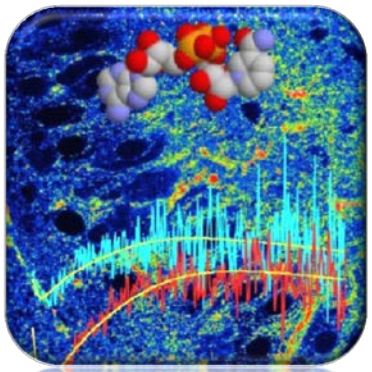
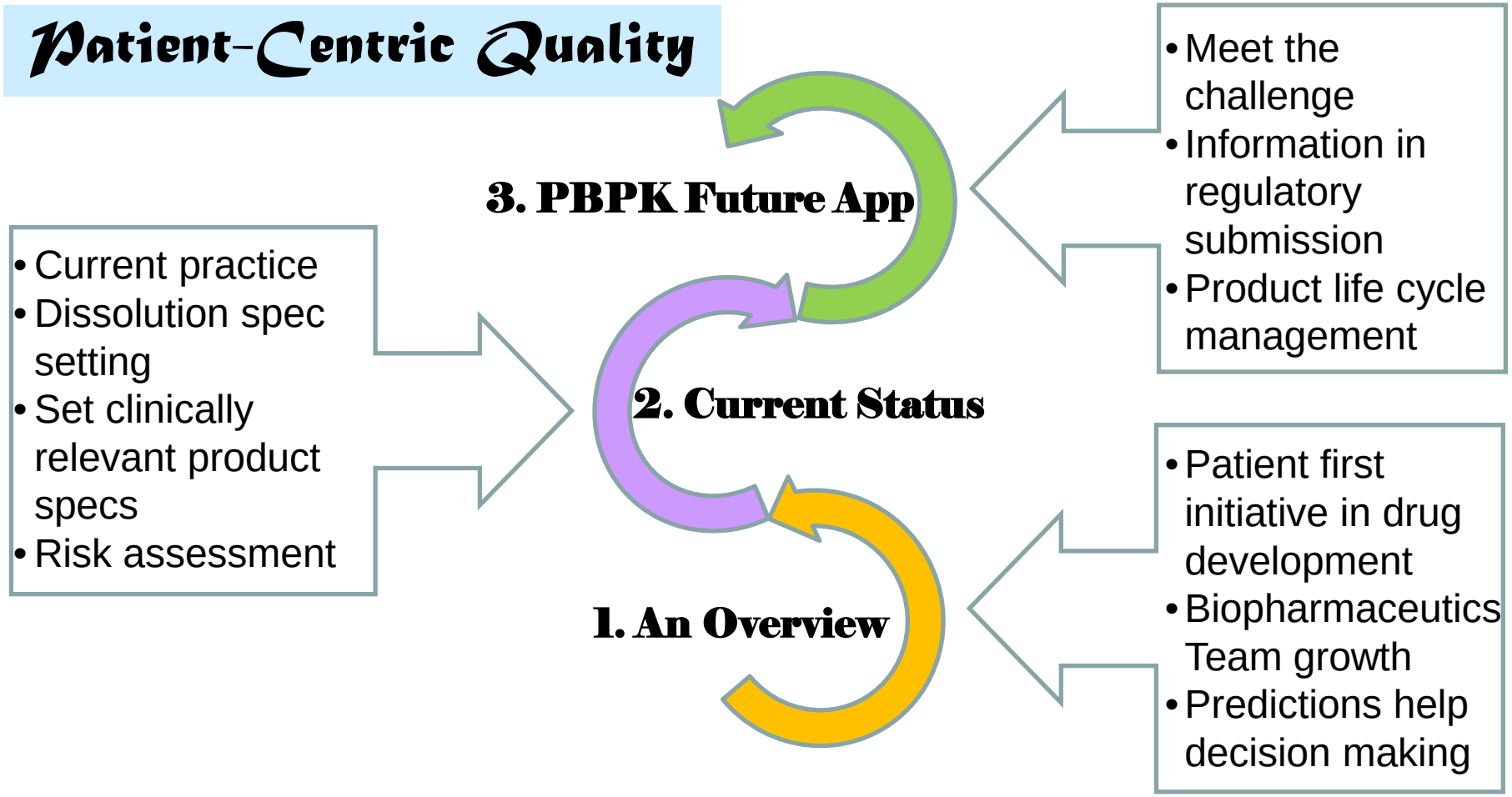



