Session Introduction

Predictive Tools for Generic Product Development and Assessment

Dr. Lanyan (Lucy) Fang

Deputy Division Director

DQMM, ORS, OGD, CDER, FDA

Dr. Ahmed Zidan

Senior Staff Fellow

DPQR V, OPQR, OPQ, CDER, FDA

Public Comments for Session 2
Predictive Tools for Generic Product Development and Assessment

In Person Comments:

- ***Huong Huynh, PhD, Director of Regulatory Science, and Shu Chin Ma, PhD, VP of MIDD & Quantitative Medicine, Critical Path Institute (C-Path)***
- ***Sandra Suarez-Sharp, PhD, President, Regulatory Strategies, Simulations Plus, Inc.***
- ***Anuj Chauhan, PhD, Professor, Colorado School of Mines***
- Elad Berkman, PhD, CTO PhaseV
- Sebastian Melgar, MPH, Lead Associate Booz | Allen | Hamilton
- Brian Eden, Vice President, Global Life Sciences Technical Operations Capgemini Group
- Sandhya Polu and Anil Bhatta, Contracts Manager, Deloitte Services LP
- Anthony Cristillo, PhD, MS, MBA, Partner, Digital Health
- Sarah Ferko, MS, PMP and Ally Lu, Senior Managing Consultant, Artificial Intelligence & Analytics, IBM Consulting
- Ashlee Brunaugh, PhD, Assistant Professor, Pharmaceutical Sciences, University of Michigan
- Jinxiang Xi, PhD, Associate Professor of Biomedical Engineering, University of Massachusetts, Lowell
- Guilherme Garcia, PhD, Assistant Professor, Marquette University and The Medical College of Wisconsin
- Darragh Murnane, PhD, Professor of Pharmaceutics, University of Hertfordshire (Informix Pharma)
- Jeff Schroeter, PhD, Senior Scientist, Applied Research Associates

Virtual Comments:

- Ravendra Singh, PhD, Director of Pharmaceutical Systems Engineering Rutgers
- Sebastian Polak, PhD, Professor Jagiellonian University
- Maxime Le Merdy, PhD, Associate Director, Research and Collaboration Simulations Plus, Inc.
- Stephan Schmidt, PhD, Professor, University of Florida
- Guenther Hochhaus, PhD, Professor, University of Florida
- Yu Feng, PhD, Associate Professor, Oklahoma State University
- Maria Malmlöf, PhD, and Per Gerde, PhD Director of Projects Inhalation Sciences
- Laleh Golshahi, PhD, Associate Professor of Mechanical and Nuclear Engineering, Virginia Commonwealth University
- Rodrigo Cristofoletti, PhD, Assistant Professor, University of Florida

CRITICAL PATH INSTITUTE

Using Innovative Quantitative Methodologies to Improve Generic Drug Development and Assessment of Bioequivalence

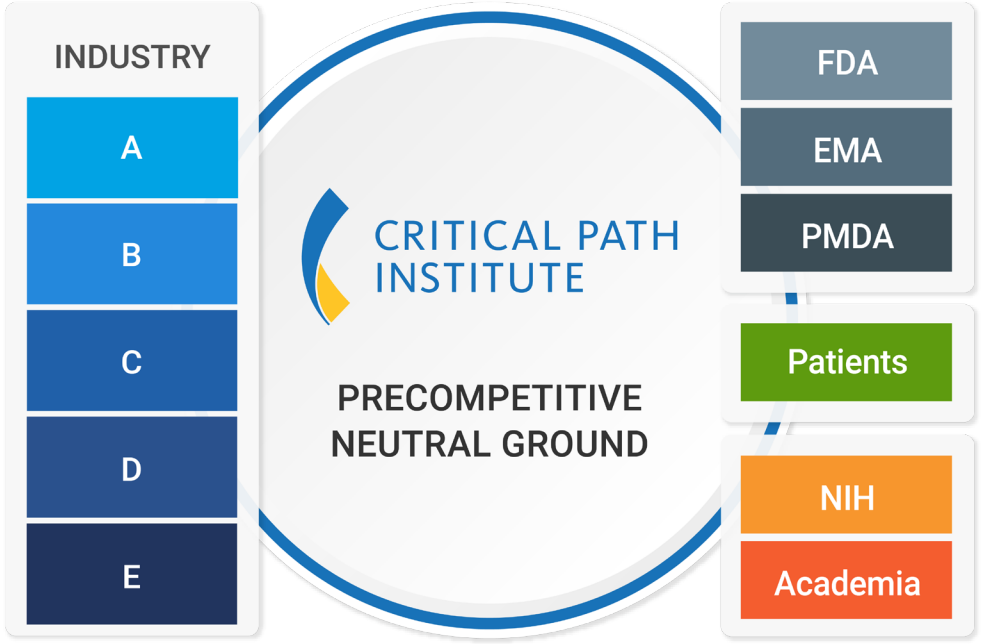
Huong Huynh, PhD, Director of Regulatory Science

Shu Chin Ma, PhD, VP of MIDD & Quantitative Medicine

20 May 2024

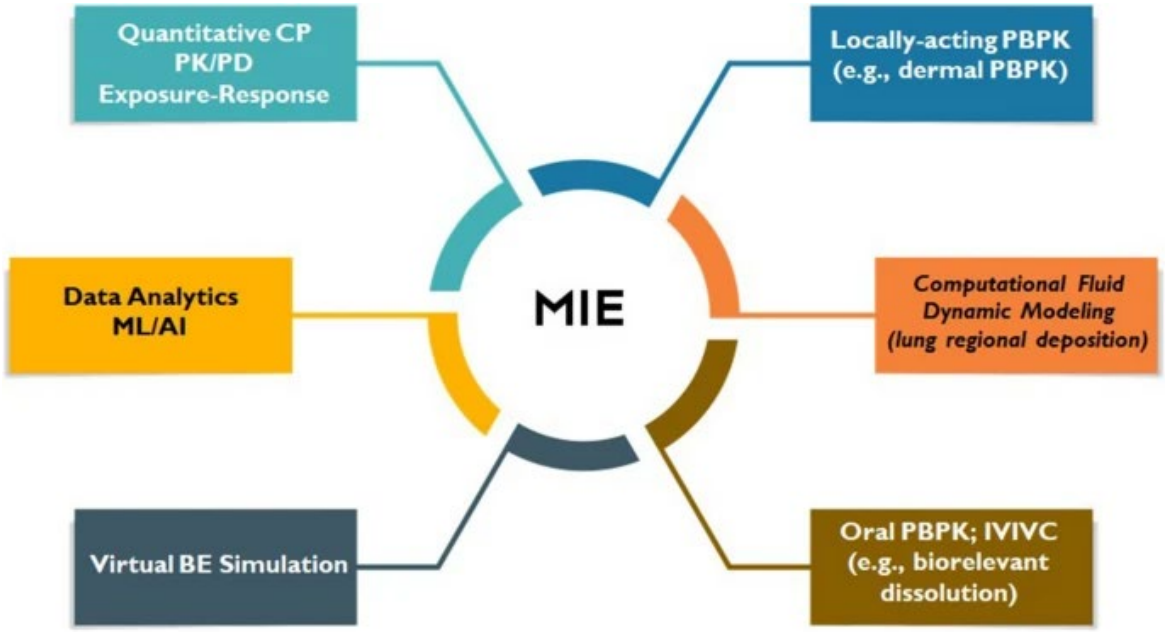
Public-Private Partnership Model

- Foster **development of new evaluation tools** to inform medical product development and regulatory decision-making
- **Convene** scientific consortia of industry, academia, and government for **sharing of data/expertise**
  - ✓ Active consensus building
  - ✓ Shared risks and costs
  - ✓ The best science
  - ✓ The broadest experience
- **Enable iterative EMA/FDA/PMDA participation** in developing new methods to assess the safety and efficacy of medical products
- **Obtain official regulatory endorsement** of novel methodologies and drug development tools



Drug Development Solutions for Regulatory Decision-Making of Generic Products

NDA Requirements	ANDA Requirements
1. Labelling	1. Labelling
2. Pharmacology/Toxicology	2. Pharmacology/Toxicology
3. Chemistry	3. Chemistry
4. Manufacturing	4. Manufacturing
5. Controls	5. Controls
6. Microbiology	6. Microbiology
7. Inspection	7. Inspection
8. Testing	8. Testing
9. Animal Studies 10. Clinical Studies 11. Bioavailability	→ 9. Bioequivalence



CP – Clinical Pharmacology; PBPK – Physiologically-based pharmacokinetics; BE – Bioequivalence
PK/PD – Pharmacokinetics/Pharmacodynamics; ML – Machine Learning; AI – Artificial Intelligence
IVIVC – In Vitro-In Vivo Correlations; BE – Bioequivalence

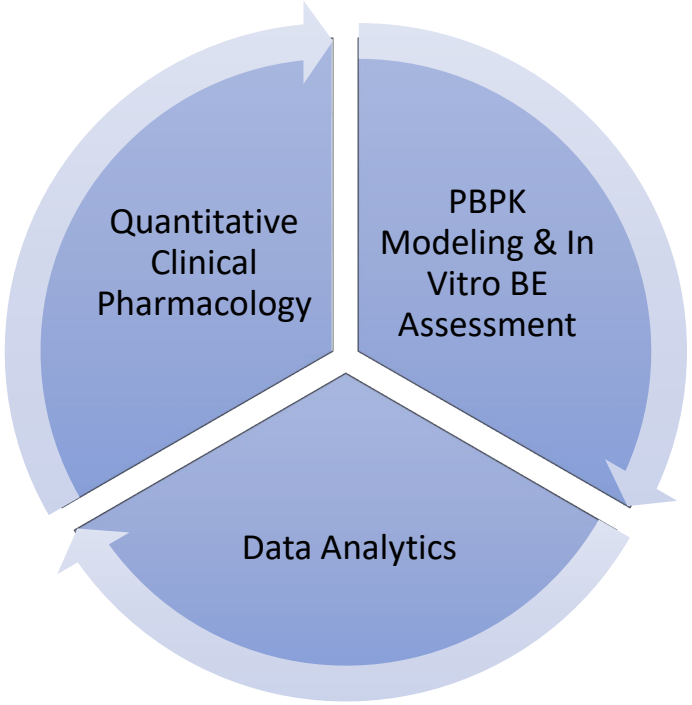
https://link.springer.com/article/10.1208/s12248-023-00884-5

Potential Application of Quantitative Solutions

CRITICAL PATH INSTITUTE

Challenges

- PK repeats, sample selection bias
- Potency and formulation uniformity
- *In silico, in vitro, in vivo* correlations and integrations
- Model standardization, validation, utilization
- Long term bioavailability



Opportunities

- Efficient BE study design
- PK metrics determination
- Evaluation of alternative BE approaches
- PBPK model as alternative approach
- Clinical relevancy of *in vitro* BE studies
- BE space determination for *in vitro* characterization
- Leveraging artificial intelligence and machine learning technologies to modernize ANDA review
- *In vitro* BE method development
- Post-marketing surveillance

Potential Applications

- Use federated data to generate drug development tools
- Use validated quantitative models from approved drug products
- Develop framework for education and sharing validated models
- Use learnings from published data and data from similar drug class
- Monitor safety of use of drug products

https://www.researchgate.net/figure/Commonly-used-MIDD-toolsets-in-generic-drug-development-Abbreviations-BE_fig3_360559059

CRITICAL PATH
INSTITUTE

Advancing Drug Development.
Improving Lives. Together.

c-path.org

SimulationsPlus

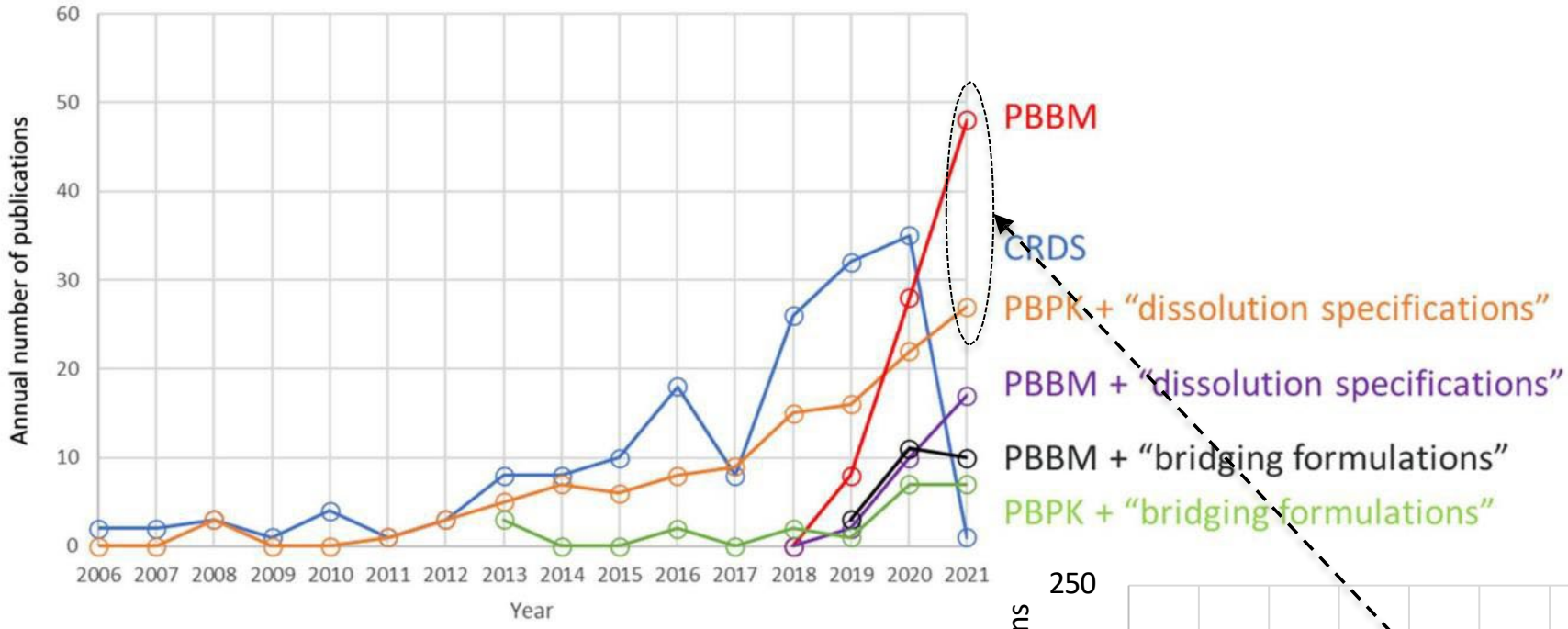
Predictive Tools for Generic Product Development & Assessment – Research Input

Sandra Suarez Sharp, Ph.D.,

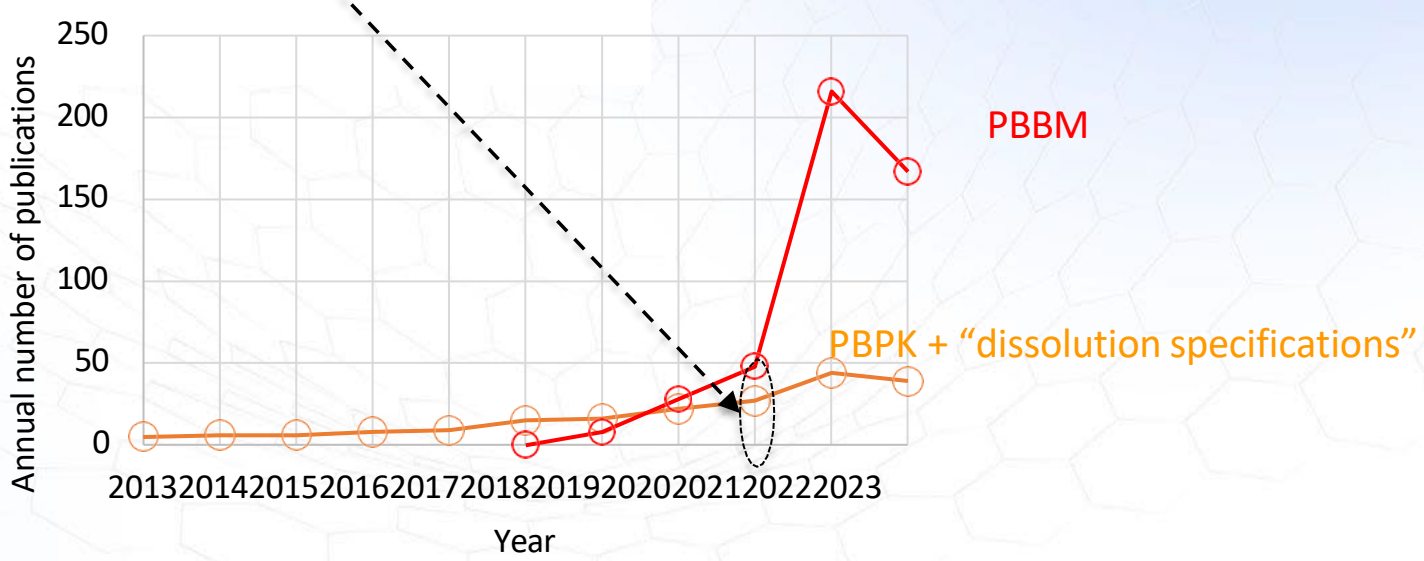
President, Regulatory Strategies

May 20, 2024

The Growth of PBBM

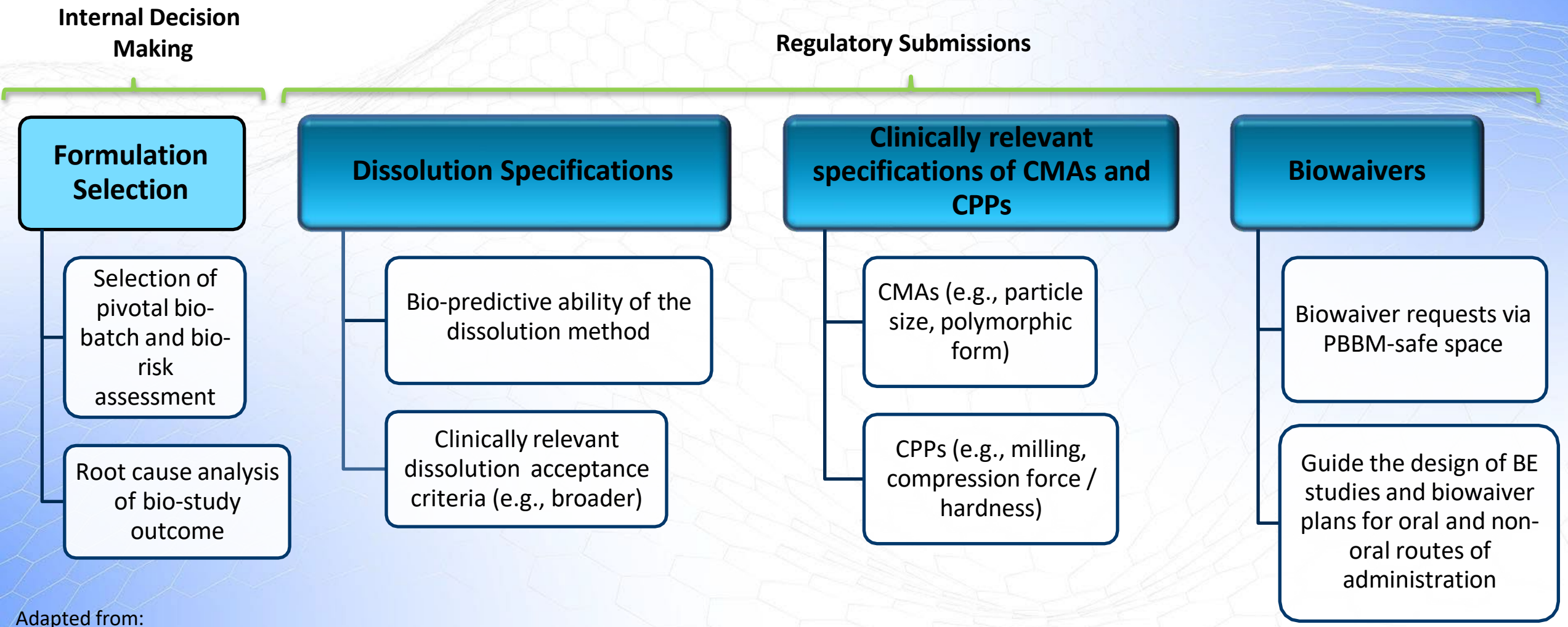


Exponential increase in the number of publications on PBBM/PBPK application in support of drug product quality



Anand, O., et al., The Use of Physiologically Based Pharmacokinetic Analyses—in Biopharmaceutics Applications -Regulatory and Industry Perspectives. Pharmaceutical Research, 2022. https://doi.org/10.1007/s11095-022-03280-4

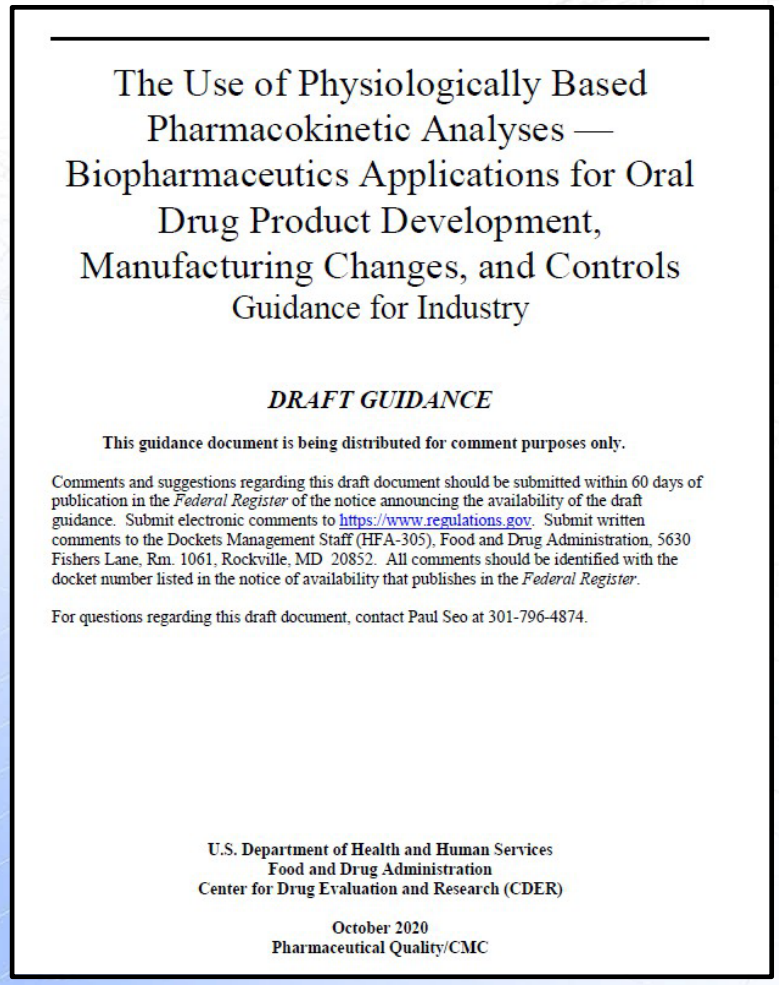
Common Applications of PBBM in Support of the Develo
Regulatory Approval of Generic Products



Adapted from:

1. Fang Wu. OGD Perspective on PBBM applications for generics. 2023 FDA/M-CERSI PBBM Workshop https://cersi.umd.edu/sites/cersi.umd.edu/files/D3-2_905AM_FangWu.pdf
2. S. Suarez-Sharp. 2019 AAPS meeting Annual Meeting. San Antonio, TX
3. Liang Zhao, et al. Generating Model Integrated Evidence for Generic Drug Development and Assessment. ASCPT, Nov 2018, https://doi.org/10.1002/cpt.1282

FDA Guidance: The Use of PBBM in Support of Pro



The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Paul Seo at 301-796-4874.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2020
Pharmaceutical Quality/CMC

We strongly recommend that sponsors demonstrate the model's predictive performance based on PK data from batches **exhibiting unacceptable BA**

Model validation acceptance criteria for a mechanistic IVIVC model to support biowaivers should comply with the **criteria provided in the IVIVC guidance**

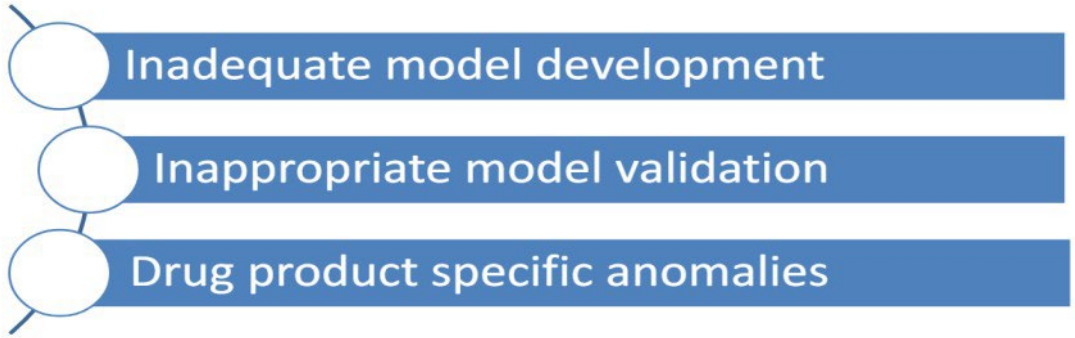
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-physiologically-based-pharmacokinetic-analyses-biopharmaceutics-applications-oral-drug-product

Common PBBM Deficiencies/Acceptance Rate

Summary for Case Example 2

- PBPK/PBBM modeling and simulation was used to evaluate the impact of faster dissolution profile of lower strength compared to higher strength on in vivo performance.
- The model should be sufficiently validated before being used to evaluate such impact.

Observed Deficiency Categories



Case Example 3: PBPK Absorption Modeling/IVIVC to Evaluate BE for ER Tablets

Deficiencies identified on the submitted PBPK/IVIVC model

For PBPK

- There is a lack of non-BE batch to challenge the PBPK model. The Applicant is recommended to use available or theoretical non-BE batch/formulation to evaluate the sensitivity and demonstrate the bio-discriminating capability of the model.

PBBM Snapshot

- An estimated **50** A/NDA and IND submissions involved PBPK modeling/simulations to support Biopharmaceutics
- **48%** of the PBPK modeling/simulations to support Biopharmaceutics were found acceptable

Fang Wu. OGD Perspective on PBBM applications for generics.
2023 FDA/M-CERSI PBBM Workshop
https://cersi.umd.edu/sites/cersi.umd.edu/files/D3-2_905AM_FangWu.pdf

Kimberly Raines. Applications of Physiological Based Biopharmaceutics Modeling (PBBM) in Regulatory Submissions: FDA2023 FDA/M-CERSI PBBM Workshop
https://cersi.umd.edu/sites/cersi.umd.edu/files/D3-6-1_1115AM_KimberlyRaines.pdf

Gaps in Knowledge (Examples)

1. Meeting the PBBM-based IVIVRs/IVIVCs validation criteria (i.e. +/- 10%) may be challenging
   - ***Research is needed to determine the appropriate criteria for model validation that is applicable to PBBM- based IVIVCs/IVIVRs***

2. The need for non-BE data to confirm the predictive ability of the model is challenging and could restrict the model application: safe space applications limited to interpolations between non-BE and BE batches
   - ***Research is needed to evaluate the risk of model extrapolation beyond knowledge space***
     - ***In which situations is it possible to extrapolate with low risk? What data are needed? How far can one extrapolate with confidence?***
     - ***Evaluation of biowaiver implications, particularly for drug products containing BCS class 1/3 drug substances***

Thank you !

Modeling Ophthalmic Drug Delivery from solutions, complex formulations and devices

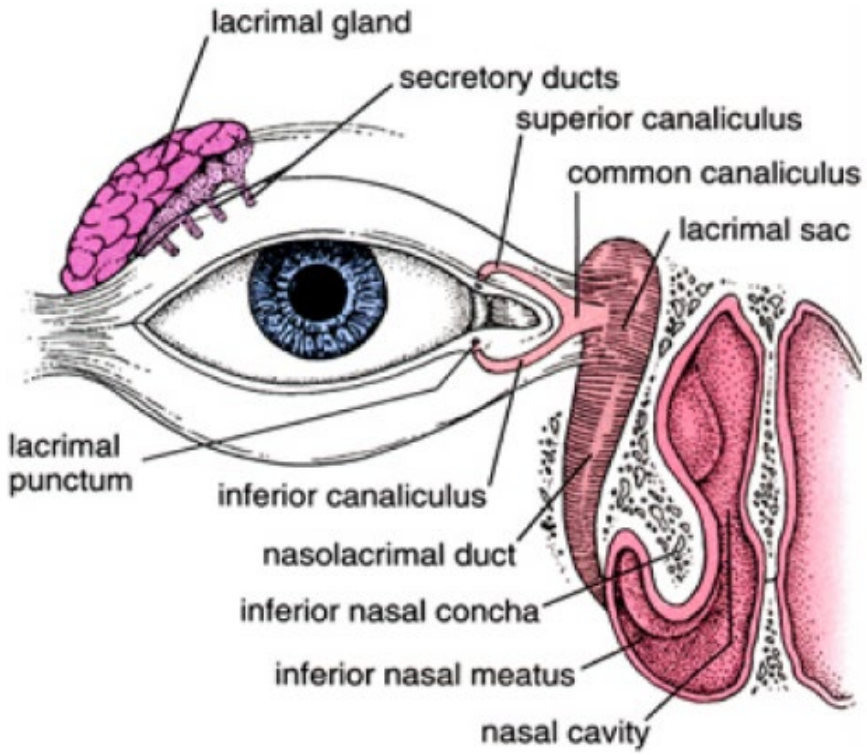
Suggested Research Topic

Enhance the Efficiency of Equivalence Approaches for Complex Drug-Device Combination Products for Ocular Drug Delivery by using physiologically based PK (PBPK) models

Anuj Chauhan

Professor, Chemical and Biological Engineering, Colorado School of Mines
Chief Scientific Officer, Freya Ophthalmics (freyaophthalmics.com)

PBPK Model for Ophthalmic Drug Delivery by Solutions



$$\frac{d(c_{tear}V_{tear})}{dt} = -c_{tear}\left(K_{conjuctiva}A_{conjuctiva} + K_{cornea}A_{cornea}\right) - c_{tear}q_{drainage}$$

Drug mass balance in tears

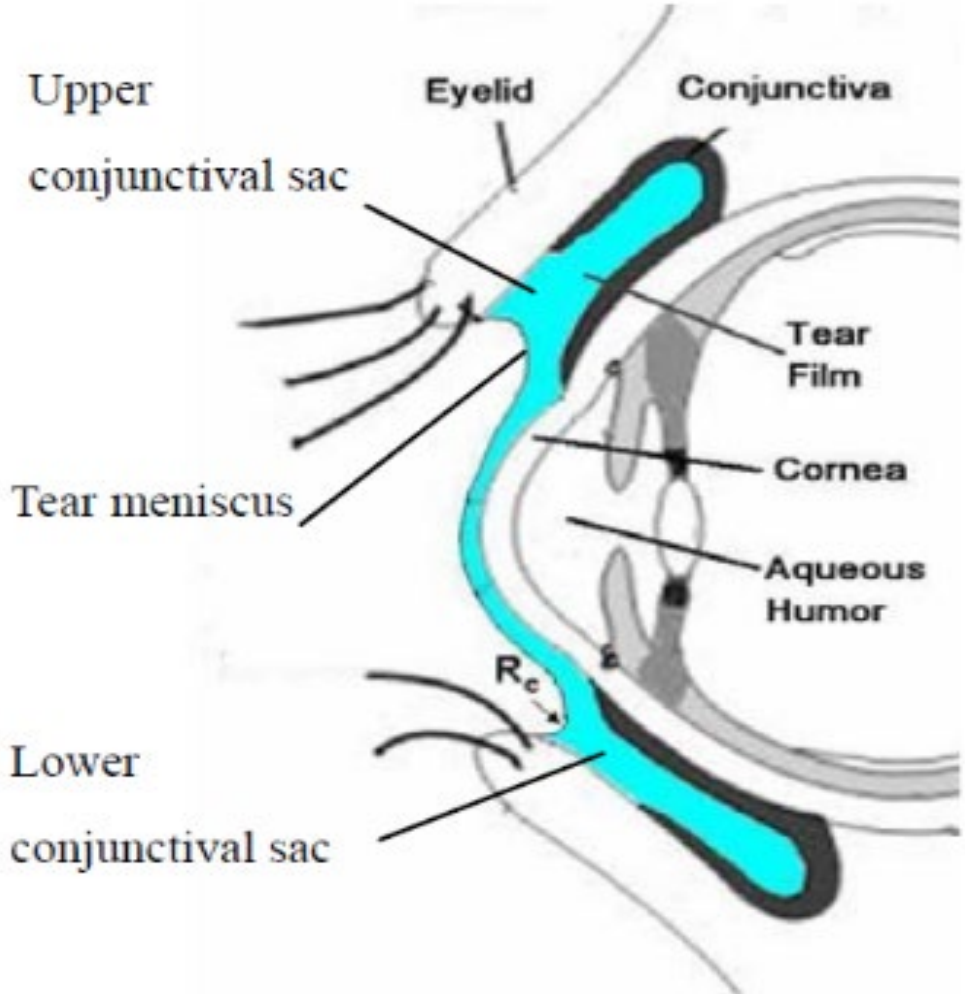
$$\frac{dV_{tear}}{dt} = q_{secretion} - q_{drainage} - q_{evaporation} - J_w S_{conj}$$

Fluid mass balance in tears

$$V_{aq}\frac{d(c_{aq})}{dt} = c_{tear}(K_{cornea}A_{cornea}) - c_{aq}q_{outflow}$$

Drug mass balance in Aqueous Humor

Tear Drainage

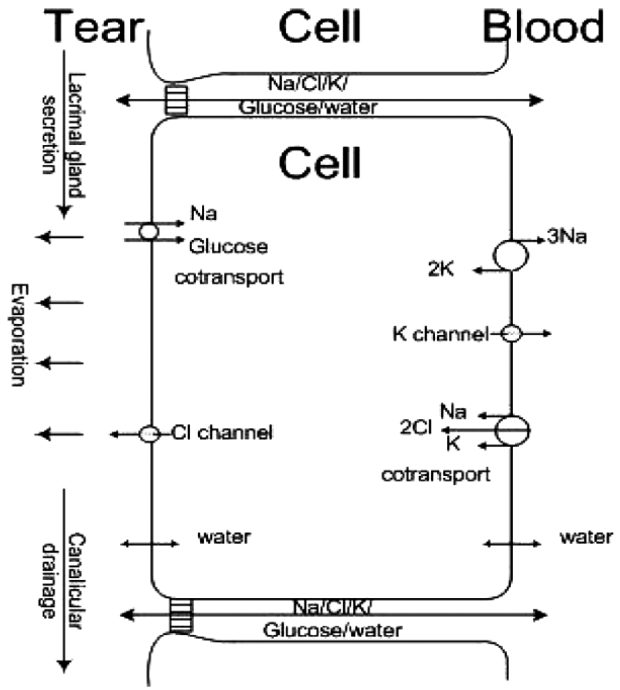


$$q_{drainage} = \frac{\Delta V}{\Delta t} = \frac{\Delta(\pi R^2 L)}{\Delta t} = \left(\frac{\pi L}{t_c}\right)\left(R_{ib}^2 - R_b^2\right)$$

$$= \left(\frac{\pi L}{t_c}\right)\left(\left(\frac{R_0}{1 + \frac{\frac{\sigma}{R_m} R_0}{bE_c}}\right)^2 - \left(\frac{R_0}{1 + \frac{R_0 p_{out}}{bE_c}}\right)^2\right)$$

Zhu H, Chauhan A. A mathematical model for tear drainage through the canaliculi. Curr Eye Res. 2005 Aug;30(8):621-30. doi: 10.1080/02713680590968628. PMID: 16109641.

Conjunctiva Transport – Water and Ion Transport



$$J_w = P_{w,1-2} v_w (Osm_2 - Osm_1) + v_w r_{eo} F \sum z_{ion} J_{ion,paracellular}$$

$$J_{ion,12} = \frac{P_{ion} z F V_{12}}{RT} \left[\frac{C_{ion,1} - C_{ion,2} exp\left(\frac{-zV_{12F}}{RT}\right)}{1 - exp\left(\frac{-zV_{12F}}{RT}\right)} \right]$$

$$J_{pump} = J_{pump,max} \left(\frac{C_{Na,c}}{C_{Na,c} + K_{pump,Na}} \right)^3 \left(\frac{C_{K,b}}{C_{K,b} + K_{pump,K}} \right)^2 * (-5 * 10^{-3} V_{cb} + 1.25)$$

$$J_{Na-K-Cl} = J_{Na-K-Cl,max} \left(\frac{C_{Na,b}}{C_{Na,b} + K_{Na,\,Na-K-Cl}} \frac{C_{K,b}}{C_{K,b} + K_{K,\,Na-K-Cl}} \frac{C_{Cl,b}}{C_{Cl,b} + K_{Cl,1,\,Na-K-Cl}} \frac{C_{Cl,b}}{C_{Cl,b} + K_{Cl,2,\,Na-K-Cl}} \right) - \frac{C_{Na,c}}{C_{Na,c} + K_{Na,\,Na-K-Cl}} \frac{C_{K,c}}{C_{K,c} + K_{K,\,Na-K-Cl}} \frac{C_{Cl,c}}{C_{Cl,c} + K_{Cl,1,\,Na-K-Cl}} \frac{C_{Cl,c}}{C_{Cl,c} + K_{Cl,2,\,Na-K-Cl}}$$

Model Equations

$$\frac{d(C_{i,tear}V_{total})}{dt} = q_{secretion}c^{0}_{i,tear} - q_{drainage}c_{i,tear} - (J_{i,channel} + J_{i,paracellular})S_{conj}$$

$$\frac{d(C_{i,cell}V_{cell})}{dt} = (\sum J_{i,channel}\, S_{conj}) - r_i c_{i,cell}$$

$$\frac{dV_{cell}}{dt} = (J_{w,transcellular,tear} - J_{w,transcellular,blood})S_{conj}$$

$$\frac{dV_{tear}}{dt} = q_{secretion} - q_{drainage} - q_{evaporation-} J_w S_{conj}$$

$$J_w = (J_{w,paracellular} + J_{w,transcellular,tear})$$

$$\frac{d(c_{tear}V_{total})}{dt} = -c_{tear}(K_{conjuctiva}A_{conjuctiva} + K_{cornea}A_{cornea}) - c_{tear}q_{drainage}$$

$$V_{aq}\frac{d(c_{aq})}{dt} = c_{tear}(K_{cornea}A_{cornea}) - c_{aq}q_{outflow}$$

Zhu H, Chauhan A. Tear dynamics model. Curr Eye Res. 2007 Mar;32(3):177-97. doi: 10.1080/02713680601186706. PMID: 17453939.

Tear Drainage – Validation of Drainage Rate

Experiment: Measured drainage rate in rabbits per blink: 0.58 mm^3 for the lower canaliculus.

Model: The model prediction for the drainage rate is 0.4001 mm^3

Zhu H, Chauhan A. A mathematical model for tear drainage through the canaliculi. Curr Eye Res. 2005 Aug;30(8):621-30. doi: 10.1080/02713680590968628. PMID: 16109641.

