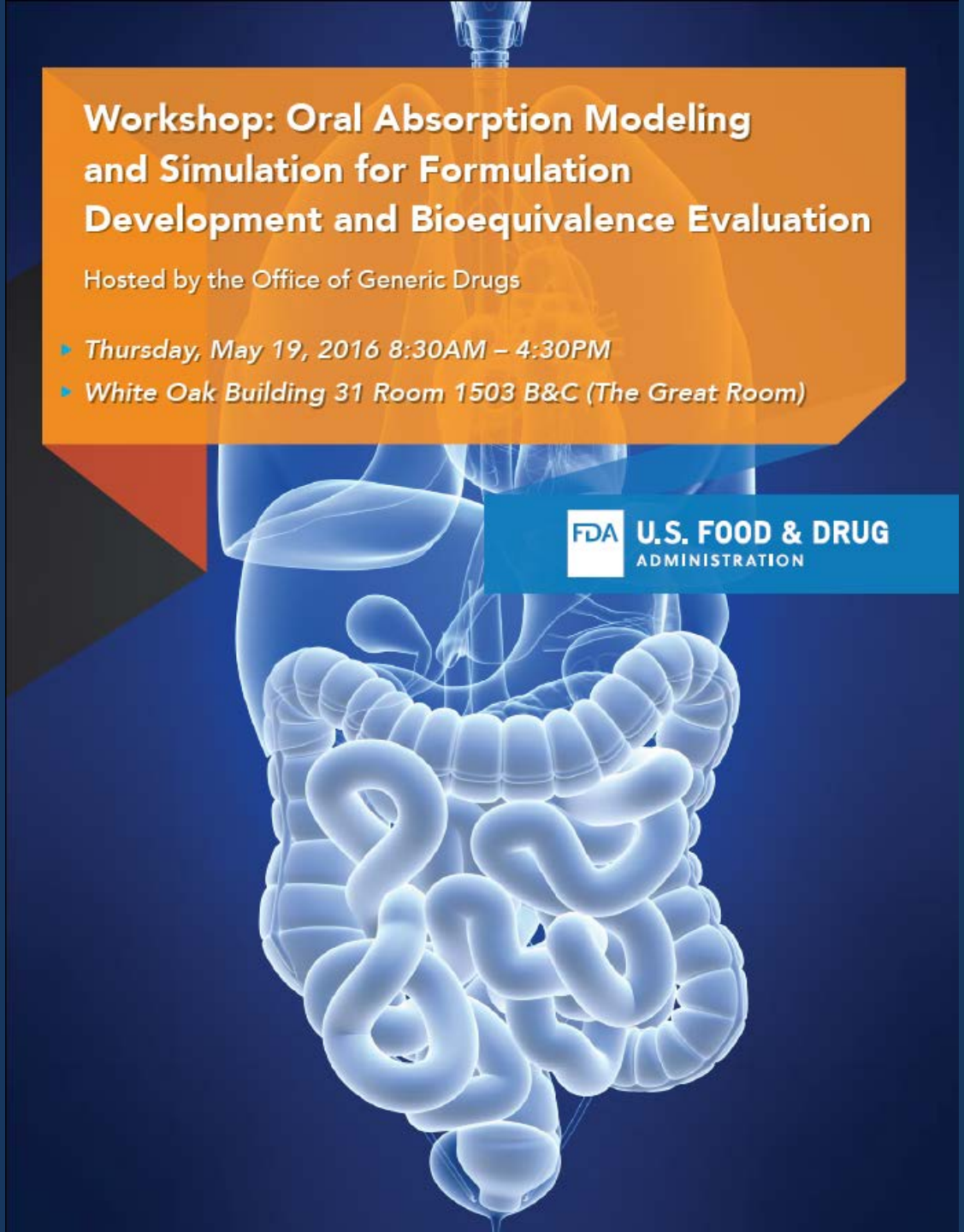
Workshop: Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation

