I guess,
2 now at the FDA, and a programming consultant
3 colleague of mine, Judy Price. We published this a
4 year ago.
5 I want to show we fit the gastric emptying
6 curves to a 4H series. I'm not going to get into
7 any of the details. It's in the paper. But then
8 when we computed the bioequivalence
9 implications -- and you don't have to look at the
10 details here, but we computed the expected
11 variation, expected when we simulated a
12 bioequivalence trial.
13 What we did here is we simulated 5,000 or
14 10,000 -- I don't remember the
15 number -- simulations to get the so-called
16 population average, and then we simulated samples
17 of 26. From that population, we took samples of
18 26, and what you can see here is the number of
19 potential failures that would occur just due to
20 gastric emptying rate, nothing to do with plasma or
21 absorption, just gastric emptying.
22 There's significant variation in our in vivo

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1 bioequivalence studies just because of the
2 variability in the gastrointestinal process. We'll
3 continue to study that and determine how we can
4 come up with better bioequivalent standards, better
5 and, in some cases, simpler which is kind of a
6 regulatory nirvana, cheaper and better.
7 We know that's true for BCS Class I drugs if
8 they dissolve rapid enough. Now, can we extend
9 that? That's what we're saying. How far can we
10 push that science of in vitro bioequivalence?
11 What about GI inputs? This is going to be
12 the point, and maybe I'll be interested in how the
13 simulation presentations talk about this. But the
14 key is going to be the input function. What is the
15 concentration profile of drug along the
16 gastrointestinal tract delivered from the product?
17 Because that absorption profile is what
18 determines absorption, absorption rate and then
19 subsequently, if the absorption rate of two
20 products -- remember, we're talking about products
21 with the same drug. We often forget that. We're
22 not talking about bioavailability. We're talking

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1 about bioequivalence, and I think we're
2 establishing a new bioequivalence science.
3 The difference is because we're talking
4 about relative bioavailability, two products, same
5 drug. The pharmacokinetics are the same, with some
6 exceptions, but they're the same. So we're talking
7 about a product effect, not a bioavailability
8 effect. So we've got to talk about the input and
9 look at that more carefully.
10 I'm going to give one example here that my
11 brother Greg has done as we're working on this
12 contract, and this is the USP dissolution test, on
13 the left of the RLD, the reference-listed drug
14 product. It dissolves at 10 minutes 100 percent.
15 That's the USP method, but when we use a
16 more -- I'm going to say more because this is not
17 fully bio irrelevant, but when we use a bicarbonate
18 buffer, 15 millimolar, we now know the buffer
19 strength is much less. It takes 60 minutes to
20 dissolve in a more biorelevant media.
21 Now, I'm not saying this is bio predictive
22 yet, but it just shows you the huge difference of

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1 dissolution rate. I think we also have to develop
2 a better semantics talking about dissolution. We
3 often talk about dissolution, but there's so many
4 variables that affect that. So we need to get more
5 specific when we're talking about dissolution and
6 particularly when we want it to be in vivo
7 predictive of what's happening in vivo. We're
8 making progress on that. I think that's a major
9 step.
10 On the left, we have a USP dissolution
11 apparatus. On the right, we have what we're
12 calling an in vivo predictive dissolution
13 apparatus, which was developed by a generic
14 company, by one of my former students, because they
15 did a BE study and failed. They wanted to know
16 why. I mean, they should determine that before
17 they do the study, right? So that's what we're
18 trying to do.
19 Now, this is in no way going to be a quality
20 control device, but it can help you set your
21 quality control specifications. It can be used for
22 product development and for understanding how your

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1 product and the critical product and manufacturing
2 variables.
3 So think this what I'm calling IPD in vivo
4 predicted dissolution method, which we're extending
5 basically from the ASD that has been developed and
6 published in the literature and we basically added
7 another beaker to their device and call it GIS,
8 gastrointestinal simulator. That's one of the
9 projects we're working on, because we want to
10 develop -- you need an experimental input function
11 for your simulation. We need something that we
12 think is relevant in vivo. We need the evidence to
13 show that, and that's what we're doing now.
14 Some ways where we can extend biowaivers
15 based on IPD and subsequent quality control
16 specification, can we slow dissolution for BCS
17 Class I, even Class III? I saw that question
18 earlier today. Likewise, the quantitative versus
19 qualitative differences that we can allow for BCS
20 Class III and, of course, BCS Class II and IV and
21 I'll talk about them more in a minute, but I'm
22 going to propose subclasses, acid, base, neutral,

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1 because we know that makes all the difference in
2 the world to product performance, the in vivo
3 product performance.
4 I'm proposing that we at least start talking
5 now not only about BCS class, but BCS subclass.
6 Principally, I propose for II and IV, but it could
7 also be relevant for I and III, particularly III
8 where permeability and solubility, particularly
9 permeability, can vary along the intestine because
10 the pKa if it's in the physiologic range. We need
11 a subclassification at least as the next step in
12 talking about in setting dissolution standards,
13 even IPD, but also quality control standards.
14 I'm proposing that we use acid, base,
15 neutral, because if you're a development scientist,
16 you not only want to know that, you want to know
17 everything else related to your product, but that's
18 one of the things you want to know.
19 This is just a very preliminary step.
20 Actually, when we first tried to publish this
21 paper, which was published about a year ago, it was
22 rejected, and I'm the editor of the journal. But

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1 it's because dissolution specifications are so darn
2 hard. Dissolution specifications, you've got to
3 think, it's almost product dependent. Certainly,
4 it's subclass dependent, but we're making progress
5 at some general recommendations about dissolution
6 methodology that would be predictive for
7 subclasses. We're still working on that, and I'm
8 working closely with Greg Amidon to do that and
9 develop that as part of this FDA research grant
10 effort.
11 I'm going to conclude with my key point.
12 The key to predicting in vivo is predicting the
13 input concentration profile of the drug at the
14 absorbing site in the GI tract. It's also true in
15 other routes, too, but it's more complicated
16 because of local effects there. But at least for
17 the gastrointestinal tract, we want to develop a
18 methodology that we think will reflect the in vivo
19 dissolution conditions and the variable conditions
20 of the gastrointestinal tract.
21 That's where I think we're going to go
22 today. That's what we're trying to develop today,

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1 and I think this conference -- and I think one of
2 the things that the mechanistic simulation
3 approaches that we're talking about here are really
4 bringing those fundamental mechanistic questions to
5 the forefront. We're beginning to ask what those
6 questions are and determine methods for determining
7 what are the key crucial variable controlling
8 product performance for clinical performance to the
9 patients.
10 Finally, I just want to say, of course, this
11 is a picture from my colleague, Gus Rasagna, on my
12 real BCS, you're either in heaven or purgatory,
13 depending on what you have for BCS class and, I
14 would say, now subclass. But I think that what
15 this initiative which was actually started in the
16 early '90s, 20 years ago, by FDA-funded research at
17 Michigan and at the University of Uppsala to
18 develop the permeability database that subsequently
19 became used for the biowaiver BCS guidance, which
20 has evolved today.
21 I think there's a draft guidance, now nearly
22 in final form, revising the guidance, which is very

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1 satisfying to me to see the scientific -- seeing
2 the uptake of the scientific approach by the FDA,
3 and then, of course, there's many considerations
4 around that, especially at the FDA where you've got
5 public policy, as well as science considerations
6 that impact how the agency has to operate.
7 It's been a real pleasure. I think I
8 actually finished ahead of time, because I think I
9 talked faster than I usually do.
10 (Laughter.)
11 DR. AMIDON: I want to thank you again for
12 the opportunity to present here. Thank you.
13 (Applause.)
14 DR. L. ZHAO: Thank you, Dr. Amidon.
15 With this, I want to thank again all the
16 speakers in the morning. Thank you to download
17 your thoughts, your guiding principles in the PBPK
18 field, and to make the meeting exciting and
19 valuable.
20 So we are looking forward for this
21 afternoon, and we have another three presentations,
22 followed by a panel discussion.

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1 Thank you, Dr. Amidon, for giving us extra
2 time.
3 I think everybody, in BE terms, are in the
4 fasting condition. So we'll have a one-hour break,
5 and please be mindful about the time, to be coming
6 back in time. We will reconvene at 12:30. Thank
7 you. See you soon.
8 (Whereupon, at 11:22 a.m., a luncheon recess
9 was taken.)
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1 AFTERNOON SESSION
2 (12:30 p.m.)
3 DR. L. ZHAO: Hello, everyone. I think the
4 majority of people probably -- the key people are
5 here. More people may come in once the meeting is
6 in session.
7 I will introduce the next speaker,
8 Dr. Masoud Jamei, a vice president from R&D,
9 Simcyp, the first presenter from software
10 developers.
11 Presentation – Masoud Jamei
12 DR. JAMEI: Thank you very much for the
13 introduction and, of course, for the opportunity to
14 be here.
15 I have considered three main topics for our
16 discussions in terms of the opportunity and the
17 challenges. The first one is the IVIVE-linked PBPK
18 absorption modeling. The second one is
19 physiologically-based or mechanistic IVIVC, and
20 then bioequivalence and PBPK modeling.
21 I'm trying to do some parallels between the
22 success that we have in the PBPK in other areas and

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

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

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

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1 you look at the color, the purple color is the
2 density changing, and in this case, it shows the
3 distribution of three or four in the GI tract. We
4 have to have this type of information to be able to
5 provide in the model.
6 One thing that is very important when we are
7 building individual, because we are dealing with
8 virtual individuals, we can do one-color sampling,
9 which is very common. If you open any paper, they
10 say, "Oh, we'll be using one-color sampling."
11 If you want to create a subject using one-
12 color sampling, this may happen. You are putting
13 different size of individual, so the individual
14 will not be a proper individual. But you have to
15 do correlated sampling.
16 If you do correlated, then you keep the
17 correlation between the different physiological or
18 anatomical or even biological aspects. It is the
19 same if you change the subject and then you can do
20 that, but moving from the left to the right is a
21 huge amount of work.
22 I think in the morning we got a good mention

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1 that gastric emptying by its own can affect the
2 plasma concentration. When we were developing this
3 seven years ago, we had that question. If the pH
4 in the stomach in some subject is 2, is the
5 duodenum pH going to be affected or not? If
6 somebody's stomach pH is 5, is it going to affect
7 the duodenum pH or not? I understand for motility.
8 At the time and still, we haven't found the
9 evidence, which is fine, so we can independently
10 generate this, but if there is any evidence that
11 they are correlated, then we have to incorporate
12 those.
13 So we have to do this. Another question
14 when we're developing the pediatric absorption
15 model was that is gastric emptying related to the
16 age. Is it changing by age? So we had the post
17 doc. She collected six months or nine months
18 of -- to collect all the data, and the data didn't
19 show any relationship between gastric emptying and
20 age. But there was a good correlation between the
21 type of food and gastric emptying.
22 This type of information is very important

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1 if you want to generate realistic mechanistic
2 modeling, but they are taking time. Another thing
3 which is very important is the amount and the way
4 that the fluid dynamic is changing in the GI tract,
5 because everything, as we know, is going to be
6 affected as part of that one.
7 If you look at the MRI data, these data are
8 coming from Werner Weitschies in Germany using MRI.
9 He generated the data, and if you look after one
10 hour, they gave the individual 150 milliliters of
11 water, after one hour, on median, you have 85
12 milliliters of water, which is very low, very low
13 compared to what sometimes we are using.
14 We were a bit skeptical, and then you see
15 the data that is coming out of, again, Gordon
16 Amidon's group and Marciani's collaboration, you
17 see that the variability is very high. So we will
18 see that the variability is there.
19 Another thing is that after one hour, the
20 mean value is almost the same. This is the reality
21 that we have, and you don't have the static fluid;
22 it is changing by time. So it goes up and comes

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1 down, and if we ignore this, you will not know how
2 many of the parameters can be affected.
3 We know, in reality, there is a fluid
4 dynamic that happens, and considering that one
5 allows us to consider many other factors, like
6 variability, how much of the water they have taken,
7 the dynamic of the dilution and viscosity, because
8 we want to know what is the viscosity and how it is
9 changing to be able to look at the effect of
10 formulation, if you are adding any specific
11 excipient, how are you going to be affected.
12 Precipitation and supersaturation, they are going
13 to be affected by the level of fluid. These are
14 very important for us to know.
15 These two slides are from Professor
16 Yamashita from Japan. He presented these last
17 year. They are very interesting. He did a survey
18 of 500 people and how much water they are drinking
19 with a tablet. If you see, the mean value is 80,
20 and we are doing most of the control study by 250
21 milliliters. This is the reality, and you see
22 there can be some disconnect between what we do in

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1 clinic and what people are doing at home.
2 There are direct effects. Again, he checked
3 for three different drugs, and he saw the impact.
4 The Cmax is different, the AUC is different, as
5 well as the Tmax, they are changing.
6 It is not only dissolution. Permeability
7 has almost the same story. These are the data that
8 I think Gordon mentioned the lucky gut at
9 experiments. You see that there are good level of
10 variability from 10-fold, 11-fold, fivefold and
11 fourfold, that they are happening for permeability
12 of different drugs.
13 There are models that we can get some idea
14 from as to some of the drug. If you look at the
15 metoprolol, we are able to come up with some idea
16 of the prediction mechanistically to be able to get
17 some idea of the variability of dose.
18 Another aspect, as I said, is that IVIVE
19 side. One thing that we are doing at the moment,
20 not everybody, but the most common practice is that
21 we do some experiment in a different shape, so
22 different pH, different RPM, and then we get those

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1 data and we directly plug them into a PBPK model.
2 This is good, but it's not good enough. We
3 see what we are missing from that one. If, rather
4 than doing that one, we put many of these data
5 together and we model them, mechanistically we
6 model them, then we can separate whatever is
7 related to the in vitro and what is related to the
8 API or even formulation.
9 The next step would be formulation. We are
10 separating the system data from drug data, and then
11 we can put them back. If we don't have to put them
12 back, then they allow us to extrapolate. You don't
13 need to do so many different experiments to be able
14 to get to the point that you want. If you extract
15 the in vitro intrinsic parameter, you will be able
16 to do it.
17 We have been doing this one for metabolism,
18 for transfer, for induction, for inhibition. We
19 know how to do those, and now our idea is to bring
20 it and do it for the absorption side. Is it
21 working or not? As part of the OrBiTo that
22 Filippis is going to explain, we have been working

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1 with different groups. So there are some data. We
2 are running different experiments, and then we
3 combine all those data and together, we fit them
4 and then we input them into the PBPK model.
5 Then when you combine these, there are some
6 data that Christos Reppas from Athens University,
7 they have measured the duodenal concentration, and
8 then when you put it in the model, you see that it
9 is possible -- at least in this case, we were lucky
10 for ketoconazole to get a close prediction or
11 simulation of what is happening. It is a close
12 relationship between what is observed and what is
13 predicted.
14 Moving to the IVIVE side, again, what we are
15 doing, usually, we go from plasma concentration.
16 We directly go from the deconvoluted, but we can
17 deconvolute only the absorption profile or most of
18 the time absorption profile. If you have the
19 first-pass effect or you have got a different
20 location for the permeability, when you want to
21 link in vitro and in vivo, then you will come up
22 with some complex IVIVC, because we are linking the

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1 dissolution with absorption or absorption with
2 absorption. That is complex.
3 If you use the PBPK model that we have, then
4 we can separate each of these processes, because we
5 have information for those. We can separate
6 first-pass effect. Metabolism, we can remove it.
7 We can remove the permeability side, and we get
8 only the dissolution part and then make the
9 connection.
10 In many cases, it comes up with the simpler
11 IVIVC that allows us to extrapolate and change the
12 formulation, which is an advantage. This is one
13 case that we have been working on this one. In
14 this case, we are using metoprolol data, and this
15 specific graph, we use the PBPK. You see that for
16 three different formulations, we managed to get a
17 solid line for IVIVC, but any other method that we
18 try to get, it was always biased. It was always
19 biased.
20 The method that was published in 2002, in
21 1998, and, again, we repeated, the bias is there,
22 which is obvious, because the absorption is not

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1 necessarily the same as dissolution. But if you
2 use PBPK, it allows us to go back and get the
3 dissolution profile.
4 This is very good work that Marilyn and
5 Bipin did to do PBPK IVIVC and look at various
6 scenarios, what happens. So it's a huge amount of
7 work even to this one, and it should come out very
8 soon. They use a PBPK model for IVIVC, the same
9 metoprolol data, but we had individual data. That
10 was the good thing. The individual data was
11 available.
12 Then they tried various scenarios to look at
13 the consequence of choosing different options on
14 the outcome. Like if you use a waiver function,
15 how you choose the alpha and beta and which you
16 fit, it has some consequences for you. If you are
17 using different fitting module or if they are using
18 different rating algorithm, then it's going to have
19 a different impact. If you are looking considering
20 fitting gastric emptying or if you are not
21 considering that, again, it can have some impact as
22 with the importance of the population variability