Validation of concentration transients in tears

TABLE 8 Decays of tear volume, concentration and solute quantity after instillation

	Experiment	Model
Volume decay (15μl instillation)	300 s [56]	1115 s
	>600 s [57]	
Concentration decay (~40μl instillation)	4800 s [58]	2401 s
Quantity decay (25μl instillation)	~ 1000 s [59]	1454 s
	>900 s [60]	
	~ 900 s [61]	

Zhu H, Chauhan A. Tear dynamics model. Curr Eye Res. 2007 Mar;32(3):177-97. doi: 10.1080/02713680601186706. PMID: 17453939.

Incorporation of Emulsion and Suspensions formulations in model

$$\frac{4}{3}\pi R^3 \frac{d(c_{oil})}{dt} = -4\pi R^2 k_{mt}\left(\frac{c_{oil}}{K_{o/w}} - c_{tear}\right)$$

$$Sh = \frac{k_{mt}(2R)}{D} = \sqrt{4 + 1.21Pe^{2/3}}$$

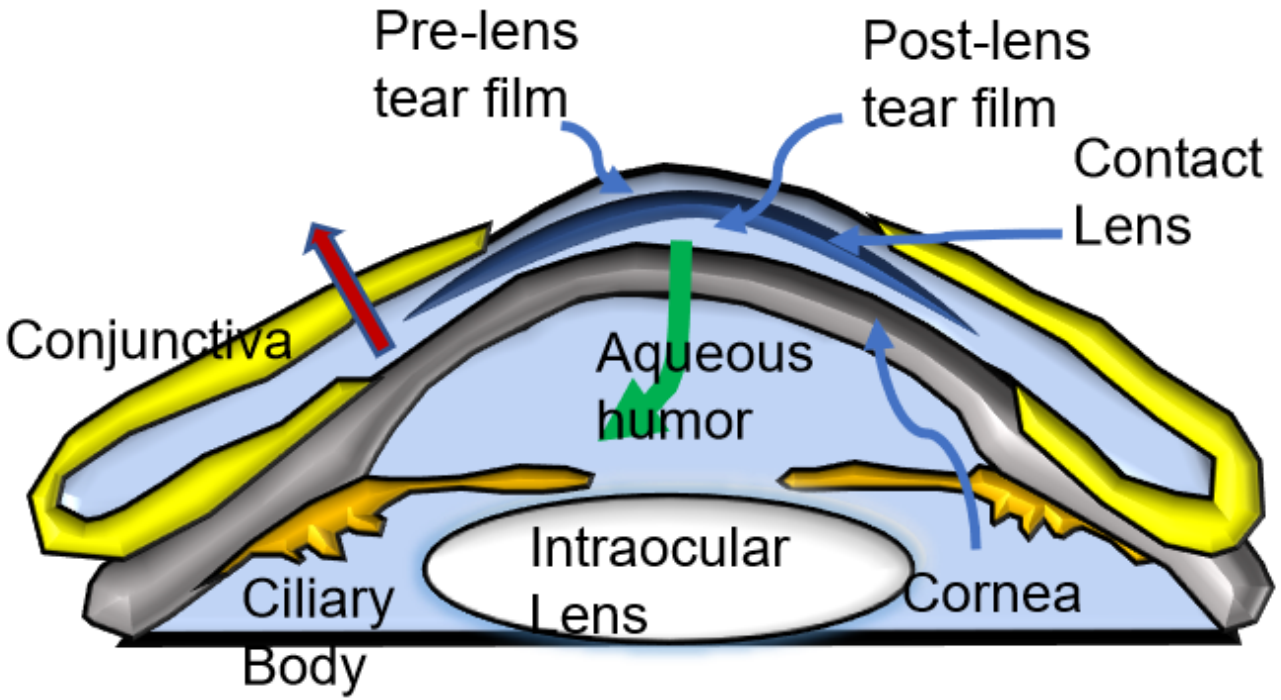
$$\frac{d\left(c_{tear}V_{tear}\left(1 + K_{o/w}f_{oil}\right)\right)}{dt} = -c_{tear}\left(K_{conjuctiva}A_{conjuctiva} + K_{cornea}A_{cornea}\right) - \left(c_{tear}\left(1 + K_{o/w}f_{oil}\right)q_{drainage}\right.$$

$$j = k_{mt}(c_{sol} - c_{tear})$$

$$Sh = \frac{k_{mt}(2R)}{D} = \sqrt{4 + 1.21Pe^{2/3}}$$

$$N4\pi R^2 k_{mt}(c_{sol} - c_{tear}) \sim c_{tear}\left(K_{conjuctiva}A_{conjuctiva} + K_{cornea}A_{cornea}\right)$$

Incorporation of devices such as contact lens



Other Devices: Puncta Plugs, Fornix Inserts, Subconj Injection, Intravitreal Injections, Intracameral Injections, Devices in Anterior and Posterior Chamber

Posterior Segment Drug Delivery by Contact Lenses – Model

$$\frac{\partial C_l}{\partial t} = D_l \frac{\partial^2 C_l}{\partial y^2}$$

$$V_t \frac{dC_t}{dt} = -D_l \frac{\partial C_l}{\partial y}(y=0) A_{cont} - q_d C_t - P_{t-blood} A_{conj,pal} C_t - P_{t-ScCh} A_{conj,bul} \left(\frac{C_t}{K_t} - \frac{C_{ScCh}}{K_{ScCh}}\right)$$

$$V_{ScCh} \frac{dC_{ScCh}}{dt} = q_{uvsc} C_{aq} - q_{uvsc} \frac{C_{ScCh}}{K_{ScCh}} + P_{t-Sch} A_{conj,bul} \left(\frac{C_t}{K_t} - \frac{C_{ScCh}}{K_{ScCh}}\right) - CL_{Ch} C_{ScCh} - A_{globe} P_{SCh-ret} \left(\frac{C_{ScCh}}{K_{ScCh}} - \frac{C_{ret}}{K_{ret}}\right)$$

$$V_{ret} \frac{\partial C_{ret}}{\partial t} = A_{globe} P_{SCh-ret} \left(\frac{C_{ScCh}}{K_{ScCh}} - \frac{C_{ret}}{K_{ret}}\right) - A_{globe} P_{ret-vit} \left(\frac{C_{ret}}{K_{ret}} - \frac{C_{vit}}{K_{vit}}\right)$$

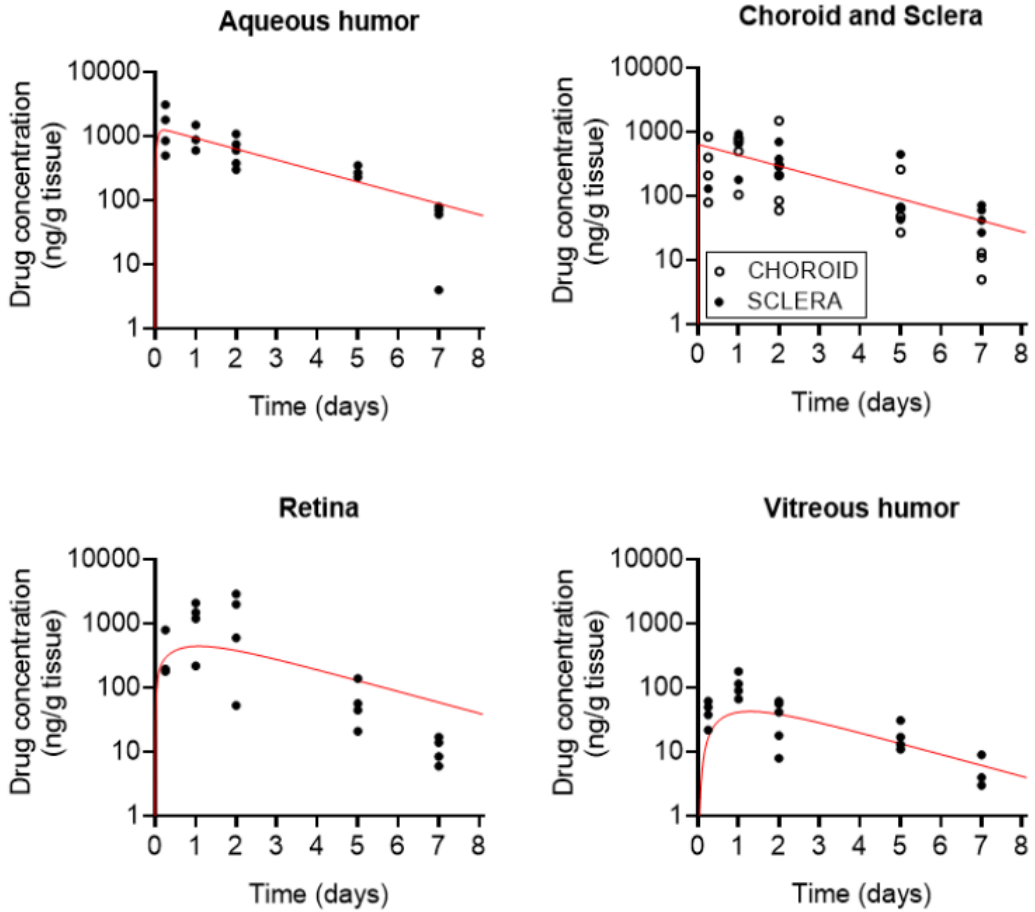
$$V_{vit} \frac{\partial C_{vit}}{\partial t} = A_{globe} P_{ret-vit} \left(\frac{C_{ret}}{K_{ret}} - \frac{C_{vit}}{K_{vit}}\right) - A_{vit-aq} P_{vit-aq} \left(\frac{C_{vit}}{K_{vit}}\right)$$

$$V_{aq} \frac{\partial C_{aq}}{\partial t} = A_{vit-aq} P_{vit-aq} (C_{vit}) + A_{cornea} P_{t-aq} \left(\frac{C_l(y=H)}{Kl} - C_{aq}\right) - q_{aq} C_{aq}$$

$$C_{epithelium} = \frac{(K_{ep/aq} C_{aq} + K_{ep/t} C_t)}{2}$$

Toffoletto N, Saramago B, Serro AP, Chauhan A. A Physiology-Based Mathematical Model to Understand Drug Delivery from Contact Lenses to the Back of the Eye. Pharm Res. 2023 Aug;40(8):1939-1951. doi: 10.1007/s11095-023-03560-7. Epub 2023 Jul 27. PMID: 37498499; PMCID: PMC10447275.

Validation



Toffoletto N, Saramago B, Serro AP, Chauhan A. A Physiology-Based Mathematical Model to Understand Drug Delivery from Contact Lenses to the Back of the Eye. Pharm Res. 2023 Aug;40(8):1939-1951. doi: 10.1007/s11095-023-03560-7. Epub 2023 Jul 27. PMID: 37498499; PMCID: PMC10447275.

Summary

1. Physiology Based Pharmacokinetic Models can utilize in vitro data and anatomical and physiological parameters to predict tissue concentrations, and hence Bioequivalence
2. Parameters can be obtained from literature or measured in vitro, ex vivo, or estimated based on fitting.
3. Validation by comparison with experiments is critical.

Suggested Research Topic

Enhance the Efficiency of Equivalence Approaches for Complex Drug-Device Combination Products for Ocular Drug Delivery by using Physiologically Based Pharmacokinetic (PBPK) models

Thank you!

Public Comments for Session 2
Predictive Tools for Generic Product Development and Assessment

In Person Comments:

- Huong Huynh, PhD, Director of Regulatory Science, and Shu Chin Ma, PhD, VP of MIDD & Quantitative Medicine, Critical Path Institute (C-Path)
- Sandra Suarez-Sharp, PhD, President, Regulatory Strategies, Simulations Plus, Inc.
- Anuj Chauhan, PhD, Professor, Colorado School of Mines
- Elad Berkman, PhD, CTO PhaseV
- Sebastian Melgar, MPH, Lead Associate Booz | Allen | Hamilton
- Brian Eden, Vice President, Global Life Sciences Technical Operations Capgemini Group
- Sandhya Polu and Anil Bhatta, Contracts Manager, Deloitte Services LP
- Anthony Cristillo, PhD, MS, MBA, Partner, Digital Health
- Sarah Ferko, MS, PMP and Ally Lu, Senior Managing Consultant, Artificial Intelligence & Analytics, IBM Consulting
- Ashlee Brunaugh, PhD, Assistant Professor, Pharmaceutical Sciences, University of Michigan
- Jinxiang Xi, PhD, Associate Professor of Biomedical Engineering, University of Massachusetts, Lowell
- Guilherme Garcia, PhD, Assistant Professor, Marquette University and The Medical College of Wisconsin
- Darragh Murnane, PhD, Professor of Pharmaceutics, University of Hertfordshire (Informix Pharma)
- Jeff Schroeter, PhD, Senior Scientist, Applied Research Associates

Virtual Comments:

- ***Ravendra Singh, PhD, Director of Pharmaceutical Systems Engineering Rutgers***
- ***Sebastian Polak, PhD, Professor Jagiellonian University***
- ***Maxime Le Merdy, PhD, Associate Director, Research and Collaboration Simulations Plus, Inc.***
- ***Stephan Schmidt, PhD, Professor, University of Florida***
- *Guenther Hochhaus, PhD, Professor, University of Florida*
- Yu Feng, PhD, Associate Professor, Oklahoma State University
- Maria Malmlöf, PhD; Per Gerde, PhD Director of Projects Inhalation Sciences
- Laleh Golshahi, PhD, Associate Professor of Mechanical and Nuclear Engineering, Virginia Commonwealth University
- Rodrigo Cristofoletti, PhD, Assistant Professor, University of Florida

Digital twin model: a faster and economical way to modernize the generic drug product manufacturing

Ravendra Singh

C-SOPS, Department of Chemical and Biochemical Engineering
Rutgers University, NJ, USA

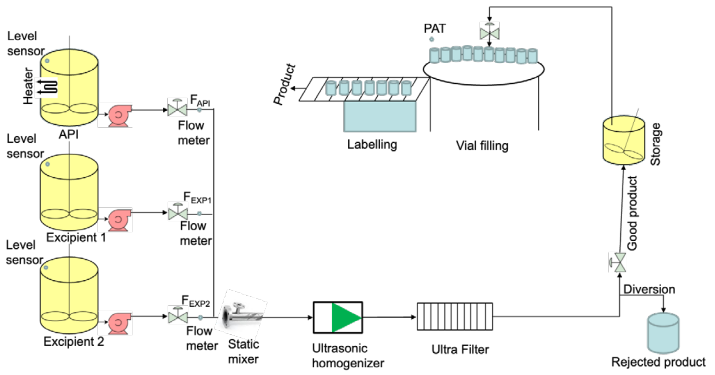
RUTGERS

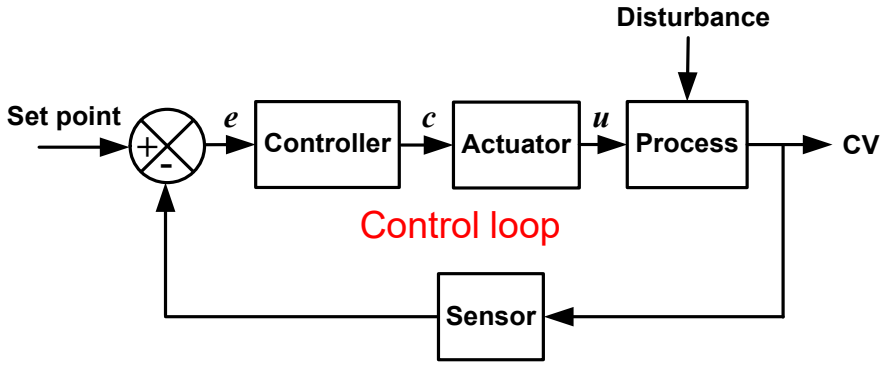
Contact: ravendra.singh@rutgers.edu

Introduction and applications of digital twin model

- Simulation
- Process control
- Optimization
- Process design
- Digital DOE screening
- Material traceability
- Disturbance analysis
- Soft sensing
- Identification of CPPs and CQAs
- Sensitivity analysis
- Scenario analysis
- Risk assessment
- Feasibility and flexibility analysis
- Ingredient selection
- Could be part of regulatory filing
- Natural knowledge reservoir

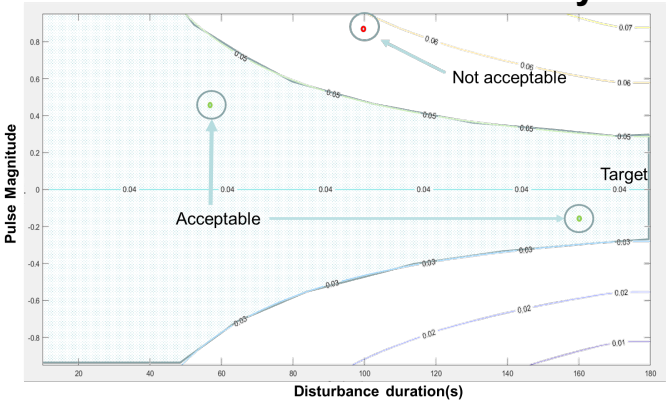
Injectable manufacturing



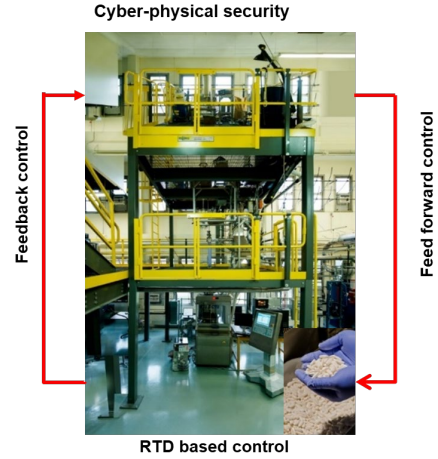


Total simulations: 2601

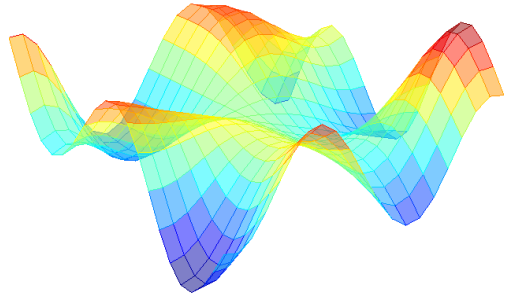
Disturbance analysis



Tablet manufacturing



Optimization



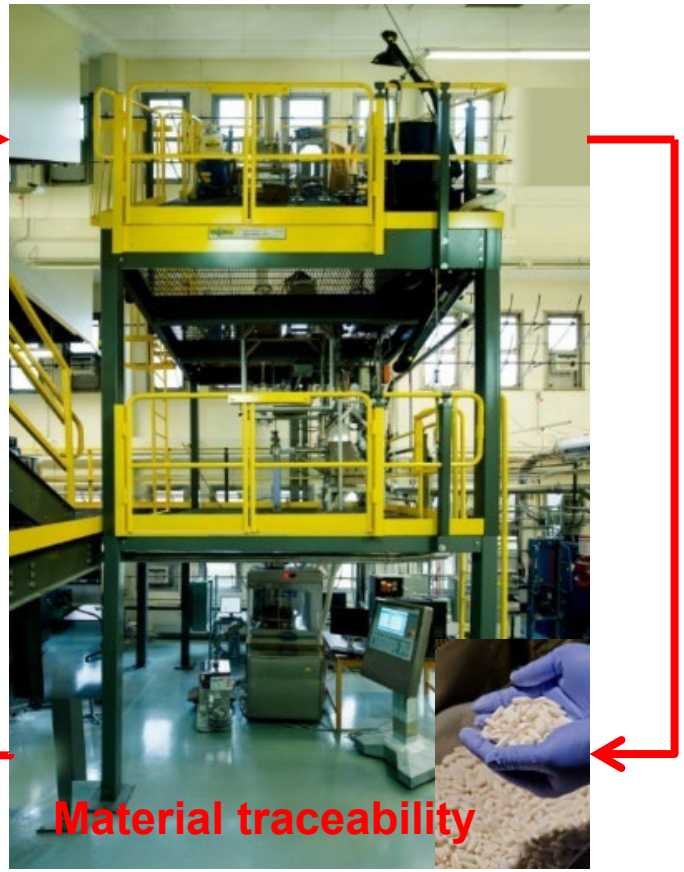
RUTGERS

Implemented digital twin in tablet manufacturing process

Artificial intelligence/Machine learning

Cyber-physical security

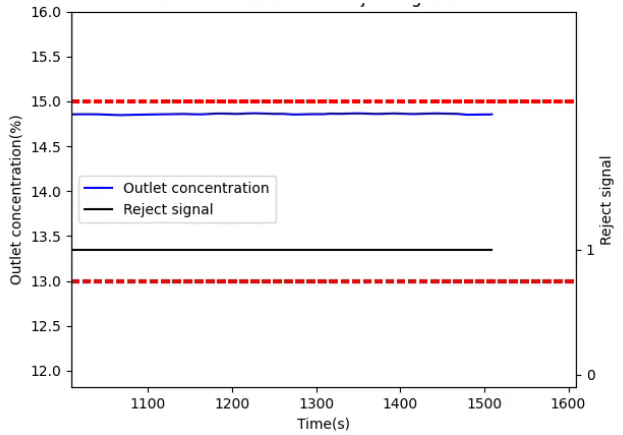
Feedback control

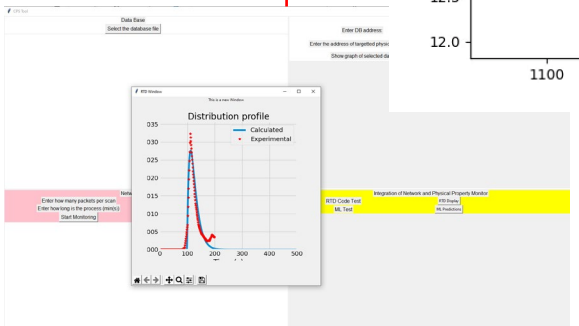


RTD based control

Feed forward control

RTD based diversion





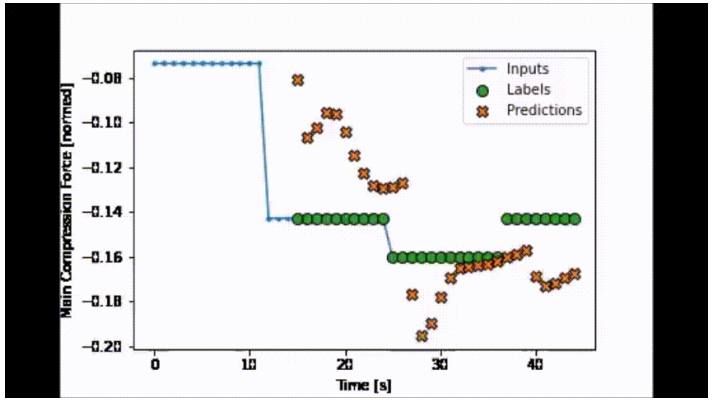
AI/ML

Output in '.csv' format

SIMATIC PCS 7 SIEMENS

DELTAV

Plant



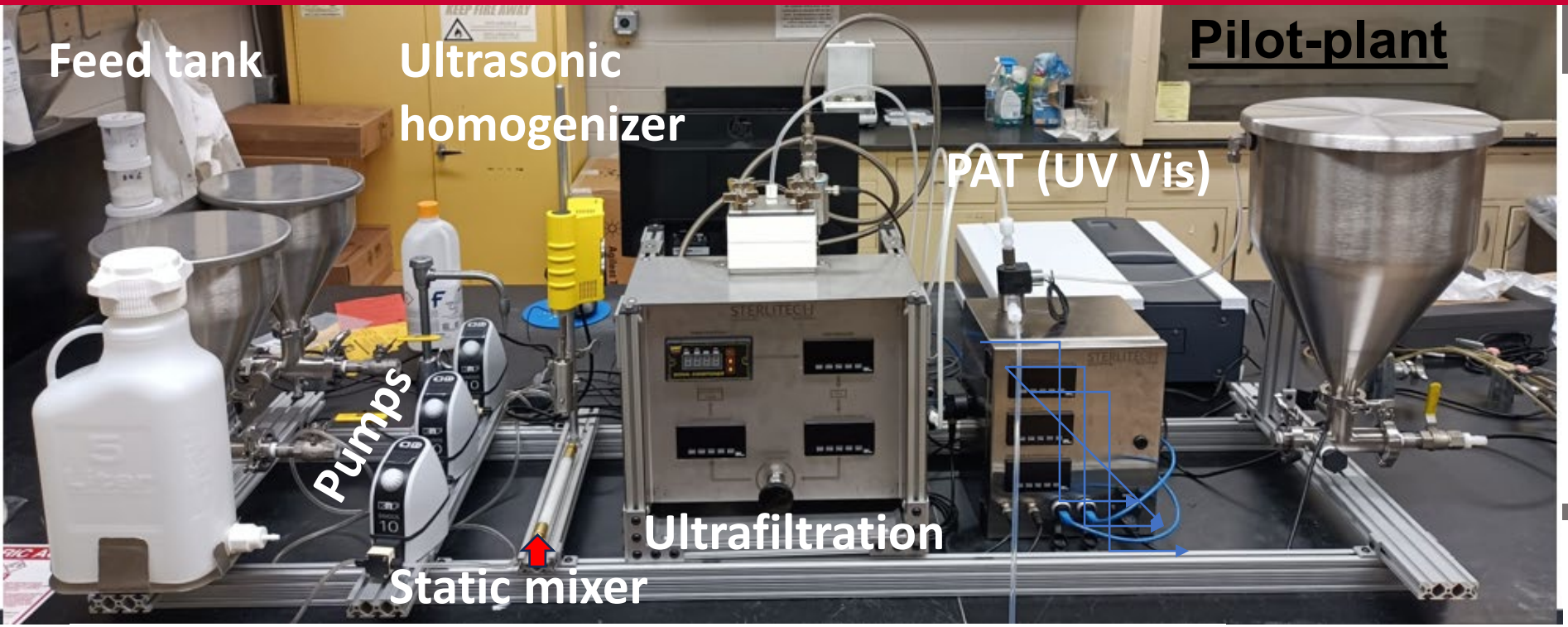
Predictions and saved in '.csv' format

Data

AUTOMATION

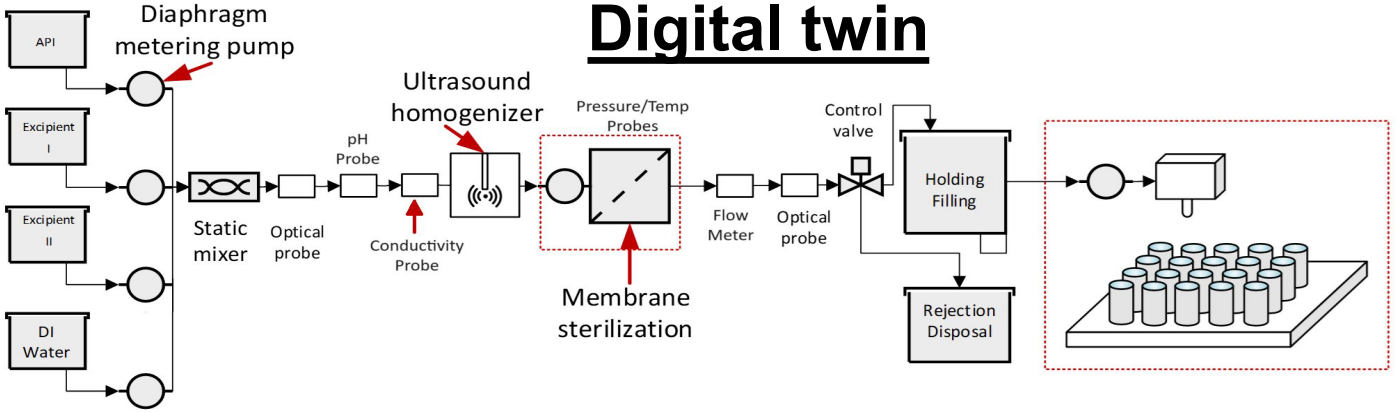
RUTGERS

Injectable drug product manufacturing



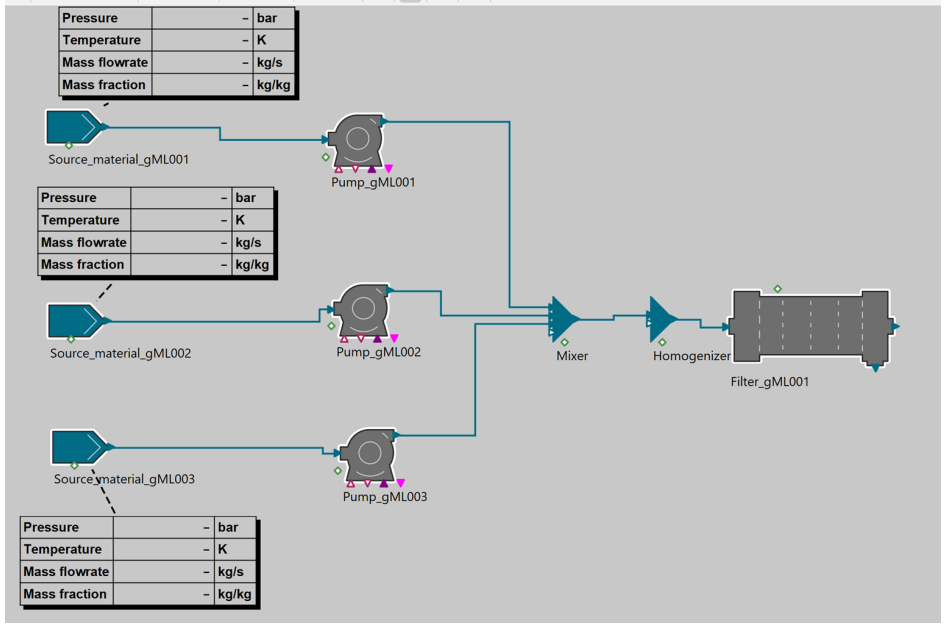
Vial filling and capping

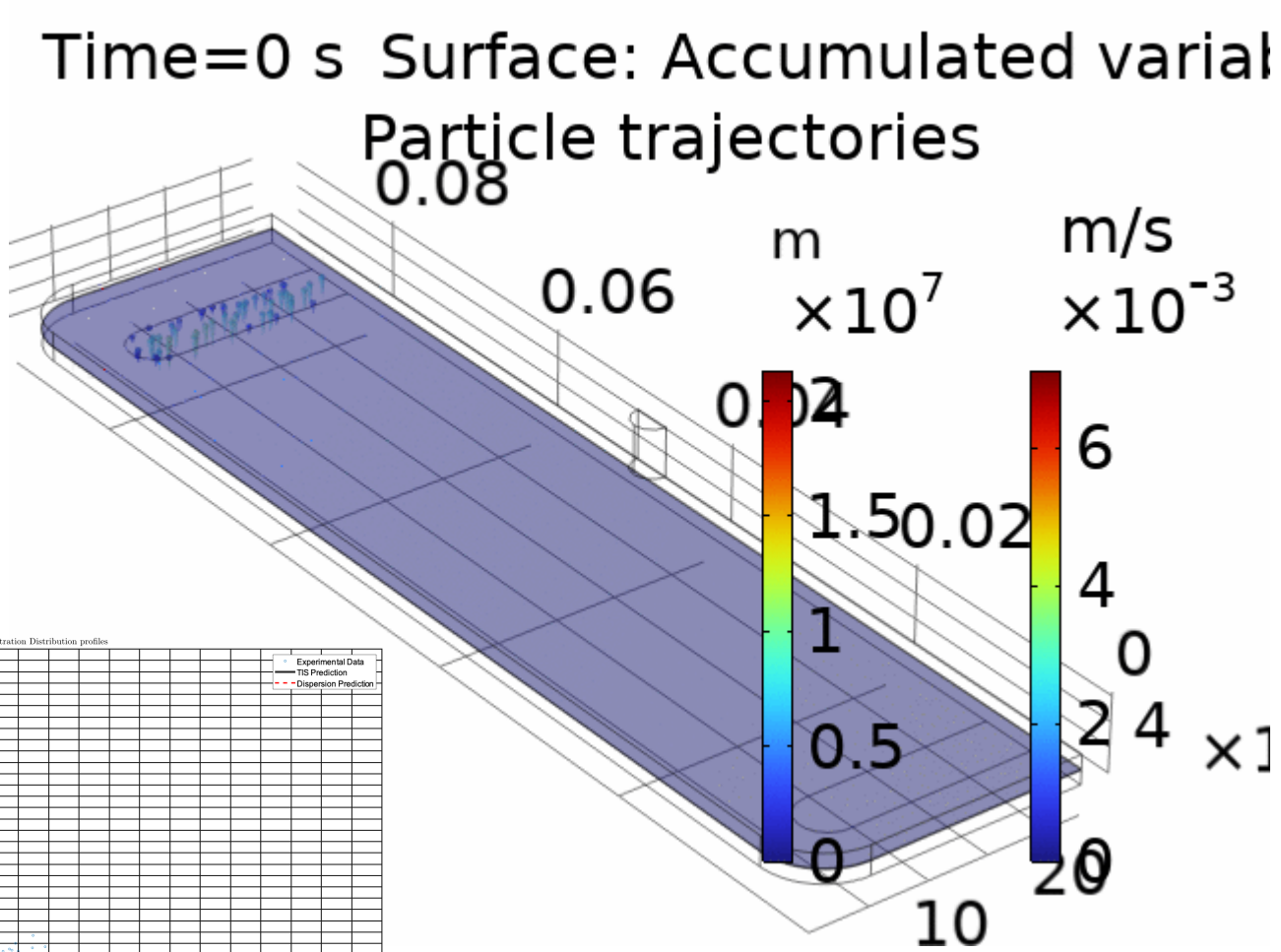
Digital twin

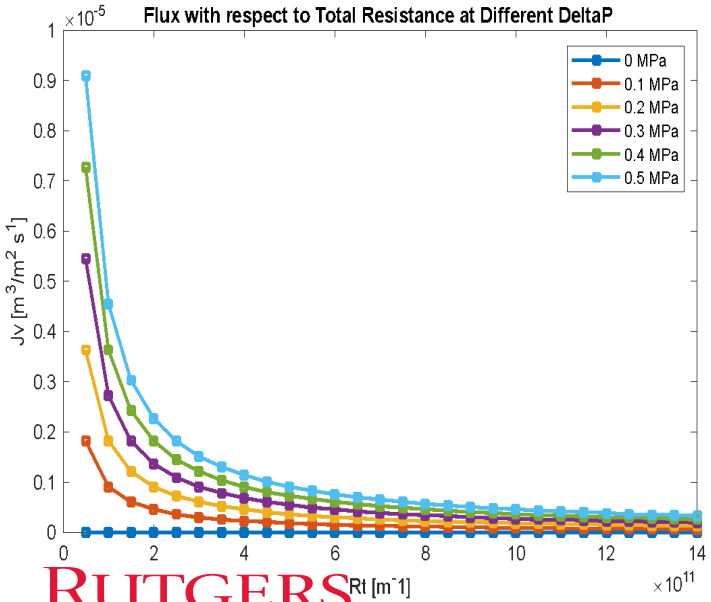


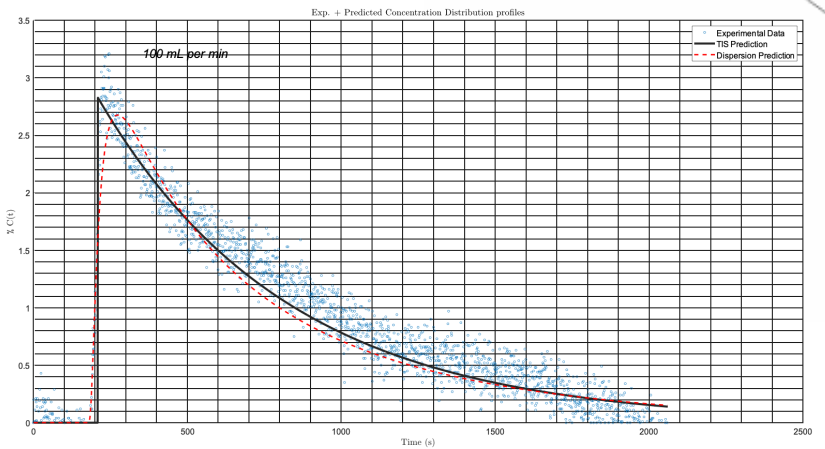
RUTGERS

Modelling of injectable manufacturing process

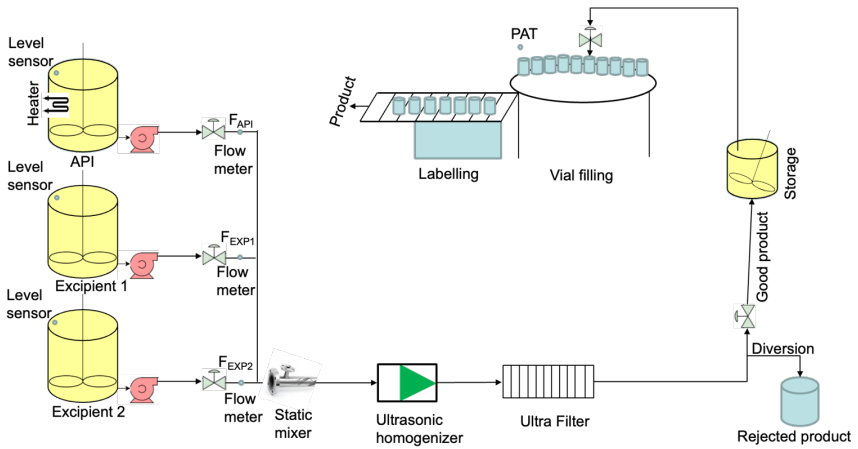








Automation and control for real time quality assurance

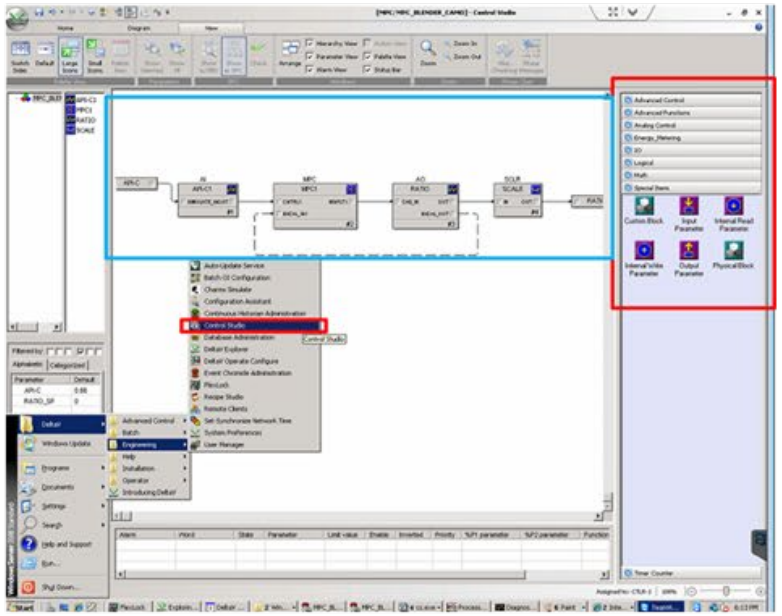


Serial ports, OPC

PROFIBUS

Switch

Control platforms



Sensors

UV VIS

Real time monitoring

Real time control

CERTARA

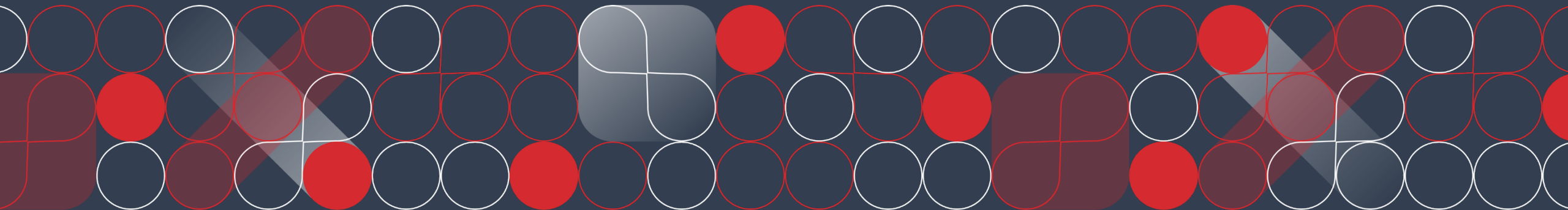
ALL MODELS ARE WRONG AND YOURS ARE USELESS

what is needed to make predictive models accepted for regulatory decision making – focus on complex generics