Hosted by the Office of Generic Drugs

- *Thursday, May 19, 2016 8:30AM – 4:30PM*
- *White Oak Building 31 Room 1503 B&C (The Great Room)*

FDA U.S. FOOD & DRUG ADMINISTRATION



FDA Public Workshop

Mechanistic Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation

Docket Number FDA-2016-N-0668

May 19, 2016

Agenda

8:00 – 8:30 am	**Registration**
8:30 – 8:35 am	**Welcome and Logistics** Liang Zhao, PhD, Director, FDA/OMPT/CDER/OGD/ORS/DQMM
8:35 – 8:45 am	**Opening Remarks** Kathleen (Cook) Uhl, MD, Director, FDA/OMPT/CDER/OGD
8:45 – 9:00 am	**Introduction and Objectives of the Workshop** Liang Zhao, PhD, Director, FDA/OMPT/CDER/OGD/ORS/DQMM
9:00 – 9:25 am	John Duan, PhD, Acting Branch Chief, FDA/OMPT/CDER/OPQ/ONDP/DB/BBIII
9:25 – 9:50 am	Xinyuan Zhang, PhD, Scientific Lead, FDA/OMPT/CDER/OGD/ORS/DQMM
9:50 – 10:15 am	**Break**
10:15 – 10:40 am	Filippos Kesisoglou, PhD, Senior Principal Scientist, Merck, PQRI/BTC
10:40 – 11:05 am	Jasmina Novakovic, PhD, Scientific Leader, Apotex
11:05 – 11:30 am	Gordon Amidon, PhD, The Charles R. Walgreen Jr. Professor, University of Michigan
11:30 am-12:30 pm	**Lunch** (not provided)
12:30 – 12:55 pm	Masoud Jamei, PhD, Vice President of R&D, Simcyp (a Certara company)
12:55 – 1:20 pm	Viera Lukacova, PhD, Team Leader, SimulationsPlus
1:20 – 1:45 pm	Thomas Eissing, PhD, Head of Systems Pharmacology CV, Bayer Technology
1:45 – 2:10 pm	Xavier Pepin, PhD, Principal Scientist, AstraZeneca R&D, ORBITO
2:10 – 2:30pm	**Break**
2:30 – 4:00 pm	Panel Discussion
4:00 – 4:30 pm	Questions and Comments from the Audience for Panel Discussion
4:30 – 4:40 pm	**Closing Remarks** Robert Lionberger, PhD, Director, FDA/ OMPT/CDER/OGD/ORS

Apologies, Filippos to present

Panelists

US FDA

- Dale Conner, Pharm.D., Director, FDA/CDER/OGD/OB
- John Duan, Ph.D., Acting Branch Chief, FDA/CDER/OPQ/ONDP/DB/BBIII
- Liang Zhao, Ph.D., Director, FDA/CDER/OGD/ORS/DQMM
- Mehul Mehta, Ph.D., Director, FDA/CDER/OTS/OCP/DCP1
- Paul Seo, Ph.D., Director, FDA/CDER/OPQ/ONDP/DB
- Ping Zhao, Ph.D., Scientific Lead, FDA/CDER/OTS/OCP/DPM
- Robert Lionberger, Ph.D., Director, FDA/CDER/OGD/ORS
- Xinyuan Zhang, Ph.D., Scientific Lead, FDA/CDER/OGD/ORS/DQMM

Non-US FDA

- Filippos Kesisoglou, Ph.D., Senior Principal Scientist, Merck, PQRI/BTC, OrBiTo
- Gordon Amidon, Ph.D., Professor, University of Michigan
- Jasmina Novakovic, Ph.D., Scientific Leader, Apotex, GPhA
- Masoud Jamei, Ph.D., Vice President of R&D, Simcyp (a Certara company)
- Thomas Eissing, Ph.D., Head of Systems Pharmacology CV, Bayer Technology
- Viera Lukacova, Ph.D., Team Leader, SimulationsPlus