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1 and how you incorporate the dose.
2 At the end, the good thing is when you are
3 using PBPK IVIVC, then you can extrapolate. So in
4 this case, we are looking at metoprolol, and most
5 of the individuals in the study, they were
6 extensive metabolizers of 2D6. Then you can change
7 it to a poor metabolizer and see if the formulation
8 is changed, how it's going to affect other
9 population that they haven't been in your study.
10 Moving to the bioequivalence work, some have
11 a similar approach. They're first starting to
12 develop a good model for the drug without going to
13 any complexities, and using the clinical
14 observations to assess the performance. So
15 whatever, again, we learn from the PBPK in other
16 areas, that's when we develop a model, we have to
17 qualify it. We have to see if it can predict the
18 cases that it hasn't been used to fit the model or
19 to improve the model.
20 When you do, then you can start to develop a
21 physiologically-based IVIVC module. The next step
22 is that we have to have some idea about inter-

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1 location variability, and this is one of the
2 challenges that we don't have much of a grip on
3 this type of information.
4 Assuming we have those, then we can conduct
5 the bioequivalent, and we can determine the
6 solution limited specification or safest space
7 design. All of these can come out of this
8 approach.
9 This is what my colleague, Shriram, did for
10 tramadol. He went through systematic work, and
11 then what you see on the left, he did lots of
12 different simulations based on the Weibull function
13 that he fitted for in vivo dissolution. Then he
14 came up with a range that's in vitro dissolution is
15 acceptable, and it's keeping the IVIVC valid.
16 One thing that we have to always remember is
17 that there are -- we have to be realistic. There
18 are things that we don't know what is happening.
19 There are some data that we don't know them, so we
20 have to fit some parts, but when we are doing a
21 bottoms-up approach, if it's not working and if you
22 are using the clinical studies, then we have to be

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1 careful when we go for the next step forward
2 extrapolation.
3 When we are fitting or we are assuming
4 parameter, those assumptions and those fitted
5 parameters we are using, we have to declare them,
6 because sometimes we may make four or five or six
7 different assumptions, but we forget to declare
8 them. It can cause confusion.
9 Sometimes we are going beyond the range that
10 the model can predict, and you get disappointing
11 results. And then you blame the model. However,
12 the model, I think Filippas in the morning said,
13 modeling is not wrong. The assumptions that they
14 use and then afterward we try to extrapolate, they
15 may not be correct.
16 Of course, sensitivity analysis, so in the
17 morning, I think John showed the value of
18 sensitivity analysis. As I said, we agree that
19 there are parameters that they are not certain. So
20 we can do sensitivity analysis.
21 Sensitivity analysis is a very good tool to
22 assess the impact of these uncertainties or the

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1 fitted parameters or unknown even type of
2 phenomenon to see what is the range, what is the
3 scope of under-prediction or over-prediction.
4 Sensitivity analysis is a very important factor.
5 This is the work, the joint work with
6 Nikunj Kumar and Jennifer Dressman from University
7 of Goethe and Cristofolletti from a Brazilian agency
8 that they are in the process of submitting this
9 one. They tried posaconazole and ketoconazole, and
10 they wanted to see bioequivalence assessment. They
11 want to see what situation is the most striking or
12 differentiated between the two cases.
13 So they run various simulations. If you
14 look at the top, you have ketoconazole with the
15 fasted considering only bulk pH for the dissolution
16 or the next to that one, they're using more common
17 multi-climate pH that improved the predictions.
18 Then you go for fasted and fed for the posaconazole
19 or if you come down, for ketoconazole, if you have
20 PPI, what happens? If you have fed for ketoconazole
21 or PPI on posaconazole, what happens?
22 They investigated various scenarios all in

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1 the population and considering the variabilities.
2 This is, I think, a good outcome out of that study
3 there.
4 Now, you want to see when you are doing this
5 virtual bioequivalence which conditions are going
6 to be the most reflective of each scenario or which
7 one is the worst case scenario that you want to do.
8 So at the top, you have ketoconazole, you have fed,
9 fasted-plus soft drinks and you have fasted-plus
10 water or achlorhydria.
11 We have those information, so we can model
12 them. You see that in the fasted state for
13 ketoconazole plus water, it was almost borderline,
14 but for achlorhydria, it was very different. You
15 see for posaconazole, in the case of achlorhydria,
16 again, it was different. So these two cases for
17 both drugs are very different, but for
18 posaconazole, the fed state was the worst part.
19 You expect them, because they are very
20 similar, to be the same, but even small changes in
21 the properties can have an impact on which
22 bioequivalence is going to be most differentiated,

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1 why the -- I think for the test, as well as the
2 reference data, there were two different particle
3 sizes.
4 This is another study from the same group.
5 This one is putting the question of bioequivalence
6 a bit higher, because most of the time, we are
7 looking at the PK side. In this case, they said,
8 "Okay, let me get the PD side, what happens,"
9 because the ultimate aim is that you want to get an
10 effect.
11 For the case of ibuprofen immediate release,
12 at the top, it is for pediatric, and at the bottom,
13 the graph is for adults. If you look at the left
14 side, you see almost linearity for the two cases,
15 but if you look at the left, for one endpoint,
16 which is the pain relief, you get almost, again,
17 bioequivalence, if you want to call it that. But
18 if you go to the temperature reduction, you see
19 that there is a significant difference.
20 While in PK we may get bioequivalence, in
21 PD, we may not or we may. Dependent on what you
22 are looking at, there can be a difference between

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1 those.
2 Looking at the extrapolation, because at the
3 very beginning, I said that if we go for the system
4 separations of the data and drug, we will be able
5 to extrapolate. These are some cases. Again, the
6 first one coming from Cristofolletti, they looked at
7 many from the simulation side at what are the
8 impacts going to be in the children.
9 In the second one, coming from Roche
10 colleague, that they investigated the PBPK and the
11 impact on pediatric. And the bottom one is,
12 Trevor [ph], my colleague with AstraZeneca, they
13 did. They developed an IVIVC model in adults, and
14 they use it for extended-release module for
15 pediatric.
16 When we say pediatric, they are adolescents.
17 They're not really 4 years old or 3 or 2 years old.
18 So they are from 10 or 11 years up to 15 years, but
19 it works.
20 The same for the food effect, so food
21 effect, this morning it was mentioned. They are
22 cases that we have been able to predict. Even if

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1 you look at the middle one that, again, Nikunj did
2 for nifedipine, even formulation, when we manage
3 bottom-up to predict the food effect, which was
4 very encouraging. Maybe it was lucky that in
5 nifedipine it worked for that case or dose
6 formulation, it was a good prediction.
7 Overall, there are lots of opportunities to
8 use PBPK and for mechanistic absorption, but at the
9 same time, there are lots of challenges and maybe
10 we should be aware of the challenges.
11 Extrapolation to population, we are using it
12 for other cases, it will be great if we can do it
13 in the absorption side. Better understanding of
14 formulation performance in vivo. Determining the
15 product clinical qualities. Prediction of food
16 effect, of course, is very desirable. PBPK IVIVC
17 that potentially can expand the application of the
18 IVIVC and virtual bioequivalence, as well.
19 There are lots of gaps in our knowledge
20 about digestive systems, different parameters, and,
21 hopefully, the work that Gordon is doing and FDA
22 support will allow to fill in some of the gaps.

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1 It is very important that we spend time on
2 the education side. This is a new area, so
3 everybody will have to learn how to deal with
4 those, and, of course, colonic absorption.
5 I would like to thank all the people who
6 contributed to the work from Simcyp's side, as well
7 as many of the regulatory, as well as the academic
8 colleagues that provided those data. I would like
9 to thank them and, of course, the OrBiTo that is
10 providing a forum for advancing the absorption.
11 Thank you.
12 (Applause.)
13 DR. L. ZHAO: Thank you, Dr. Jamei.
14 The next speaker to have us fight against a
15 food coma probably is Dr. Viera Lukacova from
16 SimulationsPlus.
17 Presentation – Viera Lukacova
18 DR. LUKACOVA: Thank you, Liang.
19 As you might have noticed, my slide deck had
20 quite a few slides in there, but fortunately, all
21 the speakers ahead of me already described half of
22 those slides, so we'll be moving through quite

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1 quickly.
2 I won't be spending too much time on this
3 initial slide. Jasmina did a very nice job
4 describing the opportunities for including the
5 modeling and simulation in the generic drug
6 development starting from identifying your
7 products, identifying the initial formulation all
8 the way up to use of modeling and simulation during
9 the scale-up process.
10 What I will be focusing a little bit on is
11 some outlines of where modeling and simulation
12 again can help in the formulation design, describe
13 a little bit more details on the mechanistic
14 simulation models and some of the case examples on
15 IVIVC's equivalence trials, food effects, and also
16 describe an example of a biowaiver study that we
17 were involved in.
18 Again, I think it was the first presentation
19 by John Duan, who already highlighted some of these
20 utilities of simulation in the formulation
21 development, starting from helping with the
22 development of the dissolution method to help you

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1 get a method, which is more biorelevant, which is
2 better discriminative, which gives you better
3 information about the possible in vivo performance
4 of your formulation through the design of the
5 formulation; evaluating what are the possibilities
6 or what you need to have, what kind of release
7 profile you need to achieve bioequivalence, as well
8 as establish the dissolution specifications,
9 evaluate what deviations from the brand product you
10 can afford to still have a bioequivalent product.
11 This article I'm pointing out was coming out
12 from the OGD group back in 2011, where they nicely
13 highlighted the process of the mechanistic
14 absorption model development to be used in the
15 formulation design, starting from collecting the
16 information about your compound, collecting
17 information about the drug and formulation through
18 finding information about the PK of the compound to
19 build the mechanistic absorption and
20 pharmacokinetic model.
21 This model needs to be validated, of course,
22 before you use it for your formulation development.

<p style="text-align: right;">Page 141</p> <p>1 So we would be using additional datasets to 2 validate the model and make sure that it's 3 capturing the assumptions that are relevant for 4 your formulation. And finally, the validated model 5 can be used to do the sensitivity analysis, to do 6 deconvolution, to figure out your target profile 7 for your formulation, to simulate different dosing 8 regimens, to finally conducting the virtual 9 bioequivalence studies to evaluate the probability 10 of success when you go with your formulation into 11 the clinic. 12 GastroPlus helps you to follow that type of 13 paradigm, where, just like with the other 14 mechanistic absorption and PBPK models, you are 15 linking the physicochemical properties and 16 formulation properties of your product and your 17 drug with the physiology itself. Starting with the 18 information about your compound-specific physical 19 properties and information about the formulation 20 about the drug product, you can start predicting 21 your regional absorption, where the drug actually 22 may be getting absorbed in the different regions of</p>	<p style="text-align: right;">Page 143</p> <p>1 compartmental absorption transit, model. It's 2 split into nine different compartments. The 3 intestine is split into nine different 4 compartments, each of them defined by its own 5 properties, by its own pH, volume of fluid, transit 6 times and so on, which allow us to describe the 7 ever-changing environment in the intestine going 8 from stomach, through the stomach, intestine, all 9 the way down to colon. 10 The drug and all of these arrows that you 11 are seeing through the figure are representing 12 different processes that are happening in the 13 intestine, and I'll be describing those arrows in 14 the next slide. But once the drug makes it through 15 the enterocytes and gets collected by the portal 16 vein, the portal vein carries it through the liver 17 into systemic circulation. Here, you have options 18 to describe the disposition via the simpler 19 compartmental model or a full PBPK model. 20 To look a little bit more closely on what 21 all of these individual little arrows mean, the 22 processes that we are accounting for are, of</p>
<p style="text-align: right;">Page 142</p> <p>1 the intestine. 2 Filling in additional information on the 3 pharmacokinetic description, which is very 4 important since your evaluation is based on plasma 5 concentration, so having correct PK description is 6 important in having an accurate evaluation of your 7 formulation performance. So once you get your PK 8 filled in, you can start using this model to create 9 deconvolution to come up with your desired in vivo 10 dissolution profile in order to match the 11 formulation performance. 12 This would help you to get your first 13 formulation, and once you get the first 14 formulation, the initial pilot study, you can use 15 the data from the initial pilot study to possibly 16 create an IVIVC, maybe come up with a better 17 in vitro dissolution test, which gives you better 18 correlation, and, finally, evaluate the 19 bioequivalence trials or possibility of 20 bioequivalence for your final formulations. 21 Within GastroPlus, we are using the ACAT 22 model, which is the next generation of the CAT,</p>	<p style="text-align: right;">Page 144</p> <p>1 course, transit through the intestine. This could 2 be transit of the drug from the previous regions of 3 the intestine or the dose if we are talking about 4 the stomach. As the drug is moving into a specific 5 region of the intestine with its own local pH, 6 specific concentration of the bile salts, the 7 actual amount of fluid that's available for 8 dissolution at a given place and time, the drug can 9 undergo dissolution. 10 In many cases, especially as we are talking 11 about basic compounds, you might see a significant 12 precipitation. You might have chemical 13 degradation. We all know about compounds, which 14 are not stable except in pHs; again, something that 15 needs to be accounted for. 16 The dissolved drug can get absorbed, and 17 again, here, you might need to account for 18 different processes for the absorption, passive 19 diffusion, transporter effects, uptakes, efflux 20 transporters and so on. 21 In the enterocytes, you may have metabolism, 22 and, finally, the drug may be getting into portal</p>

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1 vein through, again, passive or carrier-mediated
2 processes. The rest of the compound is moving to
3 the next region of the intestine, and the success
4 of how much drug actually makes it into systemic
5 circulation is really just a matter of different
6 rates of these processes and how these processes
7 are competing for the drug and which of these
8 processes is most favorable.
9 Even if you are dealing with the generic
10 product development, you make assumptions that the
11 rates of the processes affecting your API will stay
12 constant, but, of course, the rate for your
13 dissolution will have to compete with these rates.
14 You still need to make sure that you are properly
15 accounting for what is happening with the API so
16 that any small differences in that input function,
17 in how quickly your drug is dissolving, can be
18 properly accommodated and predicted by the model.
19 One of the topics that actually wasn't
20 covered much yet were the saturable processes
21 happening in the enterocytes, and this is, again,
22 something that may be very important, especially if

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1 you are trying to describe or look at the
2 bioequivalence across different doses or in case of
3 transporters if you are dealing with a narrow
4 absorption window and so on.
5 These are just some of examples showing
6 nonlinearity in these processes. This is the
7 classic example of midazolam, which undergoes
8 saturable intestinal metabolism. And as you are
9 going from doses from 7.5 up to 30 milligrams, the
10 model is able to account for the saturation of the
11 metabolism and increased bioavailability due to
12 increased fraction escaping the intestinal
13 metabolism.
14 Similarly, for the transporters, you may
15 need to account for these effects. These examples
16 showing experimental data published for
17 valacyclovir for different dose levels showing
18 nonlinearity in the overall absorption and, again,
19 the mechanistic model utilizing the in vitro K_m
20 values for the interaction with the transporters
21 was able to account for the nonlinearity in the
22 absorption.

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1 When it comes to mechanistic absorption and
2 mechanistic models, it's a possibility to expand
3 these to other administration routes, as long as we
4 can describe the other route of administration by
5 similar models as we were working with the
6 intestine. It really comes down to knowing the
7 physiology.
8 Right now, the models are probably more in
9 the stages of helping us figure out what we don't
10 know about these routes yet, but as we go,
11 hopefully, they'll make it to the process with a
12 similar predictability with the oral absorption
13 routes.
14 One of the applications for the mechanistic
15 absorption models, of course, is doing the
16 in vitro-in vivo correlations, where, again, with
17 the mechanistic models, what we are trying to do is
18 to deconvolute the in vivo dissolution. Masoud
19 already did a very nice job describing this, so
20 this is just a different version of the point that
21 he was trying to get across, that as the drug is
22 being dissolved, there are other processes that

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1 govern the absorption of the compound.
2 In the passive diffusion transporter
3 effects, you can have metabolism in the intestine,
4 the rest of the drug hitting portal vein. The
5 portal vein will carry it through the liver, where
6 you can have additional metabolism, and, finally,
7 getting the drug into systemic circulation.
8 The advantage of the mechanistic absorption
9 models in this deconvolution is that it's really
10 trying to deconvolute the dissolution in the
11 intestine. All of the other processes are handled
12 by the model parameters themselves. It's just for
13 a very quick comparison of what you are
14 deconvoluting with the more traditional methods,
15 where everything is lumped into one rate of
16 appearing in systemic circulation.
17 This is one example of publication from 2012
18 where the authors were evaluating the more
19 traditional method with the mechanistic IVIVC, with
20 the mechanistic deconvolution, and their
21 conclusions were with the internal validation, the
22 models did perform in a similar way. But when it

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1 comes to external validation, the GastroPlus model
2 had a greater prediction accuracy and will be wider
3 applicability domain.
4 Another article published for Class II
5 compounds, again, utilizing GastroPlus model,
6 where, again, for risperidone, they were able to
7 build a nice mechanistic IVIVC properly predicting
8 the Cmax, as well as AUC for the test formulation.
9 For virtual bioequivalence trials, again,
10 it's very nice to show your mean simulation, how
11 they are matching between the test and the
12 referenced product, but eventually, it comes down
13 to running a trial in the clinic.
14 The virtual bioequivalence trials are a nice
15 tool to help you evaluate or predict the
16 probability of success, help you predict how close
17 you might be when you account not only for
18 differences between formulations, but account also
19 for variability in the subjects, inter-subject
20 variability, as well as possible variability in the
21 formulation itself, how close you might be with the
22 bioequivalence there.