Sebastian Polak

MAY 20-21

2024



the source of presentation title

and how to translate it to the drugs realm

npj | precision oncology

Comment

Published in partnership with The Hormel Institute, University of Minnesota

https://doi.org/10.1038/s41698-024-00553-6

All models are wrong and yours are useless: making clinical prediction models impactful for patients

Florian Markowetz

KEY OBSERVATIONS

- *focus on in silico models with potential use in the clinical settings*
- *success in academia is not the same as success in the clinic*
- *successful models use data that are available in routine practice*
- *successful models are linked to actions*

Box 1 | A checklist for useful clinical prediction tools

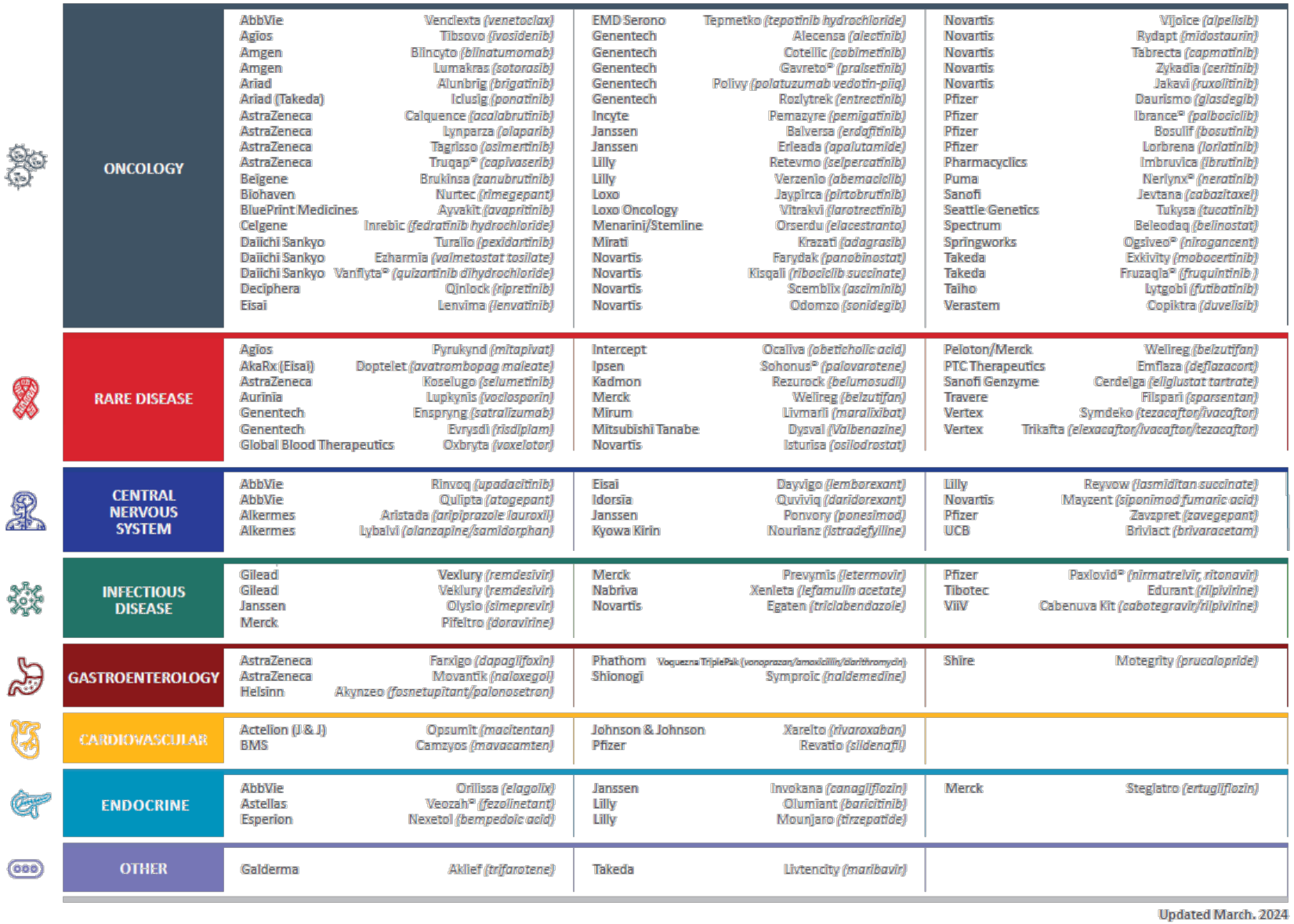
1. Do you address a clear clinical decision point?
2. Does your tool output parameters that help in that decision making?
3. Do you address a clear clinical decision point? Are you sure? Better go and talk to a clinical collaborator who is a domain expert.
4. Are the input parameters used in common clinical practice?
5. Do you address a clear clinical decision point? Are you really, really sure? Better go and get advice from a large and diverse group of experts and stakeholders.
6. Is the interface easy to use, both for input and output?
7. What value does your model add to current clinical judgement?
8. Is your tool better than existing tools?
9. What is your implementation plan?
   a. What needs to happen for doctors to actually use this tool?
   b. What is the path through medical device regulation?
   c. Is the medical environment ready for it?

simulating virtual patients and waiving clinical studies

>115 Novel Drugs

and 375+ individual label claims, approved

by global regulators using predictions from the Simcyp Simulator in lieu of clinical studies



ONCOLOGY	AbbVie — Venclexta (venetoclax)	EMD Serono — Tepmetko (tepotinib hydrochloride)	Novartis — Vijoice (alpelisib)
	Agios — Tibsovo (ivosidenib)	Genentech — Alecensa (alectinib)	Novartis — Rydapt (midostaurin)
	Amgen — Blincyto (blinatumomab)	Genentech — Cotellic (cobimetinib)	Novartis — Tabrecta (capmatinib)
	Amgen — Lumakras (sotorasib)	Genentech — Gavreto® (pralsetinib)	Novartis — Zykadia (ceritinib)
	Ariad — Alunbrig (brigatinib)	Genentech — Polivy (polatuzumab vedotin-piiq)	Novartis — Jakavi (ruxolitinib)
	Ariad (Takeda) — Iclusig (ponatinib)	Genentech — Rozlytrek (entrectinib)	Pfizer — Daurismo (glasdegib)
	AstraZeneca — Calquence (acalabrutinib)	Incyte — Pemazyre (pemigatinib)	Pfizer — Ibrance® (palbociclib)
	AstraZeneca — Lynparza (olaparib)	Janssen — Balversa (erdafitinib)	Pfizer — Bosulif (bosutinib)
	AstraZeneca — Tagrisso (osimertinib)	Janssen — Erleada (apalutamide)	Pfizer — Lorbrena (lorlatinib)
	AstraZeneca — Truqap® (capivasertib)	Lilly — Retevmo (selpercatinib)	Pharmacyclics — Imbruvica (ibrutinib)
	Beigene — Brukinsa (zanubrutinib)	Lilly — Verzenio (abemaciclib)	Puma — Nerlynx® (neratinib)
	Biohaven — Nurtec (rimegepant)	Loxo — Jaypirca (pirtobrutinib)	Sanofi — Jevtana (cabazitaxel)
	BluePrint Medicines — Ayvakit (avapritinib)	Loxo Oncology — Vitrakvi (larotrectinib)	Seattle Genetics — Tukysa (tucatinib)
	Celgene — Inrebic (fedratinib hydrochloride)	Menarini/Stemline — Orserdu (elacestrant)	Spectrum — Beleodaq (belinostat)
	Daiichi Sankyo — Turalio (pexidartinib)	Mirati — Krazati (adagrasib)	Springworks — Ogsiveo® (nirogacestat)
	Daiichi Sankyo — Ezharmia (valmetostat tosilate)	Novartis — Farydak (panobinostat)	Takeda — Exkivity (mobocertinib)
	Daiichi Sankyo — Vanflyta® (quizartinib dihydrochloride)	Novartis — Kisqali (ribociclib succinate)	Takeda — Fruzaqla® (fruquintinib)
	Deciphera — Qinlock (ripretinib)	Novartis — Scemblix (asciminib)	Taiho — Lytgobi (futibatinib)
	Eisai — Lenvima (lenvatinib)	Novartis — Odomzo (sonidegib)	Verastem — Copiktra (duvelisib)
RARE DISEASE	Agios — Pyrukynd (mitapivat)	Intercept — Ocaliva (obeticholic acid)	Peloton/Merck — Welireg (belzutifan)
	AkaRx (Eisai) — Doptelet (avatrombopag maleate)	Ipsen — Sohonus® (palovarotene)	PTC Therapeutics — Emflaza (deflazacort)
	AstraZeneca — Koselugo (selumetinib)	Kadmon — Rezurock (belumosudil)	Sanofi Genzyme — Cerdelga (eliglustat tartrate)
	Aurinia — Lupkynis (voclosporin)	Merck — Welireg (belzutifan)	Travere — Filspari (sparsentan)
	Genentech — Enspryng (satralizumab)	Mirum — Livmarli (maralixibat)	Vertex — Symdeko (tezacaftor/ivacaftor)
	Genentech — Evrysdi (risdiplam)	Mitsubishi Tanabe — Dysval (Valbenazine)	Vertex — Trikafta (elexacaftor/ivacaftor/tezacaftor)
	Global Blood Therapeutics — Oxbryta (voxelotor)	Novartis — Isturisa (osilodrostat)	
CENTRAL NERVOUS SYSTEM	AbbVie — Rinvoq (upadacitinib)	Eisai — Dayvigo (lemborexant)	Lilly — Reyvow (lasmiditan succinate)
	AbbVie — Qulipta (atogepant)	Idorsia — Quviviq (daridorexant)	Novartis — Mayzent (siponimod fumaric acid)
	Alkermes — Aristada (aripiprazole lauroxil)	Janssen — Ponvory (ponesimod)	Pfizer — Zavzpret (zavegepant)
	Alkermes — Lybalvi (olanzapine/samidorphan)	Kyowa Kirin — Nourianz (istradefylline)	UCB — Briviact (brivaracetam)
INFECTIOUS DISEASE	Gilead — Vexlury (remdesivir)	Merck — Prevymis (letermovir)	Pfizer — Paxlovid® (nirmatrelvir, ritonavir)
	Gilead — Veklury (remdesivir)	Nabriva — Xenleta (lefamulin acetate)	Tibotec — Edurant (rilpivirine)
	Janssen — Olysio (simeprevir)	Novartis — Egaten (triclabendazole)	ViiV — Cabenuva Kit (cabotegravir/rilpivirine)
	Merck — Pifeltro (doravirine)		
GASTROENTEROLOGY	AstraZeneca — Farxiga (dapagliflozin)	Phathom — Voquezna TriplePak (vonoprazan/amoxicillin/clarithromycin)	Shire — Motegrity (prucalopride)
	AstraZeneca — Movantik (naloxegol)	Shionogi — Symproic (naldemedine)	
	Helsinn — Akynzeo (fosnetupitant/palonosetron)		
CARDIOVASCULAR	Actelion (J & J) — Opsumit (macitentan)	Johnson & Johnson — Xarelto (rivaroxaban)	
	BMS — Camzyos (mavacamten)	Pfizer — Revatio (sildenafil)	
ENDOCRINE	AbbVie — Orilissa (elagolix)	Janssen — Invokana (canagliflozin)	Merck — Steglatro (ertugliflozin)
	Astellas — Veozah® (fezolinetant)	Lilly — Olumiant (baricitinib)	
	Esperion — Nexetol (bempedoic acid)	Lilly — Mounjaro (tirzepatide)	
OTHER	Galderma — Aklief (trifarotene)	Takeda — Livtencity (maribavir)	

Updated March. 2024

various application explored in PBPK submissions

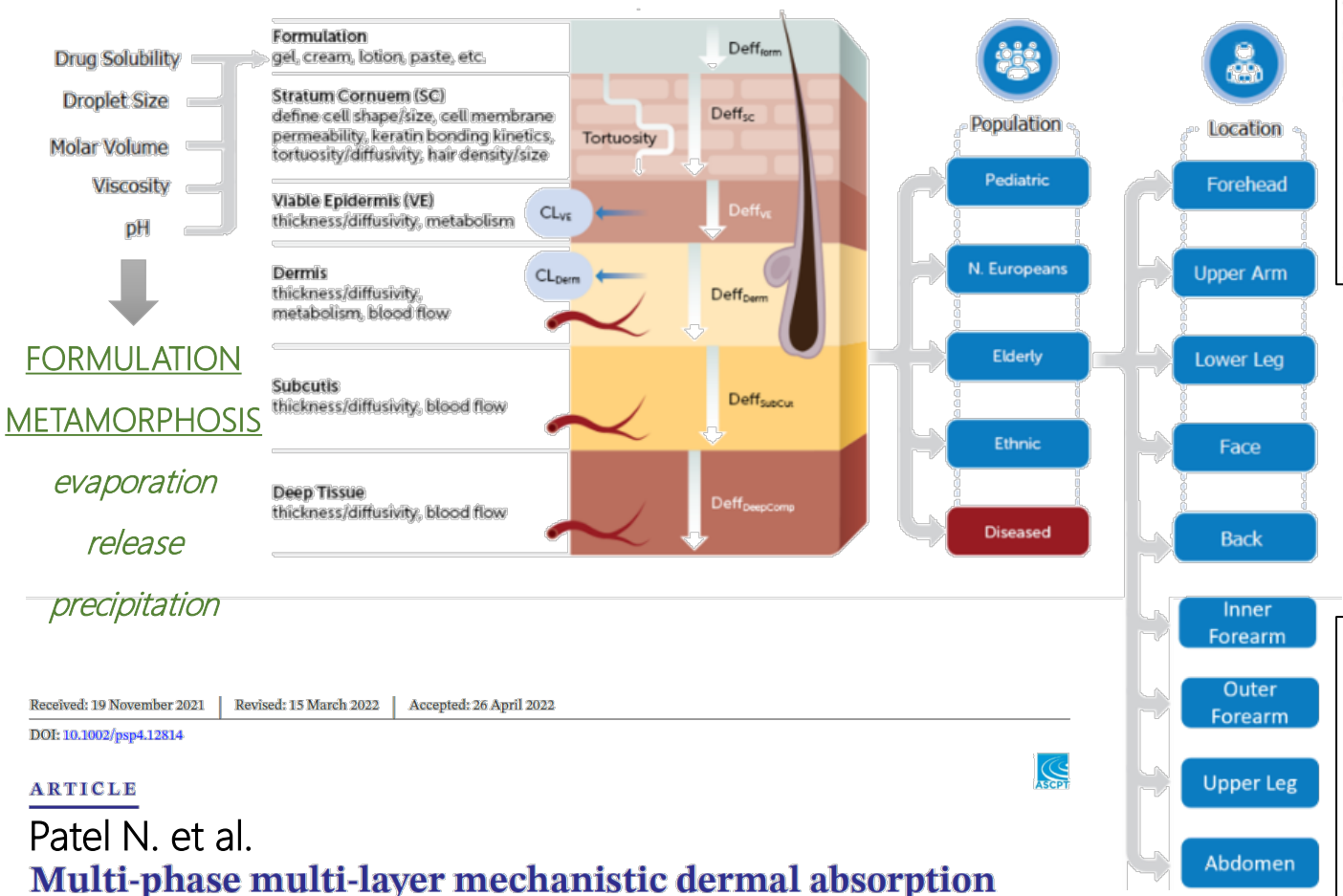
various routes of administration, therapeutic areas, drug development challenges, applications

Application	Drug (trade name)	Year
P-gp and CYP3A4 inhibition	Rivaroxaban (Xarelto)	2011
OATP1B1/3 influence on PK	Simeprevir (Olysio)	2013
Food effect	Sonidegib (Odomzo)	2015
PK in Cancer subjects	Cobimetinib (Cotellic)	2015
Hepatic Impairment	Obeticholic acid (Ocaliva)	2016
PK in children	Deflazacort (Emflaza)	2017
UGT inhibition	Ertugliflozin (Steglatro)	2017
Effect of stomach pH changes on PK	Ribociclib (Kisqali)	2017
Explain non-linear PK and ethnic differences due to OATP transporters	Letermovir (Prevymis)	2017
ADC DDI	Polatuzumab vedotin piiq (Polivy)	2018
DDI in children – **dermal application**	Aklief (trifarotene)	2019
BE (PD endpoint study waiver) – **dermal application**	Arthritis Pain (diclofenac)	2020

models allowing complex generics simulations

mechanistic models for various routes of administration – all available in **Simcyp Simulator** with GUI and **validation**

MechDermA – skin absorption model > 10 years of R&D



Received: 19 November 2021 | Revised: 15 March 2022 | Accepted: 26 April 2022
DOI: 10.1002/psp4.12814

ARTICLE

Patel N. et al.

Multi-phase multi-layer mechanistic dermal absorption (MPML MechDermA) model to predict local and systemic exposure of drug products applied on skin

European Journal of Pharmaceutics and Biopharmaceutics 178 (2022) 140–149
Contents lists available at ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics
journal homepage: www.elsevier.com/locate/ejpb

Modelling and simulation approaches to support formulation optimization, clinical development and regulatory assessment of the topically applied formulations – Nimesulide solution gel case study☆

Naresh Mittapelly [a], Sebastian Polak [a,b]

frontiers | Frontiers in Pharmacology
TYPE Original Research
PUBLISHED 01 December 2022
DOI 10.3389/fphar.2022.1007496

A mechanistic physiologically based model to assess the effect of study design and modified physiology on formulation safe space for virtual bioequivalence of dermatological drug products

J. F. Clarke[1,2]*, K. Thakur[1] and S. Polak[1,2]

Toxicology and Applied Pharmacology 459 (2023) 116357
Contents lists available at ScienceDirect
Toxicology and Applied Pharmacology
journal homepage: www.elsevier.com/locate/taap

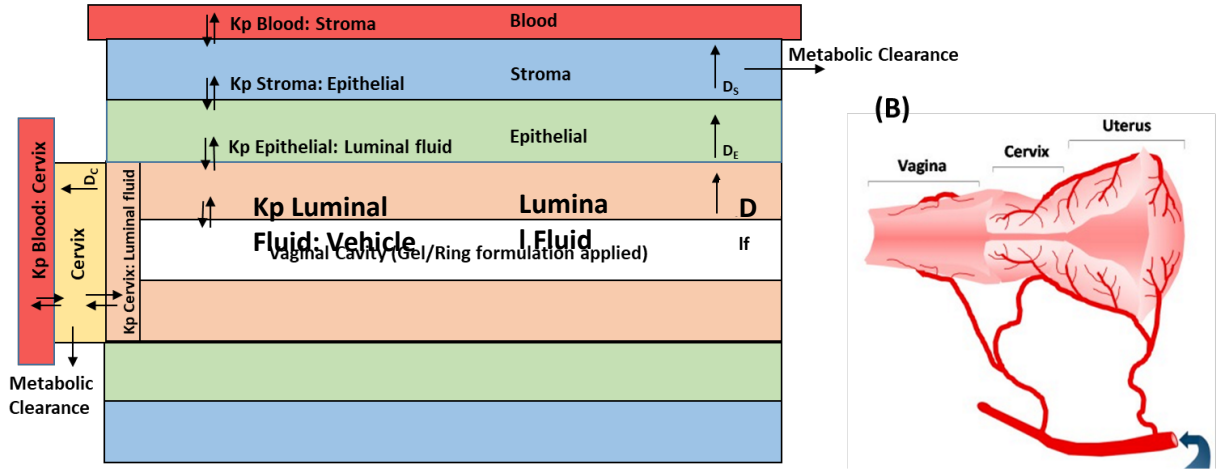
Wisniowsk B. et al.

Physiologically based modelling of dermal absorption and kinetics of consumer-relevant chemicals: A case study with exposure to bisphenol A from thermal paper

models allowing complex generics simulations

mechanistic models for various routes of administration – all available in **Simcyp Simulator** with GUI and **validation**

MechVAM – vaginal absorption model



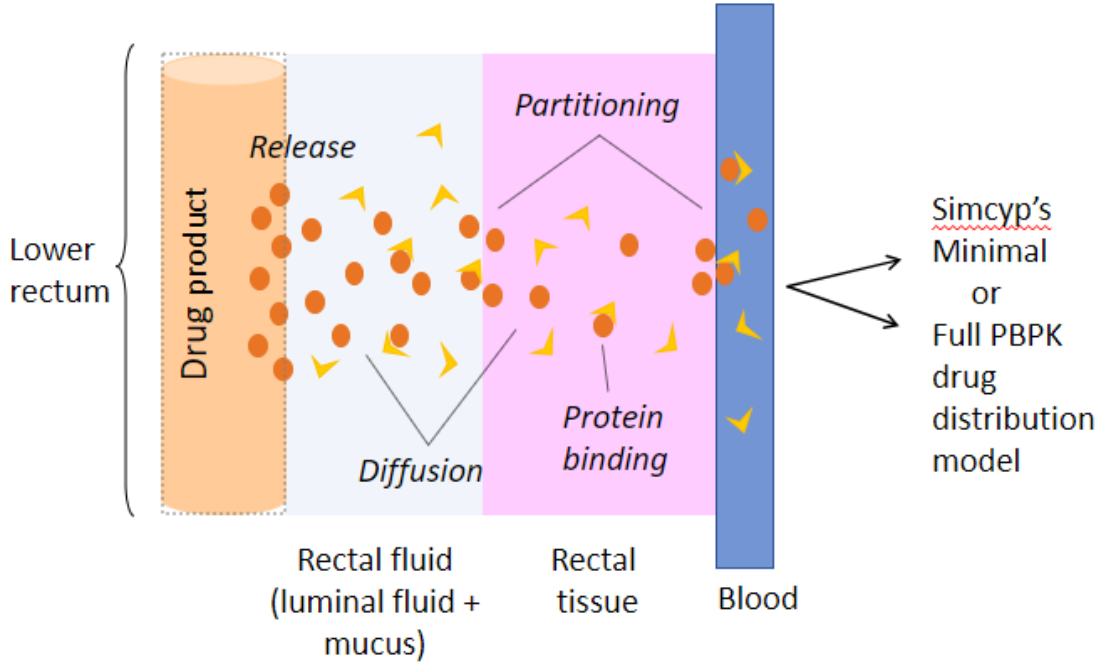
Received: 1 November 2023 | Revised: 18 January 2024 | Accepted: 22 January 2024
DOI: 10.1111/bcp.16029

ORIGINAL ARTICLE

Thakur K. et al.

Development and verification of mechanistic vaginal absorption and metabolism model to predict systemic exposure after vaginal ring and gel application

MechRAM – rectal absorption model



Contents lists available at ScienceDirect
International Journal of Pharmaceutics
journal homepage: www.elsevier.com/locate/ijpharm

Yuri Dancik [a,*], Naresh Mittapelly [a], Santosh K. Puttrevu [a], Sebastian Polak [a,b]

A novel physiologically based pharmacokinetic model of rectal absorption, evaluated and verified using clinical data on 10 rectally administered drugs

conclusions, discussion points and questions

current state and future perspectives

PBPK MODELS

- *verified, validated and widely accepted tools saved in the Model Master File form*
- *the same level of quality control as in vitro and in vivo models*
- *utilized in various areas so solve problems and answer scientific questions*

COMPLEX GENERICS

- *require new tools to support development and submissions*
- *considering advancement of the PBPK models questions arises* ***what is required for their wider acceptance for regulatory decision making?***

SimulationsPlus

Predictive Tools for Generic Product Development & Assessment – Research Input

Maxime Le Merdy, Ph.D., PharmD.

Associate Director, Research And Collaboration

May 20, 2024

Active Scientific Collaborations Between Simulations Plus and FDA

Physiologically Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development

Maxime Le Merdy,[1] Ming-Liang Tan,[1] Andrew Babiskin,[1,2] and Liang Zhao[1]

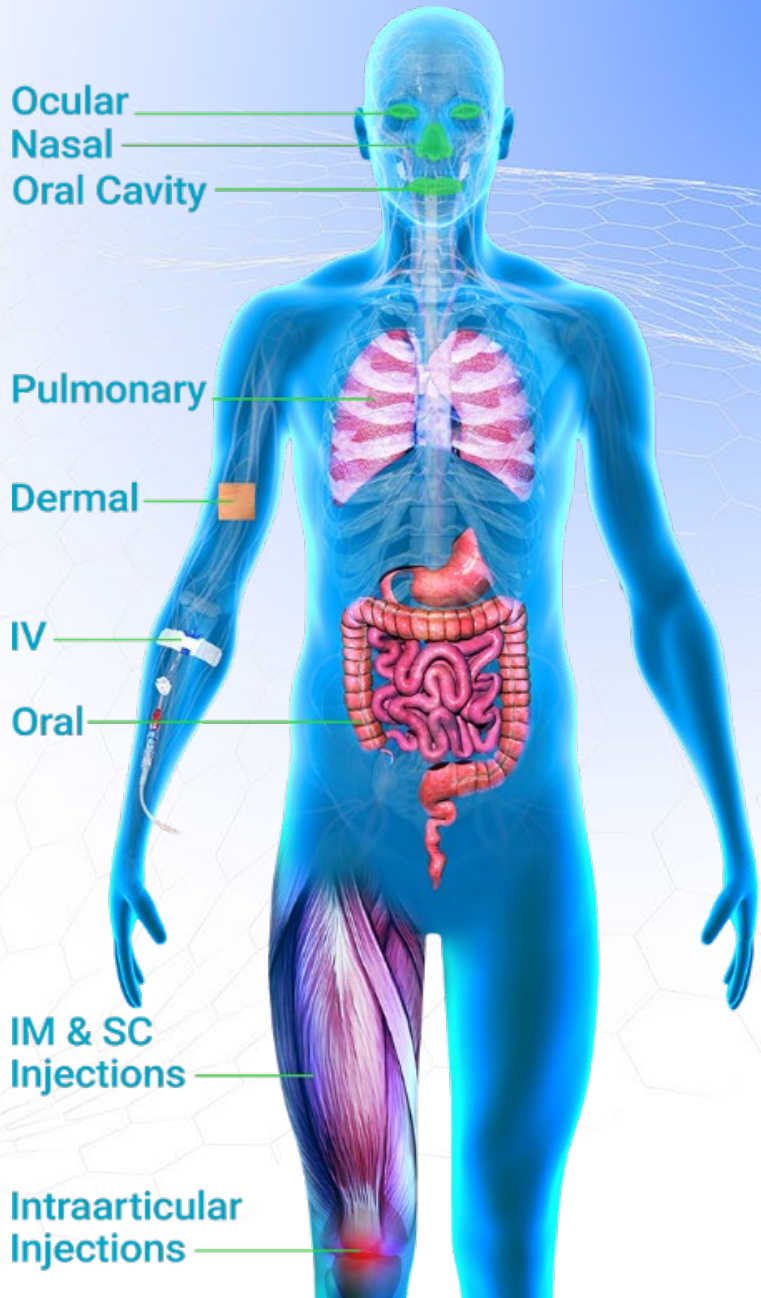
Clinical Ocular Exposure Extrapolation for Ophthalmic Solutions Using PBPK Modeling and Simulation

Maxime Le Merdy[1] · Farah AlQaraghuli[1] · Ming-Liang Tan[2] · Ross Walenga[2] · Andrew Babiskin[2] · Liang Zhao[2] · Viera Lukacova[1]

Predicting Human Dermal Drug Concentrations Using PBPK Modeling and Simulation: Clobetasol Propionate Case Study

William W. van Osdol[1] · Jasmina Novakovic[1] · Maxime Le Merdy[1] · Eleftheria Tsakalozou[2] · Priyanka Ghosh[2] · Jessica Spires[1] · Viera Lukacova[1]

- FDA: Ocular model extensions
- FDA: Oral cavity model extensions
- FDA: Pulmonary model extensions
- FDA: Dermal model extensions
- FDA: ACAT™ – GI Diseases – Local acting drugs
- FDA: ACAT™ - Modified release
- FDA: Virtual BE trial workflows
- FDA: Long-acting injection model extensions



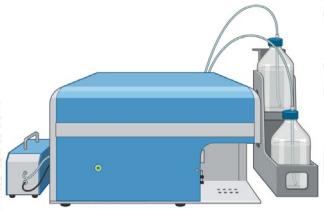
Budget Allocation

Industry – Academic Partnerships

In vivo preclinical study

In vitro characterization

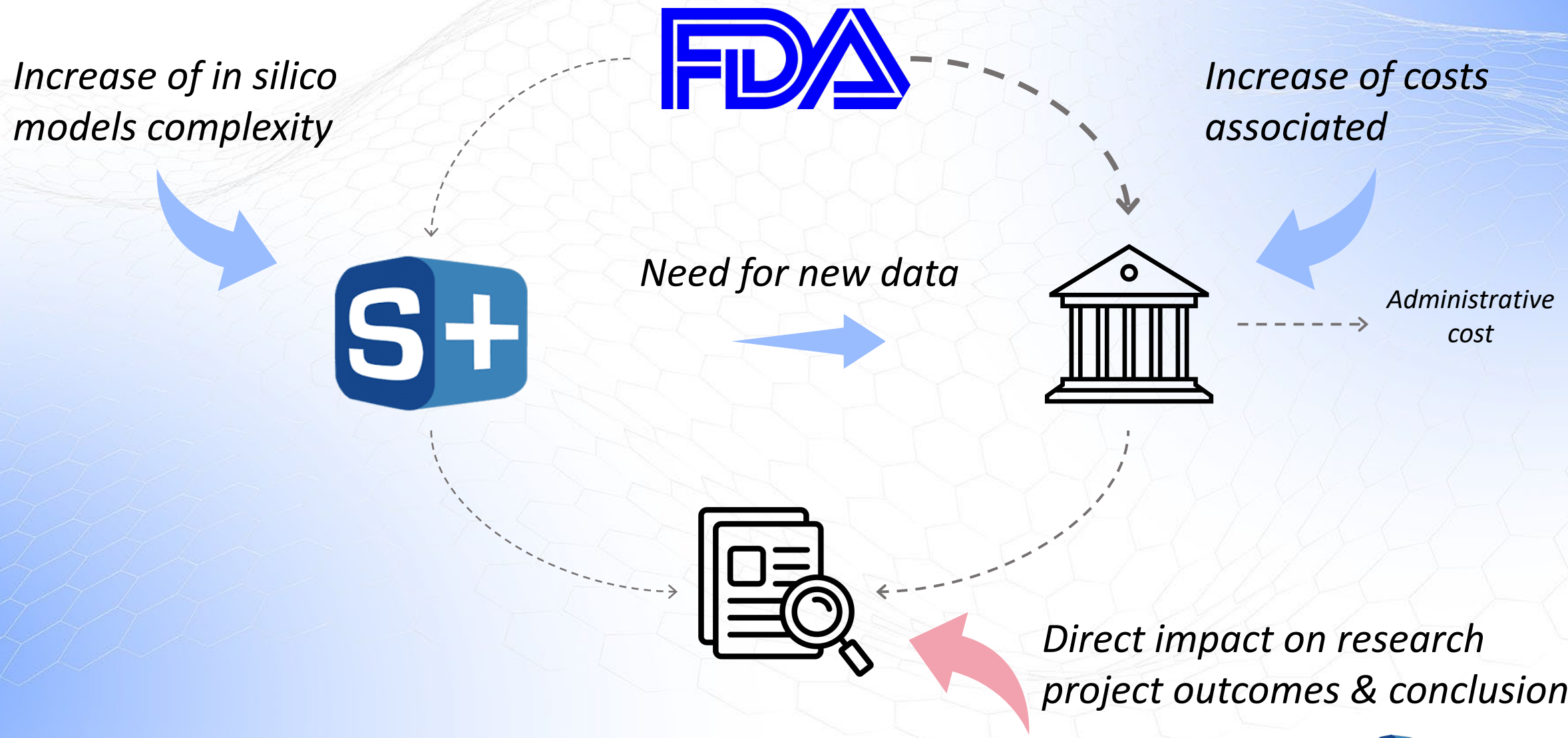
Published in vitro & in vivo data



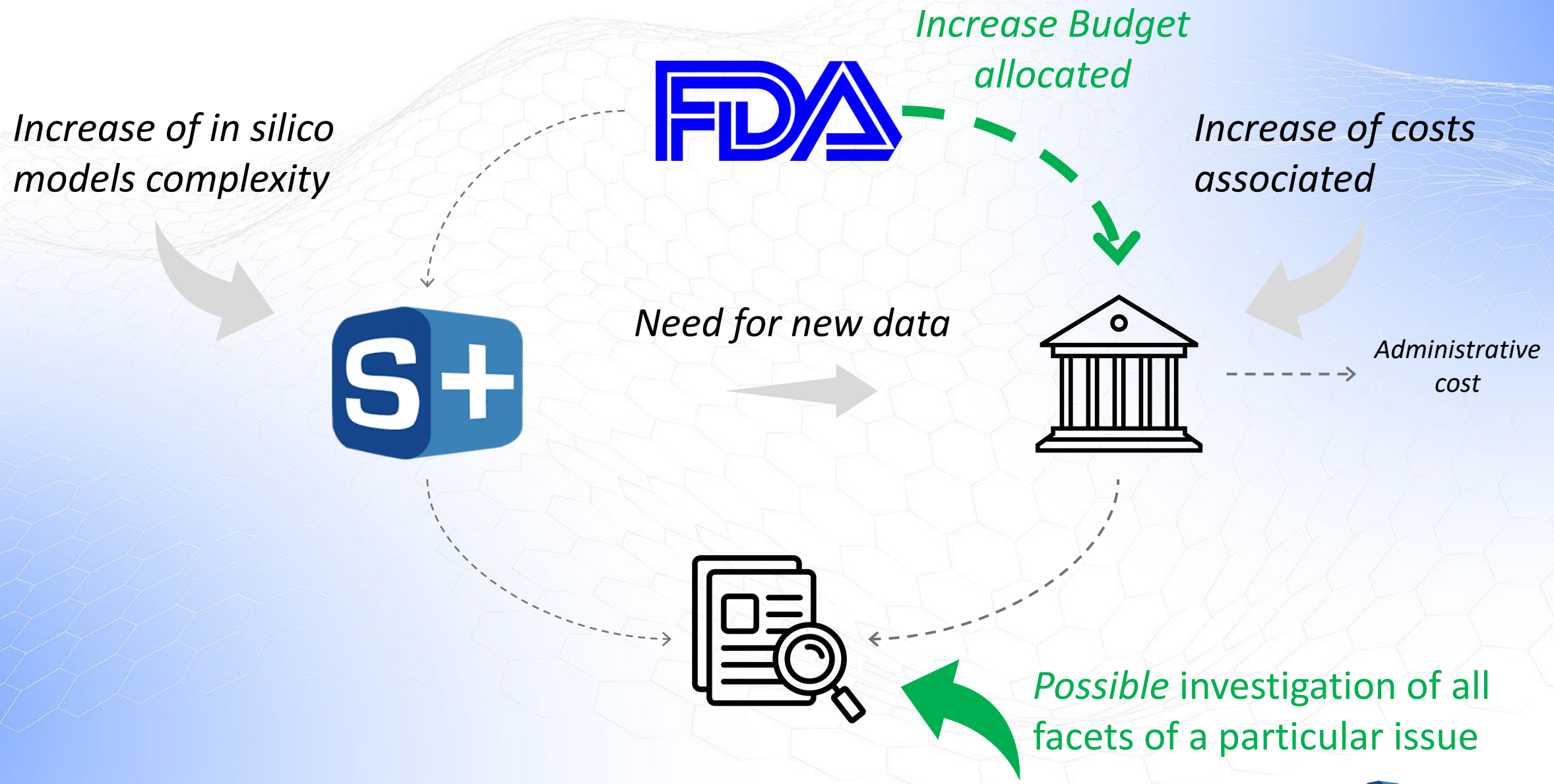
Enhancement and validation of the state-of-the-art PBPK model to support generic drug product development and regulatory assessment.

Budget Allocation

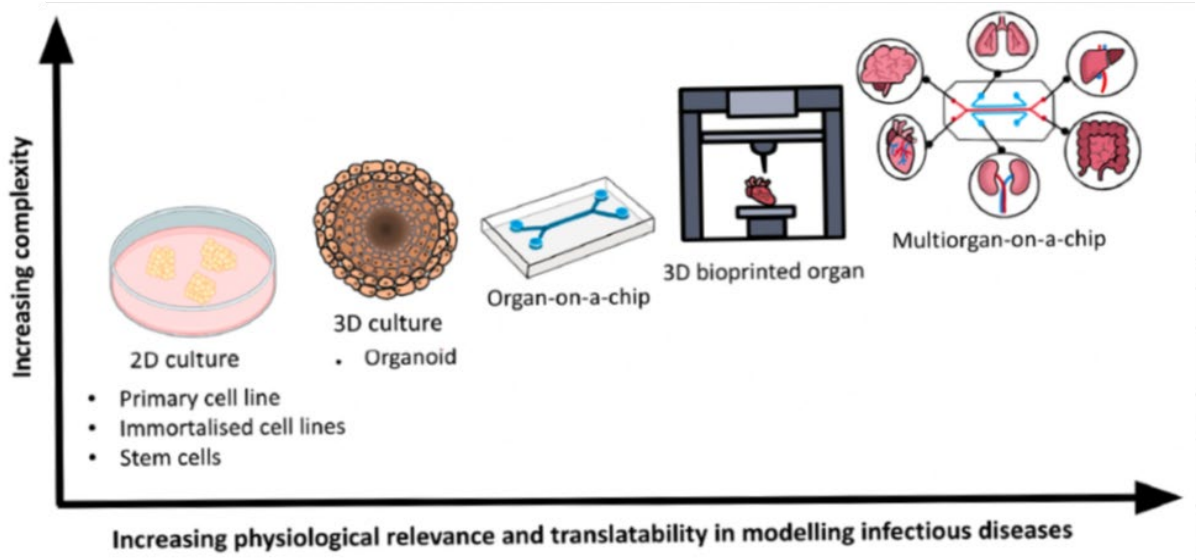
Challenges


Increase of in silico models complexity
Increase of costs associated
Need for new data
Administrative cost
Direct impact on research project outcomes & conclusions

Solution


Increase Budget allocated
Increase of costs associated
Administrative cost
Need for new data
Increase of in silico models complexity
Possible investigation of all facets of a particular issue

New *in vitro* Studies



Chia et al. Biomedicines 2022, 10, 1541.