Introduction

Liang Zhao, Ph.D., Director
Division of Quantitative Methods & Modeling
Office of Research Standards
Office of Generic Drugs

Objectives

- Share current FDA experiences on the application of mechanism-based absorption modeling and simulation in regulatory activities;

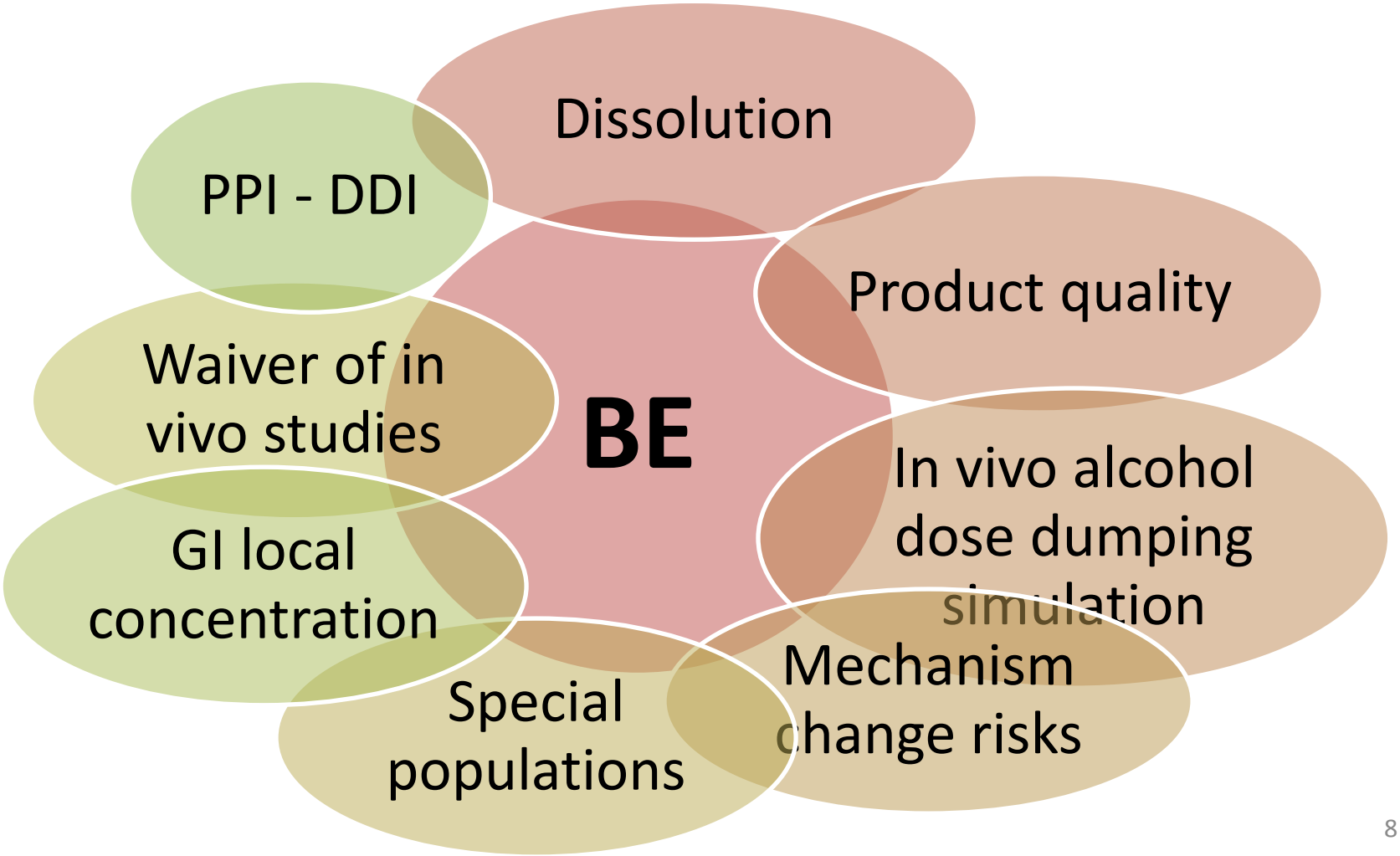
- Discuss current and future utility of mechanism-based absorption modeling and simulation in the development of bioequivalent oral drug products and regulatory reviews;