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1 Again, it is also a good tool to help you
2 with your dissolution specifications so you can
3 evaluate your range of dissolution profiles within
4 the bioequivalence trial accounting for the
5 population, as well.
6 It's, again, just an example of looking not
7 only at mean profiles and comparing the average CP
8 time profiles, but accounting for the variability
9 in the predicted CP time profiles.
10 Food effect is one of the very big aspects
11 for mechanistic simulations and, to a degree, you
12 can actually anticipate an expected food effect
13 just based on the BCS classification. But running
14 the full simulations for mechanistic absorption
15 models could help you take this predictability a
16 little bit further.
17 With the domain changes that you are looking
18 at, the standard ones, of course, come down to the
19 stomach volume, stomach pH between fasted/fed
20 state, concentrations of the bile salt in the
21 intestine as the gallbladder empties in response to
22 the meal and so on.

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1 There are also differences that you may need
2 to account for not only between fasted and fed
3 state, but also for different types of meals. The
4 high calorie meals versus low fat meals versus high
5 fat meal versus standard meal may also have
6 different parameters. Some of those expected ones
7 would be gastric emptying, stomach volumes.
8 Possibly with high fat meals, you may need to
9 account for additional aid in the dissolution of
10 your compound, in addition to the bile salt
11 concentrations.
12 This is, again, one of the examples from the
13 literature where the authors used, again,
14 GastroPlus to do the food effect, where they
15 actually tried to use the simulation to design out
16 a food effect, but they built a model that was able
17 to account for the food effect for their
18 formulations. They started using this model once
19 it was validated to explore whether there is a
20 range of formulation parameters that would help
21 them to overcome the observed food effect.
22 They've done a sensitivity analysis on the

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1 dose and particle radius. It was immediate-release
2 formulation, so particle size was the driving force
3 for the dissolution rate, and came out with a
4 conclusion that a particle size reduction might
5 help them to mitigate the food effect, even though
6 as you look at food particle size, they would have
7 to have -- I think they came down to about 50
8 nanometers maximum, so probably not a very
9 practical solution. But it did show a possible
10 sort of a blueprint for utilizing the simulations
11 for these kinds of purposes.
12 There are a variety of other publications
13 looking at other applications of mechanistic
14 simulations of GastroPlus model within the
15 pharmaceutical development either from industry or
16 even from the FDA scientists.
17 Finally, one case study for the successful
18 biowaiver case study where the virtual
19 bioequivalence was done. This was actually a case
20 where the sponsor -- and actually, since this was
21 done, it was actually presented by J&J also at the
22 AAPS last year, where they went through a

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1 manufacturing change which resulted in different
2 particle size distributions for the new lot.
3 They wanted to look at the mechanistic
4 simulation to see if they can avoid having to do a
5 bridging study by assessing the effects of particle
6 size on the in vivo and show that the difference
7 was not significant enough to actually cause any
8 difference in the exposure.
9 Of course, the modeling went through the
10 standard phases of creating the absorption and PBPK
11 model that would be accounting for the clinical
12 data available already and was validated and then
13 used the sensitivity analysis and virtual trial
14 simulations to evaluate the sensitivity to particle
15 size and predict the bioequivalence probability.
16 This is showing the particle sizes for the
17 original formulations in the table on the left
18 versus the new formulations in the new table on the
19 right. As you will see, the d50 values were
20 actually very similar. The main change was in
21 narrower and better controlled formulation with the
22 new engineered particles.

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1 So the first part was, of course, the model
2 development and model validation, and here it's
3 showing how the model was able to nicely account
4 for different doses spanning the entire range of
5 their clinical doses from 50 to 300 milligrams.
6 These were all done with actually different lots of
7 the initial non-engineered particles, and when the
8 simulation used the particle size for the specific
9 lot that was used in each of these doses, it was
10 nicely accounting for pharmacokinetics.
11 The sensitivity analysis showed that the
12 particle size starts affecting the fraction
13 absorbed once the diameter changes or increases
14 above, I think, about 30 or 50 microns. The Cmax,
15 as well, would start getting affected, as well as
16 the Tmax.
17 Finally, the virtual bioequivalence
18 simulations were performed with several different
19 lots of the original non-engineered particles and
20 compared to the new lot of the particles with the
21 new particle size distribution. Again, the mean
22 radius was well in line with many of the previous

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1 ones. It shows the distribution was a bit
2 narrower.
3 The bioequivalence trial shows that
4 for -- this is a summary for 250 virtual subjects,
5 and it is showing a big higher Cmax when the new
6 formulation was compared to one of the original
7 lots, but it was well bioequivalent with all of the
8 other original lots of the formulation of the API.
9 In summary, this simulation was not standing
10 on its own. It was part of the full submission
11 package. There was other supporting material, as
12 well, but it did help to make the point that the
13 new formulation or the new manufacturing process
14 did not create enough difference to affect the PK.
15 The sponsor's biowaiver application was approved.
16 To sum this up, the modeling and simulation
17 can help you gain insights into absorption of your
18 compound or of the drug that you are trying to
19 model; can help you guide formulation, design; can
20 help you to evaluate probability of success once
21 you go into the clinic by running the virtual
22 bioequivalence trials, hopefully speeding up the

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1 drug development process so you have fewer failed
2 trials before you find the one that's actually
3 working on. I think that's all.
4 (Applause.)
5 DR. L. ZHAO: Thank you, Dr. Lukacova, for
6 your excellent talk.
7 Next speaker, Dr. Thomas Eissing from Bayer
8 Technology.
9 Presentation – Thomas Eissing
10 DR. EISSING: Thanks a lot. First of all, I
11 would like to thank the organizers for inviting me
12 to this interesting workshop. It's a pleasure to,
13 last but not least, talk as a PBPK software
14 provider.
15 I will keep the introduction on PBPK
16 modeling short. I think Masoud and Viera already
17 introduced the general concepts also on oral
18 absorption and dissolution modeling. I will then
19 provide examples and, hopefully, at the end, also
20 provide a glimpse of how that looks like.
21 One point, in PK-Sim, similar to GastroPlus
22 and Simcyp, we also have a large database of

<p style="text-align: right;">Page 157</p> <p>1 relevant physiological information in order to 2 parameterize physiologically-based models that 3 describe the distribution, metabolization and 4 elimination, and, of course, also the absorption, 5 which we'll focus on later. 6 At one point, I again would like to pick 7 up -- I think Masoud already focused on 8 that -- that in PBPK, you have a clear distinction 9 between properties which characterize the organism 10 and properties that characterize the drug, and I 11 think, therefore, PBPK provides the ideal framework 12 in order to bring these things together and 13 deconvolute information. 14 Of course, this framework also allows you to 15 learn from one drug about, for example, physiology 16 or pathophysiology how certain enzyme expressions 17 or other parameters are changed and translate that 18 use of knowledge you gained for one drug for 19 another drug, which is the basis, for example, to 20 extrapolate to specific populations or, of course, 21 also in a similar conceptual framework, to novel 22 formulations.</p>	<p style="text-align: right;">Page 159</p> <p>1 Regarding oral absorption and dissolution 2 modeling, we have a compartmental approach to this. 3 So this is kind of very closely related to the ACAT 4 model which Viera just introduced. The GI tract is 5 basically divided into different subcompartments 6 both in the lumen and on the mucosal side, and 7 there you describe how the drug is released or 8 dissolved and from there, systemic circulation. 9 General features, there is a separation 10 between liberation, transit and absorption. You 11 can account for food effects, including caloric 12 content, and enterohepatic cycling you can 13 consider. Through the mucosal blood flow, you have 14 a physiological way of absorbing your drug into the 15 systemic circulation. Of course, you can include 16 transporters and GI metabolism, as well as hepatic 17 first-pass. 18 Regarding dissolution, we offer a predefined 19 thing so as to find out are there viable first 20 order. Also, just a table reading or particle 21 dissolution, so all, again, very similar to what 22 was already presented.</p>
<p style="text-align: right;">Page 158</p> <p>1 PK-Sim is embedded into a platform. It's 2 fully compatible with our second software, MoBi, 3 which allows you to really add and change the 4 models we provide as like a standup model. It 5 provides a very flexible environment, and we also 6 have interfaces to both MATLAB and R so you can do 7 a customized coding around there. 8 Yes, all this should add to points we 9 consider for our daily work are very important, and 10 that is flexibility and reproducibility, 11 transparency. I hope I will be able to focus on 12 that during my talk in the following. 13 Pur PBPK modeling can, of course, be used to 14 address many questions during preclinical and 15 clinical development. From my perspective, the 16 most important is probably to really challenge and 17 test our understanding of a drug or drug product 18 and also to evaluate the consistency of the 19 different data that is out there. Of course, if 20 you have an incomplete understanding, it's not 21 always a problem, per se, but at least it's always 22 good to be at least aware of that.</p>	<p style="text-align: right;">Page 160</p> <p>1 In our software, it's also rather easy to 2 implement your own equations or at least you are 3 very flexible in doing that to any kind of 4 complexity. 5 Regarding passive absorption, we validated 6 our absorption model or we developed it based on a 7 collection of a 111 passively absorbed drugs, and 8 we could get a nice correlation between the 9 intestinal permeability based on molecular weight 10 and a measure of lipophilicity, an affinity in our 11 lower case. 12 Coming to examples, if we integrate 13 dissolution data, basically, here, we show eight 14 different examples, where, on the left hand, we 15 have the dissolution data where we used the Weibull 16 function to fit that and then predicted in vivo PK. 17 That worked overall pretty well. 18 Two exceptions can be understood from taking 19 a closer look. One was diclofenac, and here, we do 20 an individual fit and really consider the 21 variability in the gastric emptying time, so 0.1 22 already that is highly variable. If you really</p>

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1 take a look using such a model, you can understand
2 that inter-individual differences can provide
3 different T_{max} , which then, on the population
4 level, also lead to a decreased C_{max} , where you
5 basically get a broader shoulder. Also, a nice
6 example for how in a PBPK setting, you can
7 understand observations which might otherwise be
8 more difficult to understand.
9 Similar for furosemide, we used just one
10 Weibull function, and I didn't consider for pH
11 differences in the stomach and the intestine in the
12 first chart. If we basically take that into
13 account, we can also get a good description or
14 reasonable prediction of the data.
15 What we also looked at was cilostazol
16 kinetics. This was done in dogs. Here, there was
17 basically a published case where people published
18 in vitro dissolution data and also
19 in vivo-absorption data. And they concluded, yes,
20 there's relation between particle size, but we
21 can't really quantitatively relate that based on
22 the data alone.

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1 If we fit the particle size distribution,
2 which they published in the data, just with simple
3 distribution functions and input that into our
4 software and anchor that for one particle size
5 distribution, we basically can describe all three
6 in a very reasonable way.
7 So, yes, the rate and extent of absorption
8 based on particle size is well predicted here and
9 can be nicely described and understood. This is
10 really where mechanistic modeling helps you to get
11 an IVIVC, which can also increase your
12 understanding of what's going on.
13 Another drug, just as a quick example what
14 you can all do, here we looked at different doses,
15 and our model can nicely describe that with
16 increasing doses, our fraction absorbed decreases.
17 We have a solubility limitation here. We looked at
18 food effects, fasted/fed conditions. Different
19 doses can be nicely described with one consistent
20 model. I guess that's an important point about PBPK,
21 that you want to get to a consistent description and,
22 from one setting to another, just want to change

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1 those parameters which are also changed in the
2 experimental setting.
3 For this substance, that results in an
4 absorption site study done with [indiscernible]. So
5 really the drug is in the GI tract released at the
6 different sites, which can trigger externally. Also,
7 there, you can see that regional absorption can be
8 nicely described and understood in a PBPK setting.
9 For this drug, we also looked at the GITS
10 formulation, so where you basically have this tablet
11 with a defined pore, which releases substance, in
12 this case, particles at a basically zero rate for a
13 longer time. We could combine the zero order rate
14 release from the GITS formulation with the particle
15 dissolution function and, again, nicely describe
16 here, show population simulations where we had inter-
17 individual variability contained in our database.
18 Again, you can nicely describe that, and if
19 you have done all this for one drug, you, of course,
20 have quite high confidence that you have really
21 understood how you can model that drug in the
22 physiological, in the in vivo setting. That, of

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1 course, allows you to explore the design space if you
2 go for extended-release formulations, if you go for
3 different particle size. All kinds of questions can
4 be addressed from there on.
5 Another example is looking at food, at drug
6 interactions. Here, my colleague, Christian Wagner
7 from the University of Frankfurt, back then looked
8 at nifedipine dissolution and, also, the influence
9 of grapefruit juice, which always prolongs gastric
10 emptying, as well as reduces GI CYP3A4 activity.
11 That could also be nicely described by the model,
12 as you can see on the right-hand side, where the
13 comparison with and without grapefruit juice
14 inclusion is shown.
15 This study looked at different in vitro
16 tests, and there, again, a very important point is
17 that at least we in our model always assumed that
18 the dissolution function we get represents kind of
19 the in vivo setting. For that, of course, at least
20 biorelevant media should be used, and if you have
21 that, of course, you can also use such a setting to
22 really explore the design space.

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1 Another example which our colleagues in
2 Florida did from Stephan Schmidt's group, they
3 looked at the oral absorption in pre-term neonates.
4 We had a pre-term neonate model for the
5 distribution of drugs, and because the
6 physiological changes going on in pre-terms are
7 very complex and not enough data out there, it's
8 difficult to inform that really mechanistically.
9 They chose a simplified approach to just
10 develop equations, which describe that, and then of
11 course, in principle, you are free to combine this
12 kind of equation, which was with a mechanistic PBPK
13 type distribution model. This is just an example
14 meant to show you what is technically possible. Of
15 course, here, this example, because of the
16 challenging data situation, there's still a fair
17 bit of uncertainty left. Still, I think it's
18 interesting to explore with this technology what is
19 possible.
20 Another example where we really stretch what
21 is possible is population PBPK modeling is where we
22 really try to merge the concepts of PBPK modeling

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1 with traditional pop PBPK approaches. So we are
2 working on hierarchical Bayesian statistical models
3 to be combined with our PBPK model, which really
4 allows us then to, for example, assemble from the
5 knowledge databases you have included in the PBPK
6 software and then use, for example, Markov Chain
7 Monte Carlo methods to really both fit individuals,
8 as well as population data at the same time and
9 thereby really derive and further develop your
10 knowledge.
11 You go from a prior distribution based on
12 additional PK data. You get additional information
13 out of that. You really deconvolute your data in a
14 clear and clean setting. This is definitely still
15 challenging. Also, on the conceptual side, still
16 needs to be somewhat done, and also on the
17 implementation side, of course, PBPK models are
18 numerically more demanding than if you have a two-
19 or three-compartmental model. But yes, this looks
20 really promising, and our first example here is
21 where we applied this method to a crossover study
22 so where both IV and PO data were available and

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1 where then you can really deconvolute parameters
2 based on the PK data, so absorption parameters
3 based on the PK data.
4 This concept, again, because we have
5 separation between the properties of the organism
6 and the drug and formulation, we can really learn
7 in a systematic and more or less unbiased way
8 mathematically and further develop our knowledge
9 base.
10 I mentioned our focus is on flexibility.
11 Most of the examples I showed were, when we did
12 them, not yet easily possible in PK-Sim. Of
13 course, as we do new things, we also try to provide
14 them in a user friendly, but the first things we
15 usually do in the first versions, we also develop
16 in MoBi ourselves. Yes, this really is a very
17 flexible way of proceeding.
18 This is a screenshot from PK-Sim. You can
19 see you have full access to all the parameters.
20 You see the different building blocks, how it's
21 separated. We have a history. Every modeling step
22 you do, every parameter change is really locked.