- Development of new *in vitro* technologies (e.g., 3D cell culture..) combined with state-of-the-art in silico models allowing in vitro to in vivo extrapolation of the results.

- Role of Organ-on-a-chip could have in supporting the development and regulatory assessment of generic drug products.

Thank you!

Public Comments for Session 2
Predictive Tools for Generic Product Development and Assessment

Virtual Comments: Did not provide PPTX – no PDF available

- ***Stephan Schmidt, PhD, Professor, University of Florida***

Public Comments for Session 2
Predictive Tools for Generic Product Development and Assessment

In Person Comments:

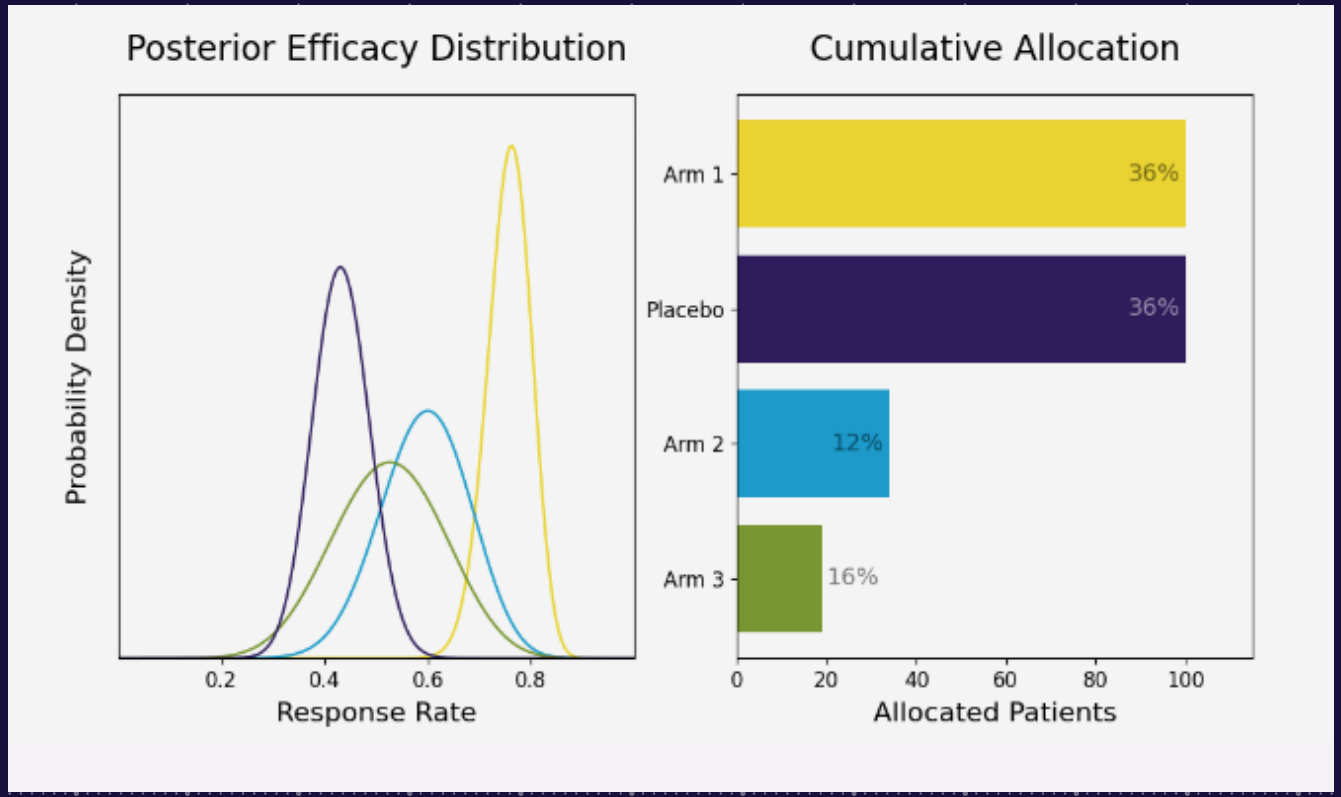
- Huong Huynh, PhD, Director of Regulatory Science, and Shu Chin Ma, PhD, VP of MIDD & Quantitative Medicine, Critical Path Institute (C-Path)
- Sandra Suarez-Sharp, PhD, President, Regulatory Strategies, Simulations Plus, Inc.
- Anuj Chauhan, PhD, Professor, Colorado School of Mines
- ***Elad Berkman, PhD, CTO PhaseV***
- ***Sebastian Melgar, MPH, Lead Associate Booz | Allen | Hamilton***
- ***Brian Eden, Vice President, Global Life Sciences Technical Operations Capgemini Group***
- ***Sandhya Polu and Anil Bhatta, Contracts Manager, Deloitte Services LP***
- ***Anthony Cristillo, PhD, MS, MBA, Partner, Digital Health***
- ***Sarah Ferko, MS, PMP and Ally Lu, Senior Managing Consultant, Artificial Intelligence & Analytics, IBM Consulting***
- ***Ashlee Brunaugh, PhD, Assistant Professor, Pharmaceutical Sciences, University of Michigan***
- ***Jinxiang Xi, PhD, Associate Professor of Biomedical Engineering, University of Massachusetts, Lowell***
- ***Guilherme Garcia, PhD, Assistant Professor, Marquette University and The Medical College of Wisconsin***
- ***Darragh Murnane, PhD, Professor of Pharmaceutics, University of Hertfordshire (Informix Pharma)***
- ***Jeff Schroeter, PhD, Senior Scientist, Applied Research Associates***

Virtual Comments:

- Ravendra Singh, PhD, Director of Pharmaceutical Systems Engineering Rutgers
- Sebastian Polak, PhD, Professor Jagiellonian University
- Maxime Le Merdy, PhD, Associate Director, Research and Collaboration Simulations Plus, Inc.
- Stephan Schmidt, PhD, Professor University of Florida
- Guenther Hochhaus, PhD, Professor University of Florida
- Yu Feng, PhD Associate Professor, Oklahoma State University
- Maria Malmlöf, PhD; Per Gerde, PhD, Director of Projects, Inhalation Sciences
- Laleh Golshahi, PhD, Associate Professor of Mechanical and Nuclear Engineering, Virginia Commonwealth University
- Rodrigo Cristofoletti, PhD, Assistant Professor, University of Florida

Adaptive Trials for Bioequivalence - FDA GDUFA Public Workshop

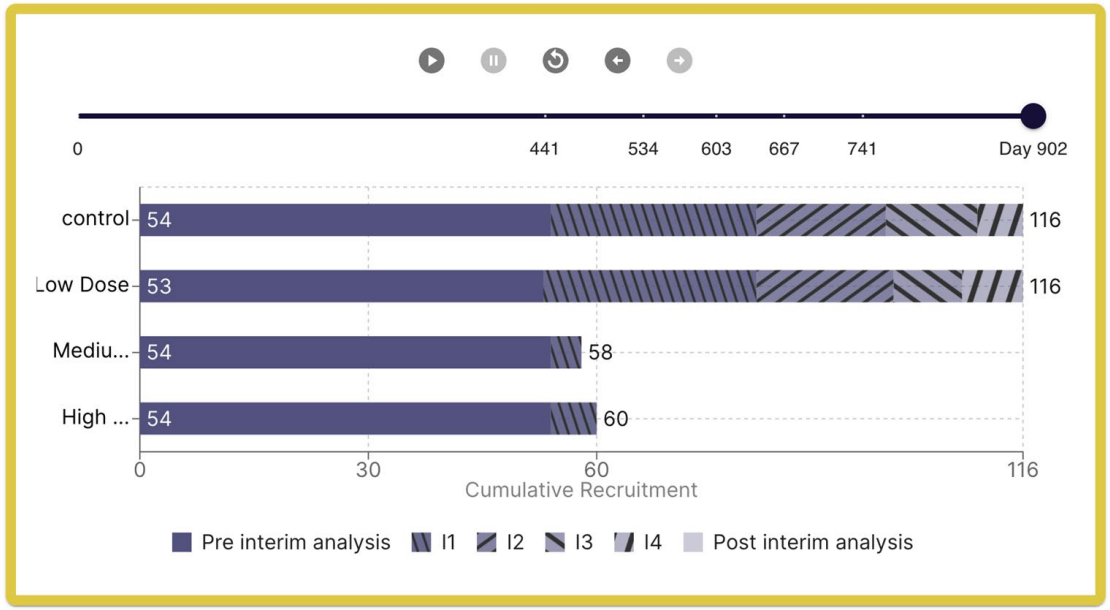
Elad Berkman,
CTO and Co-founder of PhaseV Trials



Adaptive Trials

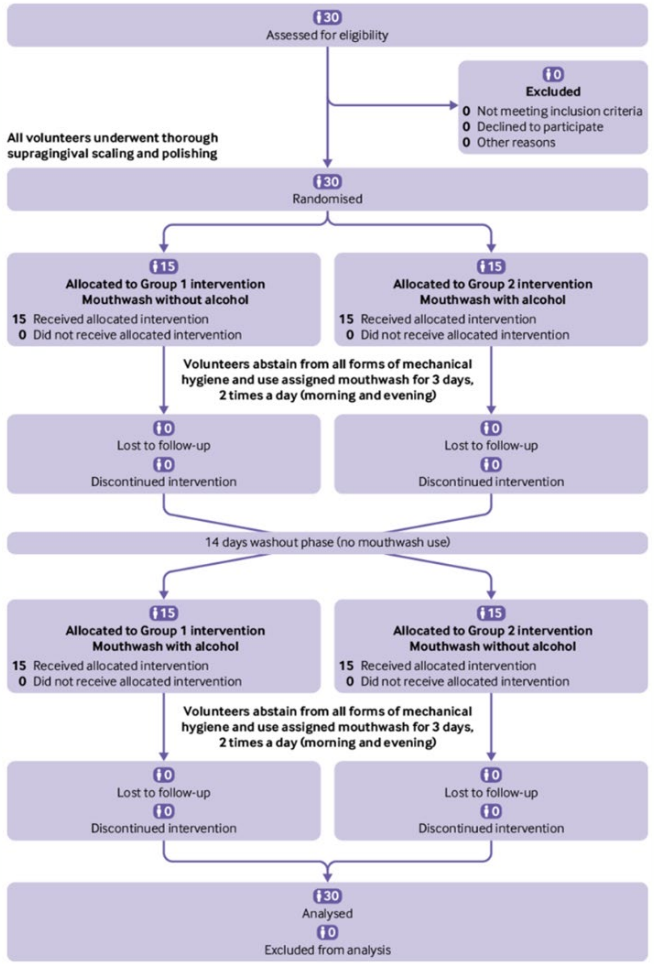
- Leverage the data collected during the trial:
  - Efficiency - Less patients, higher power
  - Time to market - stop earlier for efficacy or futility
  - Removing the guesswork
    - Variance
    - Effect size

⇒ Increased probability of success



Adaptive Trials for Generics

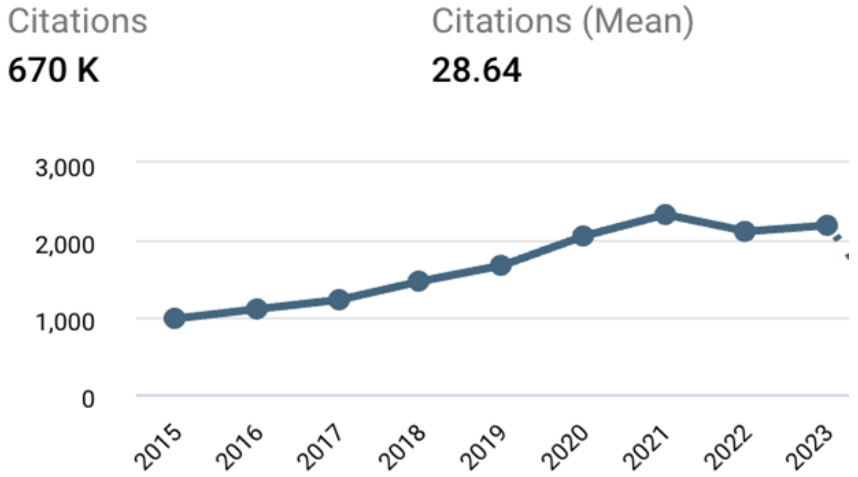
- Bioequivalence trials pose a unique challenge:
  - Small sample sizes
  - Efficiency as a key focus
  - Crossover trials
    - In-person variance - larger uncertainty
  - Relevant Historical data
    - Room for Bayesian designs
  - Bespoke approach is more challenging
    - Limited Budget

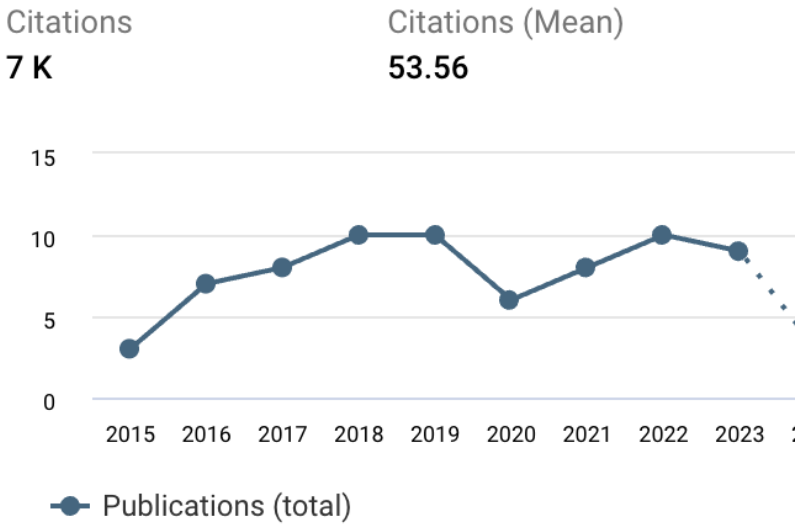


*Dwan K, Li T, Altman DG, Elbourne D. CONSORT 2010 statement: extension to randomised crossover trials

Past Work

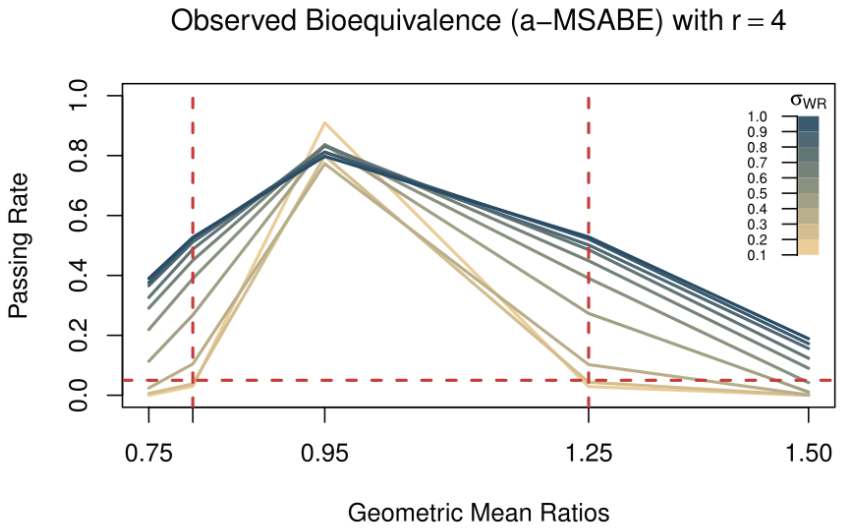
- “Sequential design approaches for bioequivalence studies with crossover designs”, Potvin et al 2008
- “Optimal adaptive sequential designs for crossover bioequivalence studies”, Xu et al 2016
- “Statistical methodology for highly variable compounds: A novel design approach for the ofatumumab Phase 2 bioequivalence study”, Jones et al 2022





Recent Example

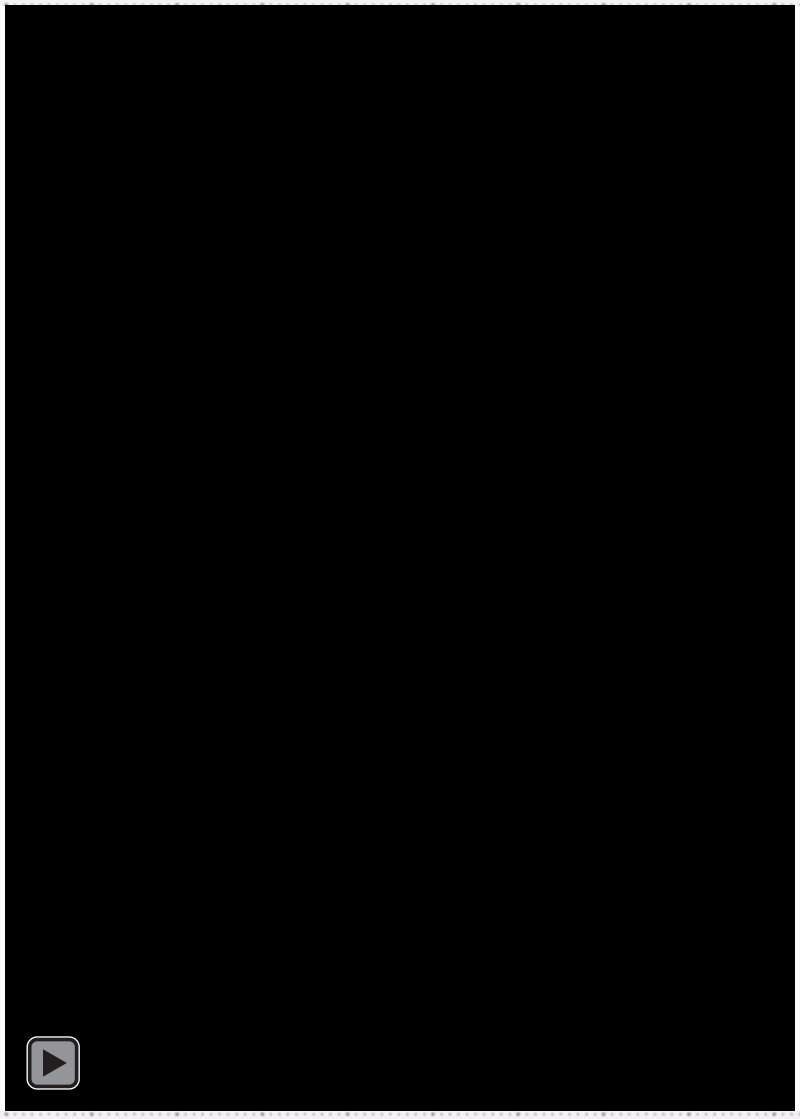
- Adaptive MSABE
  - New design combining MSABE (ABE/RSABE) with Sequential design (based on Potvin 2008)
  - Many degrees of freedom:
    - What should the initial number of subjects be (n_1)?
    - How many replicates per subject (r)?
    - What to choose α_1 and α_2?
    - What value of GMR to assume?
    - …



*Lim D, Rantou E, Kim J, Choi S, Choi NH, Grosser S. Adaptive designs for IVPT data with mixed scaled average bioequivalence

Calibration of Trial Parameters

- **PhaseV** has developed a unique method for efficiently calibrating trial parameters:
  - Start with a burn-in - run simulations with diverse parameter values.
  - Train a model on the results and update after every batch
  - Choose new parameters guided by the model
  - Establish confidence in the final choice of parameters, without needing to heavily simulate that particular setup.
- The overall number of simulations required for convergence and verification is of the order of magnitude that would be needed to verify each set of parameters (if they are simulated one at a time).



Directions for further Research

- Substantial room to innovate on trial design:
  - Additional adaptations
  - Optimal designs
  - “Building Blocks” to support easy design
    - Intuitive software

- We suggest there is room for a designated effort, utilizing the key learnings across adaptive trials to propose new, improved designs for Generic drug trials

Thank You

http://www.phasevtrials.com/

Booz Allen®

Utilization of Artificial Intelligence and Machine Learning Applications in Post-Marketing Safety, Regulatory Review, and Physiologically Based Pharmacokinetic Modeling for Generic Drug Development

Proposed Priority GDUFA Science and Research Initiatives

Booz | Allen | Hamilton®

FDA should consider prioritizing the use of artificial intelligence and machine learning to address current challenges impacting post-marketing safety, regulatory review, and pharmacokinetic modeling

Post-Marketing Safety

Regulatory Review

Pharmacokinetic Modeling

Current Challenges
Potential for Addressing Current Challenges through AI/ML
Considerations for Implementation of AI/ML
Recommendations

AI has the potential to mitigate existing challenges in conducting post-market surveillance for generic drugs, but FDA should carefully consider ethical, privacy, and patient diversity concerns

Current challenges and barriers in conducting post-market surveillance of generic drug substitution include:

- **Limited data**: There is insufficient data on bioequivalence versus real-world effectiveness due to under-reporting of adverse events
- **Lack of standardization**: Lack of a standardized reporting system can make it difficult for healthcare providers to submit adverse event (AE) reports
- **Cost**: Conducting large-scale studies to assess the real-world effectiveness and safety of generic drugs can be expensive and logistically challenging
- **System limitation:** Existing reporting can be complex to navigate, which can limit utilization
- **Data security**: Concerns over data privacy of patients' health information and data

Use of AI/ML tools can:

- Perform real-world data analyses of electronic health data to identify trends in AE. This can provide **insights into long-term safety of generic drugs**
- **Standardize and automate tasks** associated with case reporting, evaluation, and processing
- Analyze large amounts of safety data and compile aggregate reports of multiple AE for products within a specific timeframe. This **reduces the manual effort, cost, and time** compared to traditional report generation
- Train AI/ML tools on historical AE to **predict the potential for long-term effects** based on a drug's properties, patient factor, and reported events
- Provide **comparative safety analyses** of generic drugs and their potential effects

When implementing AI/ML tools, FDA should consider:

- **Patient diversity concerns** (e.g., sponsors must ensure the historical data used to train algorithms is representative of **diverse patient data population to eliminate bias** and ethical concerns
- **Regulatory compliance** (i.e., ensuring AI/ML tools meet regulatory requirements such as Good Pharmacovigilance Practices)
- **Ethical concerns** with using algorithms that have limited or little transparency, or algorithms that may have internal operations that are not visible to users or other interested parties
- **Security concerns** like improper data sharing, cybersecurity risks, and data privacy

AI/ML tools are well-suited to address the current challenges in the regulatory review process of generic drugs

Barriers/challenges for regulatory filing of generic drugs		How AI/ML tools can address these challenges
Exclusivity	• 5-Year New Chemical Entity Exclusivity • 3-Year Exclusivity for Product Improvements • 7-Year Orphan Drug Exclusivity	Automate repetitive tasks, such as document classification, information extraction, and analysis of supporting literature
Patents	Submission of correct patent certification	Analyze text from drug labels, clinical studies, adverse event reports, and regulatory submissions to extract relevant information to aid reviewers
Chemistry Manufacturing and Controls (CMC)	ANDAs need to include detailed CMC data to identify and mitigate any potential risks	Automate quality control processes by analyzing CMC data, batch records, and quality assurance reports to detect deviations, anomalies, and non-compliance issues
Sourcing API and Critical Excipients	Improper preparation of active pharmaceutical ingredient (API) Drug Master File	Learn from historical FDA data to identify potential quality risks and predict future compliance issues, enabling proactive corrective actions and ensuring adherence to regulatory standards
Risk Evaluation and Mitigation Strategies (REMS)	Insufficient REMS elements to ensure safe use of the generic drug	Analyze historical FDA approval data, including factors such as drug characteristics, submission attributes, regulatory pathway, and timeline, to predict the probability of ANDA approval

Integration of AI/ML tools can improve prediction accuracy of physiologically based pharmacokinetic modeling by overcoming current challenges relating to complex formulations, model inputs and validation

Formulation

- **Challenge**: Difficult to accurately model PK due to complex formulation or route of administration.
- **AI solution**: **Integrate data from various resources** (e.g., drug properties, excipient interactions, and dissolution profile) to improve accuracy.

Model Validation

- **Challenge**: Clinical data limitations for the validation of PBPK models.
- **AI solution**: **Impute missing data points**, **conduct neural network-based simulations** using virtual patient populations, and apply **transfer learning** technique to adapt pretrained models to specific datasets.

Model Inputs

- **Challenge**: Time intensive, costly, or infeasible data collection for generating input parameters for PBPK modeling.
- **AI solution: Predict parameters using deep learning methods** based on similar compounds or known correlations.

FDA should consider requiring explainable and interpretable AI models, rigorous validation, and robust safeguards for data and patient privacy

Require **rigorous validation** of AI-integrated PBPK models against experimental data and comparison with traditional modeling to demonstrate reliability and suitability for regulatory decision-making

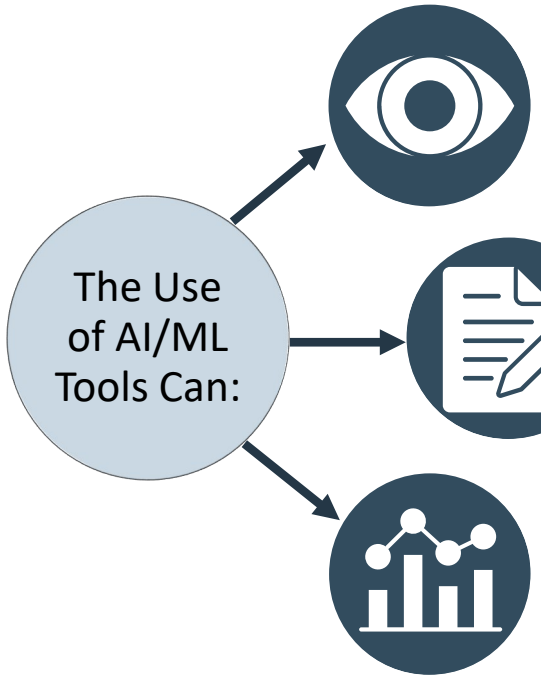
Require applicant use of **explainable models** and review results for model transparency

Prioritize **model interpretability** through quality model development practices and documentation

Consider **data privacy** and **patient confidentiality**

Implementation of AI/ML can advance generic drug development by addressing current challenges in post-market surveillance, regulatory review, and pharmacokinetic modeling

Potential Generic Drug AI Use Cases



Improve Post-Marketing Surveillance

Enhance Efficiency of Regulatory Review

Improve Accuracy of PBPK Modeling

FDA Should Consider Developing Science and Research Initiatives to Include:

- Training AI/ML tools for post-market surveillance using representative diverse patient population data
- Promoting transparency in the implementation of AI/ML tools to reduce bias and ethical concerns

- Developing standardized methodologies and protocols for using AI/ML in quantitative analyses and modeling approaches for regulatory review
- Providing training and resources for FDA staff to enhance their proficiency in using AI/ML technologies

- Supporting research aimed at leveraging AI/ML tools for improving PBPK modeling for an efficient demonstration of bioequivalence for complex generics
- Requiring explainable and interpretable models, and rigorous validation for PBPK models generated using AI/ML algorithms

Booz Allen emphasizes the continued importance of two of the Agency's existing science and research priorities for generic drug development

#7 Facilitate the Utility of Model-Integrated Evidence (MIE) to Support Demonstrations of bioequivalence (BE)

A. Advancing complementary approaches **using MIE to support an efficient demonstration of BE** specifically for locally acting products (e.g., inhalation and topical routes of delivery) as well as for LAI products

B. Establishing best practices for model standardization, validation, acceptance, and sharing (e.g., using model master files) that improve the reproducibility and reusability of quantitative pharmacology information used in BE study simulations

#8 Expand the Use of Artificial Intelligence (AI) and Machine Learning (ML) Tools

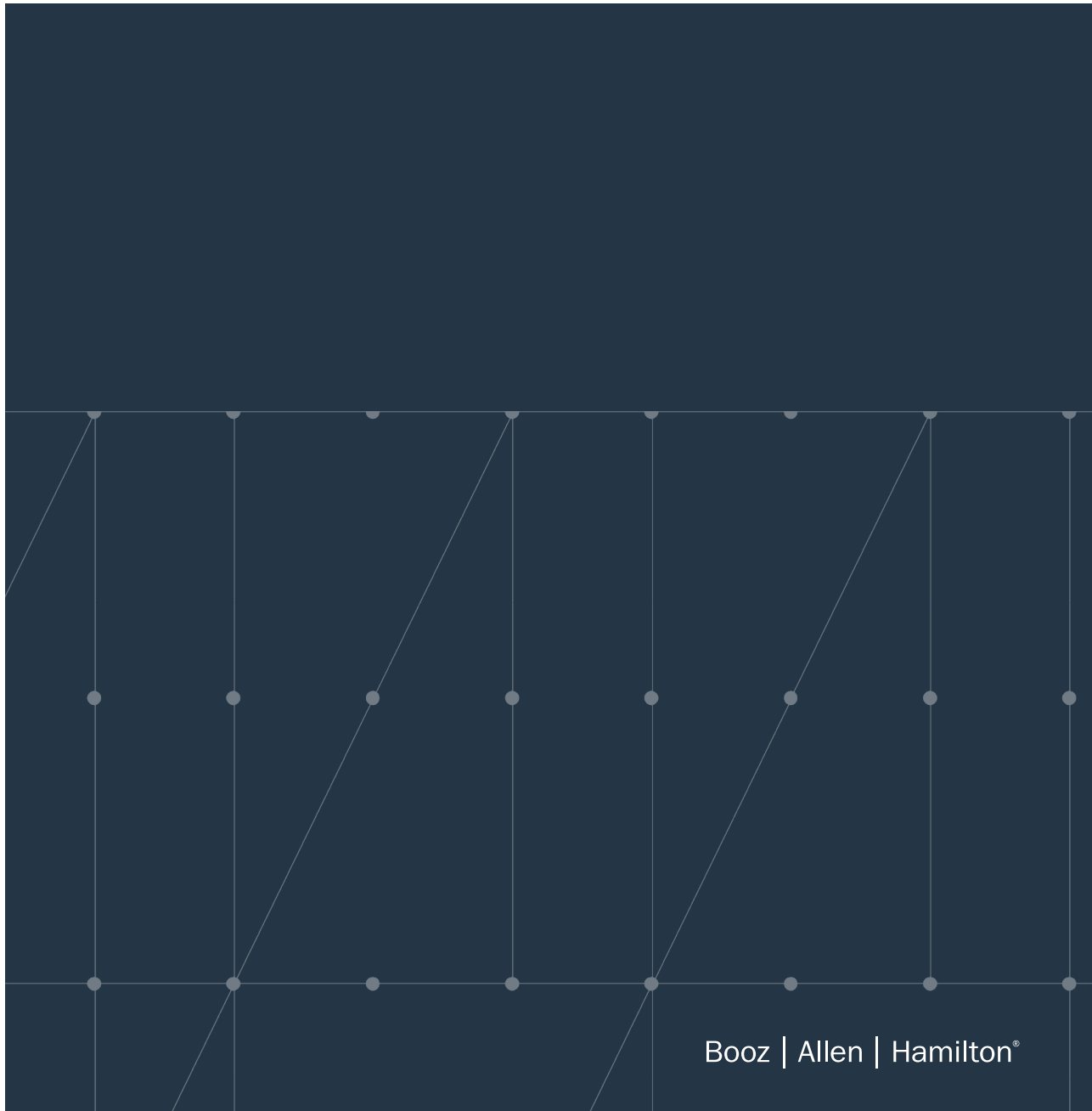
A. **Improving the use of real-world evidence for post-market surveillance** of generic drug substitution and for evaluating the impact of generic drugs on public health

B. Integrating AI/ML tools with FDA information and data to support quantitative analyses and modeling approaches that **facilitate regulatory assessments**, and identifying strategies to optimize the reliability of outcomes produced by these tools

C. Exploring the capability of AI/ML tools for a prospective applicant to be able to efficiently assess the completeness of its ANDA prior to submission, and to **enhance the efficiency, consistency, and quality of regulatory assessments** once ANDAs are submitted

Booz Allen®

As the Federal government and its agencies seek to accelerate their adoption of AI capabilities, Booz Allen stands ready to support research and implementation of secure and responsible AI.



Capgemini

Predictive Tools for Generic Product Development & Assessment

Use of Data Models and AI ML to Allow Participative ANDA Approval Interaction

May 20th, 2023

Brian Eden

VP, Global Life Sciences Technical Operations
Capgemini Group

Profile

- Three decades of operations transformation, process improvement, management consulting and leadership experience developing global Lean and Digital programs, leading global business integrations, and serving an array of pharmaceutical and medical device clients.
- Provides subject matter expertise in Manufacturing, Supply Chain, Quality and related areas across multiple dosage forms, including injectables, vaccines, oral solid dose, API and specialty forms.
- Serves as business and domain leader for digital and systems transformations, including Agile product development, SAP a and Oracle implementations and cGMP-specific MES, LES and related rollouts.
- Leads the Global Life Sciences Technical Operations Practice for the Capgemini Group, driving process and digital solutions for Pharmaceutical and Medical Device clients in Supply Chain, Manufacturing, Quality, Technical Transfer, and related functionalities.

Education and certificates

- Master of Science, Interdisciplinary Engineering, Purdue University
- Bachelor of Science, Physics, University of Connecticut
- Lean Six Sigma Master Black Belt, General Electric Company
- Agile Leader, Tata Consultancy Services
- Nuclear Engineer, United States Navy

Competencies

- cGMP Manufacturing, Supply Chain Quality, Technical Transfer
- Regulatory Affairs, Pharmacovigilance
- Transformation Management Office Leadership
- Lean Six Sigma and Digital process improvement and product development

Capgemini Group
At a Glance

Founded
1967
by Serge Kampf

TOP 5
consultancy worldwide

A Family of Brands

Capgemini invent
Fahrenheit212 Part of Capgemini Invent
idean Part of Capgemini Invent
Capgemini
frog
sogeti Part of Capgemini
Cambridge Consultants

We serve our clients in more than
100
countries

Headquarters
in Paris

350,000+
Team members

Group Chairman
& Chief Executive Officer
Aiman Ezzat

E2E-Services

- Consulting
- Technology
- Engineering
- Outsourcing & Managed Services

ANDA Filings | The Birth of the Generic Industry

FDA has enabled growth in generic, bioequivalent therapies while protecting the financial interests of innovators. The ANDA process has been improved dramically over time, further encouraging robust and timely generic competition.

Legal Basis

- Federal Food, Drug, and Cosmetic Act (1938)
- Hatch-Waxman Act (1984)
- Generic Drug User Fee Amendments (I '12, II '17, III '22)

Continuous Improvement

- ✓ Drug Competition Action Plan (DCAP)
- ✓ CDER NextGen Portal
- ✓ Biologics Effectiveness and Safety (BEST) Initiative
- ✓ Dedicated AI steering committee and proofs of concept

9 of 10 prescriptions in the US currently filled as generic and an estimated savings of $2.9 trillion over the past 10 years (generic *and* biosimilars)

Filing Challenges

Despite improvements, challenges exist limit that number/scope of approvals and total generic presence in the market.

- **Demonstrating Bioequivalence**
- **Managing Patent and Exclusivity Issues**
- **Esuring Regulatory Compliance**
- **Providing Adequate Resourcing**
- **Sharing Knowledge**

Applying Advanced Technologies to Make Improvements

Expanded, scaled cloud computing and advanced technologies can provide breakthroughs to improve patient access, reduce patient and government costs and reduce the number of drugs for which generic equivalents are not available.

Available Levers

Collect & Aggregate Data
Gather and summarize baseline information

Describe the Situation
Show what's happening in visual and statistical formats

Diagnose What Happened
Hypothesize and quantify cause and effect

Predict Behavior
Forecast what may happen in the future

Prescribe Action
Decide what to do next, advise, take action

Create Content
Develop suitable written, visual and auditory outputs

AI Branches

- Robotics
- Speech
- Knowledge Based Reasoning
- Search & Optimization
- Natural Language Processing
- Machine Learning
- Vision

Apply technology levers to optimize individual steps and to promote connection among steps

Research Recommendation

Develop and test an AI Proof of Concept (POC) of a solution allowing prospective ANDA submission risk assessment and mitigation for a targeted group of filings to allow easier, more timely approvals.

Pain Points				Primary Solution Benefits
	TRC Errors/Resubmissions	BE Challenges	FDA review time	
	Sponsor Preparation Time	**Resource Requirements**	**Overall approval timeline**	Secondary Solution Benefits

Solution Elements

- ❑ Proactive signal to screen for missing submission elements
- ❑ Submission probability of success (POS) indicator
- ❑ Suggestions of critical input parameters to raise POS
- ❑ Submission specific best practice generation
- ❑ Visual interface with which prospective filers can interact

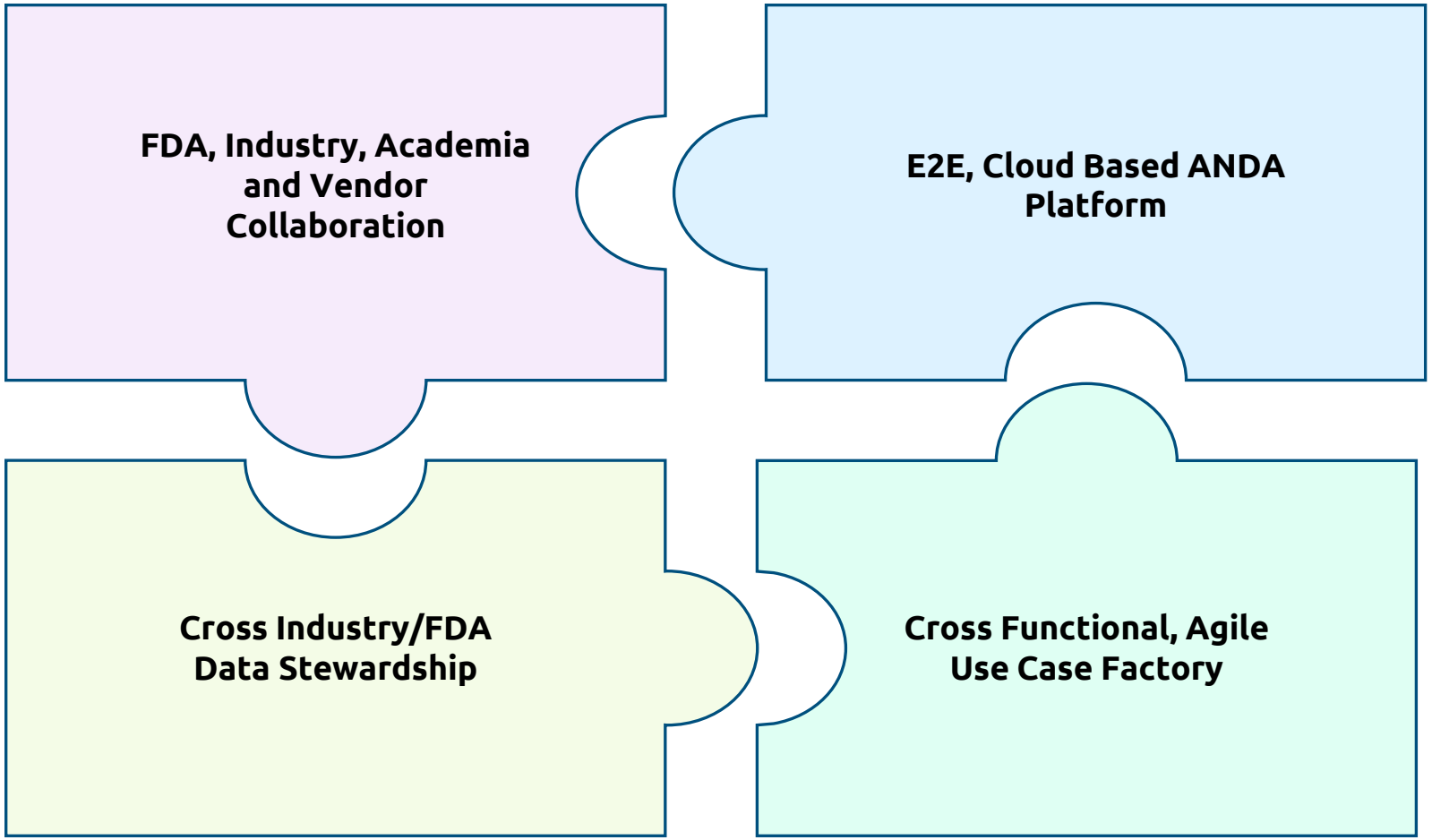
We propose a short, targeted POC to demonstrate feasibility followed by pilot launch for quick wins

Technical Requirements

- ✓ Model of submissions, review notes, regulations, numerical data
- ✓ Training for the AI/ML on all criteria
- ✓ Continuous incorporation of new data to guard against drift
- ✓ Knowledge graph to track and map available information over time and neural networkgraph to ID clusters and outliers
- ✓ … working together with a multivariate analysis/loss function to link POS cause and effect
- ✓ Front end GUI development of the prospective filer interface
- ✓ Guardrails to keep recommendations inside the range of available information

What is Required Beyond Proofs of Concept?