- Obtain input from various stakeholders on when, where, and how to conduct mechanism-based absorption modeling and simulations in the context of bioequivalent product development; and request comments on these topics.

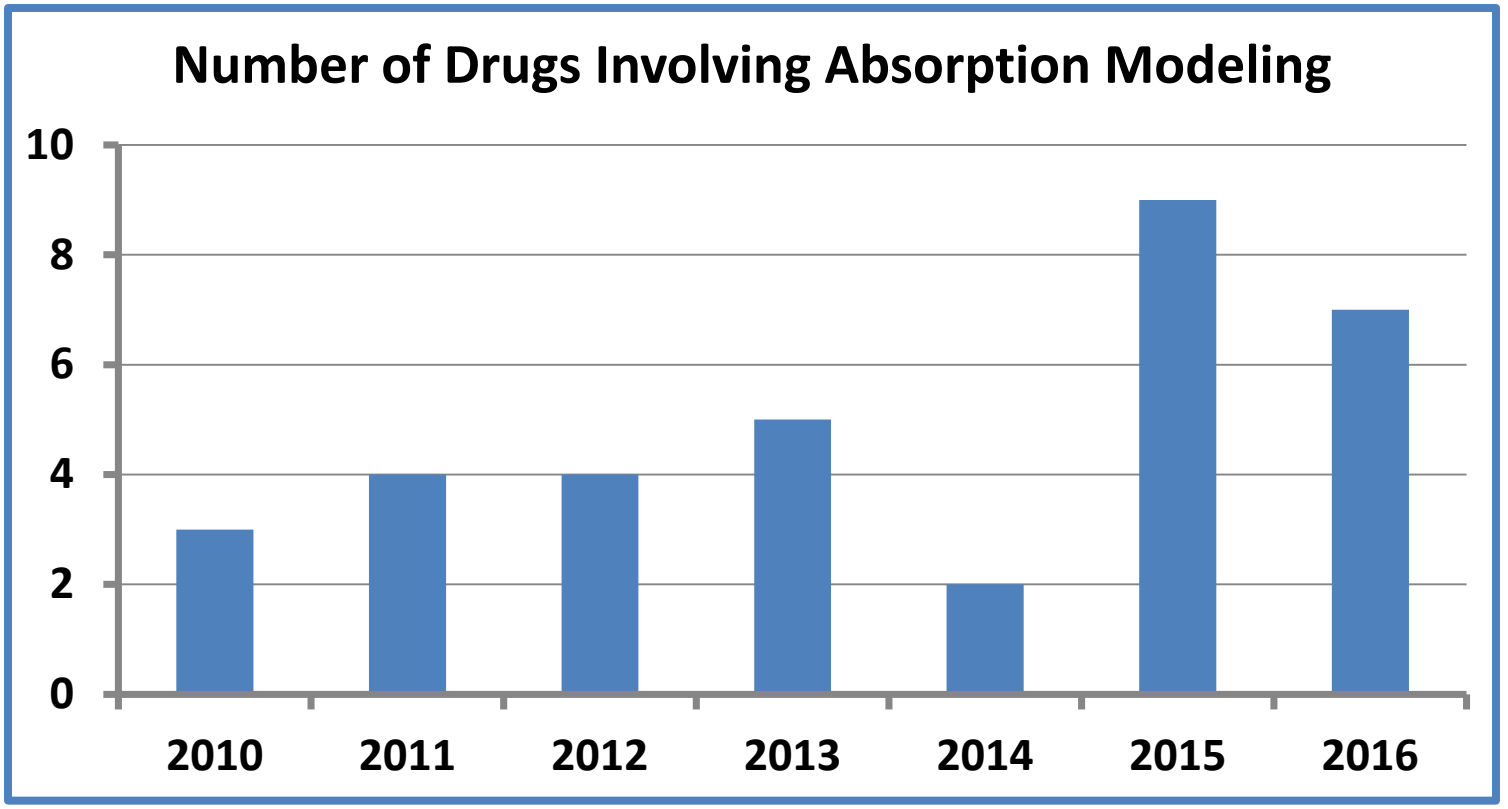
M&S Impact Various Regulatory Activities in OGD (4/1/15 to 4/1/16)