The Application of Mechanistic Oral Absorption Model in Biopharmaceutics Review

John Z. Duan, Ph.D.
Division of Biopharmaceutics /ONDP/OPQ/CDER/FDA

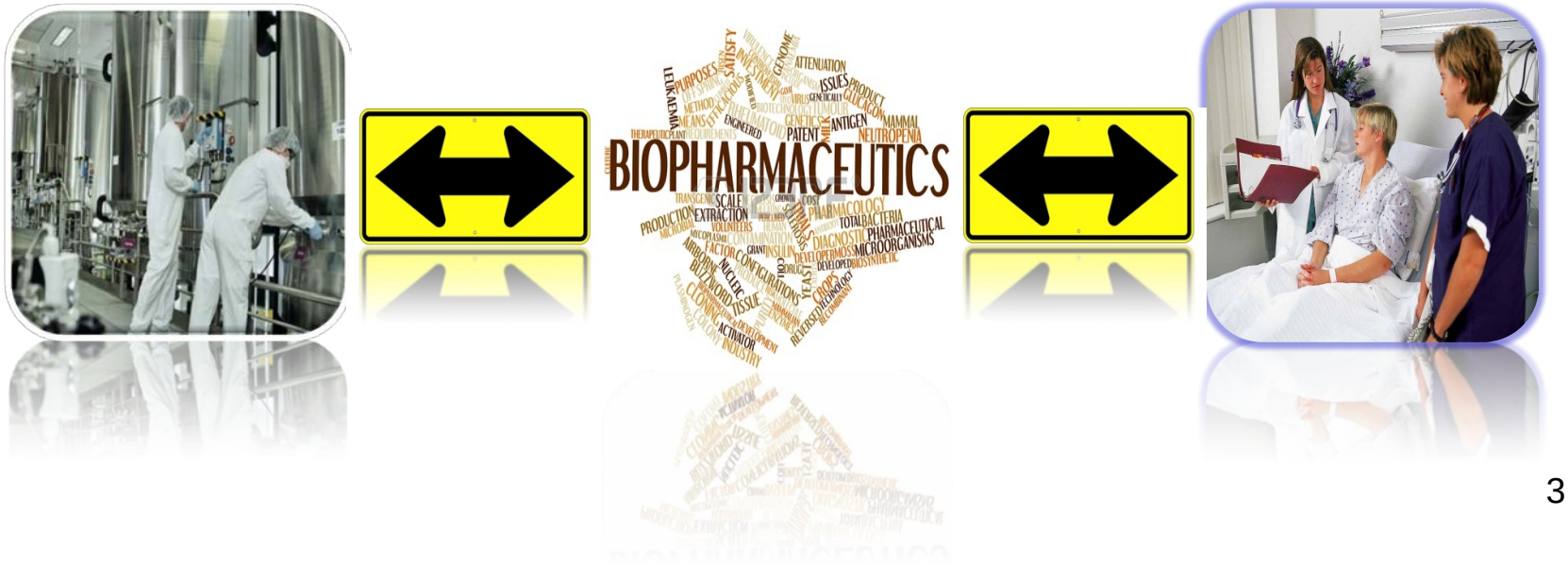



Presentation Outline



AN OVERVIEW
BIOPHARMACEUTICS ROLES IN PATIENT CENTRIC QUALITY CONTROL

CRS: CLINICALLY RELEVANT SPECIFICATION

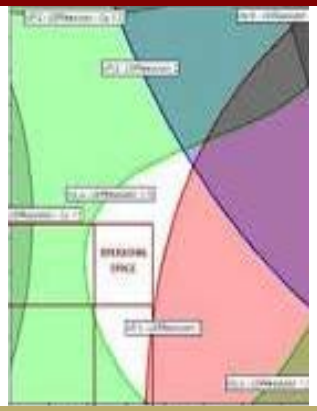


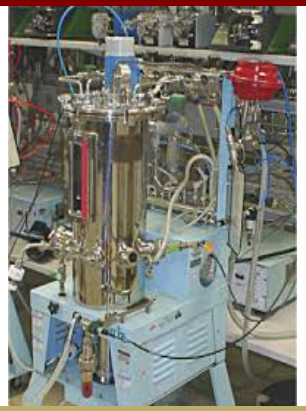
Quality Control Paradigm Shift

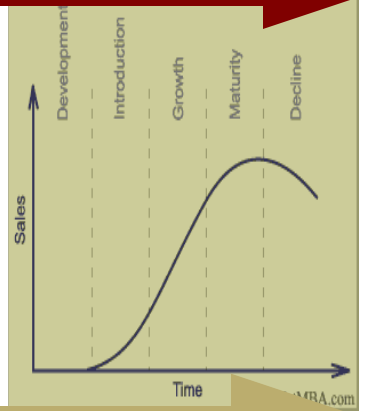
From the traditional specification compliance model to CRS paradigm.