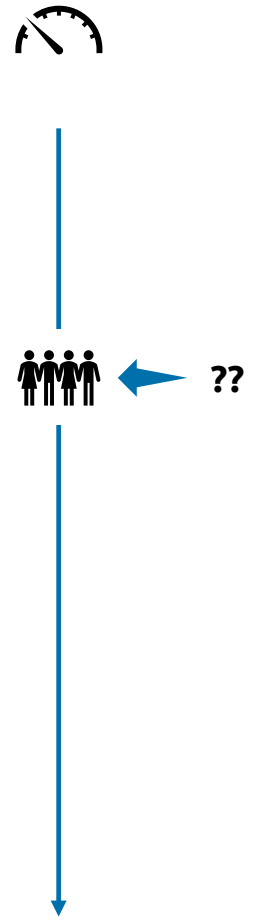
Ideation of use cases and proofs of concept are not sufficient to realize the full potential of advanced technology solutions, though. A supporting operating model and several enablers are required.



How far have we come and what's next on the journey?

Step changes in access and performance via advanced technologies are possible and now is the time to develop a cohesive vision and set of actions to chart the course for these next innovations.

Excite & Discover	Create awareness of and excitement about the potential of advanced technology solutions and set the vision and strategy. Identify and prioritize use cases, ecosystem partners and underlying technology requirements
Build	Formulate business cases, launch proofs of concept and pilots and learn from success and from failing fast. Iterate use case ID and prioritization.
	Quantify resource, timeliness and quality benefits of actions to reduce, remove, re-engineering and reimagine Estimate Implementation Costs including licensing, staffing, infrastructure and training
Scale	Create sustainable operating model, track benefits to the bottom line and continue to improve and iterate based on latest information.
	People & Culture Transformative workforce, management innovation, training and governance **Process** Agile workflows to maximize human & AI collaboration; KPIs to monitor performance **Tech & Data** Robust and sustainable platforms, close collaboration with ecosystem partners **Ethics, Legal & Risk** Coordination among entities with legal/ethics oversight to ensure compliance



A Sample of Additional Use Cases

Below are several additgional examples of practical use cases leveraging advanced technologies that can be developed and scaled today, some of which are already in ideation and pilot phases.

Use Case	Description	Levers	Benefit
Document Submission Triage	Summarize documents, automate chatbots, and establish sentiment analysis for reviewers of information as it is submitted.	Collect & Aggregate, Describe	FDA processing resource requirements Sponsor preparation and FDA review times
Technical Rejection Criteria Error Rapid Screening	Automated TRC error root cause ID and interactive problem solving between sponsors and FDA to provide early warning of possible TRC errors to sponsors	Diagnose, Predict	Submission quality Overall approval timeline Safety and efficacy
Bioequivalence Study Optimization	A supervised machine learning based approach to classify, analyze, and optimize BE study information to ensure completeness of submission and to provide early warnings for unacceptable trending	Diagnose, Predict, Prescribe	Safety and efficacy Sponsor preparation and FDA review times
Virtual FDA Review Assistant	A fine-tuned foundational GenAI model built on existing NDA and ANDA submissions with a human-like interface to answer key scientific and regulatory queries to improve speed of review and to uncover hidden insights	Diagnose, Predict, Create Content	FDA processing resource requirements Safety and efficacy

Effort toward some of these use cases is already underway

About Capgemini

Capgemini is a global leader in partnering with companies to transform and manage their business by harnessing the power of technology. The Group is guided everyday by its purpose of unleashing human energy through technology for an inclusive and sustainable future. It is a responsible and diverse organization of 270,000 team members in nearly 50 countries. With its strong 50 year heritage and deep industry expertise, Capgemini is trusted by its clients to address the entire breadth of their business needs, from strategy and design to operations, fuelled by the fast evolving and innovative world of cloud, data, AI, connectivity, software, digital engineering and platforms. The Group reported in 2020 global revenues of €16 billion.

Get the Future You Want | www.capgemini.com

Deloitte.

Generic Drug Science and Research Initiatives Public Workshop

Intelligent Postmarket Surveillance and Assessment

AI-Driven Detection and Classification of Quality-Related Signals for Generic Drugs

May 20, 2024

MAKING AN IMPACT THAT MATTERS since 1845

Postmarket Quality Surveillance Challenges

Deloitte.

Postmarket surveillance of generic drugs faces several challenges

FDA's efforts, including remote regulatory assessments and the Sentinel Initiative, support postmarket monitoring; however, challenges remain:

- FDA inspection capacity insufficient; need for advanced notice for foreign inspections
- Majority of generic drug manufacturing outside the U.S.
- Cases of falsified data from manufacturers
- Voluntary FAERS reporting by clinicians and consumers

Increasing number of FDA recall enforcement reports

- More than 1,000 drugs recalled each year; 80-90% of recalls are Class II
- 3,200+ Class I and 15,900+ Class II recalls from 2013-2023
- 300+ Class I/II recalls with cGMP deviations from 2013-2023

Existing limitations and spikes in Class I recalls **necessitate alternative approaches, tools, and data to augment inspection capacity** and **enhance postmarket surveillance**

Sources: *FDA* | *Statista* | *Health Affairs* | *GAO* | *Journal of Pharmaceutical Innovation*

Approach to Generic Drug Quality Signal Detection

Deloitte.

In line with GDUFA research priority **#8 Expand the Use of Artificial Intelligence (AI) and Machine Learning (ML) Tools,** we propose to use **advanced AI models integrated with multimodal postmarket data sources** for the detection of quality-related signals for generic drugs. This approach would prioritize and thematically categorize generic drug quality signals to enhance postmarket monitoring.

Data Sources: Public use FDA documents (483s), social media, FAERS, legal and claims data, patient advocacy forums, blogs, Google trends

Step 1: Source Data Curation

Extract, clean, deidentify data types and features

- Patient Demographics
- Drug Details: generic drug manufacturer, usage date
- Define signal events

Step 2: Exploratory Data Analysis

Perform in-depth analyses on data sources

- Examine initial trends in the signal data
- Signal Rate Calculation

Step 3: NLP Tools for Signal Identification

Develop an NLP pipeline to process unstructured data to extract relevant features

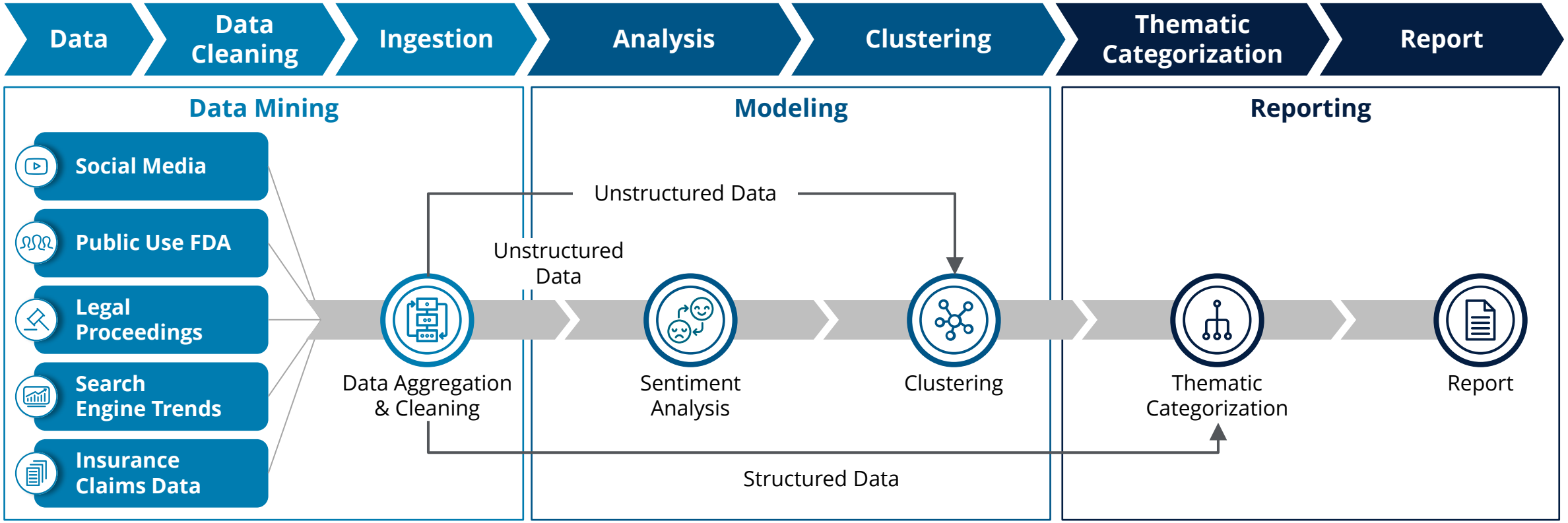
- Leverage NLP including task-appropriate Named Entity Recognition (NER) models (e.g., Bio_ClinicalBERT)

Step 4: Signal Detection and Analysis and Manual Signal Verification

Analyze rates of safety signal events and associated features:

- Apply machine learning-based anomaly detection algorithm to identify patterns in signal incidence
- Integrate human-in-the-loop review of signals for validation
- Transmit report to FDA of aggregated signal findings

various sources, which are then ingested for analysis. The analysis employ thematic categorization of sentiment, tracked over a specific period, for specific generic drugs. The goal is to **highlight quality signals that emerge before generic drugs are recalled**.



Regulatory Significance and Impact on Industry and Patients

Deloitte.

Our approach to quality signal detection for generic drugs supports GDUFA research priority **#8 Expand the Use of Artificial Intelligence (AI) and Machine Learning (ML) Tools**

Our approach would specifically support the GDUFA priority to **integrate AI/ML tools with FDA information and data to support quantitative analyses and modeling approaches that facilitate regulatory assessments** and to identify strategies to optimize the reliability of outcomes produced by these tools.

Regulatory Impact

This approach addresses an existing gap in regulatory science by **enabling proactive analysis of generic drug quality data from multimodal and nontraditional sources**. The approach would enhance FDA's surveillance capabilities by:

- Deploying AI on multimodal postmarket data
- Integrating public data with partner and regulatory data
- Leveraging technology to test and enable improved generic drug quality monitoring

Industry and Patient Impact

This approach could also **empower industry and advance patient safety** by:

- Enabling generic drug manufacturers to proactively address emerging generic drug quality signals with a feedback loop mechanism
- Advance patient safety by identifying potential quality concerns proactively and in near real time

Deloitte.

THANK YOU

QUESTIONS ?

Deloitte.

APPENDIX

Meet the Team

Deloitte.

Chris Comrack, MBA

Managing Director

Deep experience leading complex cross functional, multi-stakeholder public-health-oriented project teams; 12+ years serving in Program and Project Management leadership roles on projects at FDA

Ashwin Admala

Managing Director

20+ years experience in AI and Data Engineering solutions with expertise in leading business intelligence project implementations at FDA

Matt Crowson, MD

Specialist Leader

Surgeon and clinical informatician with expertise in applied machine learning and analytics; led academic medical teams on data science projects across all care contexts

Anil Bhatta, PhD

Manager

Leads multi-stakeholder engagement with FDA in using clinical evidence from disparate data sources to help inform regulatory decisions; expertise in the development of ML/NLP tools

Sandy Polu, PhD

Specialist Master

15+ years experience across public-private partnerships, public health data modernization, product strategy, and strategic initiatives, including at FDA

Bipendra Basnyat, PhD

Specialist Master

15+ years of experience as a data scientist, architect, and software engineer, PhD. in Artificial Intelligence and Machine Learning

Deloitte.

Leveraging AI to Expedite Generic Drug Regulatory Review

Anthony Cristillo, PhD, MS

May 20, 2024

01

ANDA Regulatory Review

Leveraging Gen AI (LLMs/RAG) for Expedited & More Efficient Abbreviated New Drug Application (ANDA) Regulatory Review

AI-Informed Routing

Drug Complexity- driven Routing

03

Higher Quality Submissions

Providing Industry leverage AI/ML/NLP tools to develop higher quality Abbreviated New Drug Application (ANDA) Submission

ANDA Regulatory Review: Challenges & Solutions

Challenges	Solutions
Manual review of a large body of literature including Phase IV surveillance data and RWE/RWD of Referenced Listed Drug (RLD) is time consuming and not always complete Detailed regulatory review of the ANDA to assess for gaps and missing information is time consuming and could delay the review process	• Leveraging Large Language Models (LLMs)/Retrieval Augmented Generation (RAG) for expedited & more efficient review of the literature, phase IV surveillance data, RWE/RWD and gaps within ANDA submission
Manual routing of the application to the appropriate FDA Reviewers can be time consuming, and delay the review process Manual compliance checks of ANDA (prior to submission) may not identify all errors/omissions, thereby creating delays in the process	• Leveraging Artificial Intelligence/Machine Learning /Natural Language Processing for drug-complexity driven routing of ANDA to appropriate review and to help drug companies develop higher quality ANDA submissions

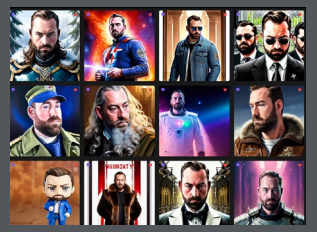
What is AI, ML and NLP?

Artificial Intelligence (AI)

The ability for computers to **imitate cognitive human functions** such as learning and problem-solving.

Through AI, a computer system **uses math and logic** to simulate the reasoning that people use to learn from new information and make decisions.

Generative AI



Generative AI refers to AI that can generate new content, such as text, images, or music, similar in style or content to a given input

Machine Learning (ML)

Subset of AI; when we teach computers to extract patterns from collected data and apply them to new tasks that they may not have completed before.

Natural Language Processing (NLP)

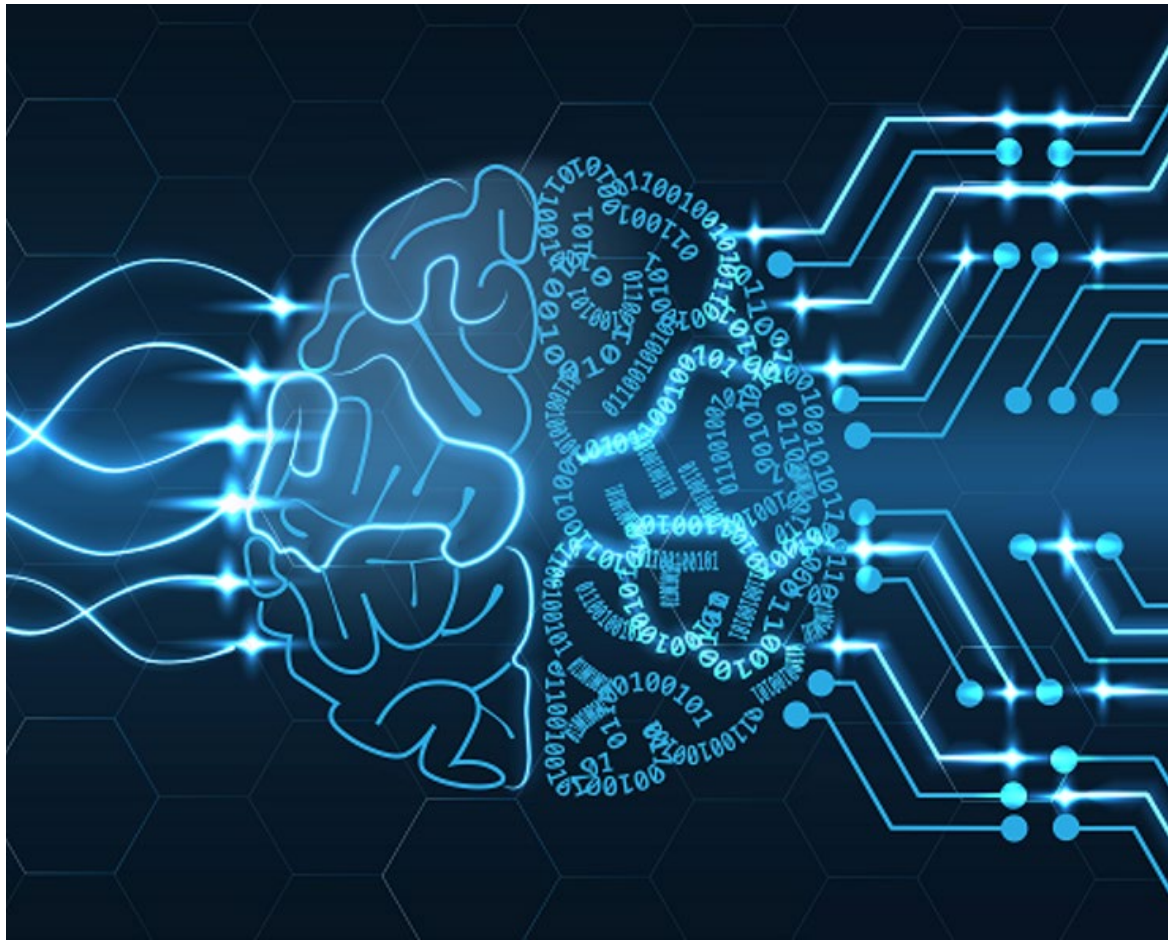
A machine learning technology primarily concerned with giving computers the ability to interpret, manipulate, and comprehend human language.

Foundation Models (FMs), Large Language Models (LLMs) & Retrieval Augmented Generation (RAG)

- Generative AI is powered by very large machine learning models (**Foundation Models - FMs**) pre-trained on vast amounts of data to understand existing content and generate original content.
- **Large language models (LLMs**) are a subset of FMs trained on trillions of words across natural language tasks
- **Pre-training LLMs**: training a model on a large corpus of text (e.g., billions of words); helps the model to learn the structure of the language, grammar, facts etc.

E.g., ChatGPT, Perplexity, BingChat

- **Fine-Tuning LLMs**: taking a pre-trained model and further training at least one internal model parameter (for a specific context/case) thereby transforming a general-purpose base model into a specialized model for a particular use
- **Retrieval-Augmented Generation (RAG):** the process of optimizing the output of a large language model, so it references an authoritative knowledge base outside of its training data sources before generating a response.

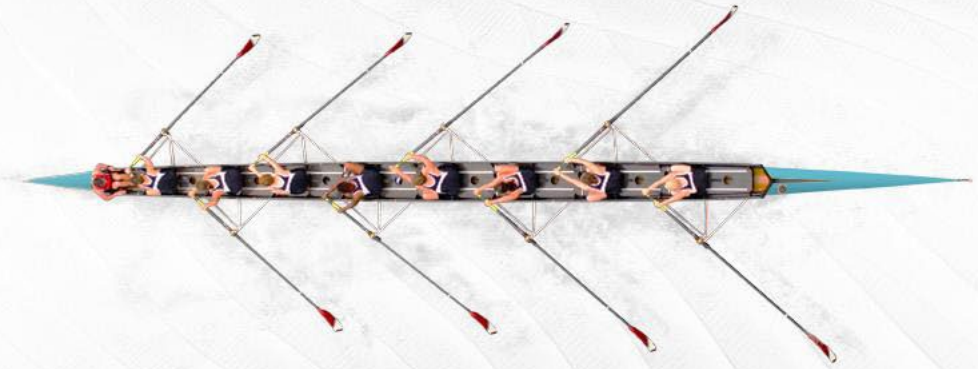


ANDA Regulatory Review: Need for More Research

Challenges	Solutions	Further Research Needed
Manual review of a large body of literature including Phase IV surveillance data and RWE/RWD of Referenced Listed Drug (RLD) is time consuming and not always complete Detailed regulatory review of the ANDA to assess for gaps and missing information is time consuming and could delay the review process	• Leveraging Large Language Models (LLMs)/Retrieval Augmented Generation (RAG) for expedited & more efficient review of the literature, phase IV surveillance data, RWE/RWD and gaps within ANDA submission	• To identify most ideal LLMs in this context • To identify most appropriate data sources for RAG • To understand and avoid hallucinations • To define the level of QC/Validation needed • To clearly define governance required
Manual routing of the application to the appropriate FDA Reviewers can be time consuming, and delay the review process Manual compliance checks of ANDA (prior to submission) may not identify all errors/omissions, thereby creating delays in the process	• Leveraging Artificial Intelligence/Machine Learning /Natural Language Processing for drug-complexity driven routing of ANDA to appropriate reviewer and to help drug manufacturers develop higher quality ANDA submissions	

Your Guide

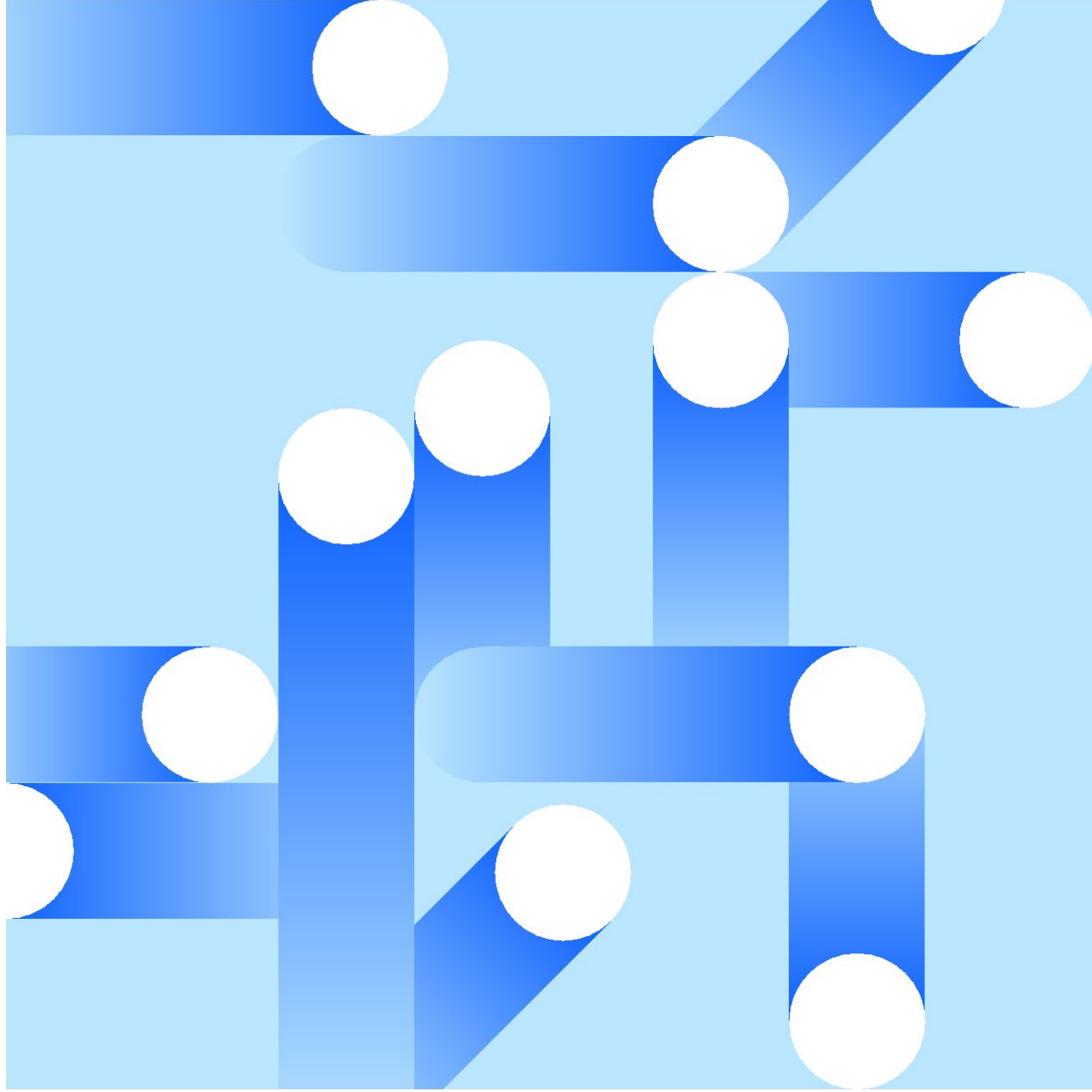
Dr. Anthony Cristillo
Partner, Digital Health
anthony.cristillo@guidehouse.com



Guidehouse
Outwit *Complexity*

GDUFA 2024 Public Workshop | *Harnessing GenAI to Enhance the Generic Drug Review Process*

Sarah Ferko, IBM Consulting
Ally Lu, IBM Consulting



GDUFA Science and Research Priority Initiatives for FY 2024

The focus area of today's presentation is initiative #8: *Expand the Use of Artificial Intelligence (AI) and Machine Learning (ML) Tools*

Source: Draft FY24 GDUFA Science and Research Priorities (fda.gov)

Introduction

IBM @ FDA

- International Business Machines (IBM) Corporation is an industry pioneer in artificial intelligence (AI), quantum computing, and large-scale modernizations, leveraging data and innovative technology to pave the way for government agencies.

- With the resources of a large company, IBM has been solving FDA's most pressing problems using cutting edge AI & data technologies and hybrid cloud solutions, underpinned by our public health and regulatory review expertise.
  - Project teams are working toward the goal of better enabling FDA for informed, data-driven regulatory decision making, supporting pre-market application review as well as post-market adverse event surveillance.

- At FDA, IBM has been providing expertise across multiple concurrent task orders for over 15 years. We are currently serving the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Tobacco Products (CTP), and the Office of Digital Transformation (ODT).

Goal: Expand the use of GenAI within OGD to support the ANDA review process

Generative AI (GenAI) is a type of AI that can generate new, original content such as text, images, music, and videos. GenAI applications offer a versatile range of functionalities, including:

- Summarization
- Semantic Search with Question-and-Answer capability
- Content Creation
- Code Creation and Conversion

Within OGD, GenAI can be used to support modernization efforts of the generic drug review process by improving the efficiency of the review of both structured and unstructured data submitted within an ANDA.

Benefits to OGD

Summarization

GenAI can be used to extract, summarize, and compare data. More specifically, within OGD:

- A GenAI application can be used to effectively extract and summarize data from unstructured PDFs.
  - Together, structured and unstructured data can be summarized to create an application-level report for the ANDA submission.

- This idea can be expanded such that data can be extracted and summarized from both ANDA and NDA data (e.g., the NME) to create a comparison report using a standardized template designed by OGD.
  - A comparison report supports the review and more effectively compare selected attributes between the two submissions.

Semantic Search with Question-and-Answer Capability

GenAI can be used to support critical tasks performed during the review of an ANDA submission, including:

- **Enhanced search capabilities and information retrieval**: GenAI can be used to more efficiently search for results across datasets and documentation submitted as part of the ANDA based on queries/questions inputted by the user/reviewer.
  - By ingesting the large corpus of data that comprises an ANDA submission, which can span multiple sequence folders within the EDR, the application can quickly parse through information and provide the user with the desired result(s), along with source information to document where the result was extracted to support traceability.

Content Creation

GenAI can be used to support critical tasks performed during the review of an ANDA submission, including:

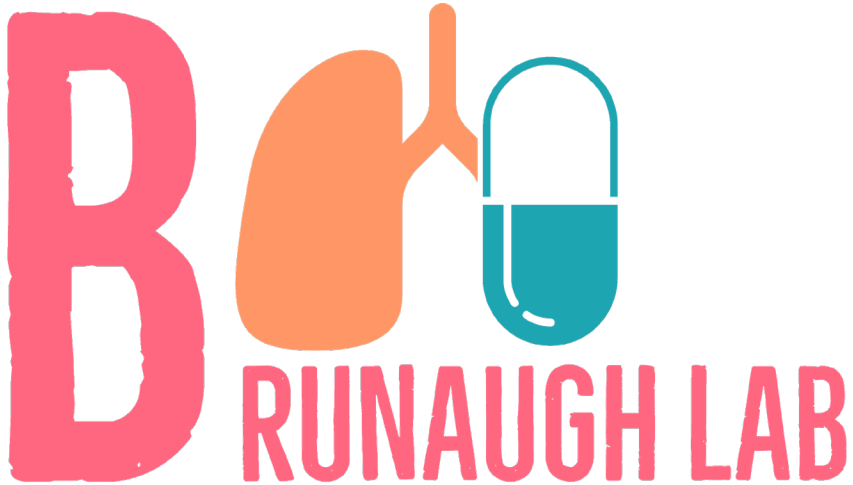
- **Drafting IR language**: GenAI can be used to draft language for Information Requests (IRs) that are sent to sponsors as needed during an ANDA review, ultimately reducing the average time needed to create and send IR information.
  - LLMs can use previously submitted IRs as the source to generate suggested text.

Code Creation & Conversion

GenAI can be used to enhance developer productivity for system development, enhancement, and maintenance by:

- Automating the process of generating code snippets or even entire programs based on requirements or patterns; [107]
- Analyzing existing code and suggesting optimizations to improve performance and readability;
- Identifying potential bugs or vulnerabilities in code and suggesting fixes or improvements; and
- Assisting in refactoring existing codebases to improve code quality, maintainability, and scalability.

Questions?



Development of models to understand and predict the impact of airway mucus on inhaled drug bioavailability

Ashlee Brunaugh, PharmD, PhD
Assistant Professor of Pharmaceutical Sciences,
University of Michigan
FDA GDUFA Public Workshop

The first generic dry powder inhalers (DPI) have entered the US market

Proprietary product	Approval year	API(s)	Generic product	Generic manufacturer	Generic approval year
Advair Diskus	2000	Fluticasone propionate and salmeterol	Wixela Inhub	Mylan	2019
Spiriva Handihaler	2004	Tiotropium bromide	LupinHaler	Lupin	2023

However, generic DPI development remains risky, high-cost endeavor

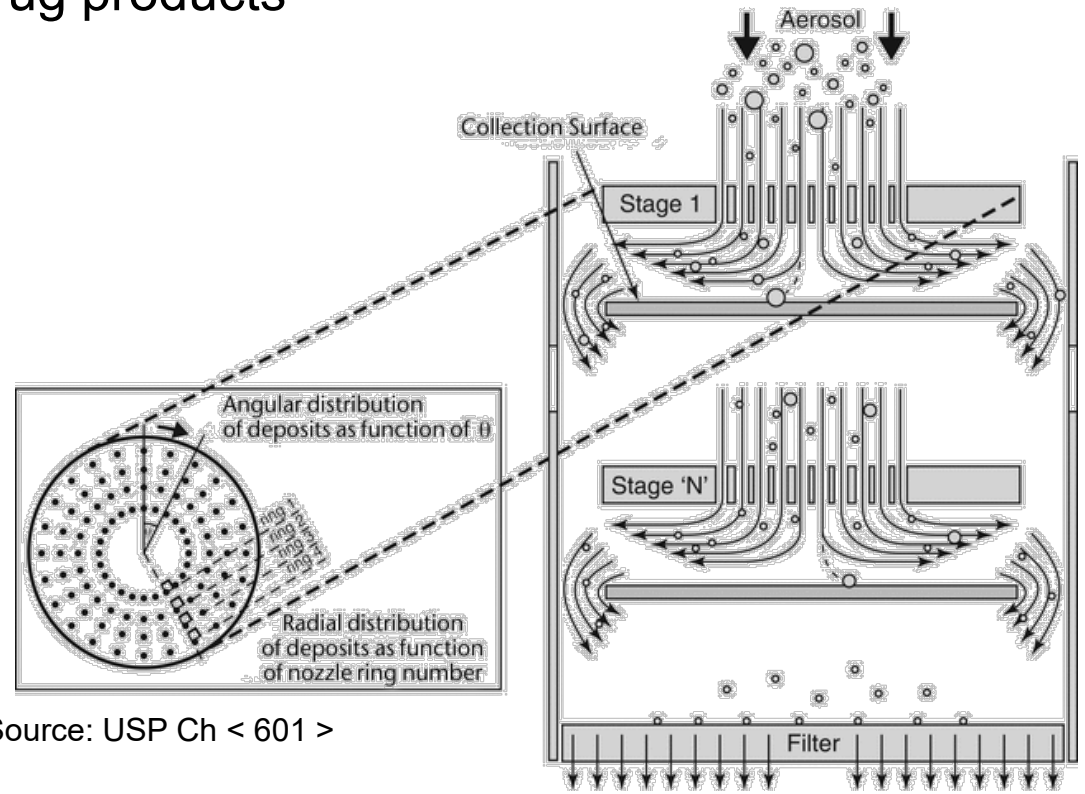

PHARMA

A $442M failure: After years of work and an FDA rejection, Novartis calls it quits on Advair copy

By Eric Sagonowsky · Jan 29, 2020 11:38am

In vitro methods for DPI performance testing lack key information related to bioavailability

Cascade impaction: Current *in vitro* gold standard for assessment of orally inhaled drug products

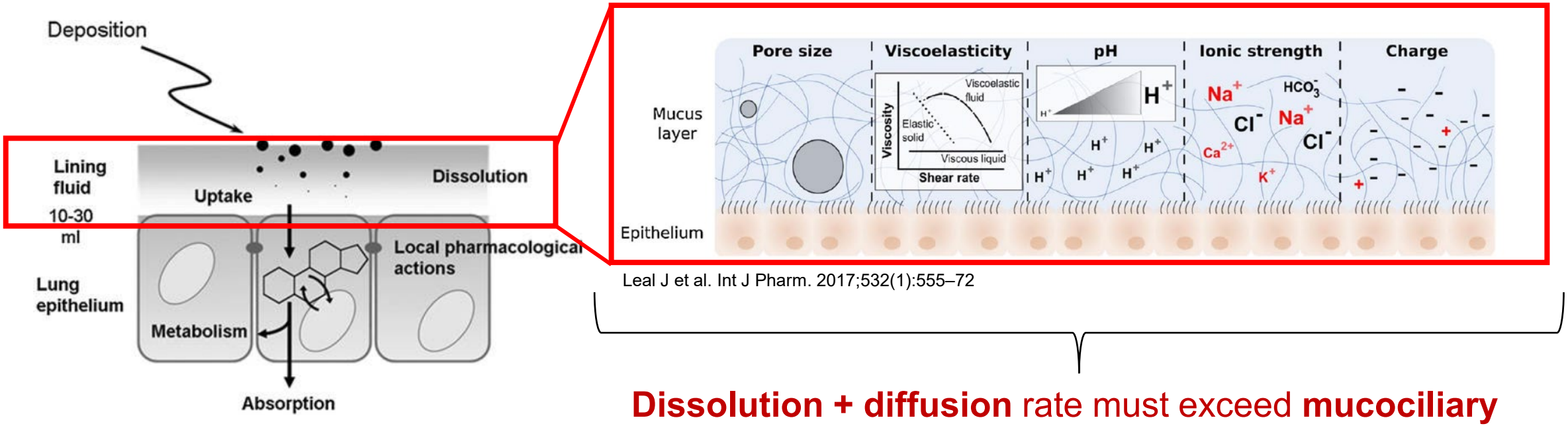


Source: USP Ch < 601 >

Output: Aerodynamic particle size distribution → insight into potential location of lung deposition

Provides no information about post-deposition particle behavior!

Prediction of inhaled drug bioavailability requires understanding post-deposition phenomenon



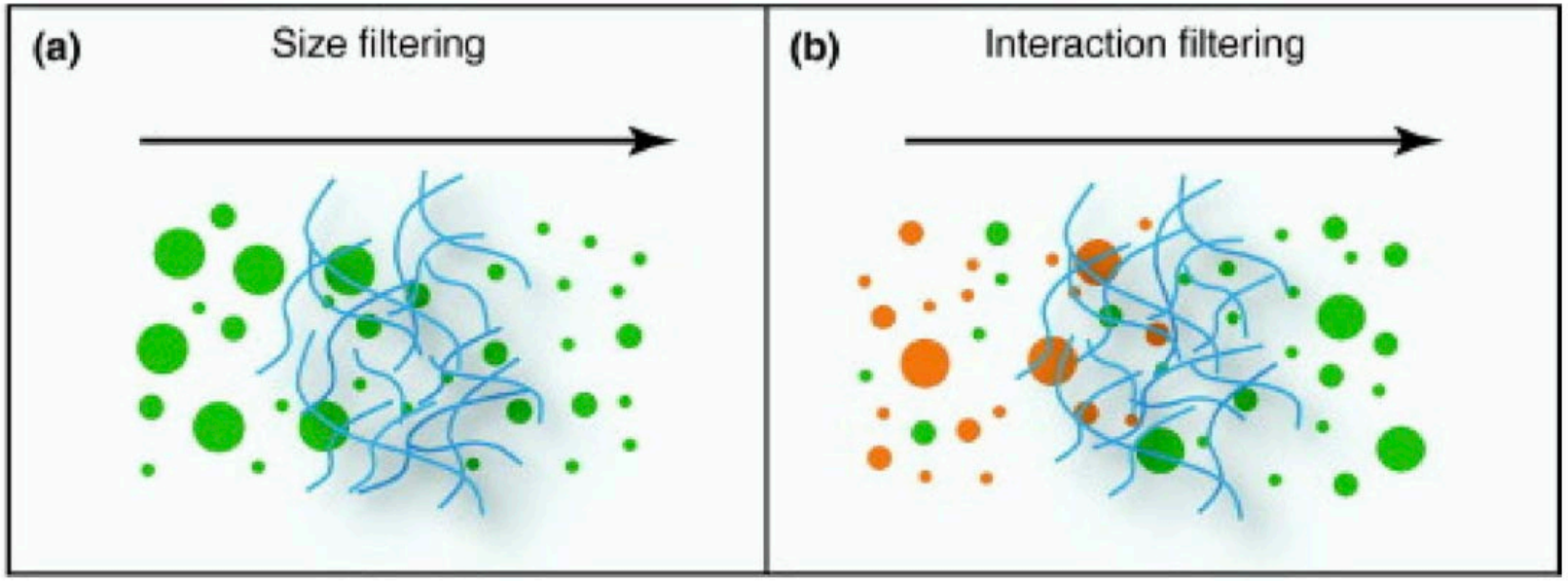
Patton JS et al. J. Aerosol. Med. Pulm. 2010;23(S2):S-71-S-87.