Type	No.	Examples
ANDA Reviews	20	❖ PD modeling and simulation for Methylphenidate ER product and asthma controllers
CP, CC, Pre-ANDA meetings	54	❖ Development of BE criteria for pain killers ❖ Assessment of BE standards for GI locally acting products ❖ Simulation of in vivo alcohol dose dumping studies
BE Guidances	33	❖ Simulations for the development of BE criteria for HVDs and NTI drugs
Regulatory Research Study	37	❖ PK/PD modeling and simulation to determine the appropriate study design and evaluate BE between generic anti-epilepsy drugs and immunosuppressant drugs in patients

PBPK in Applications for Generics



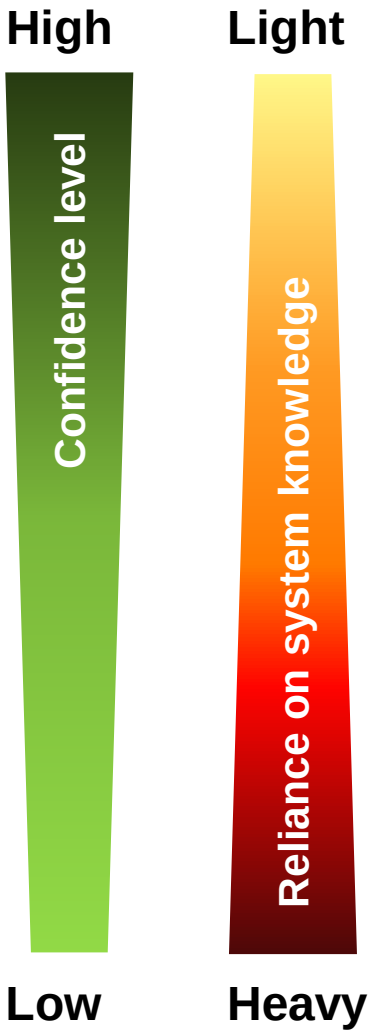
Number of Compounds Assessed Using Absorption Modeling



- IR (15), MR (19)
- Ranking: BCS 2/4 > BCS 1 > BCS 3

PBPK Applications in NDA: Current Status

	Applications	Status
Drug-drug Interactions	*Drug as enzyme substrate*	• *Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling*
	Drug as enzyme perpetrator	• *Use to confirm the lack of enzyme inhibition* • *Additional evidence needed to confirm predictive performance for positive interactions*
	Transporter-based	• *In vitro-in vivo extrapolation not mature* • *Complicated by transporter-enzyme interplay* • *Predictive performance yet to be demonstrated*
Specific populations	*Organ impairments (hepatic and renal)*	• *Predictive performance yet to be improved* • *System component needs an update*
	Pediatrics	• *Allometry is reasonable for PK down to 2 years old* • *Less than 2 years old ontogeny and maturation need to be considered*
Others with limited experiences	*Pregnancy, ethnicity, geriatrics, obesity, disease states* *Food effect, formulation change, PH effect (including DDIs on gastric PH)* *Tissue concentration*	