Risk Assessment Design Space Control Strategy

Patient Needs Product Life Cycle







Lifecycle Solutions

OFFICE OF PHARMACEUTICAL QUALITY

ONE QUALITY VOICE

One Voice:

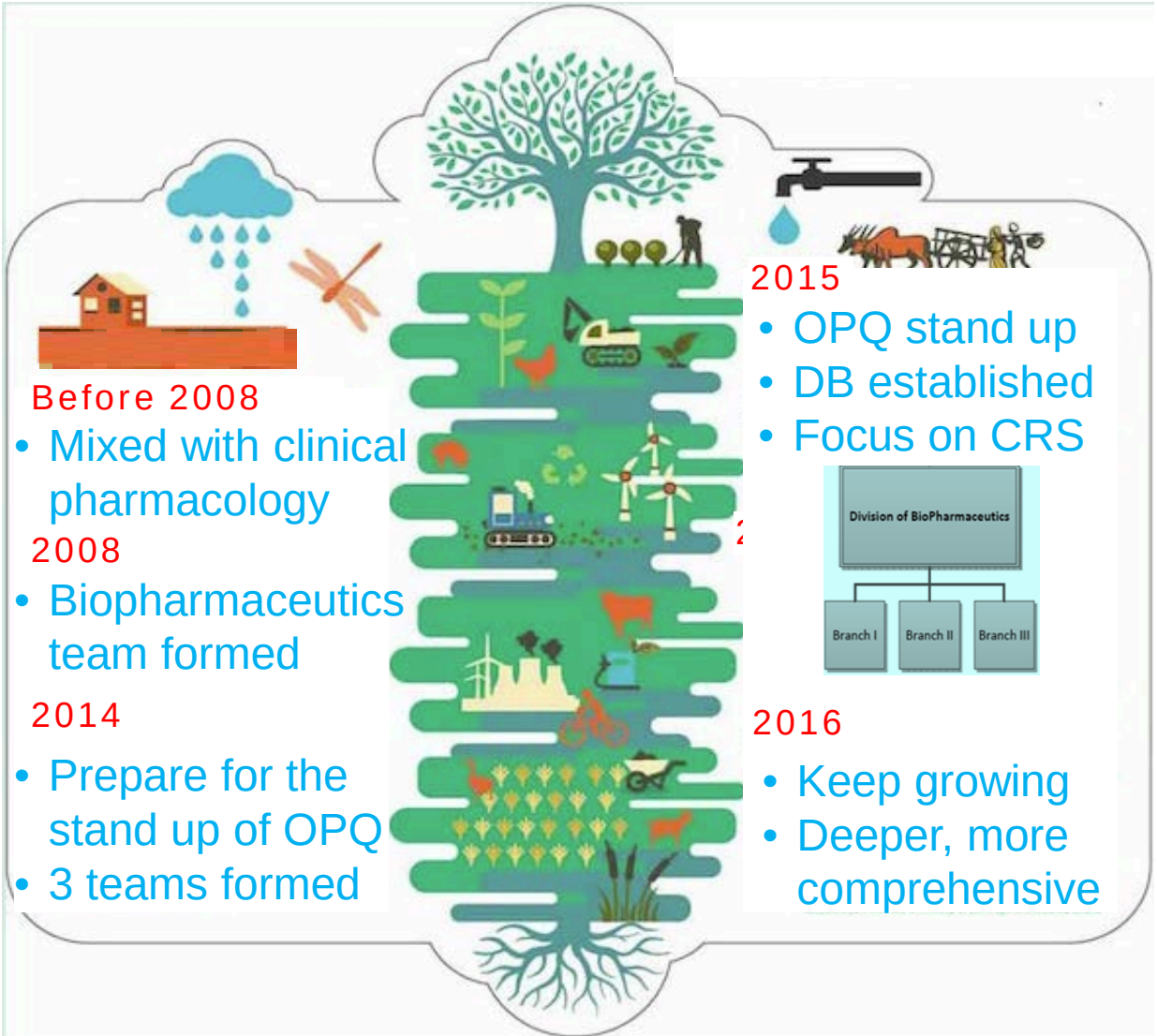
For the Patients

Mission:

To assure that quality medicines are available for the American public.

.

Decades of FDA Biopharmaceutics



Before 2008
- Mixed with clinical pharmacology

2008
- Biopharmaceutics team formed

2014
- Prepare for the stand up of OPQ
- 3 teams formed

2015
- OPQ stand up
- DB established
- Focus on CRS

2016
- Keep growing
- Deeper, more comprehensive

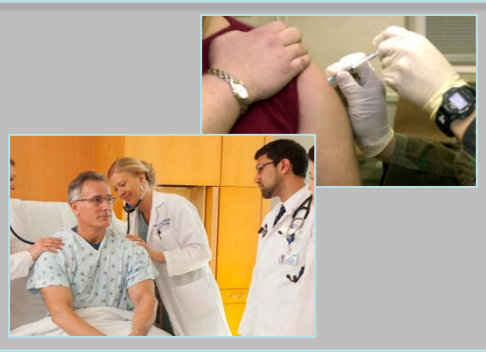
Biopharmaceutics

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.