Leal J et al. Int J Pharm. 2017;532(1):555–72

Dissolution + diffusion rate must exceed **mucociliary clearance rate** for inhaled drug to reach target in conducting airway epithelium

Interaction of inhaled particles with lung lining fluid is impacted by product attributes (e.g., particle rugosity, hydrophobicity, surface energy), but no standardized fluid exists to assess these interactions

Mucus-drug interactions are a rate limiting step in inhaled drug bioavailability

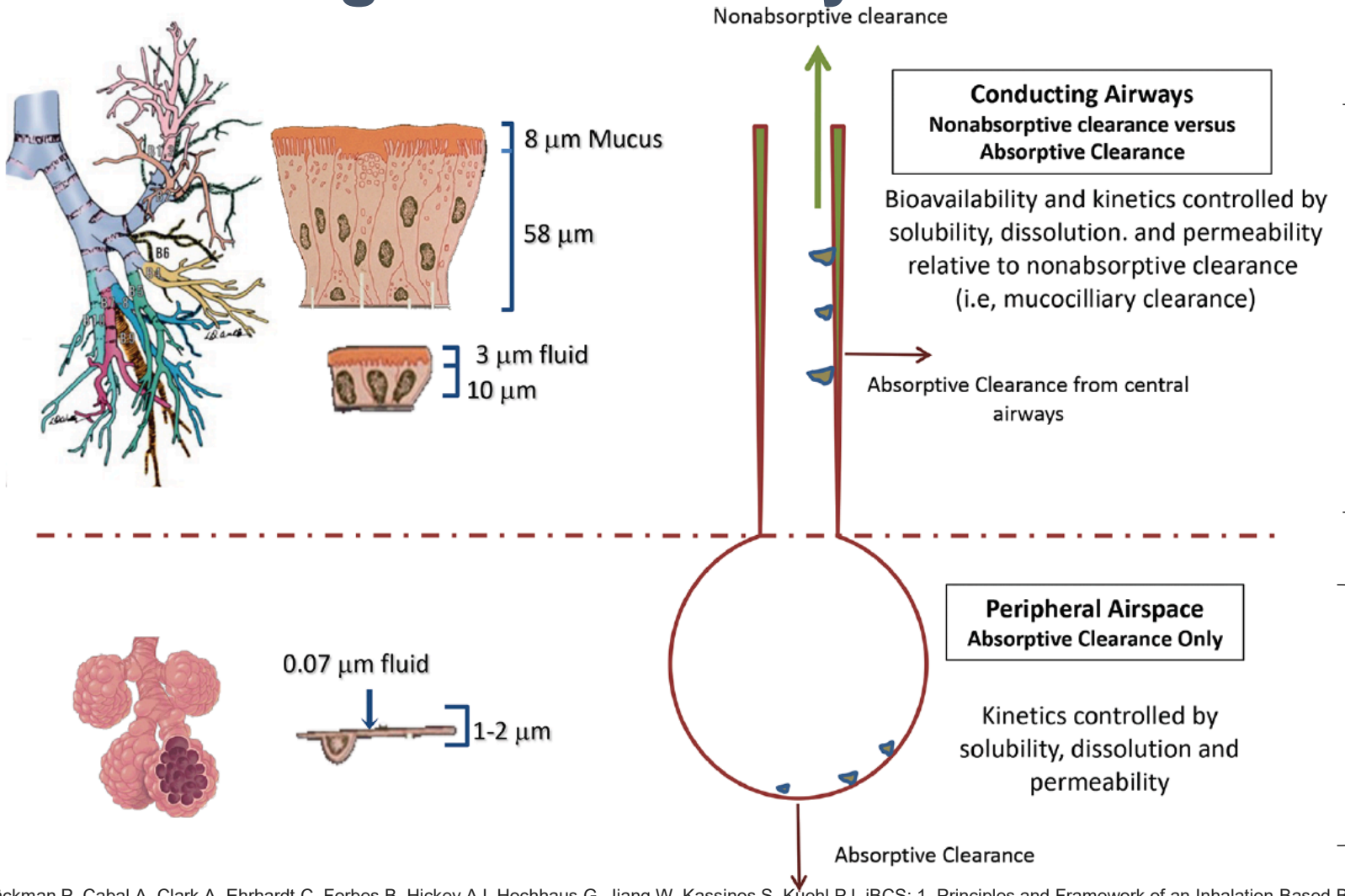


$$J = \frac{\boldsymbol{D}A(C_1 - C_2)}{\boldsymbol{h}}$$

Varies as function of anatomical location and disease

Porous, mesh-like structure – 100nm – several μm + Hydrophobic and charge-based interactions (pH 6.5-7.9) = ↓ $\boldsymbol{D}$

Mucus-drug interactions are a rate limiting step in inhaled drug bioavailability



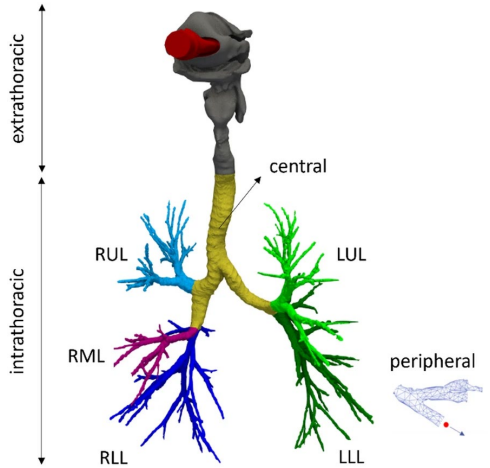
- Larger particles (slower dissolution)
- Mucus gel barrier (hindered diffusion)
- Mucociliary clearance

- Rapid dissolution (extensive blood flow, smaller particles, no mucus)

Hastedt JE, Bäckman P, Cabal A, Clark A, Ehrhardt C, Forbes B, Hickey AJ, Hochhaus G, Jiang W, Kassinos S, Kuehl PJ. iBCS: 1. Principles and Framework of an Inhalation-Based Biopharmaceutics Classification System. Molecular Pharmaceutics. 2022 May 16.

What exists:

In vitro cascade impaction



CFD

Regional deposition data in lungs

How this could be enhanced:

- Reverse engineering of healthy and diseased mucus to identify key components impacting free drug concentrations → **creation of validated artificial mucus models**
  - **Understand age, sex, environmental influence on airway mucus composition** (e.g. MUC5B:5AC)
- Elucidate relationship between particle surface properties and wetting / immersion → **critical quality attribute** for DPIs / **Q3 sameness**

Desired outcomes:

- Personalized dose and OIDP selection
- Reduced risk during preclinical – clinical transition
- Improved efficiency of OIDP generic development

Sadafi, H., Monshi Tousi, N., De Backer, W. *et al.* Validation of computational fluid dynamics models for airway deposition with SPECT data of the same population. *Sci Rep* **14**, 5492 (2024)

Questions?

Brunaugh@umich.edu

Developing an Easy-to-Use AI-Based Computational Dosimetry Prediction Model (ABCDPM) for Pharmaceutical Development and Device Testing

Jinxiang Xi, Ph.D.
Associate Professor, Department of Biomedical Engineering
University of Massachusetts, Lowell, MA

AI-Based Computational Dosimetry Prediction Model (ABCDPM)

➢ **Workflow: Inputs → ABCDPM → Outputs**

ABCDPM

CT/MRI images

Image Segmentation

Advanced Processing: SSM, Adjoint

Morphological Analysis

Navier-Stokes Eq. Solver

$$\rho g_x - \frac{\partial p}{\partial x} + \mu\left(\frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + \frac{\partial^2 u}{\partial z^2}\right) = \rho \frac{Du}{Dt}$$

$$\rho g_y - \frac{\partial p}{\partial y} + \mu\left(\frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + \frac{\partial^2 v}{\partial z^2}\right) = \rho \frac{Dv}{Dt}$$

$$\rho g_z - \frac{\partial p}{\partial z} + \mu\left(\frac{\partial^2 w}{\partial x^2} + \frac{\partial^2 w}{\partial y^2} + \frac{\partial^2 w}{\partial z^2}\right) = \rho \frac{Dw}{Dt}$$

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{V}) = 0$$

Computational mesh

Material Properties

Boundary Conditions

Hollow Cast

Airflow: P, V, T, k

Aerosols PBPK

Dosimetry: Total Regional

Velocity-informatics Analysis

Particle-informatics Analysis

Uncertainty Quantification

Drug delivery Inhalation Dosimetry

Bioequivalence Risk Assessment

User Inputs:

- Target Population
- Device Formulation
- Delivery Protocol

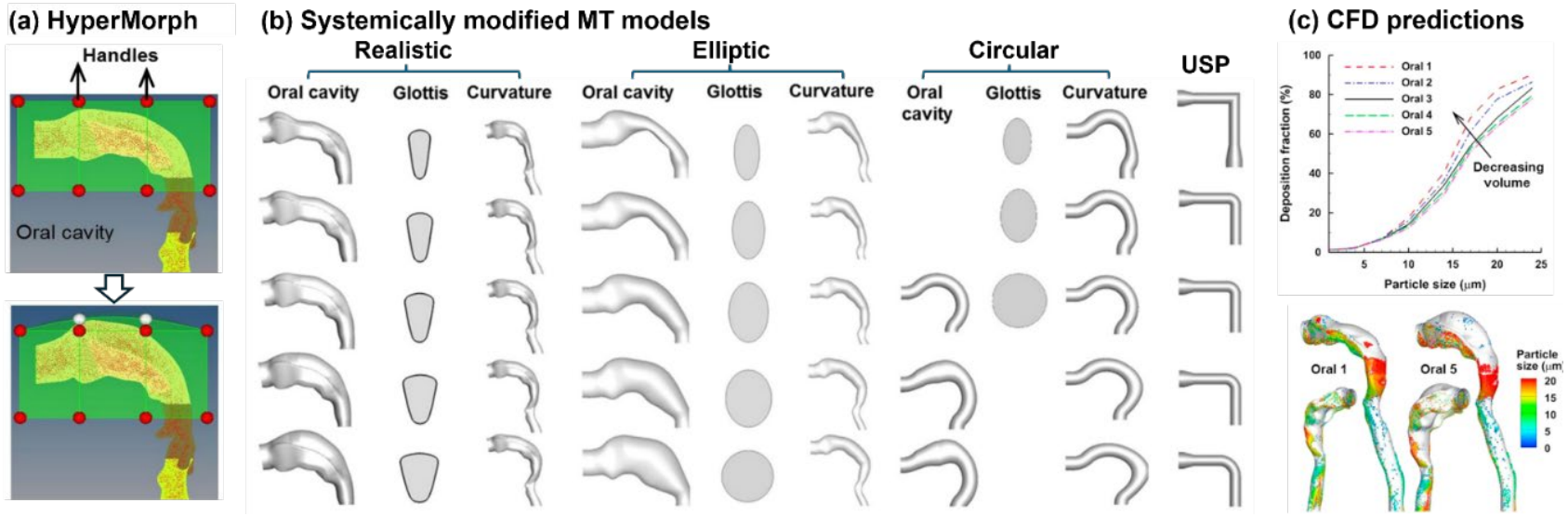
User Outputs:

- BE
- Dose
- Variability

AI-Based Computational Dosimetry Prediction Model (ABCDPM)

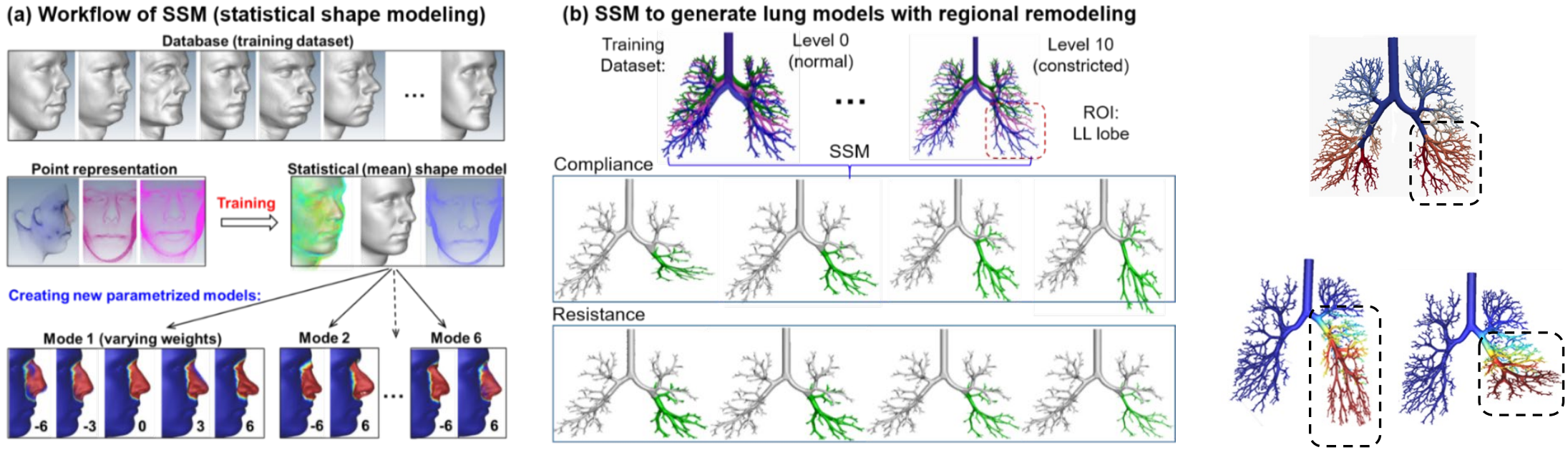
➢ Generating airway models using HyperMorph and Statistical Shape Modeling (SSM)

HyperMorph:



J. Xi, J.E. Yuan, M. Yang, X. Si, Y. Zhou, Y.S. Cheng, "Parametric study on mouth–throat geometrical factors on deposition of orally inhaled aerosols," J. Aerosol Sci, 99:94-106, 2016

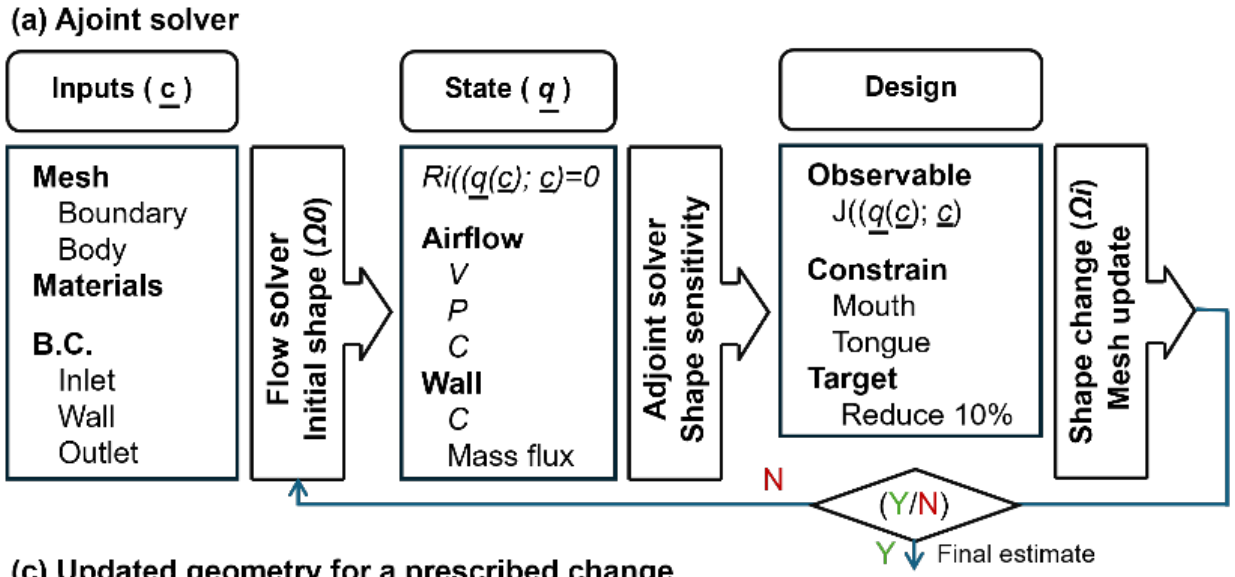
SSM:

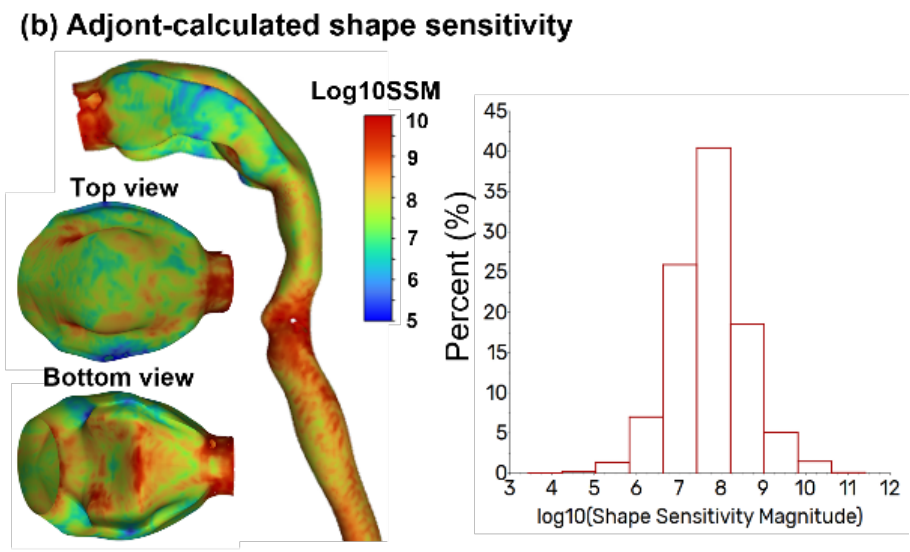


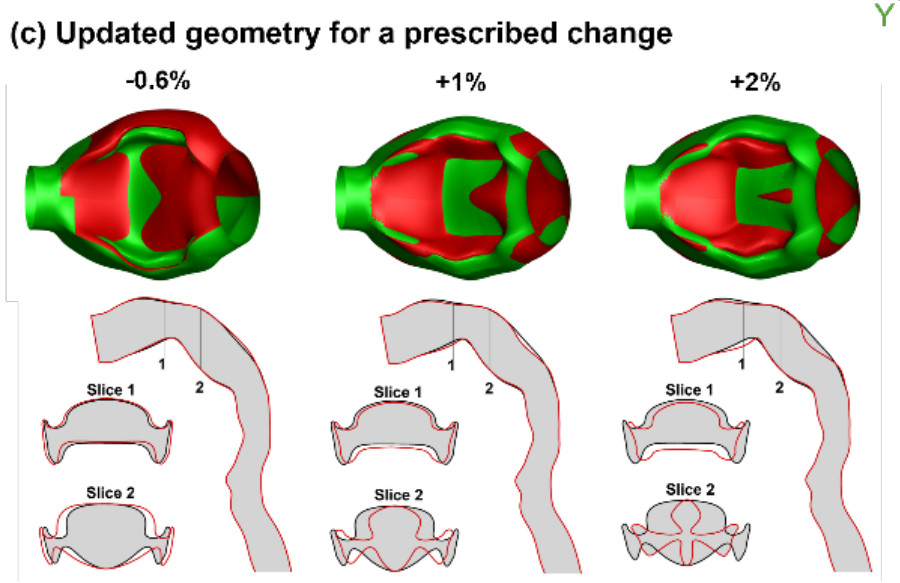
J Xi, M Talaat, XA Si, S Chandra, "The application of statistical shape modeling for lung morphology in aerosol inhalation dosimetry", J. Aerosol Sci.151, 105623, 2021

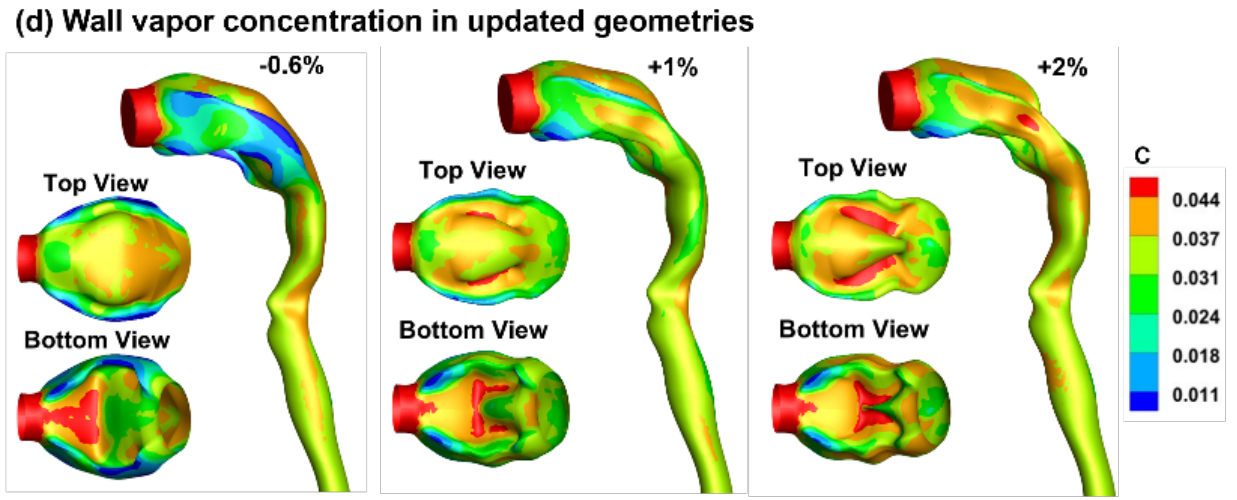
AI-Based Computational Dosimetry Prediction Model (ABCDPM)

➢ Shape Sensitivity Analysis using Adjoint Solver







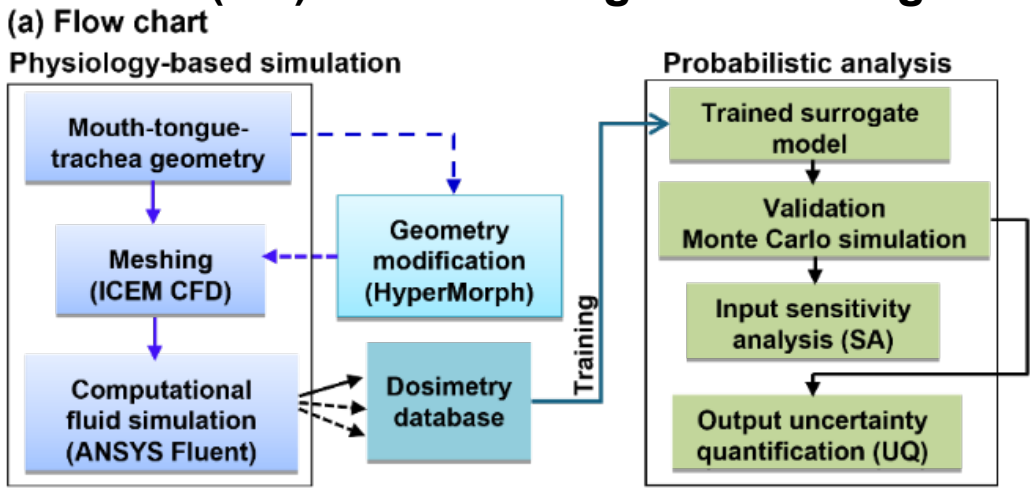


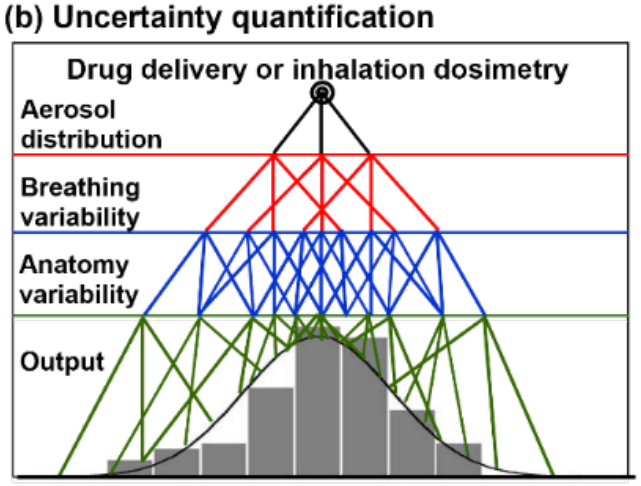
M. Talaat, X. Si, **J. Xi**, Adjoint Solver-Based Analysis of Mouth–Tongue Morphologies on Vapor Deposition in the Upper Airway, Fluids,9(5), 104, 2024

AI-Based Computational Dosimetry Prediction Model (ABCDPM)

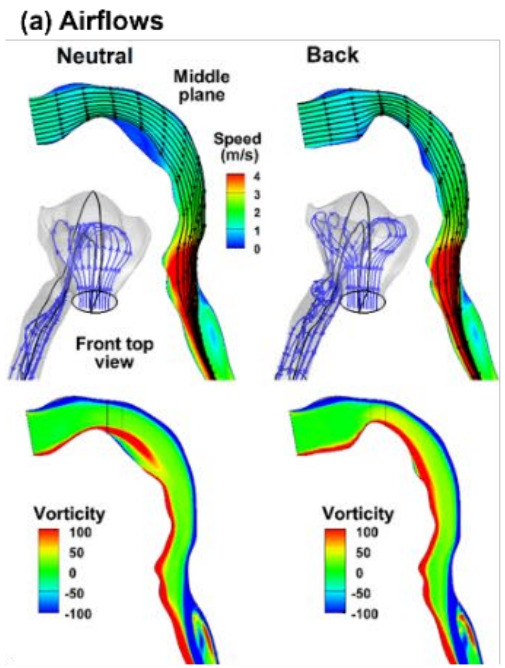
➢ Gaussian Process (GP) based Surrogate Modeling

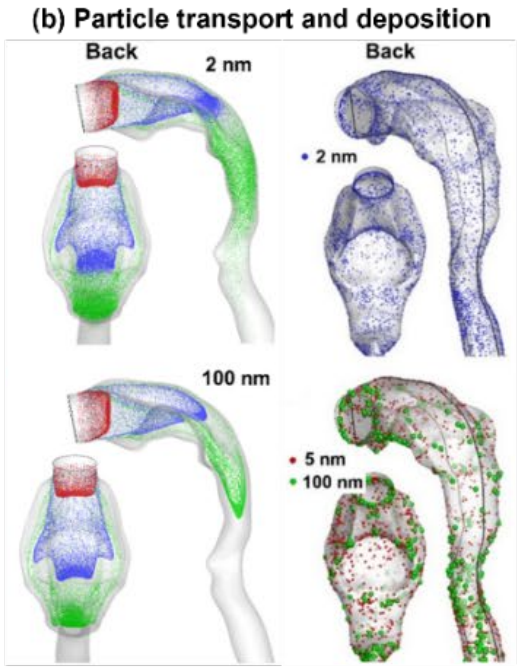
Method:

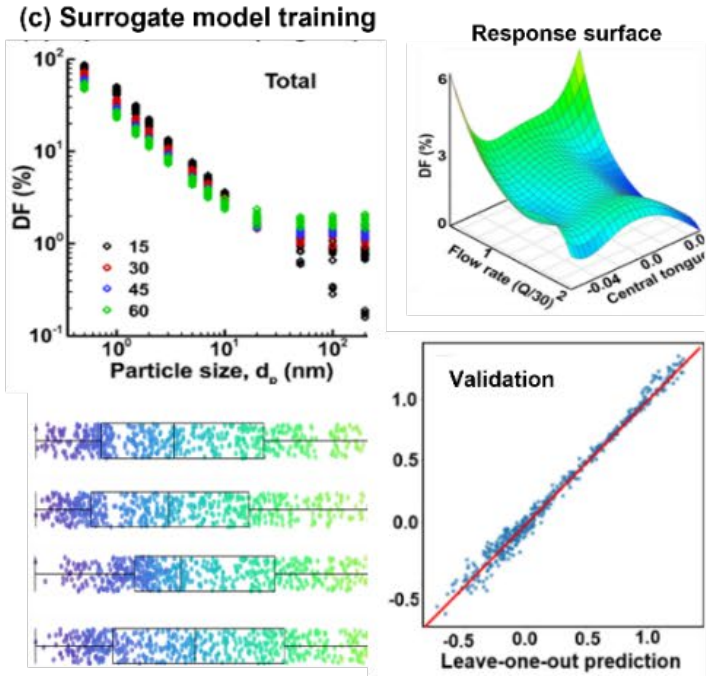


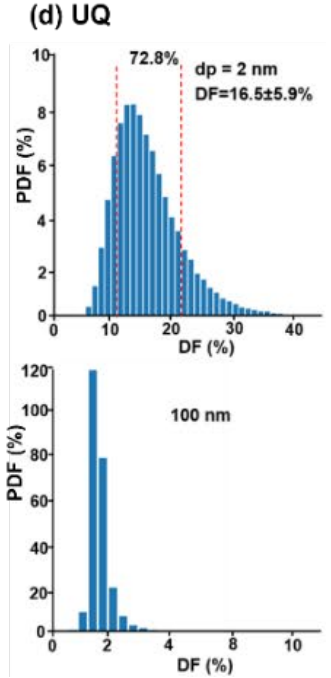


Example:





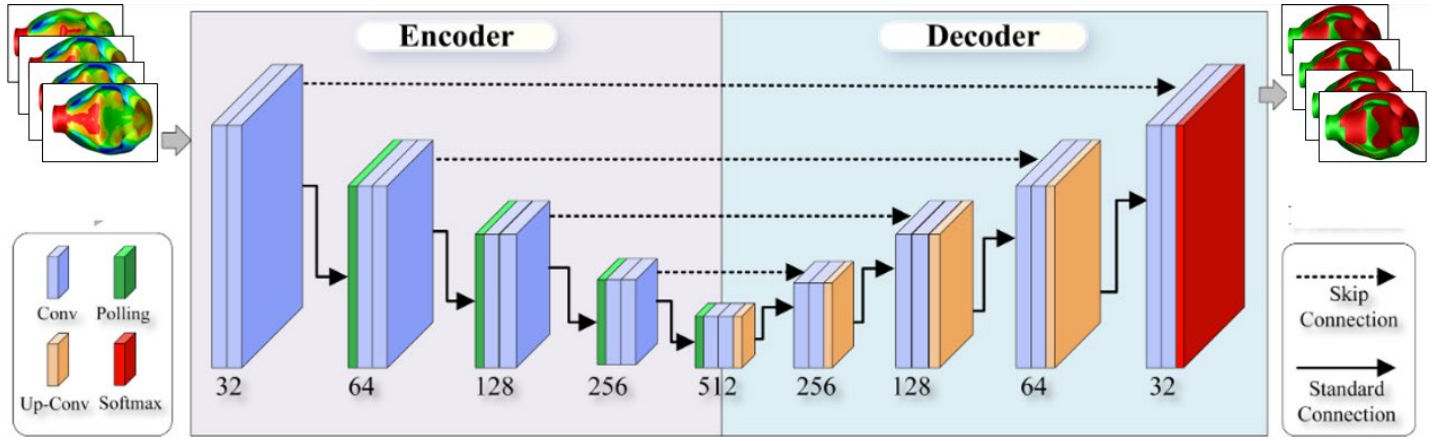




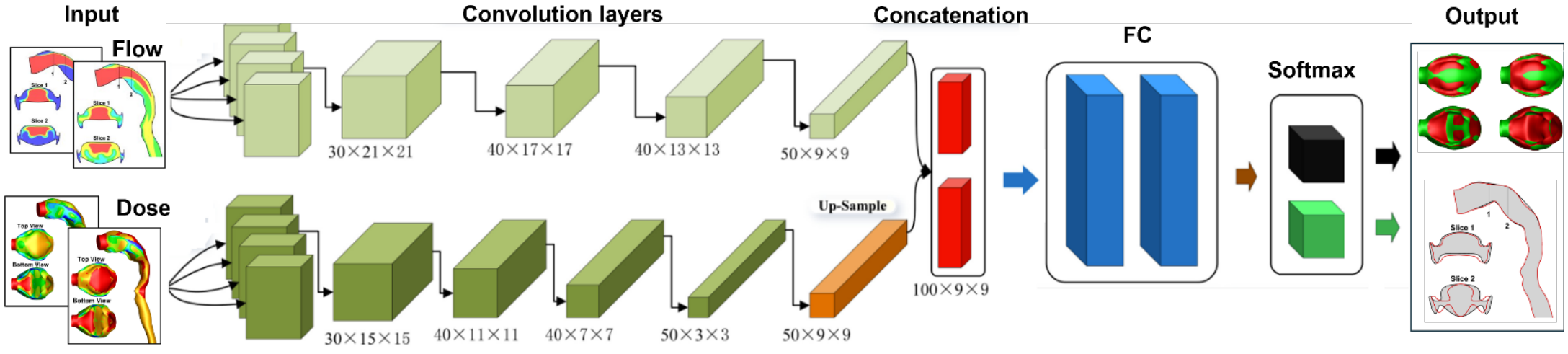
T. Yang, X. Si, **J. Xi**, Sensitivity analysis and uncertainty quantification of nanoparticle deposition from tongue morphological variations, Life,14(3), 406, 2024

AI-Based Computational Dosimetry Prediction Model (ABCDPM)

- **Machine learning of Velocity Informatics (VI) and Particle Informatics (PI) using MIScnn**



- **DeepMedic architecture to train correlating Inputs and Outputs**



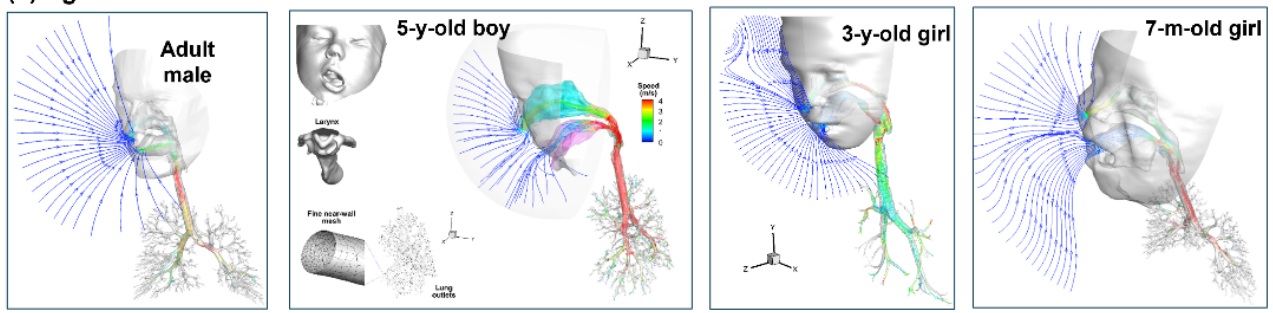
[1]. A Almeldein, **N VanDam**, "Accelerating chemical kinetics calculations with physics Informed neural networks," *J. Eng. Gas Turbines Power,145(9): 091008*, 2023.
[2]. A SubLaban, T Kessler, **N VanDam,** JH Mack, "Artificial neural network models for octane number and octane sensitivity: A quantitative structure property relationship approach to fuel design," Journal of Energy Resources Technology, 145, 102302, 2023.
[3] M. Talaat, .. **J. Xi**, "Convolutional neural network classification of exhaled aerosol images for diagnosis of obstructive respiratory diseases," J. Nanotheranostics, 4(3): 228-247, 2023.
[4]. M. Talaat, X Si, **J. Xi**, "Simulated exhaled aerosol images from normal and diseased lungs for convolutional neural network Training/Testing," Data, 8(8): 126, 2023.
[5]. M Talaat, X Si, **J Xi**, "Breathe out the secret of the lung: Video classification of exhaled flows from normal and asthmatic lung models", Journal of Respiration 3 (4), 237-257, 2023

AI-Based Computational Dosimetry Prediction Model (ABCDPM)

➢ Airway Models and Experimental Facility to Develop High-fidelity Dosimetry Database

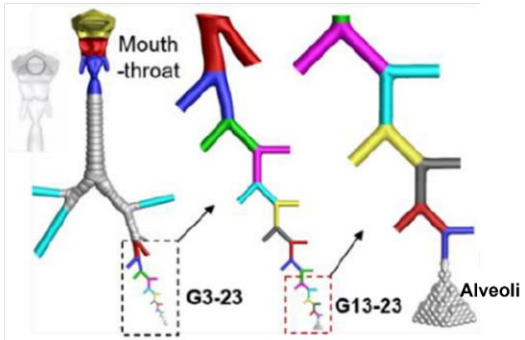
A. Age effects

(a) Age effect

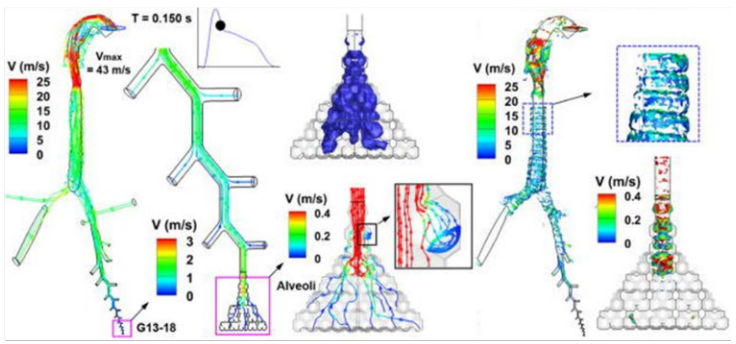


B. Lung and Alveoli

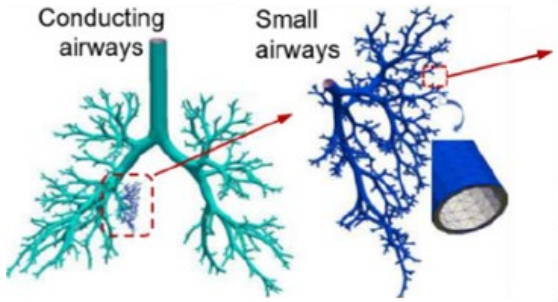
(a) Single-path whole lung model



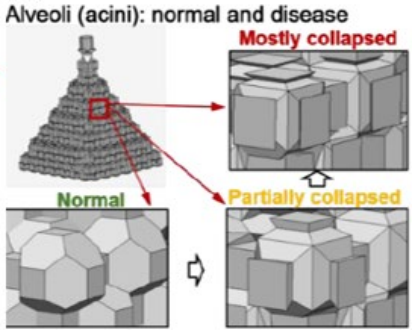
(b) CFD-predicted exhaled droplets



(a) Multi-scale airway models

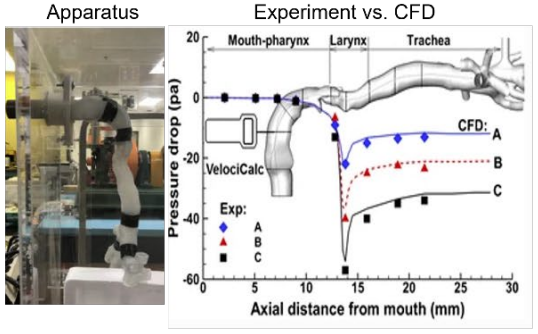


(b) Acinus

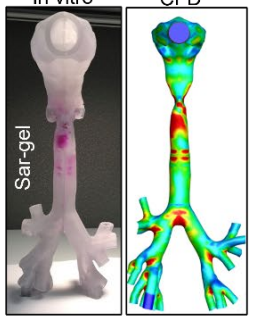


C. Experimental setup

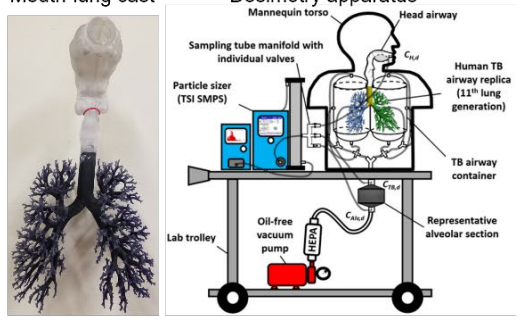
(a) Pressure



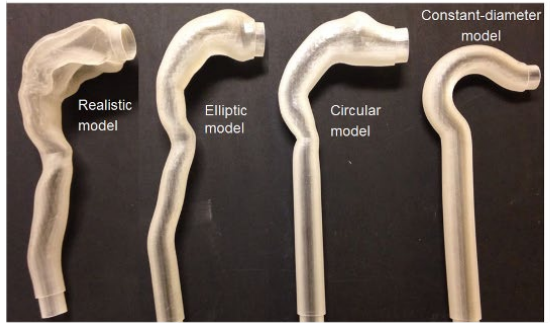
(b) Distribution



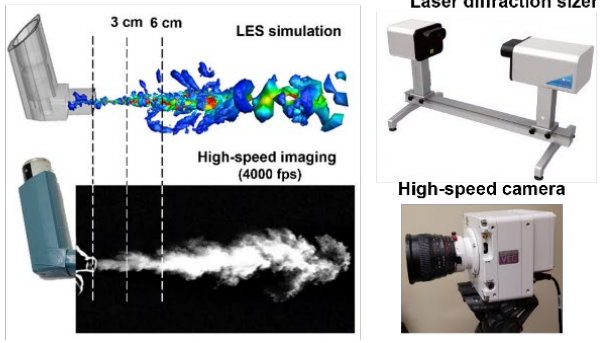
(c) Total and regional dosimetry



(d) Airway casts with detailed dimensions



(e) Visualization and quantification

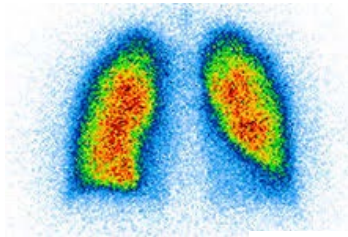


[1] .X. Si, **J. Xi**, "Deciphering exhaled aerosol fingerprints for early diagnosis and personalized therapeutics ", J. Nanotheranostics 2 (3), 94-117, 2021.