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1 You can roll back, but, of course, it also helps
2 you to really go back, what did I do, to be
3 transparent. You can compare different things. We
4 have a working journal integrated so you can do
5 additional documentation, comments on your own.
6 You can then send models you built in PK-Sim
7 over to MoBi and then customize them. There's a
8 button there. You can just press it, and then you
9 get -- although the software is the same look and
10 feel, you still have a different view.
11 In MoBi, you take more the modeling view.
12 You really see how the different things are
13 interlinked and work together. You have access
14 to -- so here, you basically have an overview on
15 the whole body scale, how the different organs are
16 connected. You can zoom into the substructure of
17 the organs, and if you look, for example, into the
18 duodenal mucosa in the intercellular space -- in
19 this case in this example, we have a metabolism
20 process entered, and you see the formula, how this
21 is done.
22 You can not only change the values, but also

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1 the formula at additional reactions, whatever you
2 want. In fact, we also use this environment to
3 really bottom-up, build up, for example, our
4 systems pharmacology, mechanistic PD models which
5 you can link or not to PBPK models.
6 In summary, I showed examples how to model
7 different formulations and the oral absorption in
8 our software environment in order to better
9 understand the PK. Yes, in conclusion, I believe
10 that our software environment has a focus on both
11 flexibility and transparency, especially together
12 with MoBi, and leaves a lot of room to explore new
13 ideas one may have. That's it. Thanks.
14 (Applause.)
15 DR. L. ZHAO: Thank you, Dr. Eissing.
16 The last presenter is supposed to be an
17 OrBiTo representative, Dr. Xavier Pepin. He cannot
18 be available, so Dr. Filippou Kesisoglou will
19 present instead.
20 Presentation – Filippou Kesisoglou
21 DR. KESISOGLOU: Thank you.
22 It's my pleasure to present on behalf of the

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1 OrBiTo team. Unfortunately, Xavier couldn't make
2 it. I cannot take credit for all of the slides.
3 He made a lot of them.
4 Throughout the day, we discussed the models
5 and their application, as well as we heard the need
6 for fundamental research to improve some of the
7 input. OrBiTo has intended to do exactly that.
8 OrBiTo stands for oral biopharmaceutics
9 tools. I will spend most of my talk giving you
10 some background of the project, how it's organized
11 and what is the research that is taking place and
12 how that feeds into some of the topics we're
13 discussing today. At the end, I will cover a
14 little bit more specifically the integration of
15 dissolution in PBPK models, which is directly
16 related to what we discussed this morning and
17 earlier this afternoon.
18 The OrBiTo vision statement is a single
19 sentence shown on the slide: To transform our
20 ability to accurately predict the in vivo
21 performance of oral drug products across all stages
22 of drug development. That's a pretty lofty goal,

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1 and throughout the day, based on the discussions, I
2 think it's becoming apparent that's a
3 multidisciplinary question. It's not easy for a
4 single person or a single scientific principle to
5 provide an answer to this.
6 So given the multidisciplinary nature, the
7 partnership, collaboration and data sharing is the
8 first part that's highlighted in the OrBiTo mission
9 statement. Through this data sharing that involves
10 both from academia and industry, OrBiTo intends to
11 develop both fundamental knowledge, which is
12 important in our developing these models, but also
13 deliver on the practical aspects, deliver
14 innovative tools that can be used to accurately
15 predict product performance. That includes both
16 the in vitro, as well as the in silico approaches
17 that can be integrated with the endpoint, improving
18 how we do drug development.
19 One step further, meeting of the objectives,
20 a lot of that is reflective of the mission
21 statement. First, the idea is to define the
22 critical physicochemical formulations and

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1 physiological factors that determine drug product
2 performance, then develop the experimental and
3 theoretical models that we can use to predict in
4 vivo performance, and then, finally, again,
5 bridging the multidisciplinary and collaborative
6 effort, to leverage industrial knowledge and
7 academic knowledge to bring our experience together
8 to validate these models and be in a better
9 position to inform future drug development.
10 How is exactly the program structured? The
11 program started in 2012, in October of 2012. It's
12 a five-year program, so we're about a year and a
13 half from completion. It's funded by the European
14 Innovative Medicine Initiative.
15 The consortium comprises 13 pharmaceutical
16 companies, listed on the slides, and 14 academic
17 centers, universities throughout Europe or subject
18 matter expert companies, such as some of the
19 software companies that are represented here today.
20 How is the whole program structured? I will
21 go from the bottom to the top of the slide. There
22 are four work packages that are looking at these

<p style="text-align: right;">Page 173</p> <p>1 major categories of tools and fundamental knowledge 2 being developed: physicochemical tools, in vitro 3 tools, in vivo tools, and in silico models. 4 For each work package, there's a co-lead 5 from the industry and a co-lead from the academia. 6 These work packages do the scientific work, the 7 data generation for the project. 8 There are a couple of governance committees. 9 The executive committee comprises the work package 10 leads, as well as key contributors from academic 11 institutions or industry. It's responsible for the 12 project leadership on an operational level, and the 13 steering committee where all the consortium 14 participants have a member there is responsible for 15 the annual reviews and also facilitating resource 16 management. 17 You can see throughout these different 18 levels of governance, collaboration between 19 academia and the industry is a key component to 20 driving success of this project. 21 In addition, all of the fundamental goals of 22 OrBiTo is the science of doing drug development.</p>	<p style="text-align: right;">Page 175</p> <p>1 development of these tools. 2 Work Package 1, physicochemical tools, 3 in vitro tools, in vivo tools, and in silico 4 models, there is a flow of information both into 5 informing the in silico models, as well as 6 informing the tools to eventually allow us to 7 develop what we call predictive models and 8 predictive experimental methods. 9 Starting with Work Package 1, Work Package 1 10 is the first building block in understanding the 11 drug product. It deals with understanding the 12 active pharmaceutical ingredient. The objective of 13 the Work Package 1 is to provide a range of 14 in vitro physicochemical tools or in silico models 15 that can be used to assess the key API properties 16 and how those may impact in vivo performance. That 17 may include excipient interactions. 18 In early drug development, especially before 19 we get into the humans, a lot of times, the API 20 supply is limited. We need to deal with all the 21 drug product, and we need to deal with small-scale 22 experiments. What Work Package 1 is trying to</p>
<p style="text-align: right;">Page 174</p> <p>1 It's not disconnected from the regulatory 2 environment. 3 There is a regulatory stakeholder board 4 where there are representatives from all the major 5 regulatory agencies, from several representatives 6 from the EMA, from the U.S. FDA and from the NIHS 7 in Japan that we will occasionally, periodically, 8 provide an update to them to make sure that what we 9 do in OrBiTo remains connected to the regulatory 10 environment, because at the end, we need the drug 11 approved. In order to influence drug approvals, we 12 need to see how what we developed during the 13 project can be leveraged also in the regulatory 14 space. 15 I will move now into describing the 16 different work packages. Again, I want to 17 emphasize although there are four work packages and 18 they are called in vitro, in silico, in vivo, and 19 physicochemical tools, in reality, there is 20 significant crosstalk between these work packages, 21 and there is data information flowing from one to 22 the other to really enable an integrated</p>	<p style="text-align: right;">Page 176</p> <p>1 deliver is tools that at those early stages can be 2 used to develop early drug development decision 3 trees, expanding on the drug classification or the 4 drug developability classification system to 5 facilitate those early decisions before we start 6 going into more classical drug product development. 7 Then again, obviously, API is important for 8 the models. It informs both in vitro tools. We 9 need to understand the API first before we start 10 adding dissolution of the drug product, as well as 11 key physicochemical parameters for the PBPK 12 modeling that were mentioned throughout the talks 13 today. 14 The second work package deals with in vitro 15 tools, mostly dissolution systems. There are a lot 16 of dissolution systems. Everyone probably in each 17 company has their favorite tool to use for drug 18 product performance, but we heard from Dr. Amidon 19 that in vitro, the predictive dissolution system, 20 there are transfer systems, systems with an 21 absorptive compartment like this cell monolayer, 22 biphasic systems or even much more public systems.</p>

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1 This is the TNO system that's intended to mimic the
2 entire gastrointestinal tract.
3 How do we go about using them in drug
4 development? Which one is the best to use for its
5 purpose? The intent is not to declare the best
6 system, but basically to declare -- to understand
7 what information we get out of each one of them.
8 Again, eventually everything feeds to building
9 predictive models.
10 The goal of Work Package 2 is to optimize
11 these tools to have maximum predictability for oral
12 absorption. Ideally, develop a decision tree to
13 select the most appropriate in vitro tools and
14 provide the data for the PBPK modeling. I'll come
15 back to the dissolution incorporation in a few
16 slides.
17 Each work package has published in the last
18 one to two years a review of the current status of
19 the science in the field. I just happened to
20 highlight here the one from the Work Package 2 that
21 summarizes the current state of the art on in vitro
22 tools for prediction of in vivo performance, but if

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1 you go to the European Journal of Pharmaceutical
2 Sciences, you'll find similar review articles for
3 all the other work packages.
4 Work Package 3 deals with the in vivo tools.
5 You can think of Work Package 3 as the one that
6 generates most of the fundamental knowledge on the
7 system that we're trying to model. The idea is by
8 understanding the in vivo system and the
9 physiology, we can then start improving our tools.
10 We can start better understanding the in vivo to in
11 vivo animal to human translation or in vitro-
12 in vivo correlations.
13 Going into a little bit more detail, the
14 gastrointestinal system, we already heard today
15 from Dr. Amidon about motility and fluid volumes.
16 That's also studied under the OrBiTo. Intestinal
17 fluids and composition, how can those translate to
18 dissolution media? Clearly, there is a lot of
19 variability in each one subject of the intestinal
20 composition, and OrBiTo is intending to
21 characterize the variability and help us develop
22 better predictive dissolution media.

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1 Finally, a lot of the stuff we discussed
2 today and most of the examples we showed were
3 around predicting PK out of a dissolution input or
4 a particle size input. However, what we are really
5 trying to predict as far as the dosage form goes is
6 how does that behave in the gastrointestinal tract.
7 However, it's not an easy measurement to
8 measure what actually happens to a tablet or a
9 capsule upon ingestion. We rely on PK because it
10 is something we can measure, but in reality, direct
11 behavior of a dosage form is what you see in the
12 gastrointestinal lumen.
13 In OrBiTo, there are specific studies being
14 conducted where upon dosing of different dosage
15 forms, there is some link of the gastrointestinal
16 fluids to better understand how in vivo dissolution
17 is actually taking place. Hopefully, by having
18 this data, we can then drive even better predictive
19 models on the in vivo dissolution part.
20 Finally, Work Package 4 is the in silico
21 tools, is the integration of all the knowledge and
22 all the data to drive a predictive mathematical

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1 model. Several efforts have been started earlier
2 on with a database creation. As I mentioned, an
3 important part of this exercise was data sharing
4 and knowledge sharing across the partners of the
5 consortium. It did take a significant amount of
6 work out of the Work Package 4 team to put all this
7 data together in a database to be able to be used
8 for those projections.
9 I know it's hard even within a single
10 company to get information together to drive
11 decisions. You can imagine how difficult it is to
12 do this against 13 pharmaceutical companies and 14
13 universities to gather all the information.
14 Based on these databases, the next step was
15 an initial gap analysis. You can think about this
16 as a blinded bottom-up PK projection analysis.
17 What can we basically see if people are giving
18 given datasets, how can they actually drive PK
19 models.
20 This effort has been completed, and now the
21 team is in the steps of evaluating the needs for
22 improvements into the models and identifying the

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1 gaps in our knowledge of the model that we should
2 be implementing moving forward.
3 Some brief highlights of progress to date, I
4 mentioned the reviews already. I will encourage
5 everyone who's interested, these are summaries of
6 the state-of-the-art in each of these topics.
7 The database, so you can see this is top of
8 the database, 90 compounds, almost 600
9 formulations, 500 studies, 25,000 data points.
10 It's a lot of information that we can tap in to
11 understand better how we're doing drug development
12 and how we're developing these models.
13 For the in vivo studies, again, these are
14 not trivial to develop, but standardized protocols
15 have been developed for sampling of
16 gastrointestinal fluids. Many of the studies have
17 been completed, and some of them are already
18 published. Compositions of human intestinal fluids
19 was also recently published, and some of the
20 studies on the in vivo characterization, such as
21 non-absorbable markers to define the transit time,
22 novel MRI methods to measure the water content,

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1 have been completed and also recently published.
2 I will move to my last part of the
3 presentation, which is the integration of
4 dissolution profiles in the PBPK models. The
5 challenge is that this beaker appears a little bit
6 simpler than the gastrointestinal tract. We need
7 to be able to translate dissolution data that we
8 generate in vitro to the in vivo situation.
9 As I mentioned, in vivo dissolution is very
10 challenging to determine. We infer what it looks
11 like based on some mathematical models, but we
12 actually almost never measure the in vivo
13 dissolution.
14 Why are we doing that? First of all, for
15 the majority of the formulated projects, when we
16 are not dosing API partner solution, which we
17 typically don't do other than some early clinical
18 studies, the dissolution modeling based on the API
19 properties doesn't agree with the observed
20 dissolution data. We need to figure one way to
21 incorporate formulation information into the model.
22 Second, as I mentioned, there are a lot of

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1 different dissolution methods, a lot of different
2 media. We need to be able to use the data
3 regardless of the source to drive a model. Can we
4 use modeling to eliminate some of these system
5 parameters for the dissolution interest? Finally,
6 I think we discussed it already quite well, the
7 facilitation of development of bio predictive
8 dissolution methods.
9 Again, multiple dissolution systems, this is
10 not even half of what's being probably used in
11 practice. How does each one of these data points
12 go into informing a model?
13 I think I stole this slide from Masoud.
14 Here, you saw it already. The idea here is, again,
15 we typically talk about deconvolution when we do
16 IVIVCs, and we're trying to deconvolute the oral
17 profile against the IV profile. In this case,
18 we're talking about the deconvolution of the
19 in vitro data where we separate the system data,
20 meaning the dissolution apparatus, the media, the
21 rotational speeds from the API and the formulation.
22 Once we have that, we convolute that back

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1 into the in vivo system for a PBPK projection. So
2 why that might be important, let me go through a
3 case study, and through this case study, we'll also
4 highlight some of the questions that I asked
5 earlier in the morning model selection and how do
6 we validate models.
7 This is a compound. It's neutral, for the
8 most part, of the physiological pH range. So the
9 media is -- it's a simple system where with the
10 factor here that's being used. There are different
11 API lots with different particle sizes from this
12 API.
13 Using the standard Noyes-Whitney equation
14 that's, again, available in all of the commercially
15 available software, we can simulate the dissolution
16 profiles based on the API particle size
17 distribution. We can compare, at least for some of
18 them -- I'm not showing all of them here -- the
19 dissolution simulation, which is on the left-hand
20 side, against the experimental data, on the right-
21 hand side, and we see that that model works which
22 is expected. These models were published, I think,

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1 more than 100 years ago, and for the most part,
2 they work as intended for API powder. So this
3 looks pretty good.
4 If you look at most of the papers in the
5 literature in the PBPK modeling, they use the
6 particle size distribution-based model to do a
7 projection. This was done here for the case of
8 this exercise. We take the different particle size
9 dissolution as projected from the model. You plug
10 them in your favorite PBPK software, and you get a
11 projection of the different sizes.
12 Although all the projections are clearly so
13 small an impact on what the dissolution shows,
14 which is not unusual, but you start seeing some
15 differences. As you move to the animal API, Cmax
16 is delayed for a few hours. It's down by 20,
17 30 percent. One could say that maybe these are
18 milled material, and I might have an issue with PK.
19 If someone didn't do anything else and they
20 used the API PSD model, they might conclude, well,
21 I need to mill my compound to I get PK exposure.
22 Let's look now at how the dissolution of the

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1 compound looks once it's formulated in the final
2 product. So what we see when you finally formulate
3 the compound is that smaller particles actually
4 dissolve relatively fast as formulated product.
5 It's slightly slower than what the API particle
6 size model suggests, but because you make granule,
7 it does take a little bit longer for it to dissolve
8 compared to the net API of a couple of microns.
9 What we also see is that the larger
10 particles actually, once you put in the
11 formulation, either break down due to the
12 compression or if you are doing a well regulated
13 product, part of it might dissolve, in which case
14 you would get faster dissolution profile from the
15 product than what your API model suggests.
16 If someone was to do a projection based on
17 this -- and I'm not showing this since everything
18 is on top of each other -- they would see no PK
19 impact, and then from a practical standpoint, this
20 means one can actually have more relaxed API
21 requirements as far as the particle size control
22 goes.