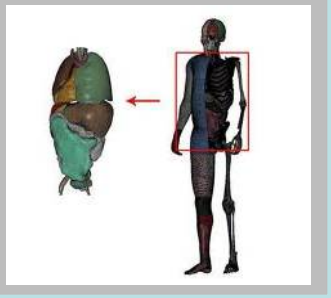
Translating in vitro to in vivo

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

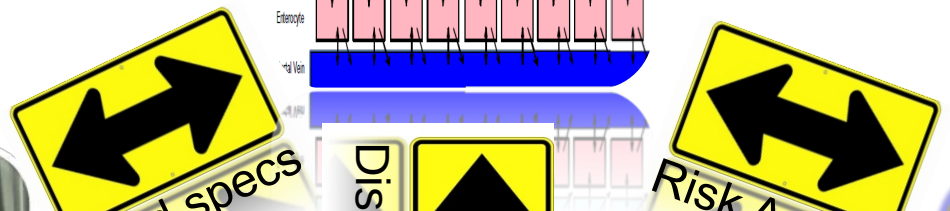


Mechanistic Absorption Model

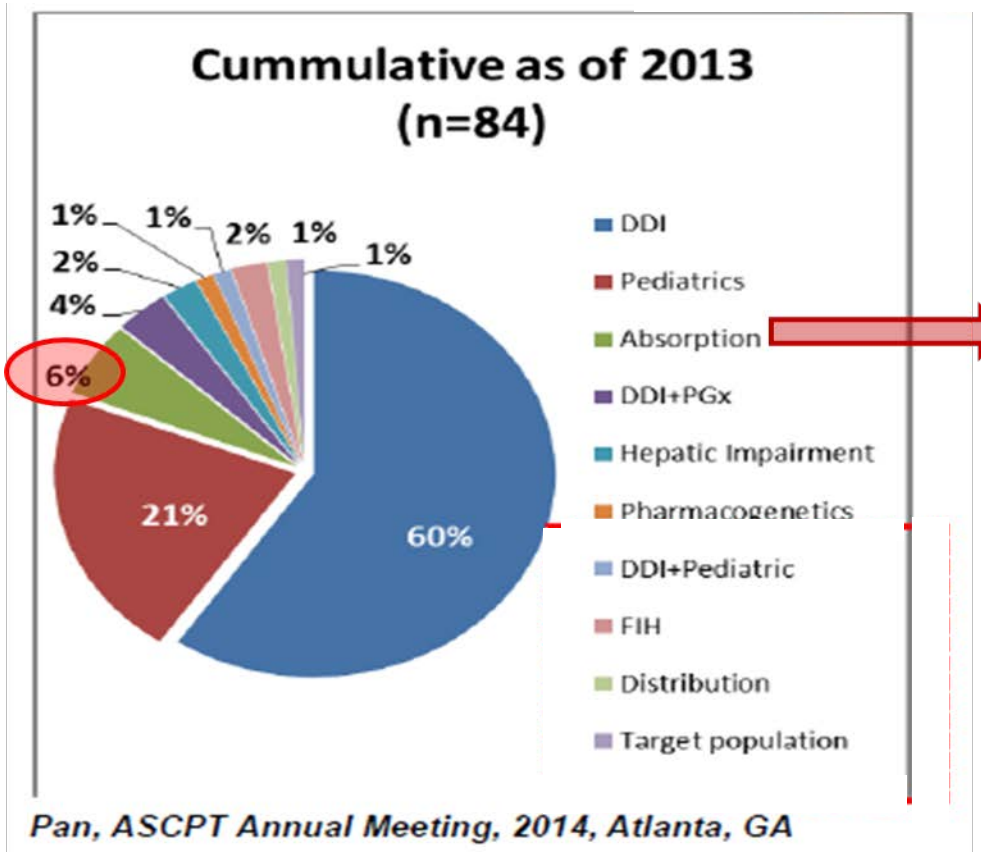
Integrate anatomical and physiological parameters, physicochemical properties of drug substances, and formulation properties of drug product to predict in vivo performance quantitatively in a mechanistic platform



CURRENT STATUS



Absorption Model: a Small Portion



Only 6%!