[2]. X. Si, M Talaat, **J Xi**, " SARS COV-2 virus-laden droplets coughed from deep lungs: Numerical quantification in a single-path whole respiratory tract geometry", Phys Fluids 33, 023306, 2021

AI-Based Computational Dosimetry Prediction Model (ABCDPM)

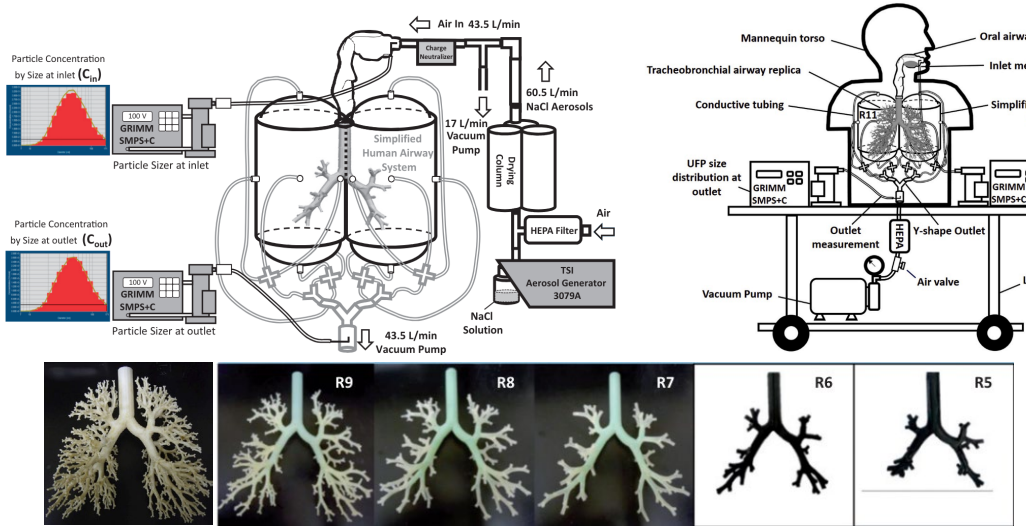
➢ Data-Driven High-Fidelity In Vitro-In Silicon Inhalation Dosimetry Model with Interpretability



➢ **In Vivo data**:
Low spatiotemporal resolution + Noise + Ethic issues

➢ **In Vitro data**:
Low spatiotemporal resolution + Noise + Labor Intensive

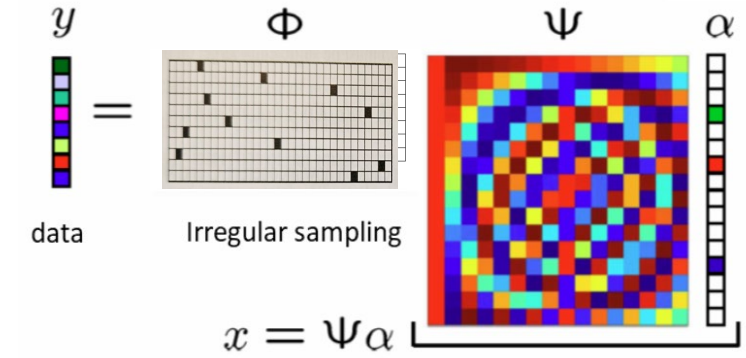
➢ **In Silicon data**:
High-resolution
Uncertainty in parameters (B.C.)



➢ **Further actions:**
Discovering hidden low-dimensionality in data
→ Data-driven modeling → Improve prediction fidelity

❖ **Machine-Learning Reduced-Order Models (ML-ROM)**

❖ **Compressed Sensing:** $y = \Phi x = \Phi \Psi \alpha$



[1]. S. Brunton, N. Kutz, "Data-Driven Science and Engineering" Cambridge, 2nd Ed. 2020
[2]. WC Su, Y Chen, **J Xi**, "Estimation of the deposition of ultrafine 3D printing particles in human tracheobronchial airways", J. Aerosol Sci., 149, 105605

Thank you!

Computational methods to evaluate the bioequivalence of generic metered dose inhalers

Guilherme Garcia

1. Joint Department of Biomedical Engineering, Marquette University and Medical College of Wisconsin
2. Department of Otolaryngology and Communication Sciences, Medical College of Wisconsin

JOINT DEPARTMENT OF BIOMEDICAL ENGINEERING | MARQUETTE UNIVERSITY | MEDICAL COLLEGE OF WISCONSIN

GDUFA Public Workshop

May 20, 2024

Motivation

- Few generic metered dose inhalers (MDIs) have received FDA approval.

- New-generation MDIs using environmentally friendly “green” propellants are under development.

- In the FDA’s “weight of evidence” approach, computational models can be used as evidence to demonstrate the bioequivalence of a candidate generic MDI to a reference product.

- However, gold standard computational methods to evaluate the bioequivalence of MDIs have not been established yet, especially in the context of green propellants.

Research Areas in FY24 GDUFA Science and Research Priorities

Item 5.C.

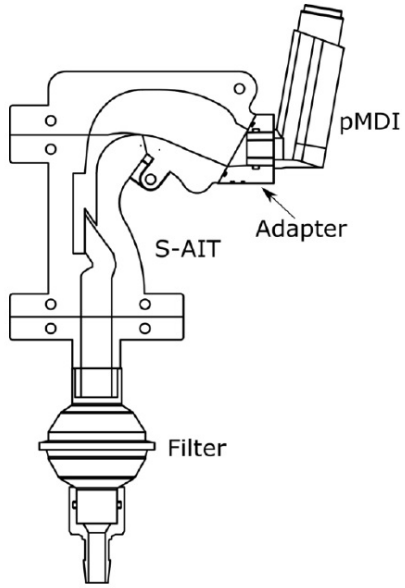
- *Developing efficient approaches to support transitions by generic products to utilize more environmentally friendly propellants.*

There are many challenges / open questions…

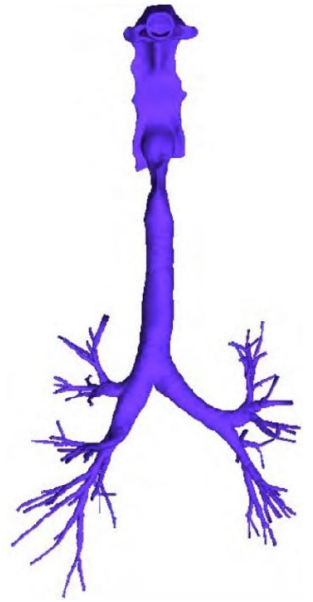
Potential study design to validate methods for testing the bioequivalence of MDIs

- Compare MDIs with currently-used vs. green propellants
- In vitro characterization (plume geometry, spray velocity, particle size distribution, etc.)
- In vitro experiments to quantify the regional doses in airway models
- Validation of CFD methods to predict regional doses
- Validation of PBPK models to estimate bioavailability

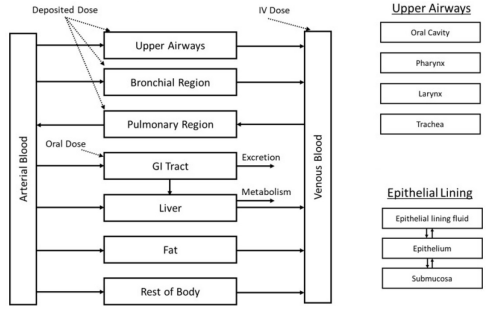
In vitro experiments



CFD models



PBPK models

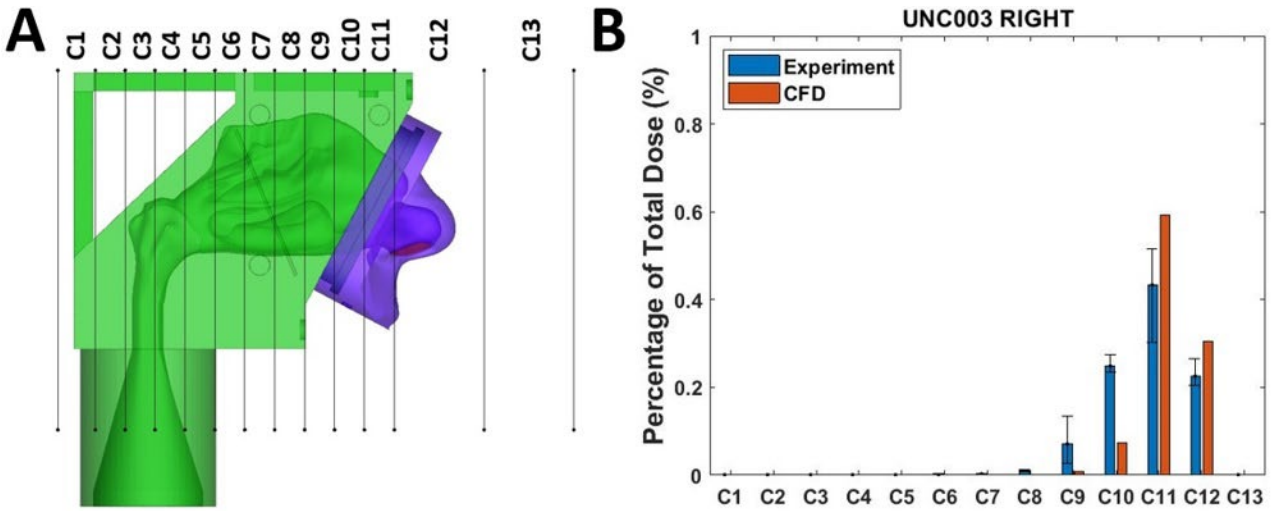


Recommended Areas of Research

Particle Bounce

- Particle bounce can affect the particle size distribution determined by cascade impactors [1].
- CFD simulations with a trap boundary condition underpredicted the dose of nasal sprays that penetrate the nasal valve compared to gamma scintigraphy (24 ± 14% vs. 46 ± 15%, p=0.0002, n=12 models) [2].

➡ There is a need to validate wall-film boundary conditions for CFD simulations of pharmaceutical aerosols.



[1] – Doub et al. (2020) AAPS PharmSciTech (2020) 21, 239.

[2] – Garcia et al., in preparation.

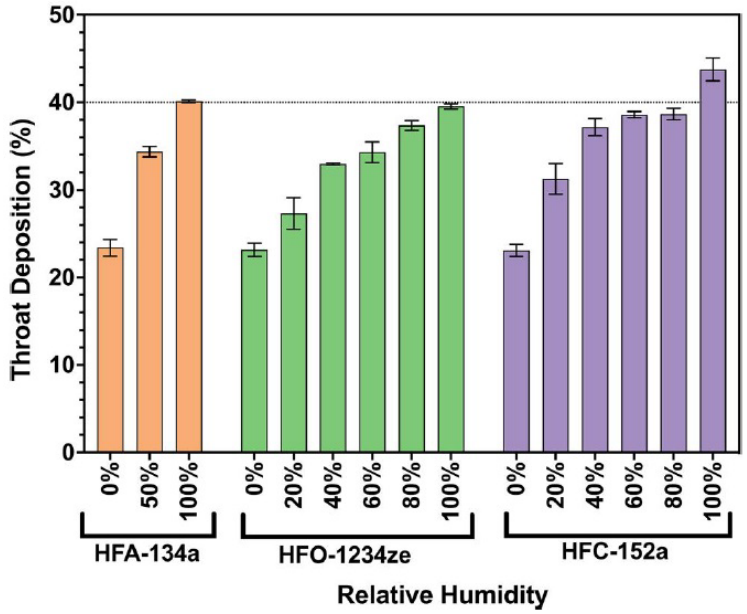
Recommended Areas of Research

Effect of air humidity

- MDIs are often characterized in laboratory conditions with room air, while inhaled air is quickly humidified to 100% relative humidity in the human respiratory tract.

- Wang et al. (2024) reported that relative humidity has a significant impact on the dose of MDIs that deposit in the USP induction port [3].

There is a need to develop CFD methods to estimate the impact of air humidity on regional doses delivered by MDIs.



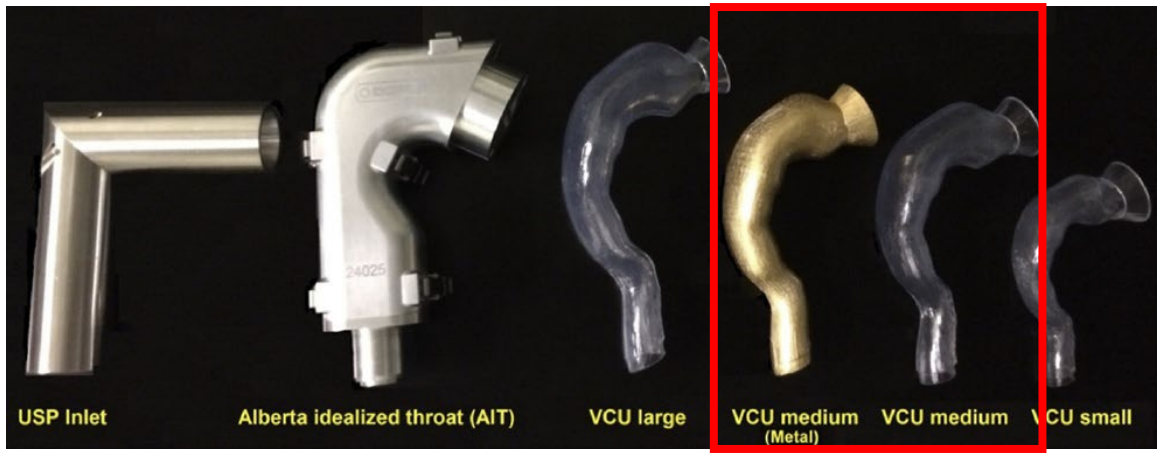
[3] – Wang et al. (2024) Aerosol Sci. Tech. 58, 115-133.

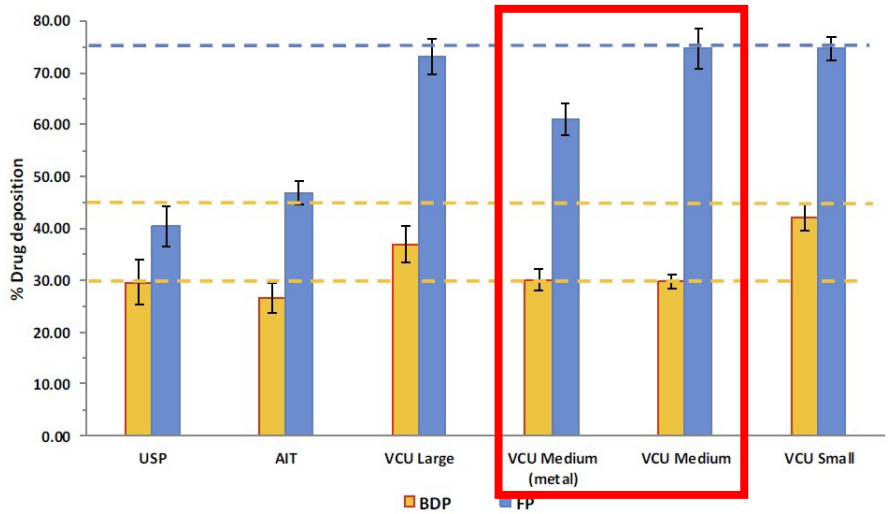
Recommended Areas of Research

Effect of electric charges

- Kaviratna et al. (2019) compared the dose of two MDIs in metal vs. polymer mouth-throat (MT) models [4].
- The fluticasone propionate MDI had higher deposition in the polymer MT model.

There is a need for more research (experimental and theoretical) to understand how electric charges affect regional doses in airway models.





[4] – Kaviratna et al. (2019) AAPS PharmSciTech 20, 130.

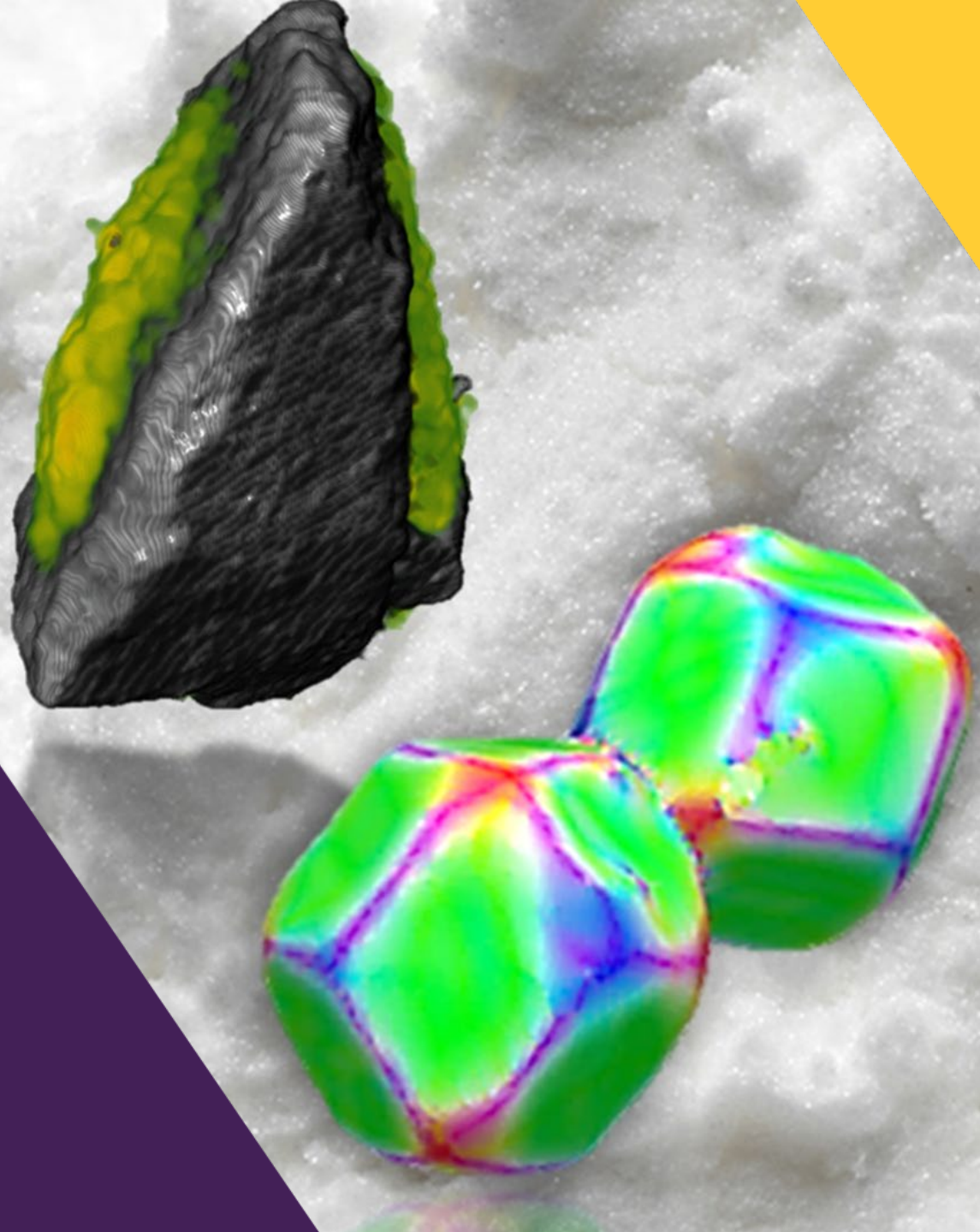
Thank you!

Contact: ggarcia@mcw.edu

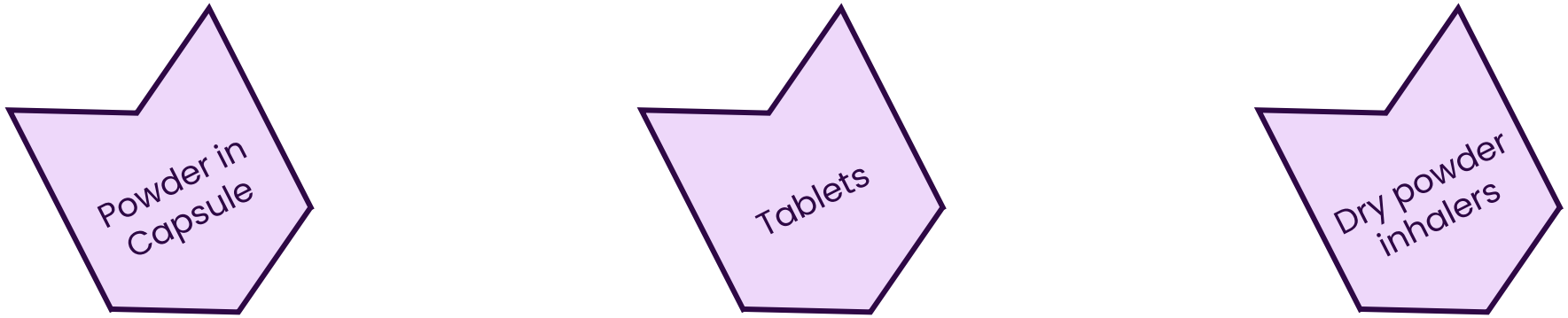
Multiscale X-ray Computed Tomography

Unlocking the power of seeing inside particulate products across multiple length scales

INFORMIX PHARMA

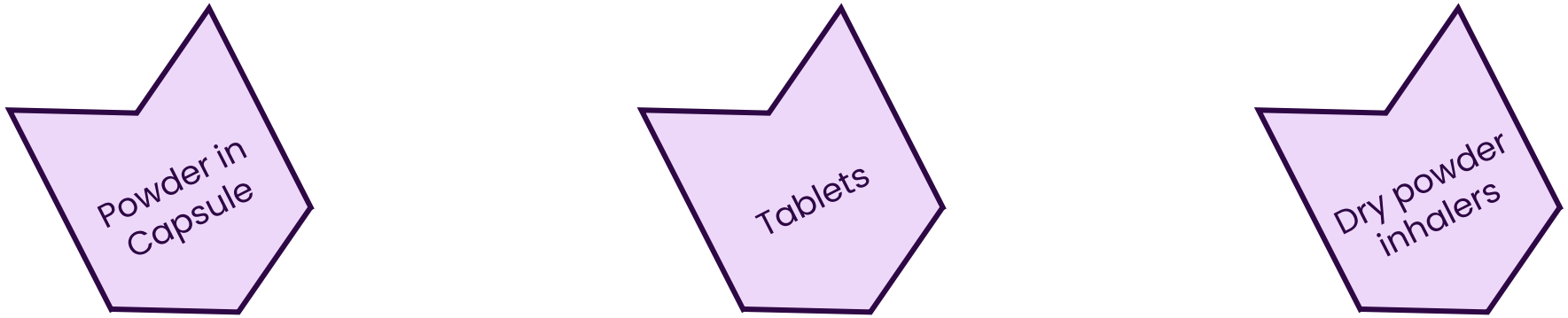


Formulating micronized and low dose products



- Micronized API essential for inhaled products & beneficial for poorly soluble APIs
- Reproducible manufacturing is technically challenging – segregation, physical instability
- Content uniformity creates bioequivalence challenges

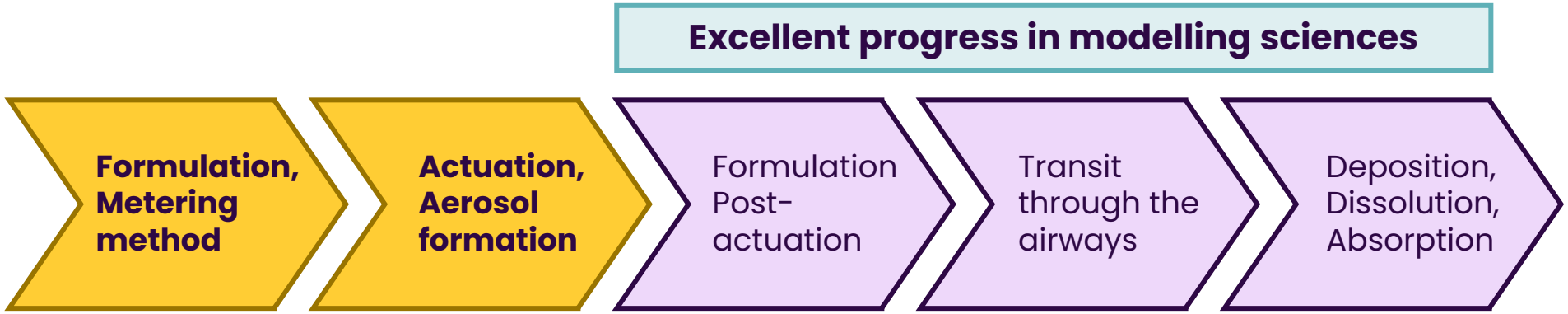
Formulating micronized and low dose products



- Micronized API essential for inhaled products & beneficial for poorly soluble APIs
- Reproducible manufacturing is technically challenging – segregation, physical instability
- Content uniformity creates bioequivalence challenges

How can imaging science contribute to predicting performance?

DPIs: Exemplar of low dose, micronized blending

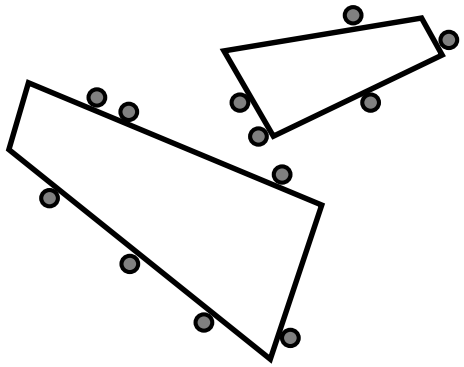


DPIs: Exemplar of low dose, micronized blending

Excellent progress in modelling sciences

Formulation, Metering method → **Actuation, Aerosol formation** → Formulation Post-actuation → Transit through the airways → Deposition, Dissolution, Absorption

Models are highly idealized

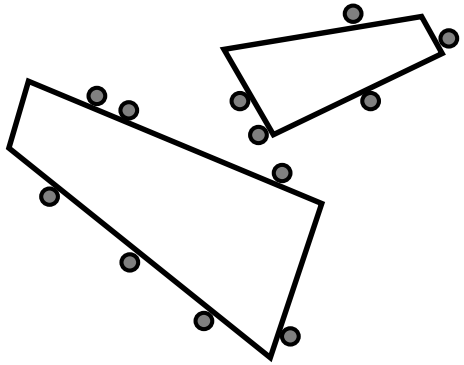


DPIs: Exemplar of low dose, micronized blending

Excellent progress in modelling sciences

Formulation, Metering method → **Actuation, Aerosol formation** → Formulation Post-actuation → Transit through the airways → Deposition, Dissolution, Absorption

Models are highly idealized



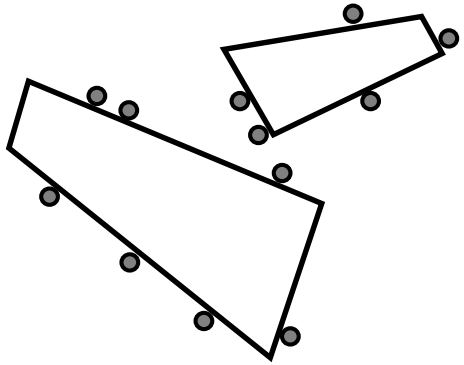
Pre-actuation formulation

- Are there meaningful links between structure and drug delivery?
- How does manufacturing affect the pre-actuated structure?
- Is there a sampling method that maintains the agglomerated state of the bulk powder?

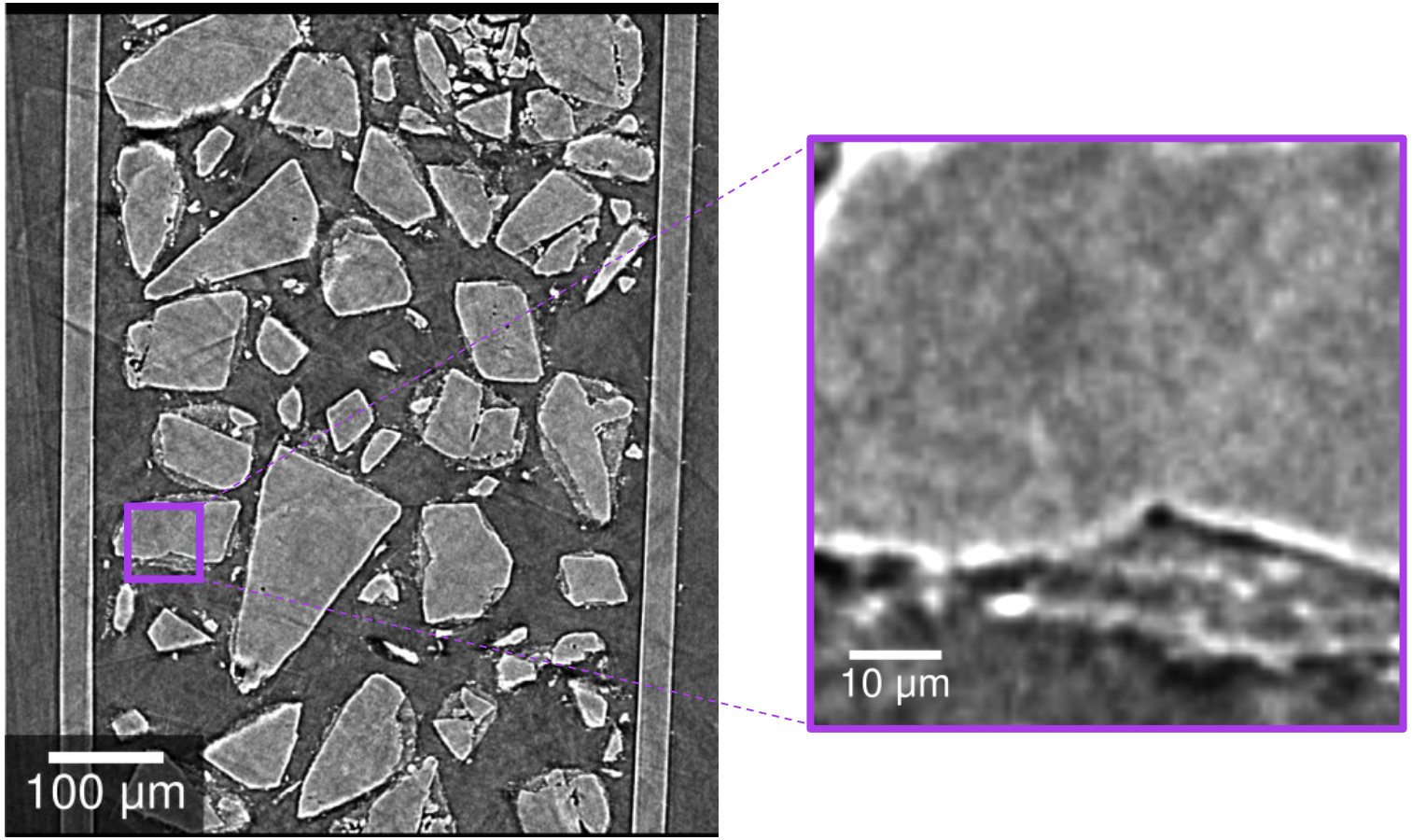
DPIs: Exemplar of low dose, micronized blending

X-ray Computed Tomography?

- Key challenge of different length scales
- Need to image on 10^{-8} to 10^{-3} m within one sample

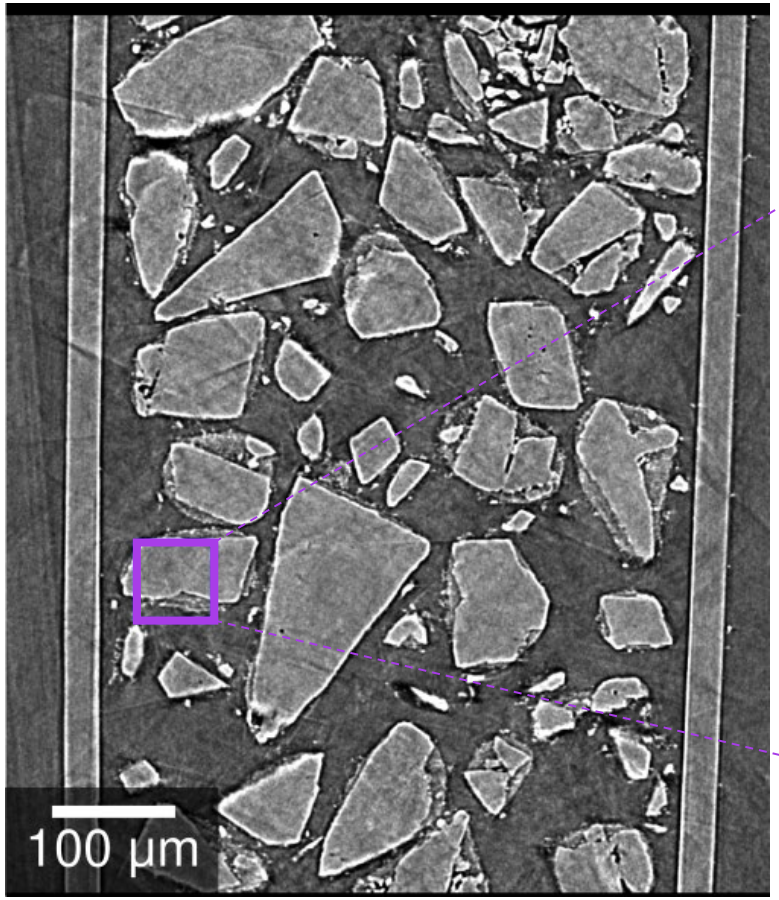


Standard XCT imaging and image analysis

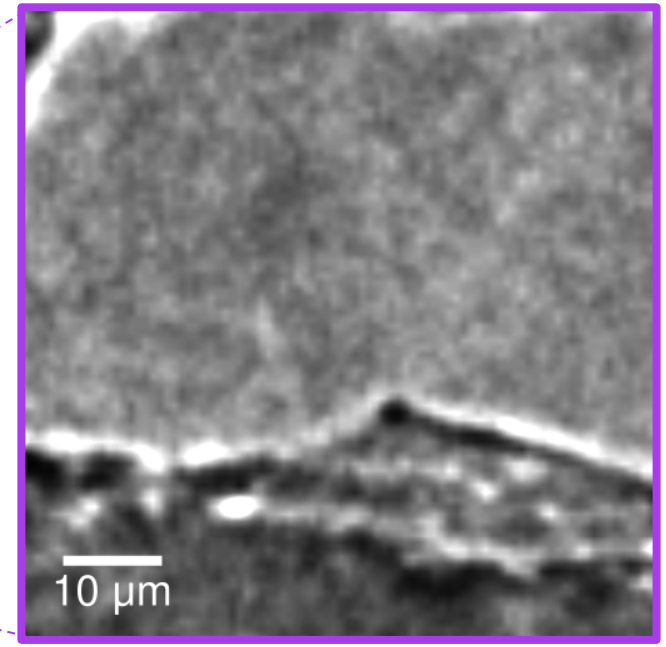


- Laboratory instruments lack resolution to image micronized drug particles
- Laboratory and synchrotron imaging is too ‘noisy’ for accurate analysis of micronized drug particles

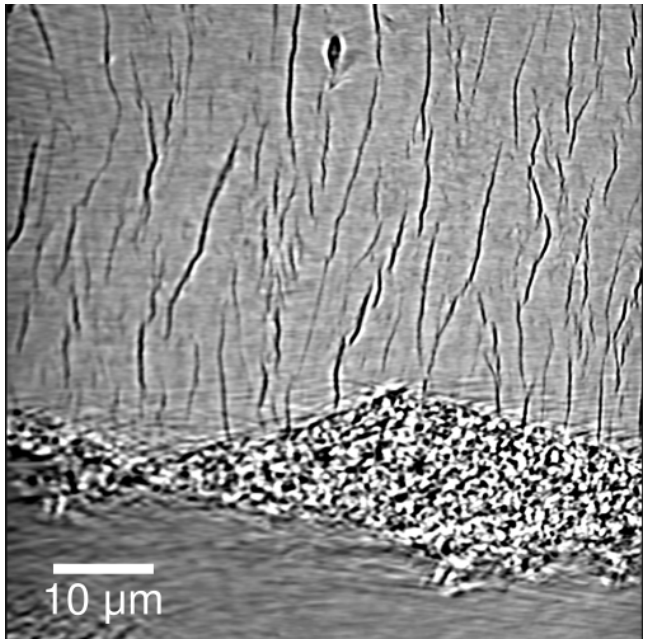
Inhalation blends: Combining nano- and micro- XCT



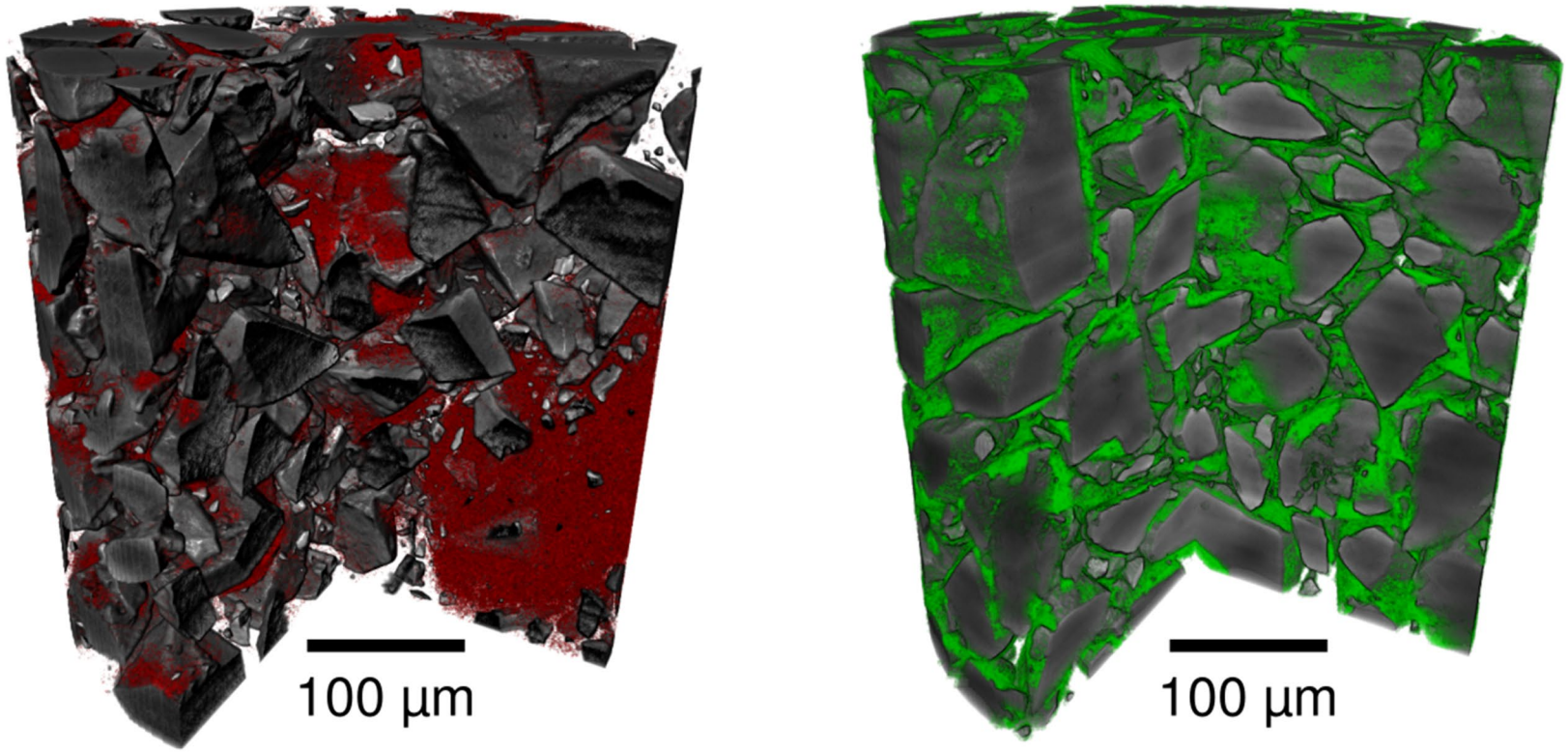
Current Standards



Informix Imaging



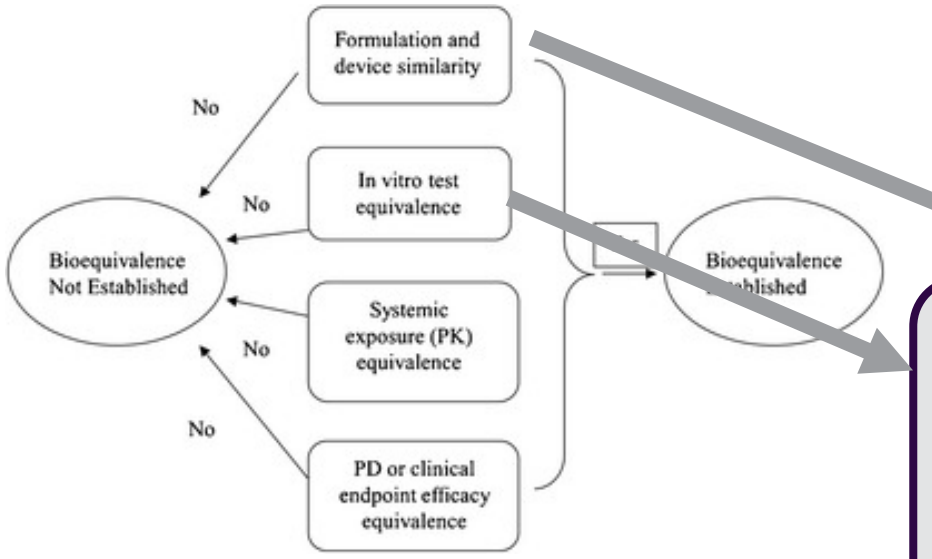
Inhalation blends: Imaging over multiple length scales



Characterizing powder microstructures

Generic Development Challenge to be Solved?