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1 I think that also talks to about
2 understanding what model we should use for one
3 question. If someone were to use the API particle
4 size model without generating the dissolution data
5 and they ran a PK study, they might conclude that
6 the model was wrong, because you would have
7 projected differences while there is no difference
8 in vivo. But in reality, you need to generate all
9 these data points and the dissolution to really
10 understand what the true impact of particle size on
11 the PK response.
12 I showed this slide, so I'm not going to go
13 through this in detail again. What I'm really
14 thinking is that incorporation of dissolution into
15 PBPK models can really drive what I term
16 bio predictive methods that will really ensure
17 future product quality.
18 With that, I will acknowledge Xavier, Mark
19 and Masoud for their help with the slides and the
20 many, many OrBiTo contributors that have generated
21 a lot of data. I think in the next year and a
22 half, you're going to see even more of the data

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1 coming out in publications that will really help
2 with driving this field moving forward.
3 Thank you for your attention.
4 (Applause.)
5 DR. L. ZHAO: Thank you again to all the
6 speakers, and I congratulate everyone that we still
7 have full stroke after lunch.
8 After another break for 20 minutes, we will
9 start at 2:30 sharp. We will start another
10 exciting session. Especially for the panel
11 members, we like challenging, controversial
12 questions, so we are looking forward to the
13 discussion.
14 (Whereupon, at 2:06 p.m., a recess was
15 taken.)
16 Panel Discussion
17 DR. L. ZHAO: We're going to shoot up the
18 first question, and once you're being seated, you
19 can start to think about it, especially for the
20 panel members.
21 At 4:00, we have a half-hour session opening
22 to the floor to all the audience. If you have

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1 comments or questions, feel free to participate in
2 that session. Given the time is very short, we
3 probably can only accommodate three, four
4 questions.
5 Then for the panel members, first of all, I
6 want to thank again all the speakers to deliver
7 such an outstanding talk, in my opinion. We've
8 already received several comments from the audience
9 and they're highly positive. They like the talk,
10 the content, the technical side of the
11 presentations.
12 It's also a very rare and valuable event for
13 FDA OGD to have all the top experts in the field to
14 get together to brainstorm, to share ideas.
15 Dr. Robert Lionberger also mentioned earlier
16 that, hey, we'd like to see the panel discussion to
17 be controversial, challenging. So we are not here
18 just trying to be friends, even though we are in
19 the same field being colleagues, but for the
20 impact, we need to be critical.
21 We'll go with the first question. For the
22 available list of areas, sub-areas, which ones do

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1 we have the highest confidence in using
2 physiologically-based absorption modeling for oral
3 dosage forms?
4 We do not have a list. It's kind of a super
5 long list, but I trust your knowledge, your
6 expertise, and your brain. You probably have an
7 even longer list.
8 With that, I will open the floor to the
9 panel members. Since the talk of the meeting is
10 transcribed, so I would like to ask you to identify
11 yourself one more time when you start having your
12 input. Thank you.
13 DR. LIONBERGER: I'll start. This is Rob
14 Lionberger. One thing I saw from the
15 presentations, just to encourage people to start
16 talking about this, is that there are a bunch of
17 examples that looked at particle size and
18 dissolution specifications for basically immediate-
19 release dosage forms. That seemed to me an area
20 where there were actual case examples, and,
21 hopefully, someone will agree with me.
22 DR. AMIDON: The only comment I would make

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1 there, Rob, is that the particle size you put it,
2 or is it the particle size that comes out and is
3 wetted in the intestine?
4 DR. LIONBERGER: I would suspect and I would
5 appreciate, industry colleagues, that probably
6 you're putting in your drug substance particle size
7 into these models in most cases; is that correct?
8 DR. KESISOGLOU: I think it depends on the
9 dosage form. This is Filippos Kesisoglou from
10 Merck.
11 If we have dissolution data that suggests
12 that the dosage form behaves like particle size,
13 then I think we can put it directly in the model.
14 If our dissolution data suggests that we need
15 additional processes, I think it's important for us
16 to also model that.
17 Overall, I would agree that the models for
18 particle size are appropriate for use.
19 I guess just back to the original question,
20 in my view, I would classify some areas that we
21 have more or less confidence as a blanket
22 statement. In my experience, it comes down to the

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1 specific compound and formulation. If you
2 understand how the drug product is behaving, can
3 you build a reasonable model with reasonable
4 assumptions and reasonable input to describe the
5 behavior?
6 In my view, if you can achieve that, I would
7 consider that model having confidence in doing a
8 projection. So that would be my view to the
9 original question.
10 DR. ZHANG: This is Xinyuan Zhang from DQMM.
11 I think we use particle size all the time, because
12 it's an available input parameter in the model, and
13 oftentimes when we see the prediction is off, we
14 would rather adjust solubility than particle size,
15 because we consider particle sizes that are
16 reported are relatively reliable. We have more
17 rationale to adjust solubility especially for low
18 solubility drug products where we thought the
19 in vitro measurement might not be in vivo relevant.
20 That was my experience.
21 DR. LIONBERGER: One thing I noticed, and I
22 think we've seen this and Susie's mentioned we've

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1 seen this, is that sometimes there's ambiguity
2 about the solubility as an input parameter into
3 these models, where sometimes we see experimental
4 reported data that varies and sometimes we are
5 uncertain about what the real in vivo solubility
6 is.
7 I appreciate maybe comments from some of the
8 software companies here, what do you people think
9 in terms of the solubility inputs, since that
10 especially for some of these, say, immediate-
11 release particle size applications, the solubility
12 input that you assume might be a driver of some of
13 the results that you would see.
14 DR. EISSING: Yes. I would agree that it's
15 often difficult to one-to-one, it takes a
16 solubility. We at least rarely do total ab initio
17 predictions. So usually, we start modeling when we
18 have some in vivo data available in order to anchor
19 that, and, of course, obviously, if you start, for
20 example, with the water solubility, that may be
21 really way off and you can't describe your PK data
22 with that. If you go to more biorelevant media, in

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1 my situation, that gets better, but still I would
2 always allow to fine tune that parameter based on
3 PK data.
4 Once you have anchored that for a substance,
5 of course, you would expect that it's then a
6 measure of solubility is the same as if you change
7 particle size, for example, if the other
8 ingredients are the same.
9 DR. LUKACOVA: Viera Lukacova. Solubility
10 is a simple word, but a very complex environment in
11 the intestine, right? So it comes down to either
12 having in vitro data or a model that can translate
13 across dose environments. You need to have well
14 characterized both the effect of pH on your
15 solubility, as well as the effect of bile salt on
16 the solubility so the models can properly translate
17 into how the changing bile salt concentrations, as
18 well as how the changing pH would be affecting or
19 would be changing the solubility in different
20 regions of the intestine.
21 DR. DUAN: Based on our limited experience,
22 as I showed in the presentation, the in vivo

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1 exposures do have -- it's affected by the particle
2 size, but the solubility plays a role over there.
3 As I showed in the slides, the reviewer did
4 a sensitivity analysis. The sensitivity analysis
5 showed at the lower solubility the relationship
6 between the particle size and the Cmax is very
7 sensitive. When the particle size becomes larger,
8 the Cmax becomes smaller, but when the solubility
9 becomes high, the sensitivity is not critical.
10 That's the interpretation of that data that
11 shows that's correlated, particle size and the
12 solubility effect is correlated. I didn't explain
13 that figure in detail. If you look at the figure,
14 very bottom right, the particle size of the radius
15 of precipitate, that's differentiated by the shape
16 of the symbol and do affect the relationship
17 between the particle size and the Cmax in the
18 condition of high solubility and the lower
19 permeability, at that corner. That's the
20 relationship.
21 That probably tells us the relationship is
22 interplay. Something gets together might be

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1 different from one by one, just examining that way.
2 Thank you.
3 DR. LIONBERGER: I want to raise the point
4 that in a lot of the biopharmaceutical modeling that
5 we're doing related to product development, we
6 often have some human data available. Earlier in
7 drug discovery, you may be trying to predict what's
8 going to happen in a first-in-human study, but by
9 the time you get to biopharmaceutical questions, even
10 the one that John answers for new drugs or
11 certainly for generic drugs, like generic drugs,
12 there's always human data available for us to get
13 our model into the right ballpark.
14 As we're talking about biopharmaceutics, I
15 would want people to be thinking that that's the
16 assumption, that you're working on a case where you
17 have some human data on some formulation. You may
18 be looking at asking a question about a different
19 formulation or a different patient population, but
20 you have some human data that you can check your
21 assumptions about your model against at the time.
22 In that context, I think one of the -- and I

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

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

22 DR. CONNOR: One of the things that

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

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

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

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

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

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

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

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

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

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

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1 drug-drug interaction, drug as enzyme substrate,
2 drug as enzyme protease inhibitor, transporter-
3 based absorption.
4 Then the confidence level may decrease a
5 little bit with you predict PK for specific
6 populations, then followed by effective factors
7 like pregnancy. I think that's the tough one.
8 Then obesity, also a tough one. Disease states is
9 a tough one, but it's very relevant to the field.
10 Then food effect, I don't know if this is
11 really beneficial, if the panel members can make
12 your comment, when would you trust the predictions
13 for food effect, under what scenarios you would
14 trust the predictions for food effect.
15 The other is pH effect, local, like we've
16 irreverently changed theological parameters such as
17 pH, that would lead change to solubility. It
18 sounds like solubility is the key parameter to
19 consider. Those are the comments, I think, given
20 the limit of time, so if the experts here can make
21 some input to us, really, please.
22 DR. AMIDON: I'll comment on one. The first

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1 is pH. It's not just pH. It's actually buffer
2 capacity. Buffer capacity in vivo was very low.
3 Our intestine is mostly CO₂, and the bicarbonate
4 buffer capacity is measured in Leuven about average
5 to millimole per liter per pH unit.
6 We measured actually lower than that, but we
7 don't have enough data. It's very low USP, is 50
8 millimole and nothing to do with in vivo. They
9 call it simulated intestinal fluid. Why do we let
10 them get away with that? But anyway. So, yes,
11 that's just one factor, I would say. One factor is
12 something like buffer capacity, as well as pH.
13 DR. NOVAKOVIC: Hi. Jasmina speaking. I am
14 from generic pharmaceutical company, and talking
15 about pH, I was thinking about pH from a different
16 angle. I was thinking about changes of the stomach
17 environmental pH, and I find predictions pretty
18 reliable in terms of being to identify biostudies
19 outliers based on the changes in the stomach pH, as
20 well as drug-drug interactions, because those
21 changes might be due to drug-drug interactions.
22 In my experience, it is reliable in the case

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1 that the drug is low soluble in acidic environment,
2 and, therefore, due to lack of the solubility,
3 because of the changes of the pH due to, for
4 example, administration of some PPI inhibitor of
5 any other drug that might modify environmental pH.
6 Bioequivalence for that particular patient or
7 volunteer is questioned, and bimodally, we were
8 able to provide that it was due to the change of
9 the pH in the gastric environment.
10 DR. SAO: I just have a quick comment, too,
11 and I know Rob and Liang, you guys want some
12 controversy. So I'm going to give you a
13 noncontroversial response.
14 I guess what we have -- I don't want to say
15 we have the highest confidence in a particular
16 approach when it comes to the modeling aspect, but
17 what I can say at least from the biopharm
18 discipline, what we've seen so far is out of the 15
19 and a subset of those are the ones that we found
20 successful, so to speak, a good portion of them,
21 the ask starts out with particle size, right?
22 So naturally, I think -- and the way the

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1 conversations are going here, again, I don't know.
2 I don't want to call the highest confidence, but I
3 think our experience is growing when it comes to
4 particle size and PBPK modeling. I just wanted to
5 put that out there to digest on.
6 DR. P. ZHAO: This is Ping Zhao from
7 pharmacometrics, Office of Clinical Pharmacology,
8 FDA. Responding to the question on the screen and,
9 also, I will try to allude to the points raised by
10 Liang regarding the food effect prediction, as well
11 as pH modulating prediction.
12 I'm looking at the agenda. I would say when
13 we talk about confidence, we have to further define
14 it into one I call a prediction confidence, meaning
15 that whether we are able to predict in the absence
16 of a study.
17 In another sense, whether this can lead into
18 high impact decision, for example, biowaiver. The
19 other one, which has, I'm told, a confidence,
20 rather, the entire day that all these applicable
21 sub-bullets, I would say, in terms of exploration,
22 explaining the mechanisms, PBPK modeling definitely

<p style="text-align: right;">Page 205</p> <p>1 has its role and is an indispensable role other 2 approaches cannot replace just because of the 3 ability to integrate all kinds of information. 4 Going back to the other aspect of the 5 confidence, which we, at clinical pharmacology, 6 define as predictive performance, as Liang 7 mentioned in his introduction slide, where we have 8 highest confidence with DDI, lower confidence with 9 special population, and even lower with other 10 application, I think the angle we're looking at is 11 using mechanistic model, at what stage you can say 12 this study definitely, I can just do a prediction. 13 I don't need to do an in vivo clinical pharmacology 14 study or maybe a BE study to confirm the knowledge 15 and give us some regulatory decision-making power. 16 I think looking through all the bullet 17 points, especially focusing on this food effect 18 prediction, at least throughout the discussion 19 today, I am not fully convinced that we're there. 20 I think there is still quite some mileage in the 21 coming years with the help of all the stakeholders 22 to move the field forward.</p>	<p style="text-align: right;">Page 207</p> <p>1 resource oriented. It may not be necessary for 2 every product, right? Only high-risk products 3 we're talking about. 4 In the sense if it's a BCS Class I, 5 Class III, arguably, this approach may not be 6 necessary, right? BCS in itself is clinically 7 relevant, so to speak. I just wanted to add on to 8 that. I think it's a very valid point. 9 DR. AMIDON: Can I comment again? 10 DR. L. ZHAO: Please. 11 DR. AMIDON: I would say that the particle 12 size importance will depend on BCS subclass whether 13 it's an acid, a base, depending on the pKa, as 14 well, and whether it's non-ionizable in the 15 physiologic arena. So the data has to be a 16 package. 17 DR. KESISOGLOU: I guess to the original 18 question, some of the areas you mentioned, if you 19 look at literature, there are published examples of 20 successful applications for both food effect, PPIs, 21 or specific compound. So we cannot discount. 22 These examples are out there and are at least past</p>
<p style="text-align: right;">Page 206</p> <p>1 Being negative, but I think to give it 2 another level of negativity is a challenge toward a 3 conclusion from two talks, one from the Merck 4 colleague and one from Susie with respect to our 5 confidence in predicting oral drug absorption for 6 BCSI. 7 Playing the devil's advocate, for the Merck 8 example, are we able to just use BCS to just make 9 the decision for that food effect example? Because 10 you have a very good solubility, you're going to 11 have a -- the model just isn't sensitive to respond 12 to any critical changes. 13 But having said all that, I really enjoyed 14 the whole session and I learned a lot, and special 15 applause to Susie and John for the nice update on 16 FDA examples. 17 DR. SAO: I guess I had an add-on comment to 18 that, as well. It's a good point that Ping made 19 that at least from a regulatory perspective, we 20 talk a lot about clinical relevance and clinical 21 relevant specs, but in a lot of cases, an approach 22 such as PBPK modeling, it's very intensive and</p>	<p style="text-align: right;">Page 208</p> <p>1 the peer review process. People were convinced 2 that the models were valid. 3 I will agree that at the end, it comes down 4 to the totality of your data, does your in vitro 5 data, your modeling and your clinical data support 6 what question you're trying to answer. Even from a 7 simple question as a particle size, the model will 8 always tell you the smaller the particle size, the 9 better for dissolution, but I've worked on products 10 where actually the smaller the particle size, the 11 slower the dissolution, because it gradually became 12 more dense. You have to have your in vitro and 13 your model together to drive a decision. 14 I also agree we shouldn't be doing the 15 modeling for the sake of doing modeling. BCSI, I 16 agree fully that the modeling is insensitive to 17 solubility. I guess all the model is testing is 18 gastric emptying time, for the most part. That is 19 definitely the PK profile. If it was a BCS 20 Class II compound, I think the question becomes a 21 little bit more complicated. 22 Sometimes the model just helps with</p>

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1 communication of data. Even if it's an obvious
2 answer, just having the model to explain to the
3 formulation group, explain to my clinical
4 colleagues some of these concepts, I think it helps
5 with just that sometimes, and I think we just need
6 to keep in mind that utility of the model, too.
7 DR. P. ZHAO: Just to add on to that, don't
8 get me wrong, that's proposing something that I
9 have been defending for the past eight years at
10 FDA. I'm a big fan of PBPK. I'm just saying like
11 for this particular question relevant to oral
12 absorption, if you ask me whether I would be
13 convinced that we are ready to predict food effect
14 based on at least my reading of the literature and
15 our limited experience of clin-pharm review of
16 maybe two or three submissions in NDA, just because
17 of the number of parameters that may impact the
18 final prediction, I just feel for other BCS class
19 compounds right now, there is still some ways to
20 go.
21 DR. EISSING: I would believe an example
22 like food effect for most examples, I would believe

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1 for PBPK model is able to predict it if you account
2 for the changes in the relevant parameters, but
3 there might be additional effects which none of the
4 PBPK models, I guess, consider so far.
5 For example, if, in rare cases, a drug would
6 bind to the food or something like that, I don't
7 see an easy way how you can predict that
8 beforehand. I guess at least for the time being, I
9 kind of also see that you at least need to confirm
10 what you predict to a certain extent. Overall, I
11 think, food effect based on the examples I know of,
12 usually you predict it well, but how can you
13 exclude that it's not doing something additional
14 which you don't consider in your model and which is
15 rare which you can't really predict? I guess
16 that's the challenge.
17 DR. AMIDON: Can I comment again? I think
18 we should be careful about whether we're talking
19 about bioavailability or bioequivalence. I think
20 they're separate questions. Bioavailability is
21 more complicated because it's got metabolism
22 consideration. It's elimination, the BDDCS

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1 considerations.
2 Bioequivalence, we're talking about the same
3 drug, different product, and so I think the
4 importance of particle size is potentially
5 important depending on whether it's physical
6 properties, but for both. But I do think the
7 questions are somewhat different, and we need to
8 define the bioequivalence science questions more
9 carefully to not confuse them with the
10 bioavailability questions, which are systemic
11 availability, which is our goal.
12 No one doubts that that's our goal, but it's
13 a little bit different between bioequivalence and
14 bioavailability.
15 DR. L. ZHAO: Given the time, we are not
16 leaving question number 1 yet, but if we proceed to
17 question number 2, it's kind of intertwined.
18 Number 2, I'll read out.
19 Do we have enough experience to confidently
20 apply the current PBPK absorption models to support
21 the following regulatory applications?
22 So we don't have to really go through the

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1 list, but in your opinion. I think this is a very
2 relevant question to industry, to FDA. It's kind
3 of a key component of this workshop. From this
4 regard, we really want to listen to the experts'
5 view, which area is kind of mature enough for
6 either generic drugs or new drugs, we can apply
7 PBPK absorption model to sometimes waive the study
8 or sometimes to shorten the product development
9 timeline, sometimes to just increase FDA reviewers'
10 confidence to trust in the result.
11 DR. MEHTA: Just to add to everybody else's
12 questions, on the list here, one thing I didn't see
13 being addressed by any of the presenters and I'm
14 very much interested in knowing more about it is
15 this proposition that widening the BCS III bio
16 criteria, proposing longer dissolution times and/or
17 different excipients. If we have good data to shed
18 light on that, I'd be very much interested in
19 knowing.
20 DR. AMIDON: I didn't quite understand the
21 question.
22 DR. MEHTA: One of the bullet points is that

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1 PBPK can be used to support a request to widen BCS
2 Class III biowaiver criteria, meaning recommending
3 longer dissolution time than what we are asking for
4 right now, very rapid dissolution instead of that
5 longer dissolution, and, even more important,
6 excipient aspects, different excipients.
7 DR. AMIDON: Well, I'll comment. I think it
8 depends on -- you probably have to look at A, B, C,
9 acid, base or neutral. I don't think you
10 could -- I think we need to define the BCS classes
11 into subclasses and look at the effect of an acid
12 or a base, because I think of the pH dependence,
13 the low permeability, the permeation variability
14 along the intestine, the pH variability. I don't
15 think we can really answer that today.
16 I don't think we have enough case honestly
17 to say we can relax the dissolution specification,
18 but I think we should investigate it. Maybe we do
19 for a II-C compound or something, but we need
20 to -- you, of course, the FDA, has presumably
21 bioequivalence data.
22 I think, theoretically, it could be relaxed,

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1 but I'm not sure we have a good basis for saying it
2 could be relaxed today.
3 DR. MEHTA: I just wanted to hear that, and
4 that question being posed that I thought there was
5 information to that effect, and if there was, then
6 that's what I wanted to know. So I appreciate your
7 clarification.
8 DR. ZHANG: I want to respond to that
9 question. Internally, we have a couple of research
10 studies ongoing. We want to evaluate all the
11 formulation factors for all the BCS III drug
12 products and see how different they are.
13 Externally, we have a couple of ongoing
14 studies to study excipients' impact on transporters
15 and to what level, and we also internally conducted
16 simulation studies to study hypothetically if we
17 vary the transporters' activity, but the abundance,
18 those type of parameters, how that is going to
19 impact drug absorption for specific BCS III
20 compound.
21 So I think all these components should come
22 together. We combine all the knowledge from

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1 different aspects and combine them together. So
2 maybe at the end, we can make a list of the
3 excipients that we don't have to worry about, a
4 list of drug products that have high risks.
5 I agree that we are not there yet, but there
6 is some room that we can improve.
7 DR. MEHTA. Sure we can.
8 DR. LIONBERGER: Like all the BCS guidance,
9 especially when you get to Class III, it can cover
10 a drug that's 84 percent absorbed or a drug that's
11 1 percent absorbed. I probably think that there's
12 completely different risk profiles in those two
13 different situations for some of the factors.
14 If you're going to set general criteria that
15 applies to all of them, you have to be very
16 conservative, but as you get into specific cases,
17 then I think there may be some aspects where
18 modeling and simulation can help understand what
19 the risks are, map out what the risks are at least
20 for a developer to say I want to pursue this or
21 just to understand the studies that you've done.
22 DR. MEHTA: I agree with you on that, sure.