Ping Zhao, Application of PBPK modeling and simulations in drug development. 15th international workshop on Clinical Pharmacology of HIV & Hepatitis Therapy, Washington DC, USA

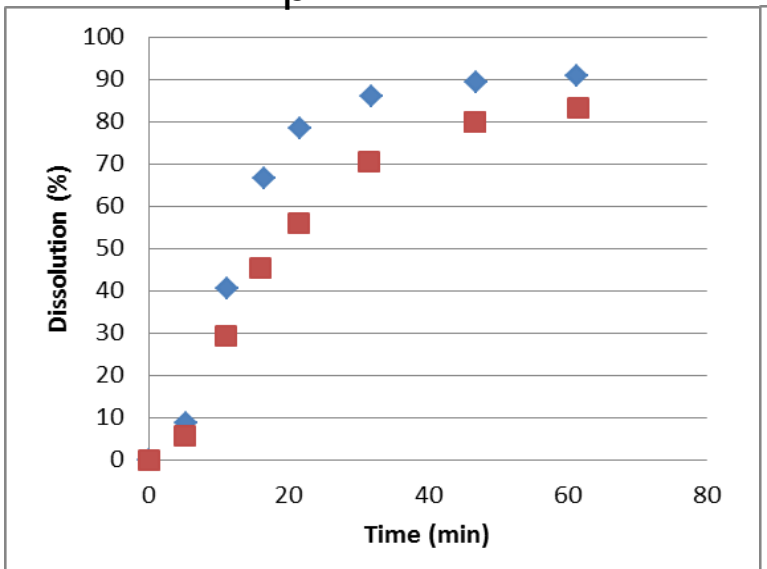
Current Status (2008-2016)

	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*

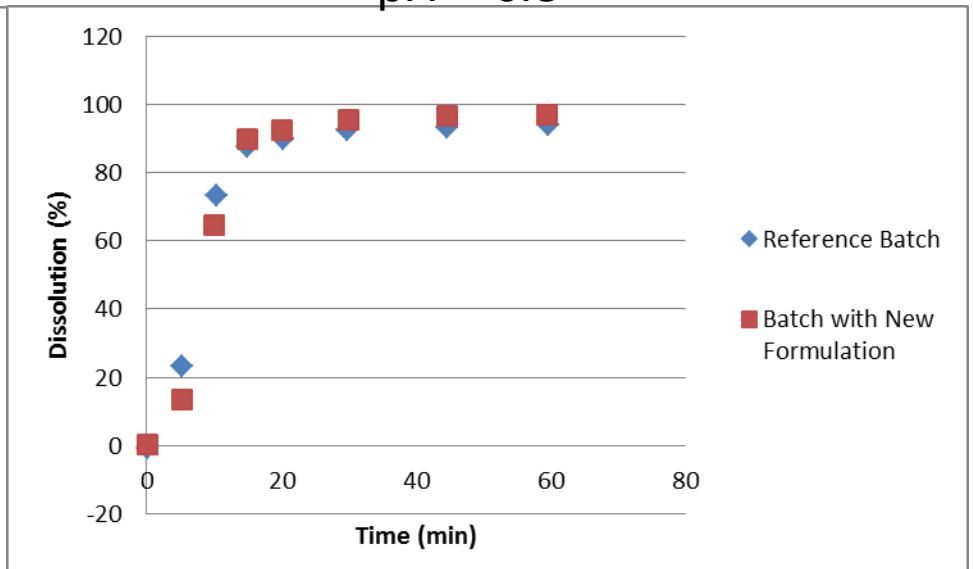
Case Example 1
Clinically Meaningful Diss Method

- Differences between target and aberrant formulation in different pH's
- PBPK simulation: the two formulations are not BE and dissolution testing in pH 2 is able to differentiate the two (Q=80% at 30 min)

pH = 2



pH = 6.8



Case Example 2

Overview:

- *In silico* absorption model accounting for differences of dosage form transit, dissolution, local pH in the GI tract and fluid volumes available for dissolution can predict the PK of non-BE batch.
- **Dissolution specification** is justified by simulation of the performance of batches with different quality**.**
- Finding the edge of dissolution by simulating a virtual batch
- Predict API **particle size distribution (PSD)** at the proposed dissolution specification.