Wagner, CPT-PSP, 2015

Slide from Ping Zhao, 2016 ASCPT

Drug labels with dosing recommendations informed by PBPK

	2009	2010	2011	2012	2013	2014	2015
Products	1 *REVATIO*	3 *CARDIZEM LA* *BILTRICIDE** *XOLEGEL**	2 *XARELTO* *EDURANT*	1 *ICLUSIG*	4 *SKYLA** *OLYSIO* *IMBRUVICA* *OPSUMIT*	7 *MOVANTIK* *CERDELGA* *JAKAFI* *ZYKADIA* *LYNPARZA* *EDURANT* *BLINCYTO*	8 *FARYDAK* *ARISTADA* *ODOMZO* *LENVIMA* *COTELLIC* *TIVICAY* *TAGRISSO* *ALECENSA*
PBPK reviews (IND, NDA, BLA)	6	12	14	16	47	38	40

**: Not a DDI application*

Slide from Ping Zhao, 2016 ASCPT

Biopharmaceutics

Biopharmaceutics: a Bridge

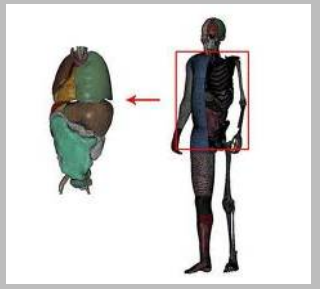
The study of the physical and chemical properties of drugs and their proper dosage as related to the onset, duration, and intensity of drug action. Construct solid biopharmaceutics discipline.

Translating in vitro to in vivo

Understanding mechanisms of in vitro release as well as physiology in relation to drug absorption, and in silico models that mimic in vivo release characteristics - potential biopharmaceutics tools to facilitate the shift

Mechanistic Absorption Model

Integrate anatomical and physiological parameters, physicochemical properties of drug substances, and formulation properties of drug product to predict in vivo performance quantitatively in a mechanistic platform



Slide from Dr. John Z. Duan

Current Status (2008-2016)

	Potential Applications	Current Status
Dissolution Method and Acceptance Criteria	*Justify/support bio-predictive dissolution method*	• *Use the verified PBPK/absorption model combined with bioequivalence clinical study and dissolution profiles generated to show that the proposed dissolution method can reject non-BE (bioequivalence) batch*
	Set clinically relevant dissolution acceptance criteria	• *Allow dissolution acceptance criteria to go beyond target ±10% range* • *Additional evidence (data) needed to validate model and confirm predictive performance*
Set clinically relevant drug product specifications for CMAs and CPPs	*CMAs (particle size, polymorphic form)*	• *Predict particle size distribution (PSD) limits which would result in similar in vivo performance to the target (clinical batch)* • *Predict the effect of polymorphic form on in vivo performance of drug product*
	CPPs (milling method, pressure force/hardness)	• *Predict the effect of milling method on the bioequivalence of drug product (e.g. pre- and post-change of milling method)* • *Used to justify specification range of compression force based on the predicted in vivo performance*
Risk assessment	*Evaluation of the risk*	• *Quantitative assessment*

Slide from Dr. John Z. Duan

Questions to the Panel

1. For the available list of area(s) or sub areas, which one(s) do we have the highest confidence in using physiologically based absorption (PBPK absorption) modeling for oral dosage forms?

Questions to the Panel

2. Do we have enough experience and confidence in applying the current PBPK absorption models to support the following regulatory applications?
   - Support particle size distribution specification for an immediate release drug product of a drug with a low solubility
   - Support dissolution specification for a modified release drug product
   - Support request to widen the BCS III biowaiver criteria (proposed longer dissolution time than very rapidly dissolve and/or different excipients)
   - Support in vitro-in vivo correlation of an API with less than three formulations with different release rates
   - Support new proposals to demonstrate bioequivalence for GI locally acting drug products

3. For the areas with middle to low confidence, what are the gaps and how to close the gaps through research?