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1 DR. AMIDON: I want to comment, Rob.
2 Absolutely, when we drafted the first BCS guidance
3 in the mid '90s, 20 years ago, it was purposefully
4 discussed and debated to be very conservative, to
5 be safe. Yes, I think the BCS Class III, I agree
6 with you completely, between 1 percent absorbed and
7 90 -- it's 85 or 80 percent, 84, there's a huge
8 difference, yes, huge range.
9 One thing I wanted to comment about, to
10 Susie's comment, is that I think the question for
11 bioavailability versus the question for
12 bioequivalence is a little bit different with
13 regard to what's happening in the transporters' pH,
14 whatever the conditions in the GI tract, because if
15 it's a bioequivalence question, then if the
16 dissolution in vivo is the same, it will be the
17 same.
18 Bioavailability is a little more complicated
19 because of metabolism, the transporter effects,
20 distribution, but even there, if the dissolution in
21 vivo is the same, they'll be the same.
22 DR. LIONBERGER: Generic products, solid

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

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

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

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

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

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

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

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

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1 they have changed independently. They are not
2 independent. Sometimes there is a dependency
3 between those.
4 A very simple example is that I have seen
5 the publication, they did the sensitivity analysis
6 on Log P, as the partition coefficient in the
7 tissue. These two are not independent. If the
8 Log P is changing, the KP is changing as well. We
9 can't independently do sensitivity analysis on
10 those two parameters.
11 DR. L. ZHAO: To be honest, I'm a little bit
12 distressed to see the experts in the field all
13 telling, okay, we need validation, we cannot
14 100 percent support, even in certain applications,
15 a specific area in regulatory review.
16 I kind of have some reservations. If we're
17 talking about validations for new drug, yes, we do
18 not need to come up much, but for generics, they
19 already accumulated experience with the compound.
20 There's some compounds do have very thorough
21 studies.
22 Then for generic drug application, the only

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1 change most likely is just the formulation. So in
2 that scenario, I think there are already some
3 clinical validations done in the NDA stage. My
4 opinion is we cannot totally rule out the bigger
5 utility of models in the realm of generics.
6 DR. EISSING: I guess it's also a little bit
7 a question of how you interpret the question. It's
8 like I believe PBPK models. Can I support all of
9 the questions in that sense that it supports
10 understanding? And you said you want to do
11 science-based decisions, and it's like only if you
12 can explain what you observe in a model, you have
13 really understood it. In that term, it can help,
14 but if you can based on the modeling alone really
15 wait for complete clinical study, I think that
16 really needs good case-by-case argumentation, and
17 justification.
18 DR. L. ZHAO: For new drug applications,
19 there are some packages with good received
20 packages. In those cases, if there is a generic
21 drug application, if there is change in
22 formulation, I think the validation already has

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1 been nicely done in the new drug application stage
2 in that.
3 Dr. Lukacova, you're looking to have
4 something to tell in this.
5 DR. LUKACOVA: Well, just to follow up on
6 that, yes, if we are both talking about generic
7 application, you are really worried only about the
8 input about the dissolution, right? If the
9 dissolution is the same, your exposure will be the
10 same.
11 The issue is how you're validating that in
12 vivo dissolution is the same, right? You are
13 comparing it to the in vivo exposure. Your in vivo
14 exposure is your target, and I'm not trying to say
15 that the PBPK model should not be used. I'm fully
16 confident that they can help with generic
17 development. But the model still needs to be
18 developed and needs to account for all of the
19 processes in order for you to have a confidence
20 that in vivo dissolution was the same for the
21 generic drug as for the brand product.
22 Unless Dr. Amidon can say that we solved the

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1 problems with an in vitro dissolution assay that
2 can predict the in vivo dissolution and we'll all
3 be happy and we can start using them. But I'm not
4 sure we are there yet.
5 I'm definitely believing the PBPK models can
6 help with the generic drug development, but still
7 needs to be validated to make sure the drug
8 properly accounting for your compound, because CP
9 time profile is what is your target where you are
10 measuring.
11 DR. CONNOR: I'm not sure that dissolution
12 is the only thing. I go back to Rob's comment.
13 It's not just disintegration plus the drug
14 dissolving. There are excipients in there which
15 are assumed to be inactive. But they aren't
16 necessarily all inactive.
17 The way we have of evaluating their
18 so-called inactivity is probably old by now and
19 could be improved, because we assume or a company
20 assumes, oh, well, I've used this excipient 10
21 times in my last 10 products, no problems at all.
22 But there is a theoretical problem.

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1 I use it in number 11. It gives me a lot
2 less or even a lot greater bioavailability than my
3 target, assuming I'm a generic sponsor, than my
4 target product, very surprisingly, because I
5 assumed it was simple and this was inactive. That
6 doesn't even address the fact that, in theory,
7 although I don't know any cases of this, in theory
8 that two seemingly inactive ingredients combined
9 together in the same product could actually
10 interact and create a surprising result as well.
11 Just simply getting the drug to dissolve in
12 the body isn't necessarily the whole story. Most
13 of the time it is, but not always.
14 DR. P. ZHAO: Just responding to Liang's
15 sort of unsatisfied comment, I had to say upfront
16 that my comments around all of these are definitely
17 taking a lot of consideration about new drug
18 development. What you said is valid. There might
19 be situations where this model will be sufficient
20 for you to make a decision in generic drug
21 development, but that has to be, as you strongly
22 believe, a verification or validation of a

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1 particular application is needed.
2 This can be easily done, and we have done
3 that with DDI. As you set the conditions, let's
4 take the first bullet, for example, poor particle
5 size distribution specification for IR drug product
6 with a low solubility. Then you say, okay, what
7 does it take for me, you go from bottom to top.
8 What does it take for me to make a biowaiver based
9 on what I know from the NDA experience, right?
10 You have a generic coming in. What kind of
11 study do I need in the middle in order to say,
12 okay, now I have enough confidence with what I know
13 about this particular API and in this new generic
14 formulation and then in the innovator's different
15 formulations? I know the PK there.
16 How much does it take for me to feel
17 confident instead of doing a BE study, I can just
18 stop here with an in vitro dissolution with my
19 knowledge about the drug and my knowledge about a
20 PBPK software platform in terms of the capability
21 of handling the interaction between excipients and
22 the physiology condition? It's robust enough.

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1 You can already imagine this middle level of
2 this workflow, you need some data to support that.
3 Maybe you need to try five different APIs. You
4 have to observe the data. You do a blind
5 prediction. You tell the world that, look, any
6 software can do this or a couple of software. We
7 have experience in-house or in the scientific field
8 that we can do this.
9 I think that could apply to all of your
10 bullet points, so set the condition.
11 DR. AMIDON: A different direction, looking
12 at the five sub-points there, the two that I have
13 the most concern about would be supportive
14 dissolution for a modified-release product, because
15 dissolution does not account for gastrointestinal
16 motility and variability effects along the
17 intestine from stomach all the way to the colon.
18 That's where I would have the least confidence in a
19 dissolution spec, at least as we think of USP.
20 That's a whole other thing.
21 Then the last one with locally acting drugs,
22 one of the questions there is where, what part of

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1 the intestine. I think both of those are more
2 complicated than maybe the other ones. They're all
3 complicated.
4 DR. LIONBERGER: I have a related question
5 on here. I think we saw some examples in the
6 presentations today of mechanistic IVIVC which I
7 would contrast with an empirical IVIVC essentially.
8 The mechanistic one, you sort of deconvolute
9 against the physiologically-based model to try to
10 get more factors out of it.
11 There seems to be evidence in the literature
12 that this is better. I'd like the panel members to
13 comment on that. Do you agree that mechanistic
14 IVIVCs are preferred over empirical IVIVCs, and
15 should then our expectation that is the state of
16 the science that we should really think that if
17 someone presents an empirical IVIVC, they should be
18 doing something more complicated?
19 Have we reached that state yet where we want
20 to put those on really different -- is there enough
21 scientific evidence to say that those two
22 approaches really are on different levels that we

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1 want to really endorse strongly the mechanistic
2 IVIVC as the preferred approach to --
3 DR. AMIDON: Absolutely, Rob. Absolutely,
4 but I'm an academic, so what do I know?
5 DR. DUAN: I would say depends, because
6 IVIVC, if used in the traditional way, three
7 formulations, slow, fast and medium. That's
8 validated. It's very difficult.
9 We made a survey. We have a publication
10 probably just for that. It's very difficult. From
11 that perspective, we have to go this way, for the
12 mechanistic-based IVIVC. That might be an
13 alternative.
14 DR. AMIDON: We should do both, right?
15 DR. DUAN: Right, yes. If it's the
16 traditional way, it's doing that IVIVC, that
17 probably is pretty solid. When we do the
18 mechanistic-based, that probably will get the same
19 results, but for the traditional way, it's very
20 difficult for the provability. As far as I
21 remember, it's very low. It's about 30, 40
22 something.

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1 I couldn't remember exactly the number, but
2 with that, we take another alternative way to get
3 some same interpretation. That will be a good
4 alternative.
5 DR. JAMEI: I think just to answer your
6 question, yes, the confidence is there. In terms
7 of the performance, they are better than the
8 classical one, but it doesn't mean that the
9 classical ones are useless now. There are many
10 cases, as people have viewed them, that classical
11 are enough. We don't need to force people to
12 different. Now, you have to go and do PBPK.
13 I think two years ago, we had that
14 discussion with Philippos, when we had that
15 discussion. If you start pushing this one
16 tomorrow, FDA is asking, we have to do everything
17 PBPK IVIVC, it's not necessary for all the cases.
18 There are some cases that they are improving the
19 performance, but those cases are necessary to do
20 it, but not absolutely for everything.
21 DR. KESISOGLOU: I would say I see them as
22 complementary approaches. I don't think I would

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1 declare one is always better than the other for
2 each compound. I have compounds that I develop
3 both of them, and they had similar qualification
4 performance. There's clearly, in the past, several
5 classical IVIVCs that have been proven useful,
6 right? So we cannot discount the old methodology.
7 I do think if we have -- absorption modeling
8 IVIVCs give you another tool to use to develop
9 these correlations, but I wouldn't necessarily
10 throw everything we've done in the past out because
11 it's the old way and we're doing things. I would
12 just use them as complementary, and at the end, you
13 have to use whatever makes sense and gives you the
14 best product, right?
15 DR. JAMEI: I fully agree.
16 DR. L. ZHAO: With time, we probably need to
17 proceed to question number 3. Based on the current
18 discussion, I think we need to slightly change
19 question number 3. Initially, it was for the areas
20 with middle to low confidence, what are the gaps
21 and how to close the gaps through research.
22 I don't think we are differentiating low to

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1 middle confidence. We are just asking the question
2 what are the gaps and how to close the gaps through
3 research.
4 I think what I got is that we need some
5 validation for if we are applying PBPK approaches
6 and we need to understand the system's parameters.
7 A mechanistic model is not always better than the
8 empirical model based on our limitation in
9 understanding the details of the theoretical
10 parameters' properties and DDS between property and
11 theoretical environment. That's my take on it so
12 far.
13 Any corrections? If there's no corrections,
14 please comment on how to close the gap. I think
15 here we are all doing PBPK research. With the
16 experts, hopefully, we can define a direction to
17 go.
18 DR. LIONBERGER: There are two types of
19 gaps, I think. One is there's a confidence gap in
20 what people believe and what our assessment of the
21 model is, and then there's, two, sort of things
22 about scientific understanding.

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

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

22 I think that's something that I think would

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

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

16 When we set the particle size or other
17 specifications, we put all the ANDAs together and
18 try to get a consistent model. We can imagine if
19 we can build a universal model for this block of
20 15, 17, whatever number that the ANDA block is, and
21 then the model can apply to each ANDA and predict
22 the BE study. That's where it'll be a beautiful,

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1 beautiful work, but we have not got there yet.
2 I think that OrBiTo approach, that's really
3 a good approach. That can give us some confidence
4 for the future study.

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

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

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1 model is reasonable.

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

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

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

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

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

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

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

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

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1 DR. JAMEI: I agree. I think it would be
2 able -- I think, Gordon, you mentioned that the
3 buffer issue, that we cannot. We think it is
4 possible by modeling to be able to account for that
5 one.
6 If we thought to incorporate the surface pH
7 rather than the bulk pH for the dissolution and
8 then we get some idea and there are some data on
9 what is the buffer capacity in different part of
10 the GI tract and explore those, then by separating
11 the information that we have from in vitro and
12 knowing what were the buffer capacity and translate
13 it to in vivo buffer capacity, there are hopes to
14 be able to predict.
15 DR. AMIDON: Yes, in some cases, but it does
16 depend on the drug, the PK, its solubility.
17 DR. JAMEI: Yes, absolutely.
18 DR. AMIDON: Every drug has to be looked at.
19 When we look at matching bicarbonate with
20 phosphate, it varies with the drug's solubility and
21 pKa, but yes, we can calculate that out. Then we
22 go and do the experiments to see if it worked,

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1 because there's always assumptions in your
2 transport analysis. But I think, theoretically,
3 yes, but it does vary from drug PK and solubility,
4 yes.
5 DR. JAMEI: Absolutely true. I think the
6 same approach that we are doing with PBPK, we have
7 to do more of in vitro modeling to get more
8 experience and in which cases, then we don't need
9 to do any extra in vitro experiment. We can model
10 it. There are some cases definitely that we have
11 to do the experiment so we carry on doing that.
12 One more point is that we are emphasizing
13 too much on the dissolution, but permeability is
14 another problem that we haven't sorted out. So
15 permeability and predicting permeability, regional
16 permeability, colonic permeability, they are
17 another aspect we have to look at as well. This is
18 another gap that we have.
19 DR. AMIDON: That's a gap. That's true.
20 But I would say that's why we restricted BCS Class
21 I to very high permeability, because once it
22 dissolves in the stomach, it's all gastrointestinal

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1 variabilities that are affecting it, not the
2 product. For BCS Class I, you're testing gastric
3 emptying doing BE, not product differences. But
4 when you slow down the dissolution rate, it gets
5 more complicated, yes.
6 DR. P. ZHAO: I fully agree. During the
7 presentations, Dr. Amidon and Masoud both mentioned
8 the quality of input parameter drives good
9 prediction. There's no doubt about it. I think we
10 also have a previous experience in terms of
11 predicting clearance based on in vitro system like
12 human liver microsome hepatocytes, transporter
13 systems.
14 Back to Liang's question around the
15 confidence that one should have for in vitro
16 solubility, it just seems like you can handle
17 better with solubility than a human liver
18 microsome, to my opinion.
19 But that said, there is still another
20 direction of complexity that we probably haven't
21 got the chance to talk about is the dissolution in
22 what, a little bit maybe in Filippou's presentation,