Dissolution Data in the Model

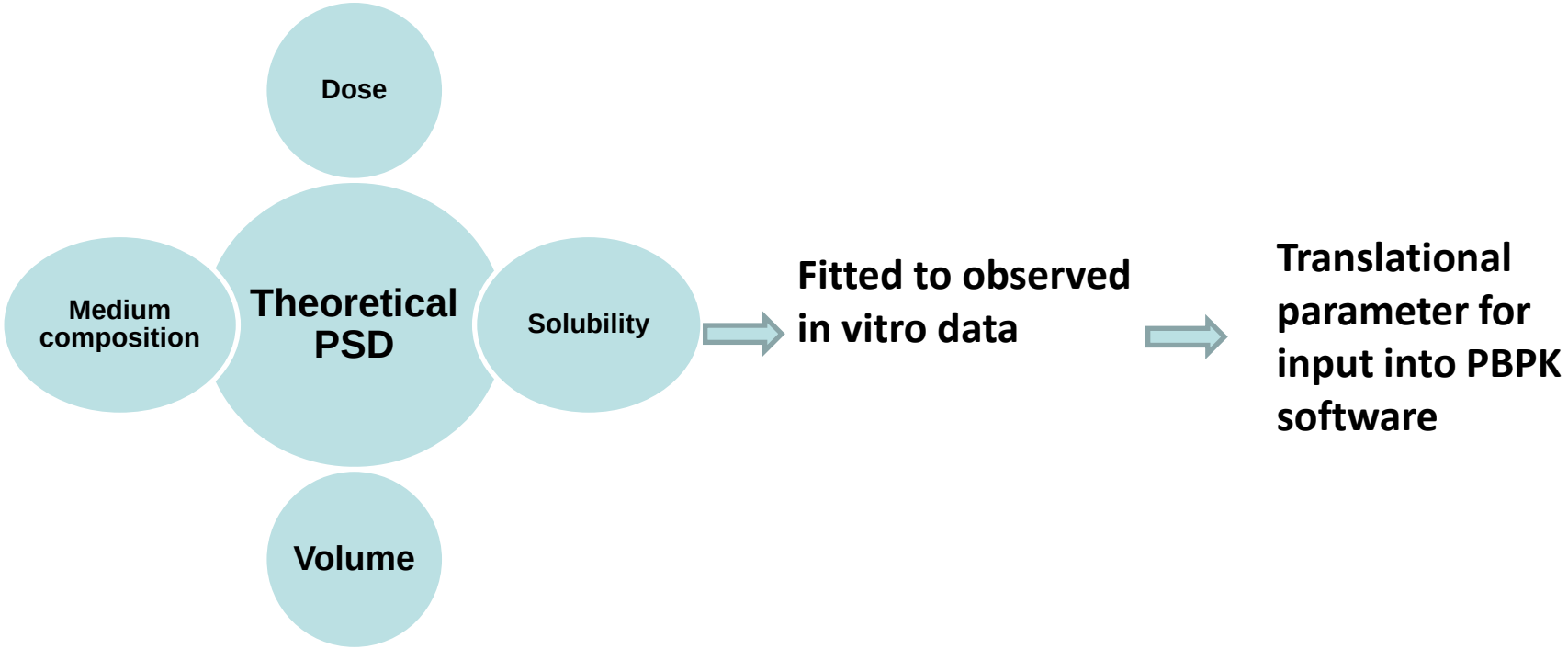
- **Option 1:** Use of in vitro dissolution data to fit particle size distribution (Dosage form: DR enteric coated tablet)
- **Option 2:** Use of in vitro dissolution data to fit Weibull function
- **Option 3:** Use of in vitro dissolution data to fit the Z-factor model (Dosage form: DR enteric coated tablet)

Option 1 verification using non BE (test) batch

- Predicted Cmax and AUC ratios were comparable to observed clinical data for test and reference batch
- Virtual BE study simulated lower Cmax and AUC for non BE batch as compared to reference batch

Option 1 was selected

Model Setup



- ACAT + Compartmental model
- Rate constants and total clearance calculated
- Gastric emptying patterns and Peff : individually fitted , disposition parameters: constant
- Total clearance was used to calculate hepatic and renal clearance
- Dosage form transit – delayed release enteric coated tablet

Model Applications

- **To set dissolution specification**
  - Batch X (bioequivalent to reference batch), reference batch and non BE batch was used
  - Virtual particle size distribution generated in excel – input for GastroPlus model
  - Batch X and reference batch - (Q≥80%) at 30 min
    Test batch - (Q ~ 60% at 30 min)
  - Virtual BE trials were performed between batch X, reference batch and test batch

	Predicted Cmax geometric mean ratio	90% CI	Predicted AUC geometric mean ratio	90% CI
Test vs reference	0.805	(0.796, 0.814)	0.876	(0.869, 0.883)
Batch X vs reference	0.987	(0.977, 0.998)	1.000	(0.990, 1.01)

- Able to reject batches which have reduced exposures in vivo and pass batches that have suitable clinical performance
- Virtual batch A : Q = 70% at 30 min was bioequivalent to reference
- **Proposed dissolution specification is justified (Q = 80% at 30 min)**

Model Applications

- **To predict the *in vivo* performance using the proposed particle size distribution**
  - Proposed PSD (test batch: virtual)
    D(v, 0.5) NMT 70 µm
    D(v, 0.9) NMT 159 µm
  - Observed measured PSD (reference batch)
    (D(v, 0.5) 23.2, D (v, 0.9) 45.9)
  - Q = 80% at 30 minutes
  - PSD was used as an input in GastroPlus using **option A** to calculate in vivo dissolution