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1 biorelevant solubility. Which one would be my true
2 input parameter?
3 I think I'm pretty sure the experience we
4 will get accumulated some years down the road, we
5 will be able to say better in terms of looking at
6 the drug characteristic and the accumulated
7 experience for drug or drug product, what should go
8 into the model.
9 Back to Susie's question, the qualification
10 of validation, I think this is really getting a
11 very general PBPK debatable area. We're developing
12 the guidance right now for clin-pharm submissions.
13 We try to shy away from this, because personally, I
14 really don't think right now there is a good way
15 that we can make some cutoff values up there and if
16 people fail, they have a lousy model, just don't
17 even submit to us. We don't look at that.
18 I think just based on the DDI prediction,
19 our experience was that, again, you focus on and
20 imagine the workflow. You focus on the end
21 product, which is a biowaiver. For us, there's
22 whether there's a need to do another DDI study, and

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1 then you trace your flow up and then decide, okay,
2 if I have 10 drugs tested in PBPK and I blind
3 myself from the observed study and this is the
4 outcome, I have maybe one or two that is beyond
5 1.25. Do I tolerate that?
6 That's something, also related to what
7 Filippou presented at the end, that might imply
8 some kind of a paradigm change, which I have no
9 authority to comment on that. I'm just proposing
10 my personal opinion or personal sort of thinking
11 around, reflecting what he said.
12 Think about clinically relevant BE. Then
13 the other advantages for generic drug development,
14 again, you have a lot of the new drug information
15 to power the model. Not like us, we probably will
16 be limited with maybe Phase 1 SAD data, multiple
17 ascending dose data, that's it. We may have
18 nonlinearity and get excited, oh, now I know
19 there's something I can deal with a model.
20 Then you go beyond that. You still need a
21 ketoconazole study to verify the model, and then
22 you say, okay, I can waive the study. There's

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1 nothing that we just do bottom-up.
2 Even for DDI, we say we have high confidence
3 there's a condition. That's why I think for all
4 these applications, we need to set a condition.
5 You identify your end question that you want to
6 address and then try to build yourself up. I think
7 that's when we do narrow the gap.
8 DR. AMIDON: I'm going to make one comment
9 about it. You have all of that NDA information.
10 The generic company doesn't have that. I think
11 that part of the problem is --
12 DR. P. ZHAO: Good point. I think I'm
13 assuming the purpose of this meeting is, also,
14 whether from the agency we can do something to
15 facilitate the broader use of the mechanistic
16 modeling. If the generic companies decide to just
17 go ahead and do the BE, I guess end of the
18 question.
19 But still you're going to run into a
20 scenario where a BE study is conducted and you get
21 puzzled by the outcome and then all this inter-
22 individual inter-variability, the patient versus a

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1 healthy volunteer, a single dose versus multiple
2 dose, those questions. That's why we're here.
3 That's my impression.
4 DR. AMIDON: I think that's a good question,
5 but it's getting into the public policy realm, I
6 think. If you can develop some internal
7 understanding from all of the NDA's information
8 and, of course, you can use that internally for
9 your decision-making, but I don't know how
10 that -- I don't know what more could be --
11 DR. P. ZHAO: That's a fair point.
12 DR. AMIDON: I think it's more of a public
13 policy issue or there's public policy issues
14 embedded in that.
15 DR. P. ZHAO: That's why I said personal
16 opinion.
17 DR. L. ZHAO: I think we almost got the
18 whole stakeholders in the field here. Actually,
19 regarding the information sharing, we are
20 sponsoring building internal PBPK database probably
21 for primary. I'm not sure whether the CRO industry
22 or the software developers have interest. I know

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1 there are already some working groups existing.
2 What is the most effective way for knowledge
3 sharing in this regard to keep continuing the
4 communication to build the PBPK future mechanism-
5 based modeling? Maybe in the future, it's not
6 called PBPK anymore once the knowledge is mature
7 enough.
8 DR. JAMEI: I just thought right now, we had
9 something around maybe 70, 80 compounds that are in
10 the simulator, but many from the metabolism side,
11 they don't have the absorption or the sophisticated
12 models. They need a database. People are
13 publishing, and maybe we have prepared a part of
14 our website that people they can upload there to
15 share between with the people who are using Simcyp.
16 It is very good to generate it, but I
17 understand from innovative company side, that they
18 expend huge amount of effort to create those ones.
19 Even if they don't want to share it, I won't be
20 able to force them. This is another thing that
21 unless they want to share it -- because
22 understandably, they have spent lots of effort,

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1 data, individual man months. They are going
2 through these.
3 We are publishing and we are publishing
4 ourselves. One of the needs the consortium has
5 asked us over the last two, three years, that we
6 curate all so they will be available.
7 Now, we have started to put all the data,
8 validation, they're all for the consortium members,
9 they are available.
10 DR. P. ZHAO: I think just to speak to that,
11 within clin-pharm, we're trying to set up a
12 repository for the submissions right now, because
13 the task will be so daunting. We haven't got to
14 the stage to put in the specific software, specific
15 model into this database, although we can trace
16 where they are.
17 In the public domain, I know several
18 journals nowadays are requesting the authors to
19 supply software-specific model files. Hopefully,
20 that will be another mechanism for us to tap into
21 the resource down the road for a specific API where
22 the model has been published.

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1 Questions and Comments
2 DR. L. ZHAO: Okay. We are almost two
3 minutes to 4:00 o'clock. We do want to give the
4 audience a chance, if you hear something which is
5 obviously wrong or you have a driving desire to
6 voice your opinion, here is your moment.
7 Unfortunately, for the people online, we
8 haven't set up the connection. We are not going to
9 address questions from online. It's more like
10 benefit to the people here in this room. Now is
11 the time if you have any comments. It's good to
12 stand up and approach the microphone. We
13 appreciate any kind of inputs.
14 DR. SUN: Duxin Sun from University of
15 Michigan, [inaudible - off mic]. As George Box
16 said, "All models are wrong, but some are useful."
17 I do agree the PBPK model is very, very useful to
18 do the prediction, especially I do agree use PPBK
19 model to set the boundary condition. I don't think
20 it's real you can actually predict the spectrum to
21 see if it makes accurate prediction, but the
22 boundary condition is very useful to do the BE

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1 study. That's one comment.
2 I think I can address the number 3, where is
3 the low confidence. Because in the model we use a
4 lot of in vitro data, then we have a plasma
5 profile. The big gap in between is the black box,
6 what is happening in vivo GI tract. But we have to
7 use the in vitro data to somewhat predict in vivo
8 what is happening, then use that data to predict
9 plasma profile.
10 When we talk about validation, what we
11 validate is use in vitro number versus PK profile,
12 plasma. We don't have data to validate what is
13 really happening in GI tract. Based on the data we
14 already have worked with the FDA -- we work with,
15 of course, Dr. Amidon, together work with the GI
16 drug concentration. We measure local concentration
17 of mesalamine. We measure the ibuprofen local
18 dissolution.
19 The data that comes out is very surprising,
20 very, very different than we thought. To give you
21 one quick example, in the stomach, the
22 concentration of both drugs, they stay in the

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1 stomach over seven hours, for very long, for very
2 high concentration. We would never predict that.
3 We never assumed that.
4 What does that mean? The in vivo real data,
5 very different from our assumption, very different
6 from our prediction. Yet, we still can't use the
7 model to predict from in vitro to in vivo PK. What
8 does that mean? Does that mean in vivo does not
9 matter or does that mean is the model perhaps wrong
10 in some way?
11 Really, I feel number 3 will be we really
12 need the in vivo data to validate. Once you get
13 that data -- right now we have a local-acting drug.
14 We complete that study. We're doing
15 immediate-release
16 drug. We're going to finish
17 within this year or next year. I think we need
18 another modified-release formulation for GI.
19 So once we get the GI dissolution data, then
20 we can really use that to validate the in vitro
21 dissolution condition, also validate the model. So
22 I feel that's fundamental. Without that data, we
can do all different validations, but it's very

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1 hard to know whether it's true or not.
2 DR. MARROUM: I think that we have --
3 DR. L. ZHAO: Can you please identify
4 yourself?
5 DR. MARROUM: My name is Patrick Marroum. I
6 work for AbbVie Pharmaceuticals.
7 I think that we're discussing a lot in PBPK
8 modeling, but I don't think we have an agreement on
9 how we define a good model. At least with the
10 classical IVIVC when the guidance was developed,
11 there was a lot of discussion and a lot of work to
12 come up with an acceptance criteria. I've seen
13 many, many PBPK models that are developed and are
14 so-called good models that have very different
15 prediction errors that deviate quite a bit from the
16 observed in vivo data. And yet they call them good
17 models.
18 As long as we do not agree on what's a good
19 model, I don't think how are we going to be able to
20 use it from an application point of view? We have
21 to first agree on what is a good PBPK model, and I
22 don't think in this discussion anybody addressed

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1 that issue really.
2 DR. JAMEI: Can we answer or we wait?
3 DR. L. ZHAO: Please go ahead.
4 DR. JAMEI: I think, Patrick, that the
5 question is maybe you're comparing two different
6 things. When you say for IVIVC we know what is the
7 criteria for success, I think you are considering
8 that look if IVIVC are in the 85 percent to 125
9 percent, then it's acceptable. If it is not, then
10 it's not acceptable. But this is not telling you
11 about the performance of the model. You are
12 accepting or rejecting is IVIVC -- you're not
13 saying anything about the model itself.
14 Exactly the same thing if you are using
15 physiologically-based IVIVC, exactly the same
16 criteria is applicable there. There are no
17 changes. If you get 85 percent, that's done. If
18 not, then it's not acceptable.
19 DR. MARROUM: Most of the models don't
20 achieve that level of criteria. Unless I'm
21 mistaken, the vast majority of PBPK models that
22 I've seen so far in that area for DDIs, for

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1 example, they say, oh, if you're within twofold,
2 you're okay.
3 But if you want to use it for bioequivalence
4 or waiving studies, either we change our definition
5 of bioequivalence or we define our models to meet
6 the relative definition of bioequivalence and be
7 able to waive it.
8 DR. JAMEI: I see this one, two different
9 things. You can say, okay, when a prediction is
10 from PBPK model, it is acceptable. This is one
11 question, which is valid and lots of discussion has
12 gone everywhere and there is some commentary on
13 that one, as well.
14 But comparing that against IVIVC acceptance
15 or rejection is not correct, from my view, because
16 they are two different things. We are not saying
17 the performance of the model is acceptable. We say
18 the formulation and everything, that way that it's
19 working is these two are bioequivalent or not. We
20 are not saying anything with the model.
21 In the PBPK, you're right. There are
22 different people that are coming with different

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1 things, and this is a good thing. I don't see this
2 one as a bad thing. The data commentary on pH in
3 clinical pharmacology and therapeutics or
4 pharmacometrics and system pharmacology, that one
5 is comparing the PK top approach against PBPK oral
6 quantitative systems pharmacology approach.
7 The purpose for them is not to match the
8 observed data. The observed data, the source of
9 the observed data we have, A, a clinical study with
10 six people or 10 people, and we say these are the
11 observed data. If you run the same study again
12 with the same people, you are not going to get the
13 same answer. Why do we expect PBPK to always match
14 10 people? So this expectation may be not right.
15 DR. MARROUM: But that's the definition of
16 bioequivalence. You're implying that we need to
17 change our definition of bioequivalence? We're
18 stuck with it. There's nothing we can do. We have
19 certain predefined criteria that we need to be able
20 to pass, and our model should be good enough to
21 give us enough certainty to determine whether we
22 pass that criteria or not.

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1 This is exactly the same problem we had 20
2 years ago when we developed the critical IVIVC
3 guidance. This is no different whatsoever.
4 DR. JAMEI: I fully agree, and I don't see
5 any reason to change that criteria. If you are
6 using numerical method or any other method you are
7 using or if you are using a PBPK model, the
8 criteria is exactly the same. There is no need to
9 change it. The same acceptance or rejection can be
10 applicable to PBPK. Because this is another model,
11 they try to match two different in vitro and in
12 vivo dissolution. The same criteria is applicable
13 to both of them.
14 DR. MARROUM: Yes. And one more comment
15 that I wanted to make is I would have a very great
16 difficulty in accepting the concept that if you
17 develop a classical IVIVC that met the stringent
18 criteria of predictability that you need to force
19 the sponsor to go back and do a mechanistic PBPK
20 model.
21 You don't need to really understand
22 sometimes what's going on. Probably sometimes you

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1 can never understand what's going on, but at least
2 if you have enough certainty and confidence in your
3 model to make a decision and relieve the burden on
4 the company, that's good enough.
5 A lot of, for example, the exposure response
6 relationship, we don't understand the initial
7 relationship, but we still use it to select the
8 dose or do something. So it is somewhat very
9 difficult to say, oh, you always have to do PBPK
10 model and it has to be mechanistic. If you have an
11 empirical model or a statistical model that is
12 predictive and robust, it's good enough.
13 DR. L. ZHAO: Thank you for that comment.
14 If there's no clear benefit to do a mechanistic
15 IVIVC or PBPK model, I don't think we would be
16 forcing that.
17 DR. MARROUM: I heard someone commenting
18 that we should go that way, I think.
19 DR. MEHTA: I thought I heard they were
20 complementary. That's what I heard.
21 DR. MARROUM: Okay.
22 DR. GOOD: Good afternoon. David Good from

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1 Bristol-Myers Squibb. Thank you for the very nice
2 panel discussion.
3 I think that we've talked a little bit about
4 the confidence levels, so just have one question to
5 supplement that. That's related to, I guess, what
6 we've been talking about and what was shown about
7 the wider adoption, the only 6 percent adoption for
8 absorption of PBPK versus things like DDI where
9 there's maybe more penetration currently. I think
10 the comments that were made about confidence
11 in vitro microsomal or hepatocyte data are very
12 poignant.
13 I think that one of the things that we have
14 in absorption that gives us this confidence and has
15 been pointed throughout multiple presentations is
16 the combination of these models with the in vitro
17 data but also the in vivo data. And it's not just
18 the validation against multiple formulations that
19 contain different excipients throughout all of the
20 clinical studies that were conducted, but it's the
21 ability to have confidence in future predictions,
22 too, by being able to leverage across species.

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1 That's something where the fundamentals of
2 absorption that we're talking about dissolution
3 rate, solubility, permeability would still apply,
4 and our PBPK models are often constructed such that
5 we can bridge across species and also be able to
6 probe new formulations and leverage that in a way
7 that for things like DDIs we can't, because the
8 mechanisms of clearance can be quite different
9 across species.
10 I guess my question is in the absorption
11 space for PBPK modeling. Does the panel feel like
12 we have additional tools to validate and to
13 demonstrate our confidence in predictability for
14 new formulations?
15 DR. AMIDON: I think it depends on BCS class
16 and subclass, so some yes, some no today.
17 DR. KESISOGLOU: I guess in the development
18 space, we often use animal data to validate whether
19 the model is directionally at least or
20 qualitatively giving us the right answer. Whether
21 it would be quantitative or not in the animal
22 model, it's a little bit more difficult question,

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1 because we typically don't measure animal-specific
2 parameters. We have the human solubility estimate,
3 but we don't have a dog solubility estimate
4 necessarily.
5 I think that you can use the data
6 supplementary in the development space. I do not
7 have an experience in regulatory application to
8 validate something against an animal model myself.
9 I cannot comment on that, but I think in the
10 development space, the totality of the data serving
11 supplementary to inform the models.
12 DR. P. ZHAO: Just responding to your last
13 question, based on experience, I'd feel cautious in
14 terms of answering absolute yes even though I'm
15 pretty optimistic. The reason I'm cautious is
16 because for the lower confidence applications that
17 Liang presented in the introduction on behalf of
18 clin pharm, we are still struggling. For example,
19 we have data around the multiple compounds with
20 regard to their PK in hepatic impairment, and this
21 is a high impact regulatory issue that we try to
22 get a good hold around it.