	Geometric mean ratio (Cmax)	Geometric mean ratio (AUC)
Test vs reference	0.998	1.000
Test vs reference		

Conclusion

- No appreciable difference was observed between Cmax and AUC for test and reference batch
- Proposed specification limits for particle size distribution are acceptable

Case Example 3

Motivation and overview:

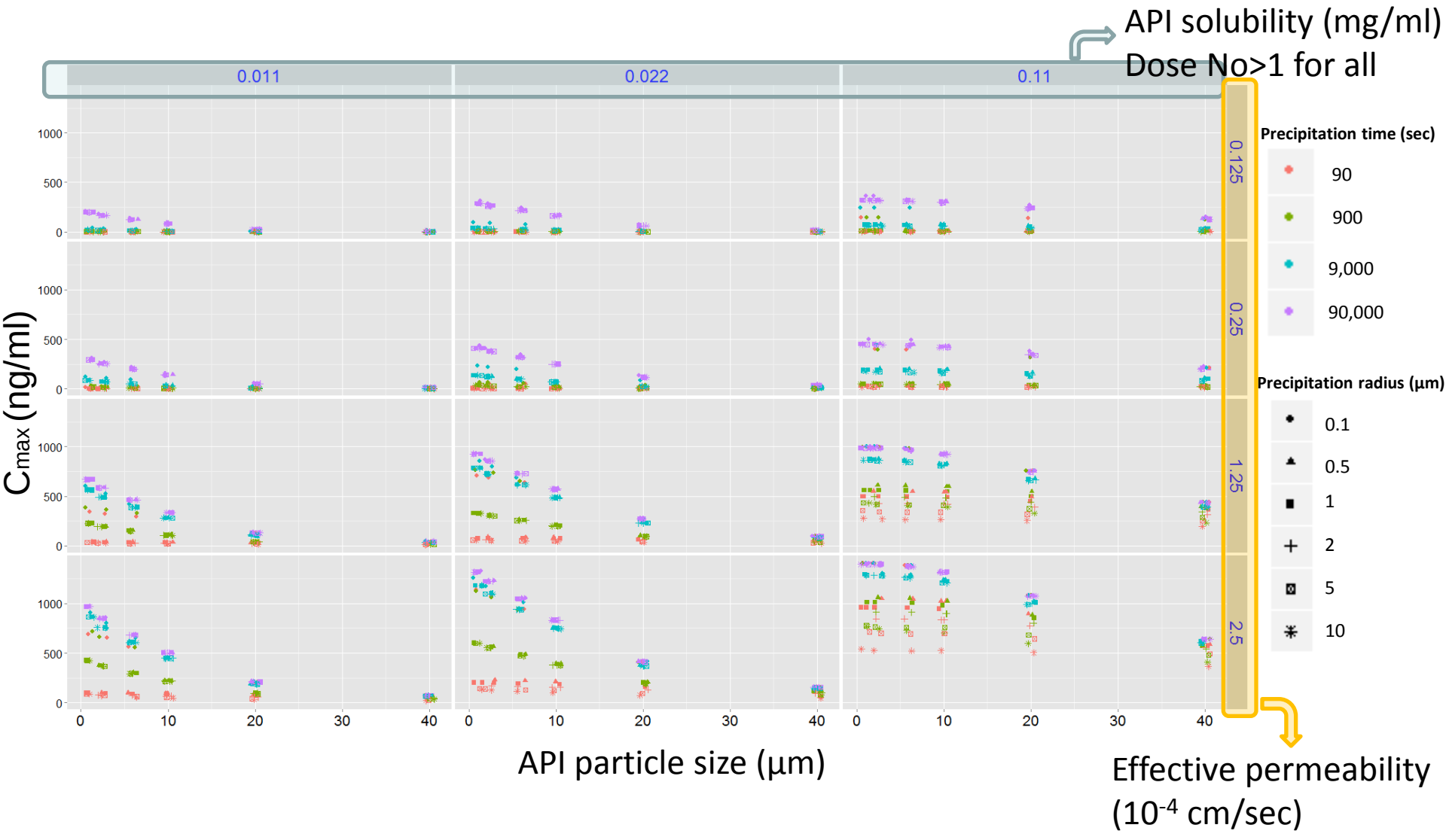
- When dealing with absorption model, inevitably several parameters are from in silicon prediction or optimization.
- The outcome of these uncertainties, especially the interplay among the uncertain parameters requires a good approach to monitor.

Parameter of interest

Parameters	Starting Value (x)	Levels	No
API particle radius	2.5	1, 2.5, 6, 10, 20, 40	6
Effective permeability	1.25	0.1x, 0.2x, x, 2x	4
Precipitation time	900	0.1x, x, 10x, 100x	4
Reference solubility	0.011	0.1x, 0.2x, 0.5x, x, 2x, 10x	6
Radius of precipitate	1	0.1, 0.5, 1, 2, 5, 10	6
Rbp	1.02	0.55, 0.8, x, 2x	4

- 4*4*6*6*6*4 = 13824 unique combinations

Multidimensional Sensitivity Analysis



Understanding the Model

Results Interpretation	Possible regulatory impact
Multi-dimensional sensitivity analysis allows tracking the interplay among uncertain and/or of interest parameters	Require further justification for the effect of uncertain parameters, when absorption modeling is used to set the product specification (e.g., particle size)
Survey of parameter values from multiple submissions allows more accurate parameter estimation and more confidence on model prediction	The reliability of the model prediction is likely to improve when the information is gathered from multiple drug applications
For low solubility drug, the accuracy of equilibrium solubility can have dramatic impact on model prediction	Sponsor may provide solubility in buffer at various pH and in bio-relevant solution (i.e. SGF, FaSSIF, FeSSIF) under 37 °C

Regulatory Implications

- Initial risk evaluation per available info
- Evaluate product quality based on clinical relevance
- Setting clinically relevant specifications
- Analyses Cross study and cross formulation
  - More knowledge and data are available, which are used for model validation. This increases confidence for improving the quality of the drug including setting of product specs.
- Combine several software to extend the ability.
  - Make full use of available information
  - Identify CQAs
  - Control the CMAs and CPPs
  - Justify the specs for quality control

Common Limitations in Submission

- Model exercises done, not used. Especially those successfully developed in the early stage not fully utilized in regulatory submissions for justification
- Detailed information not provided
- Model not fully validated
- Model files not provided
- Rationale not clear
- Justifications not reasonable

MEETING THE CHALLENGE GOING FORWARD







The Challenges

- Selection of reasonable model
- Standardization of model practice
- Model validation
- The quantitative criteria for accepting the model for different objectives
- Adequate evaluation of the sensitivity
- Population analyses, mean, SD, bound and distributions
- Risk based justifications
- Inclusion of CMA & CPP beyond dissolution
- Software improvement

Providing PBPK Information in Regulatory Submissions

- Model Information
  - **Input parameters**
  - **Optimized parameters**
  - **Software type and version**
  - **Logical description of model building & validation process**
  - **Executable model files**
  - **Simulation conditions**

- Justifications
  - **Input parameter sources & selection**
  - **Justification for Optimized parameter**
  - **Raw data to support the model validation & correlations**
  - **Rationale to support the request for regulatory actions**

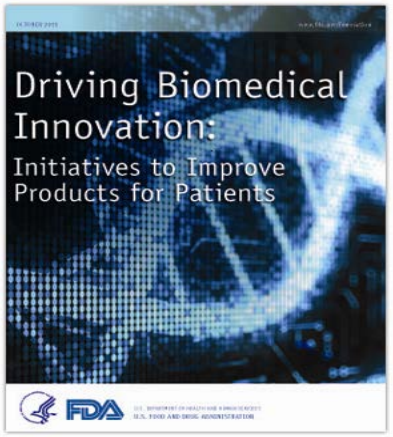
Early communication strongly encouraged

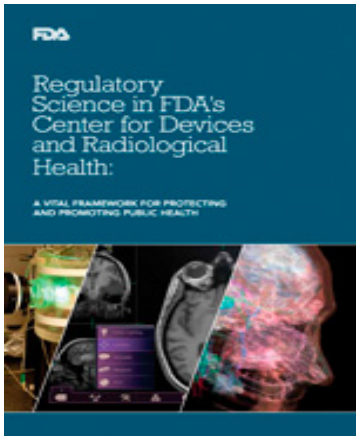
Product Lifecycle Management

- Regulatory context may be different from that for discovery and development
  - Much more knowledge and data are available, which are used for model validation. This provides more confidence for improving the quality of the drug including setting of product specs.
  - Clinical relevance of the quality control
- The knowledge gained from R&D is applicable to regulatory submission
  - Make full use of available information
  - Identify CQAs
  - Control the CMAs and CPPs
  - Justify the specs for quality control

Summary

- In vivo performance is ultimate goal and primary consideration for product quality.
- Mechanistic oral absorption modeling is a powerful tool.
- Models support decisions on product quality specification and risk assessment
- Model predictive performance needs to be demonstrated





Acknowledgments

- Reviewers:
  - Hopi Lin
  - Fang Wu
  - Sandra Suarez Sharp
- Fellows:
  - Meng Wang
  - Heta Shah
- Management:
  - Paul Seo
  - Support from ONDP Office