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1 But at the moment, the published software
2 characteristics around that already alluded to the
3 bigger problem around some physiological impact on
4 drug ADME that are not well characterized. Are we
5 at that end? I don't think so because I think
6 maybe we can further subset the question. Maybe in
7 hepatic impairment of what kind of compound, and
8 when you have what information, maybe you can use
9 PBPK.
10 We're moving towards that end, but a global
11 validation of a particular application I'd like to
12 see maybe five years down the road whether we can
13 say in confidence that, yes, we can do that.
14 Mathematically, I'm optimistic that it's just a
15 matter of getting the information.
16 You also alluded very correctly around the
17 utilization of in vivo data. I think on the one
18 hand, we need to be very critical about the input
19 in order to drive a better prediction, but also
20 once the in vivo data becomes available, this PBPK,
21 the whole point we do that is it follows this
22 predict-learn-confirm cycle. You really keep

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1 learning the system and improve the modeling.
2 Just one example, 2014, the ontogeny of
3 CYP3A4 in pediatrics had been updated. That
4 doesn't mean that the model was completely wrong in
5 2006 by different groups, but it's at least saying
6 that with updated knowledge, we know better. The
7 predictions should be narrowing us down within a
8 narrower space to give a better prediction.
9 DR. L. ZHAO: I want to add something to
10 Ping's comment. I think one thing, the technology
11 is the responsibility of both sides, both from
12 FDA's scientists and from industry. I think most
13 of the innovation should be from industry. You're
14 more than welcome to thrust new ideas or new data
15 to support the validity of model, always submit to
16 FDA or discuss with us at other venues, platforms.
17 It's kind of we together need to advance the field.
18 As we have heard from today, there are many
19 challenges, barriers. The field is still young,
20 still in infancy, so we need lots of investment.
21 DR. CHIEN: Hello. My name is Caly Chien
22 from Janssen R&D or Johnson & Johnson. I heard a

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1 comment from Ping about the prediction of food
2 effect using PBPK may be at this moment, the level
3 of confidence seems to be insufficient to give us
4 the comfort level.
5 Can you also comment on your comfort level
6 about the prediction of drug-drug interactions with
7 acid-modifying agents, like PPI or X2 antagonists?
8 I think throughout today we have listened to the
9 presenters that there are successful cases, but
10 there are also some cases that are not so
11 predictive. I would like to hear your opinion on
12 that.
13 DR. P. ZHAO: I'll try to make it quick
14 because this is a generic drug workshop.
15 (Laughter.)
16 DR. P. ZHAO: Quick answer, again, as I
17 mentioned while responding to the first question,
18 in terms of predictability, all of the bullet
19 points, we will need some more work in order to say
20 in the absence of an in vivo study, we're good.
21 Basically, I'm not convinced that if you just do a
22 software prediction in the absence of the pH

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1 modulating agent prediction, a DDI study, that you
2 can get away with it.
3 Again, conditional, there are certain
4 compounds, these behave very well in the Phase 1
5 study. We have one oncology drug that we sort of
6 gave a waiver, but it was very cautiously mentioned
7 in the label, which is panobinostat. The sponsor
8 submitted one prediction using one software. We
9 sort of retested with another software.
10 Again, that's a case where probably just
11 based on the pH and the solubility, it was sort of
12 mediocre, but it was not too bad and also has very
13 good permeability. We agreed that there's no need
14 to do a pH-dependent DDI study, but other
15 conditions, probably we wouldn't feel comfortable
16 just by accepting the model prediction.
17 DR. CHIEN: Thanks.
18 If I can, I would like to ask a second
19 question. I would like to continue to expand on
20 Susie's questions about the model validation
21 questions. I think a practical concern that I have
22 when doing this hands-on is about the prediction

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1 error of the model, comparing the predictive versus
2 the observed data, because if I'm trying to -- if
3 the application is to assess bioequivalence,
4 perhaps we would like the model to be as accurate
5 as possible.
6 At what point do I have to stop and say that
7 the model is good enough, that it can be used for
8 simulation? Can I say that a percent error, 20
9 percent is good enough, or do I have to go continue
10 until I have 10 percent? Because to go from 20 to
11 10 percent, maybe I have to spend another month to
12 build a model or maybe do a lot more experiments to
13 get to that level.
14 I would like to ask the panel members to
15 share your experience. That would be great.
16 DR. NOVAKOVIC: I can answer this question
17 because I have that experience with my case. It
18 was in the percent prediction error criteria for
19 percent prediction error exactly the same as for
20 classical IVIVC Level A which means mean prediction
21 error less than 10 percent for each parameter, AUC
22 and Cmax and individual percent prediction error

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1 may be up to 15 percent. This is exactly the same
2 as for classical IVIVC Level A.
3 DR. LIONBERGER: I think it depends what
4 you're trying to predict. If you're trying to do
5 I'm going to predict the --
6 DR. NOVAKOVIC: Biowaiver.
7 DR. LIONBERGER: Yes, but for example, if
8 I'm going to try to predict what the result of
9 giving this drug product to a particular human
10 being is, right, you're never going to get the
11 right answer from a model given the variability of
12 what the inter-subject and inter-occasion
13 variability of that person is. You're going to get
14 some statistical answer.
15 You have to be careful about what your
16 expectation is about trying to predict. Maybe in a
17 bioequivalence context is you want to have
18 confidence in your test to reference ratio that
19 you're trying to predict. If you define it that
20 way, some of the common errors may drop out, and it
21 may be much easier to achieve a 10 percent
22 prediction error on a test to reference ratio. But

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1 you're not going to be able to see a 10 percent on
2 predicting the raw, what the distribution of all of
3 the test values in your subjects are across the
4 whole population.
5 It also depends in what sense you're
6 averaging the data. Do you average it down to just
7 the mean data or the whole study, or are you making
8 a prediction about including some variation in the
9 population? I don't know that a plus or minus 10
10 percent prediction error is always right. I think
11 it's reasonable for IVIVC, but in a traditional
12 IVIVC, you have some type of sort of also model
13 normalization and correction between them at least
14 going on implicitly so it looks sort of like this
15 test to reference ratio thing that some of your
16 errors that you're fitting can cut off.
17 If you're looking for the difference between
18 the fast, slow, and the medium in your fitting
19 process, the sort of overall shifts of your errors
20 can get canceled out, too. I think you have to be
21 careful of how you define the error that you expect
22 in that way and what specifically you're trying to

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1 predict, whether it's individual subject or mean
2 data, as well.
3 DR. L. ZHAO: Yes, I think I fully agree
4 with Rob. I think there's no difference between
5 the validation of PBPK model if we are only talking
6 about data or population PK or exploratory response
7 model from pharmacometrics. I think the guiding
8 principle is the feed for purpose, depending on the
9 purpose.
10 Then if you want to do a trial simulation
11 later on, then you probably need to check all the
12 quantiles, the predicted quantiles, develop the
13 quantiles. You need not only describe the median,
14 the mean, but also the uncertainty. That's what
15 I'm thinking. I don't see any big difference
16 between PBPK model or other models.
17 DR. FANG: Lucy Fang from Division of
18 Quantitative Methods and Modeling. I want to make
19 a comment on the data available to FDA. People
20 always tell me FDA has the largest database, but
21 what people don't know is from generic perspective,
22 all the data we have actually is drug products, are

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1 so-called ideal drug products. That means they all
2 pass the bioequivalence studies.
3 This means the drug are full on one side, on
4 both sides. When we use those data to build the
5 model, then this could limit our ability to explain
6 the conclusion on those models.
7 As a modeler, I would like to see that more
8 data submission for the drugs on both sides. I
9 want the GPHA to take that into consideration.
10 DR. L. ZHAO: Lucy's from the FDA, so we are
11 not addressing that comment unless the panel wants
12 to comment.
13 DR. SUAREZ: This is Sandra Suarez from the
14 FDA. Just coming back to the question previously
15 raised about criteria for validation, we have had
16 already two or three questions about that, and I
17 was just going to somehow echo on to what Rob said.
18 That's based on my experience on my involvement of
19 several PBPK models submitted to new drugs.
20 For those limited experiences that we have
21 had, the applicants have used a criteria very
22 similar to what IVIVC guidance reflects, right?

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1 But I want to tell you, again, I don't know if it's
2 clear. I said that the applicants have used the
3 same criteria used for IVIVC, meaning 10 percent or
4 15 percent, depending on its internal
5 predictability or external predictability.
6 It's pretty similar to what the IVIVC
7 guidance specifies, but my opinion is that -- of
8 course, I agree with that, because it's a
9 conservative approach. But my opinion is that we
10 need to gather experience in terms of the use of
11 the models to really determine if 10 percent or 15
12 percent predictability is right not, and it will
13 depend on the quality of the data that's going to
14 be submitted into the NDA.
15 Again, the bottom line for me to determine
16 the right criteria for model predictability is
17 going to be based on experience and is based on
18 what kind of data the FDA gets. Just like John was
19 saying, we have data showing -- for extended
20 predictability, let's say they use bioequivalence
21 studies that fail and pass, and the model is able
22 to predict that or not. Then we will build

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1 experience to really say 10 percent is sufficient
2 or 15 percent is sufficient or not or to expand
3 those goal posts for predictability, and that's
4 what I wanted to convey to the audience here.
5 DR. WANG: Hello, everyone. I'm Meng Wang.
6 I'm from the Division of Biopharmaceutics, and John
7 Duan in the center is my mentor.
8 I want to express some of my rough ideas
9 about IVIVC. Just so we are comparing a
10 traditional IVIVC and empirical IVIVC, I just
11 thought in the last whole year, I think the
12 applications, there are only 12. The number is
13 actually very, very few.
14 I just always think about why this number is
15 very, very few. I guess maybe very, very small. I
16 guess maybe it's because there are some people from
17 company -- this is just my guess. I guess it's
18 because the success rate is very small, and another
19 reason is because I think the time is maybe more
20 precious than the money.
21 So I just wonder maybe if the IVIVC success
22 rate is very small, maybe we can use the PBPK model

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1 to do risk assessment, say, if it is feasible to do
2 IVIVC. This PBPK model may be not very, very good,
3 but maybe we can use it for the risk assessment, so
4 maybe we can shorten the time. We can increase the
5 success rate and also shorten the time to make this
6 decision. That's all.
7 Thank you.
8 DR. CHOW: Hi, I'm Edwin Chow from Division
9 of Quantitative Methods and Modeling. I want to
10 make a comment about the PBPK modeling.
11 I think it's useful in a way that it really
12 does address mechanistically how the drug is
13 absorbed. Even though for BCS Class I drug you're
14 looking for a modified-release drug, even though
15 the generic company might match Cmax and AUC, the
16 Tmax might shift. And how does that really reflect
17 therapeutically what happens?
18 NTF, an epileptic drug where the PD response
19 is really seizure risk, you can really use partial
20 AUC to identify that. If you have a generic
21 submission showing bioequivalence in terms of Cmax
22 and AUC, but you definitely see a shift in the Tmax

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1 or any shape of the response, how would that affect
2 the PD during multiple dosing? It will be in
3 question.
4 I think it's really good to use a PBPK model
5 to explain those kinds of situation. Thank you.
6 DR. PATEL: Nikunj from Simcyp. I think
7 when the panelists were getting started, I had
8 about eight points to discuss, but most of them are
9 already done.
10 So just following up on the [indiscernible],
11 it probably it looks to me that the highest
12 confidence application area looks like it will be
13 physiologically-based IVIVC, and there was some
14 discussion on what should be the qualification
15 criteria, whether it should be the same as
16 conventional. As Sandra mentioned, that it is the
17 same and also Masoud pointed out, I think we use
18 the same criteria.
19 There was a good point from Rob about how to
20 assess the prediction performance, and he actually
21 brought up a nice idea of having a challenge, a
22 competition, a blind competition. If that is the

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1 case, I think the physiologically-based IVIVC
2 database as a prediction challenge would be
3 probably a first good set to put, that you give
4 that IV data, oral solution data and control all
5 this data and see how well different people can
6 predict using different platforms, numerical,
7 physiologically-based, whatever. Then you can
8 assess.
9 That would give you confidence that it is
10 totally blind as well as it would give you an
11 unbiased comparison of numerical versus
12 physiologically based or whatever different
13 approach people used.
14 DR. L. ZHAO: Thank you, everyone. Thank
15 you for all these comments.
16 Again, I really want to show my thanks to
17 all the speakers, the panel members, also for
18 people who traveled. I see your luggage there,
19 have been sitting here listening. I hope you
20 enjoyed it.
21 At the end, I would like to turn it over to
22 Dr. Robert Lionberger, office director of research

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1 and standards, OGD, to give the closing remarks.
2 Closing Remarks
3 DR. LIONBERGER: Thank you, Liang.
4 Again, I'd like to thank the organizers of
5 this, especially you and Susie, for the work in
6 setting up this very interesting meeting and really
7 getting a diverse panel of lots of different
8 perspectives here to talk about this and advance
9 the field of modeling and simulation of
10 biopharmaceutics going forward.
11 To me, this is an essential core technology
12 area and knowledge gap for the Office of Generic
13 Drugs. Still, almost all of our products are solid
14 oral dosage forms, and the more we know about what
15 they do, the more the companies that develop them
16 can predict them, the better off the American
17 public will be.
18 Certainly, this also affects new drug
19 development, development of new formulations,
20 post-approval changes to those, as well. There's
21 broad CDER and FDA interest in advancing this type
22 of tool set. I think it's really important to keep

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1 this in mind, that we need to be continually
2 advancing these tools.
3 When we think about where we should be,
4 where we should be in the future is less
5 uncertainty, more predictability about what happens
6 to drug product factors. That should be the
7 specific focus of, I think, this audience here.
8 There are other people in FDA who have a lot more
9 interest in first-in-human questions about drug
10 absorption that are important, as well, but the
11 focus here and the challenge is to really advance,
12 as Gordon says, the product science aspects of
13 this, because as we see here, there's a lot of
14 uncertainty about that in the dissolution, the
15 interaction of the physiological environment. But
16 there's a huge upside to having a much better
17 understanding of it for both FDA's regulators and
18 for industry as product developers.
19 I think with that in mind of where we want
20 to get, you should be thinking about as we go
21 forward to the next workshops, what we'd like to
22 see in this future state. I think people from

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1 industry can speak more to this, there's things you
2 do that you don't submit in the applications to
3 FDA, just to help you develop it. If a tool is
4 useful, you're going to use it. You're not going
5 to leave things that save you effort off the table.
6 The next step beyond that is when and how do
7 these things begin to show up in your interactions
8 with FDA, and that is something that as we go
9 forward, we can begin to figure out and say, well,
10 if you describe a model, here's how we'd like you
11 to describe it.
12 We often for these model cases and I think
13 our experience for IVIVCs over the past is, yes, we
14 want to replicate. We want to say, well, do we get
15 the same answer when we run the model. We can do a
16 sensitivity analysis of our own to say does this
17 model look robust.
18 That can be an important part of that, but
19 we want to think about and have discussion about
20 what pieces that we want to see if you say, well, I
21 used a model to support my argument, it doesn't
22 have to be a waiver of a study. It could just be

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1 supporting some aspect of your application, a
2 specification, some type of argument. But you
3 include a model to support that. What types of
4 information should you include about that model is
5 an important part of the future state of
6 discussion, to have more clarity on that.
7 That will help FDA focus. We look at this
8 model. You've basically met the sort of basic
9 standards for what we expect to see in a model, and
10 that gives us the -- and then we can sort of
11 evaluate it in a more consistent manner.
12 I think that's where we want to be, and as
13 we close the workshop, I want to think about what
14 some of the next steps should be. I think the key
15 ones to me are as we go forward with this, really
16 getting the agreement on the science in the public
17 literature. What can these tools do through these
18 public competitions, tests of the models?
19 Getting agreement on where they work in
20 cases that are publicly made available through the
21 literature that people can really see, criticize,
22 analyze, that sort of scientific foundation is

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1 essential for moving acceptance of modeling and
2 simulation forward.
3 I think another thing to think about as we
4 go into the next steps is to communicate the impact
5 beyond the modeling and simulation community. The
6 importance of modeling and simulation, to try to
7 say it helps make decisions. If modeling and
8 simulation is useful, it helps people make
9 decisions, that you, as industry, developing
10 products, you have to decide what formulations
11 should I choose, what bioequivalence studies should
12 I do. Those are all decisions.
13 For us, as regulators, we also have to make
14 decisions. Is this specification acceptable or
15 not? Is this bioequivalence study acceptable or
16 not? Is this new bioequivalence approach going to
17 be valid or not? All of these are decisions.
18 Then we want to use the best tools available
19 to make those decisions. As we think about
20 modeling and simulation, we have to recognize that
21 the audience that we're trying to reach is the
22 people who are in the end making those decisions

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1 and we want to think about how we present the
2 models to those people in terms of their accuracy,
3 reliability, what they've been able to do in the
4 past, and, also, how they're just based on
5 fundamental understanding of physiology and physics
6 and mass transport and things like that.
7 No one's going to argue or people shouldn't
8 argue with things like the second and first laws of
9 thermodynamics. There's a fundamental basis for
10 the models in physics and chemistry that should be
11 solid. There's also understanding of the
12 physiology, as well, that need to be integrated.
13 We need to be thinking about how we explain
14 what the models are including as we go forward.
15 And to echo sort of the last question here, what
16 are the gaps that we need to close, so tomorrow
17 we're having a Part 15 hearing for our GDUFA
18 regulatory science program. This is an opportunity
19 where you can specifically tell us what you want
20 FDA to do.
21 To me, the thing that we really need to
22 focus on as we look at gaps, where are the

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1 new -- where are the publicly available in vivo
2 datasets that we need to move the area forward? I
3 think there's significant efforts in that in Europe
4 in the OrBiTo consortium and FDA through things
5 that we can fund through the generic drug
6 regulatory science program to generate new in vivo
7 datasets that answer and help advance the modeling
8 and simulation tools.
9 Then I think Duxin and some of the comments
10 gave about measuring the direct GI concentrations,
11 that's something that's not often available. The
12 more data you have there really helps build this
13 bridge up between the in vitro dissolution and the
14 in vivo product performance.
15 Please come tomorrow or make comments to the
16 docket about those in vivo pieces of data that
17 would be really helpful to have in the public
18 domain to advance the entire field.
19 I just want to again close by thanking
20 everyone for their time here, especially the panel
21 for your expertise and thoughtfulness about this,
22 and I hope that we will be continuing this type of

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1 discussion in many different forms going forward
2 and seeing much broader use of modeling and
3 simulation in the sort of development of generic
4 products and also the review and evaluation of
5 those application.
6 Again, thanks very much to everyone.
7 (Applause.)
8 (Whereupon, at 4:37 p.m., the meeting was
9 adjourned.)
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