Weight of evidence approach (USA)

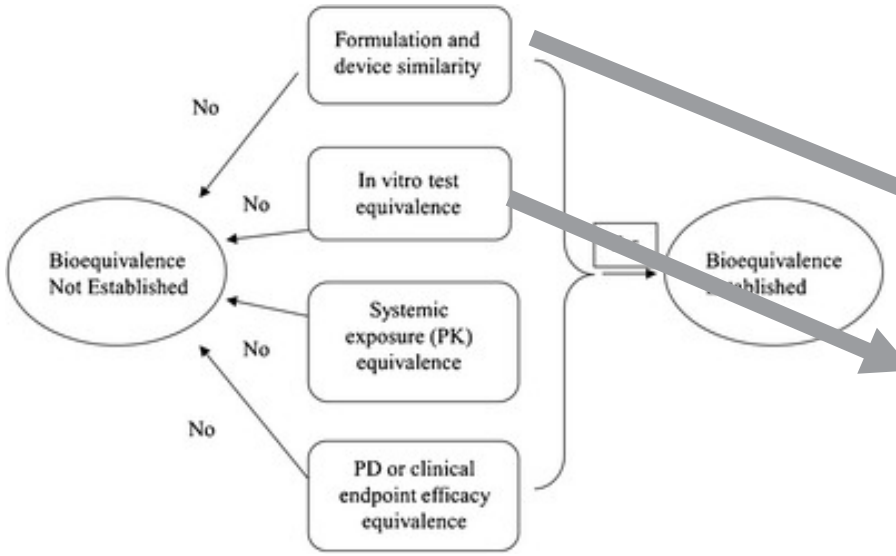


Critical quality attributes

- Q1 – Identity of components
- Q2 – Concentration and Composition
- **Q3 – Same non-equilibrium state related to the arrangement of matter**

Generic Development Challenge to be Solved?

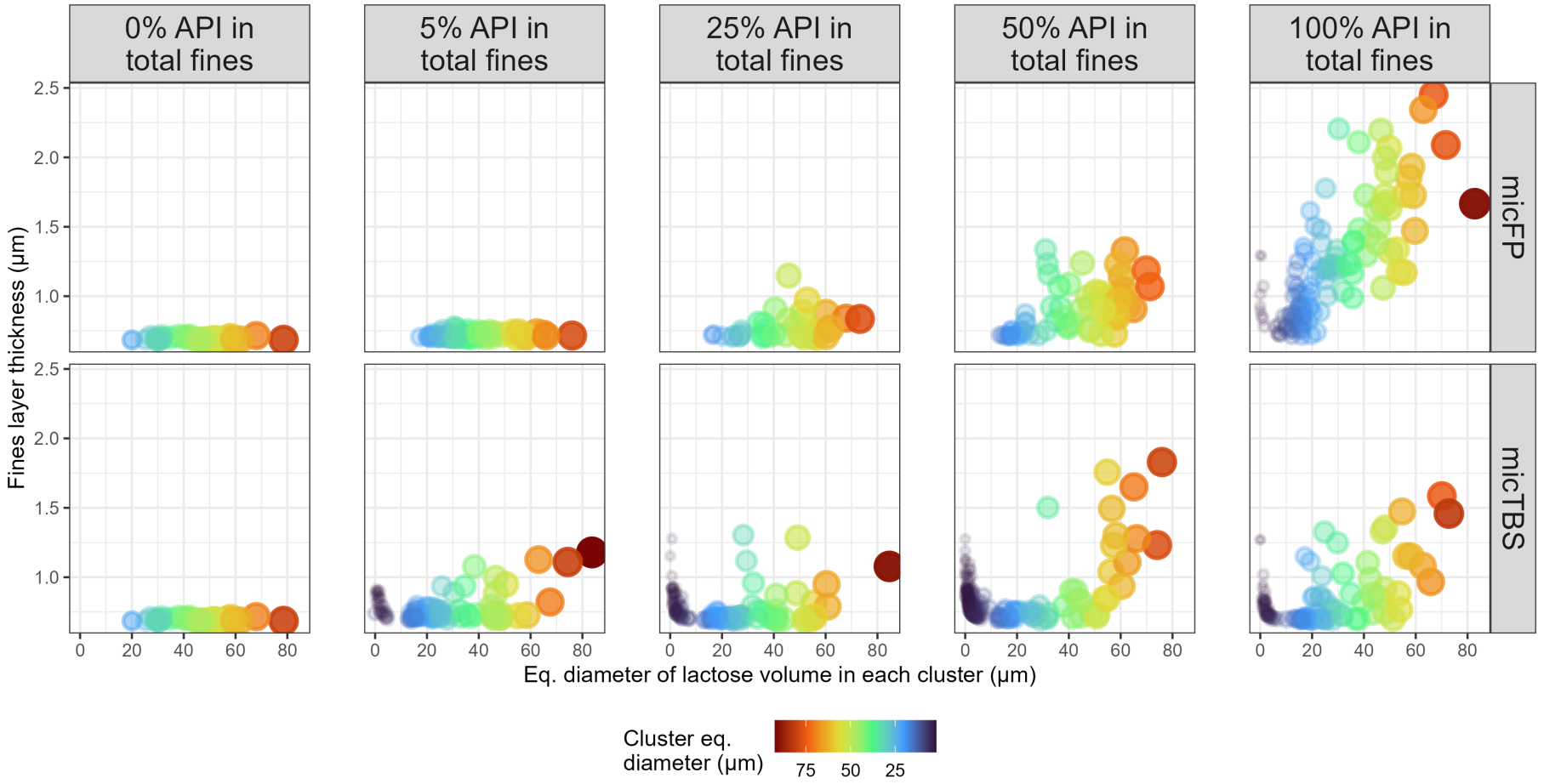
Weight of evidence approach (USA)



Non-destructive Q3 microstructural equivalence assessment for dry powder inhalation products

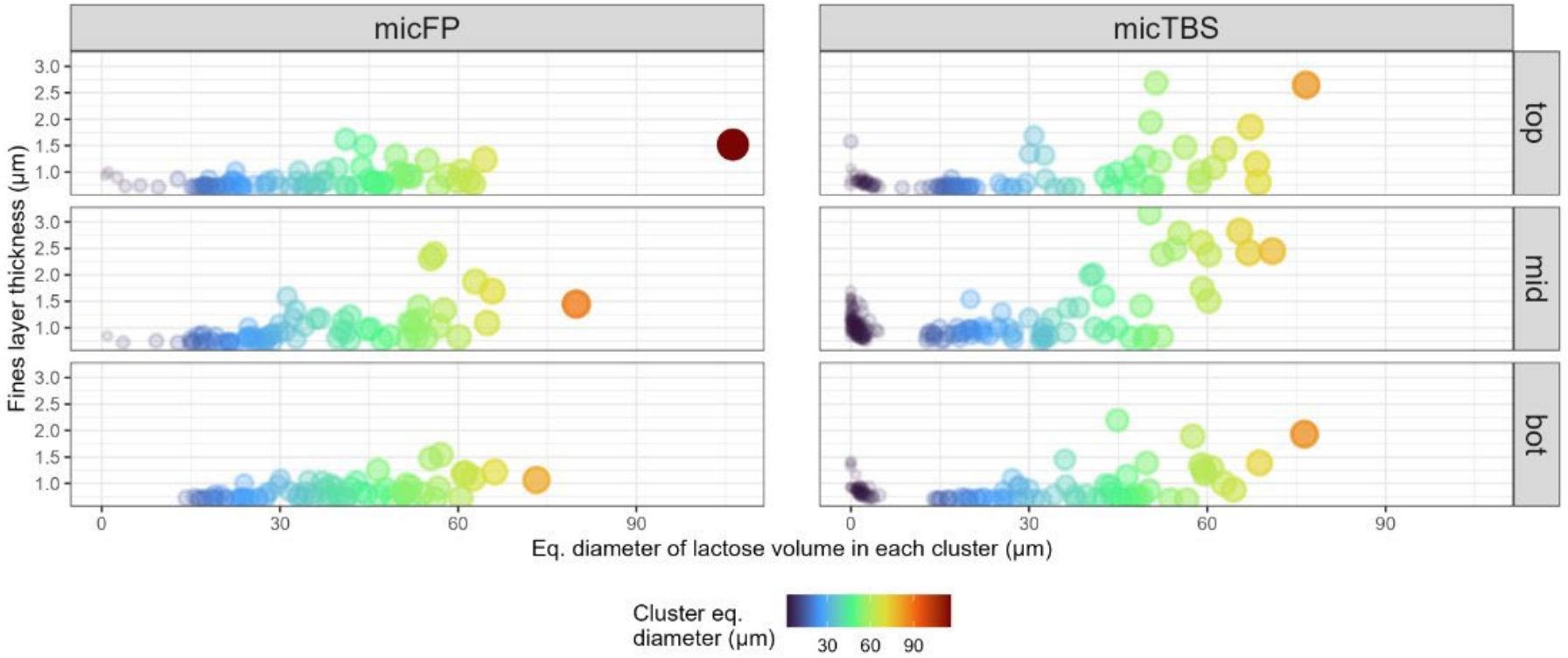
- Composition
- **Q3 – Same non-equilibrium state related to the arrangement of matter**

InformiX Analysis: Microstructural “Fingerprints”

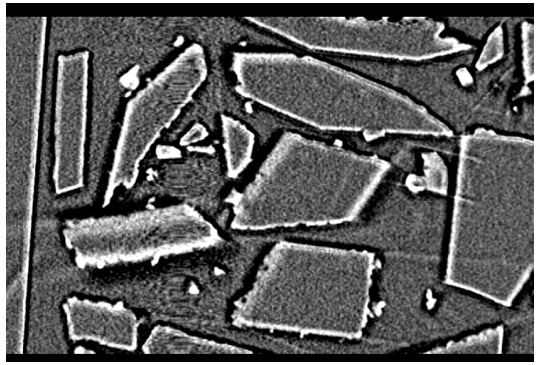


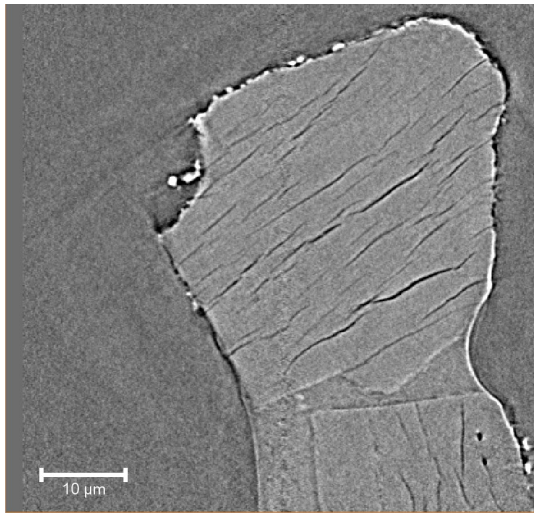
Development challenge: Intra-sample heterogeneity

- Variability in aerosolization performance is a known problem, even where unit dose content is within uniformity limits



Development challenge: De-risk raw material supplies





Nanoscale resolution of carrier lactose reveals intra-particle crystallographic faults in some commercial sources but not others

- Source of product processing failure?
- Unknown source of batch-batch variability?
- Can supply change be de-risked?

Some research questions and challenges

Knowledge and Understanding

- Does bulk microstructure correlate to aerosol microstructure?
- Will bulk microstructure equivalence equate to bioequivalence?
- Can we use bulk microstructure to build predictive digital twins?

Some research questions and challenges

Knowledge and Understanding

- Does bulk microstructure correlate to aerosol microstructure?
- Will bulk microstructure equivalence equate to bioequivalence?
- Can we use bulk microstructure to build predictive digital twins?

Technical

- What are the limits of detection for different APIs and blend types?
- How do different API chemistries affect LODs for imaging?
- What is the appropriate scale of scrutiny for assessment?

InformiX Pharma Limited is a registered company with number 14994613 and registered office at Unit 6, Church Farm, Church Road, Barrow, Bury St. Edmunds, England, IP29 5AX, United Kingdom

Thank you for your attention

INFORMIX PHARMA

E info@informixpharma.com

W informixpharma.com

May 20-21, 2024

Use of machine learning, in vitro approaches, and dosimetry models to enhance the efficiency of bioequivalence approaches for OINDPs

Jeffry Schroeter
Applied Research Associates
Rapid Presentation
GDUFA 2024 Public Workshop

ARA

Motivation

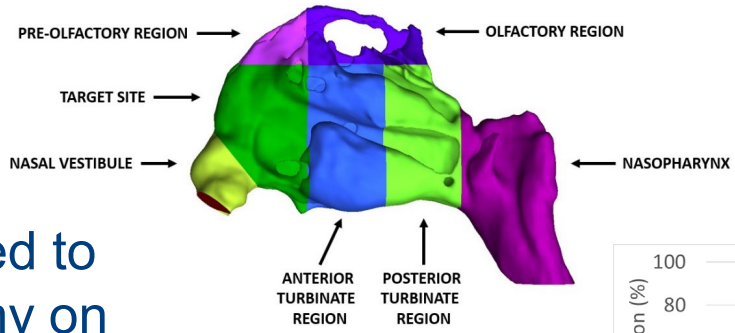
Modeling and simulation along with in vitro experiments may be used to develop product-specific bioequivalence approaches that do not include comparative clinical endpoint or pharmacodynamic studies

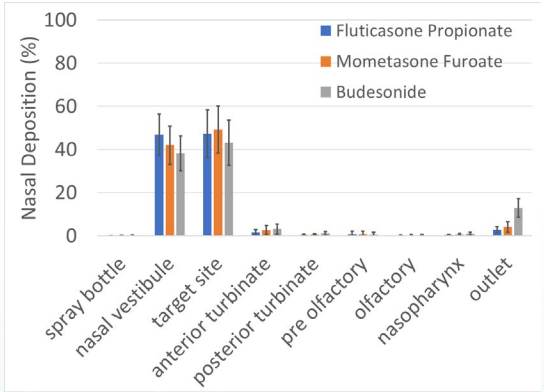
- For nasal spray products, M&S approaches have consisted of:
  - CFD models of nasal spray deposition
  - PBPK models of absorption and bioavailability

Experience

CFD models of nasal sprays

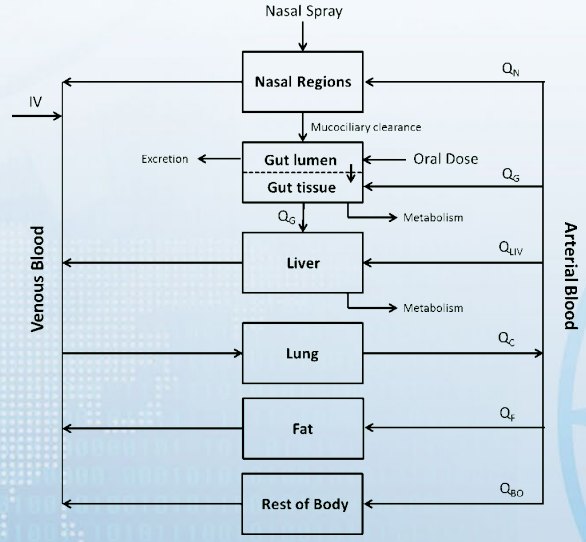
- CFD models from multiple labs have been developed to study effects of spray parameters and nasal anatomy on regional nasal deposition

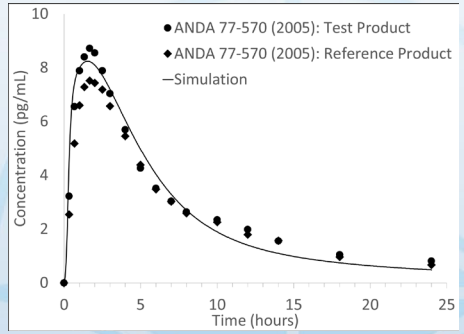




PBPK models of corticosteroids

- PBPK models from multiple labs have been developed to study drug absorption and bioavailability from nasal sprays and OIDPs (e.g., corticosteroids)





Solutions

Machine Learning Models

- Given the extensive suite of studies and wealth of data for nasal spray deposition, use ML models to gain insights into effects of CQAs on regional deposition
- Conduct further CFD studies to fill in gaps

In vitro experiments on nasal epithelial permeation

- PBPK modeling has demonstrated that systemic concentrations of nasally administered corticosteroids are highly sensitive to permeation through the nasal epithelial layer.
- Lack of model validation for tissue permeation is a current limitation of PBPK models for nasal sprays

Unified software platforms

- Various technologies (deposition data, CFD/ML results, PBPK models) can be brought together for end-to-end predictions to assess effects of nasal spray characteristics on local and systemic tissue concentrations for comparisons of generic and reference products

Thank you!

Public Comments for Session 2
Predictive Tools for Generic Product Development and Assessment

In Person Comments:

- Huong Huynh, PhD, Director of Regulatory Science, and Shu Chin Ma, PhD, VP of MIDD & Quantitative Medicine, Critical Path Institute (C-Path)
- Sandra Suarez-Sharp, PhD, President, Regulatory Strategies, Simulations Plus, Inc.
- Anuj Chauhan, PhD, Professor, Colorado School of Mines
- Elad Berkman, PhD, CTO PhaseV
- Sebastian Melgar, MPH, Lead Associate Booz | Allen | Hamilton
- Brian Eden, Vice President, Global Life Sciences Technical Operations Capgemini Group
- Sandhya Polu and Anil Bhatta, Contracts Manager, Deloitte Services LP
- Anthony Cristillo, PhD, MS, MBA, Partner, Digital Health
- Sarah Ferko, MS, PMP and Ally Lu, Senior Managing Consultant, Artificial Intelligence & Analytics, IBM Consulting
- Ashlee Brunaugh, PhD, Assistant Professor, Pharmaceutical Sciences, University of Michigan
- Jinxiang Xi, PhD, Associate Professor of Biomedical Engineering, University of Massachusetts, Lowell
- Guilherme Garcia, PhD, Assistant Professor, Marquette University and The Medical College of Wisconsin
- Darragh Murnane, PhD, Professor of Pharmaceutics, University of Hertfordshire (Informix Pharma)
- Jeff Schroeter, PhD, Senior Scientist, Applied Research Associates

Virtual Comments:

- Ravendra Singh, PhD, Director of Pharmaceutical Systems Engineering Rutgers
- Sebastian Polak, PhD, Professor Jagiellonian University
- Maxime Le Merdy, PhD, Associate Director, Research and Collaboration Simulations Plus, Inc.
- Stephan Schmidt, PhD, Professor University of Florida
- ***Guenther Hochhaus, PhD, Professor, University of Florida***
- ***Yu Feng, PhD Associate Professor, Oklahoma State University***
- ***Maria Malmlöf, PhD; Per Gerde, PhD, Director of Projects, Inhalation Sciences***
- ***Laleh Golshahi, PhD, Associate Professor of Mechanical and Nuclear Engineering, Virginia Commonwealth University***
- ***Rodrigo Cristofoletti, PhD, Assistant Professor, University of Florida***

COLLEGE OF

PHARMACY

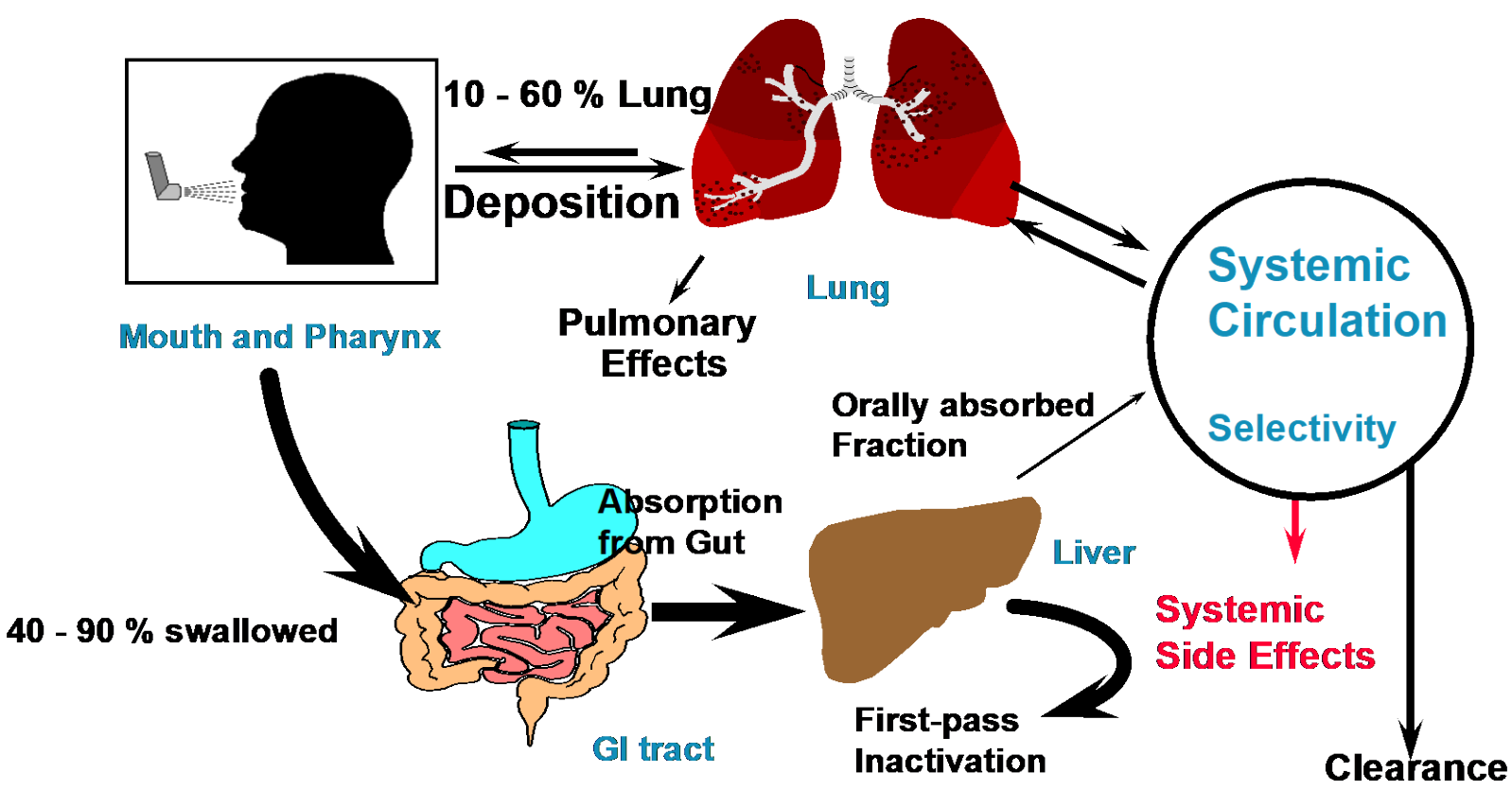
FY24 FDA GDUFA Public Workshop

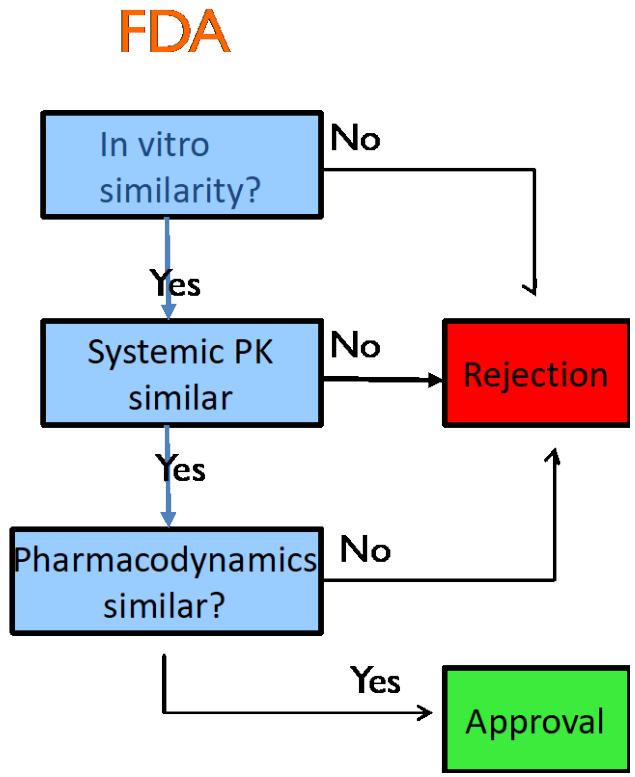
Comments from: Guenther Hochhaus, University of Florida

Hochhaus@ufl.edu

UF | College of Pharmacy
UNIVERSITY of FLORIDA

Reason for weight of evidence approach





What needs to be shown:

- **Lung Dose**
- **Regional deposition**
- **Lung residence time**

Previous Research for OINDP successfully evaluated:

- Tools to assess regional deposition
  - Use of anatomical mouth/throat models in conjunction with typical inhalation profiles observed in patients
  - Computational fluid dynamics for predicting regional deposition of inhalation drugs
- Approaches to assess post deposition events
  - Dissolution tests (integrated into PSGs of suspension nasal sprays
  - MDRS (suspension nasal sprays, very time and resource consuming)
- Methods to assess deposition/post-deposition events
  - Population pharmacokinetic evaluation (often needs iv data)
  - Physiological based pharmacokinetics

FDA released first product specific guidance mentioning PK as alternative to clinical endpoint studies.

Draft Guidance on Formoterol Fumarate; Glycopyrrolate

February 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

- APSD (ISM, MMAD, GSD)
- Single actuation content (standard)
- Spray pattern, Plume geometry, Priming and repriming
- Realistic APSD (mouth-throat models of different sizes (e.g., small and large) and weak and strong breathing profiles
- PK with and without charcoal

- Optional computational modeling studies **may** (have??) **be used** to support bioequivalence of the T and RS products (CFD, semi-empirical model, PBPK, population PK?) with the goal
  - Establishing **biorelevant limits** for bioequivalence comparison of key recommended studies, including **realistic APSD** and **plume geometry** studies.
  - to differentiate the impact of different products (i.e., device and formulation) on regional drug delivery
  - to assess the BE in terms of regional lung deposition

    by conducting virtual bioequivalence simulations

Challenge: Establish credibility of computational models through validation

- **Validation includes comparisons between predictions and data from in vivo and**/or in vitro sources including **RS** and **at least one other drug product** that is known to produce a different relevant outcome (regional deposition, systemic pharmacokinetics, or lung tissue pharmacokinetics).

- Validation might include additional in vivo studies including anatomical and physiological conditions across subjects/patients and their variabilities.
- **Thus, development** of computational methods for a specific product is **very time and resource consuming**, **potentially resulting in companies using the traditional weight of evidence approach,**

  thereby counteracting FDA's goal of streamlining

  product development.

Proposed suggestion for further streamlining BE assessments of OINDPs

- Develop *computational* models (**CFD, PBPK, popPK**) for **a range of model drugs covering the "design" space as it relates to device, formulation and physicochemical properties of the API within GDUFA sponsored research activities**

- Use these models to link differences in in vivo lung dose, residence time and regional deposition to differences in the in vitro performance **(APSD, MT-model based lung dose, dissolution rate)** as well as differences in NCA PK properties (Cmax, AUC).

- Based on this comparison define **generally applicable biorelevant limits as they relates to lung dose, residence time and regional deposition.**

- **Final Goal: allow use of standard in vitro/ PK approaches within the BE assessments of specific products without need of applying computational models**

Avicenna Alliance
Association for Data Driven Medicine

Enhancing Inhaler Development: Leveraging Machine Learning and Deep Learning with Multiscale CFPD-PBPK Models for Accelerated Innovation

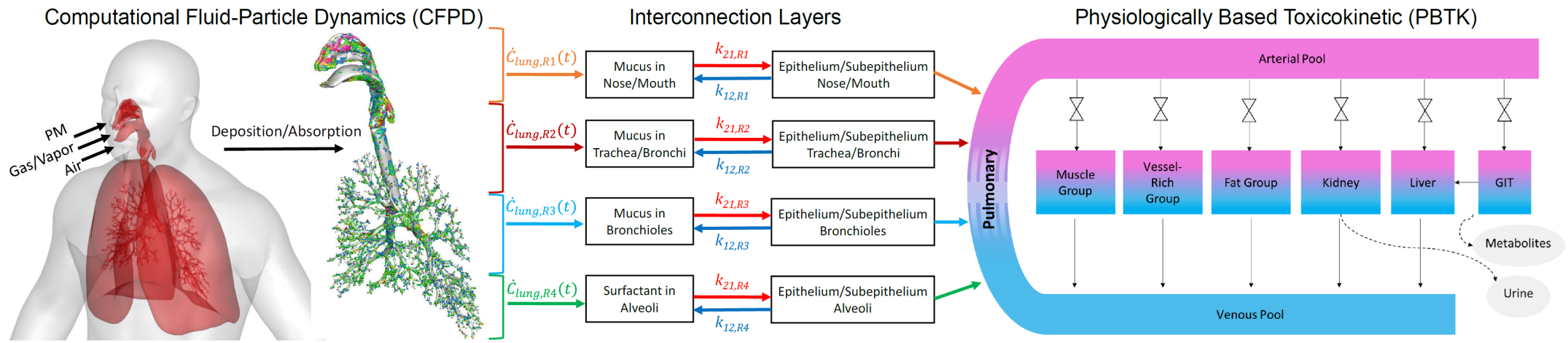
Yu Feng, Ph.D.
Associate Professor, School of Chemical Engineering, Oklahoma State University, Stillwater, OK, USA
Academic Co-Chair, Pharmaceutical (Pharma) Strategy Task Force, Avicenna Alliance

CBBL@OSU

Why CFPD-PBPK Hybrid Model is Needed

Avicenna Alliance
Association for Data Driven Medicine

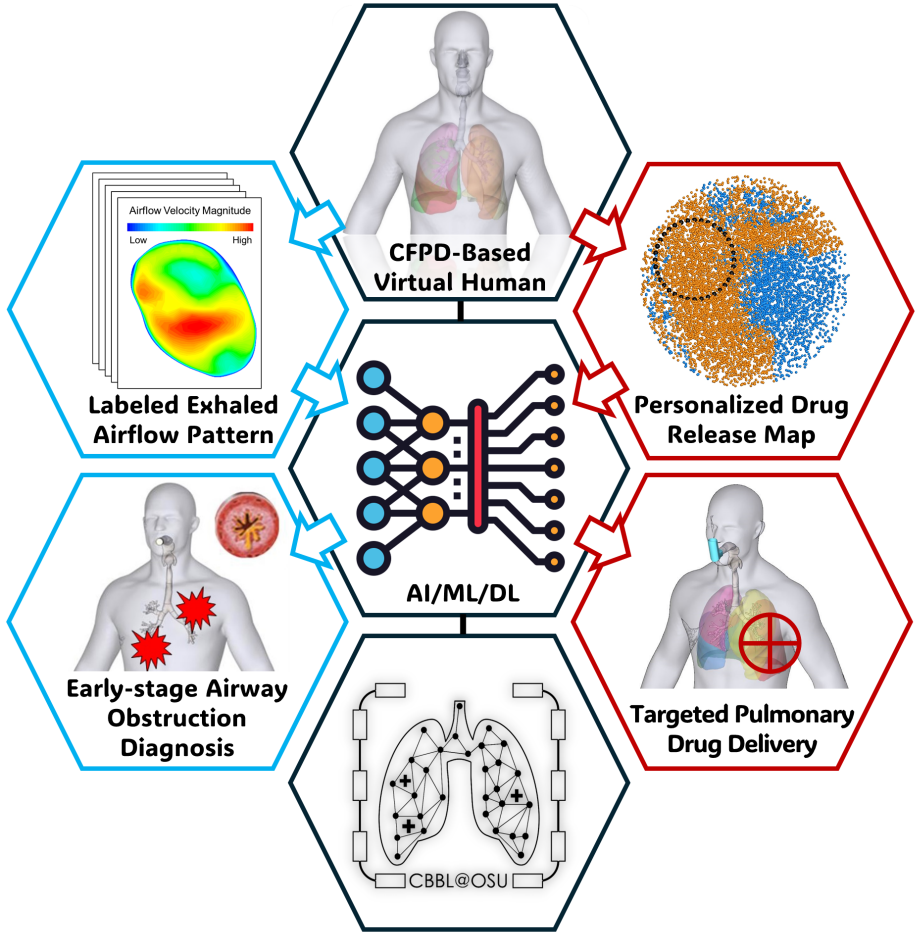
- **Capture Factors that Can Influence the Aerodynamics of Inhaled Medication and the Resultant PK/PD**
  - Inter-Subject Variability
  - Inter-Species Variability
  - Inhaler Design Parameters
  - Patient-Inhaler Coordination
- **Clinical and Regulatory Implications**
  - Maximize Therapeutic Effect
  - Minimize Overdose Risks



Why AI Integration in to *In Silico* Tool is Needed?

Avicenna Alliance
Association for Data Driven Medicine

- **Fast-running and Reliable *In Silico* Tools**
  - Faster Bioequivalence (BE) or Comparability Evaluations with Variability Studies
  - Easy-to-use *in silico* Tool empowered by AI to Accelerate Innovation Cycles in New Drug and Medical Device Development
  - More Efficient Communication between FDA and Pharma Industry Companies
- **Clinical and Regulatory Implications**
  - Maximize Therapeutic Effect
  - Minimize Overdose Risks



- Hu, P., Cai, C., Yi, H., Zhao, J., Feng, Y., Wang, Q. (2022). Aid Airway Obstruction Diagnosis with Computational Fluid Dynamics and Convolutional Neural Network: A New Perspective and Numerical Case Study. *ASME Journal of Fluids Engineering, 144,* 081206
- Islam, M.R., Liu, C., Shah, J., Cai, C., Feng, Y. (2024). A User-Centered Smart Inhaler Algorithm for Targeted Drug Delivery in Juvenile Onset Recurrent Respiratory Papillomatosis Treatment Integrating Computational Fluid Particle Dynamics and Machine Learning. *Physics of Fluids, 36,* 021912 (Editor's Pick and AIP Scilight Article https://doi.org/10.1063/10.0025061

Example 1: Capture Subject-specific Variability using CFPD-PK

Avicenna Alliance
Association for Data Driven Medicine

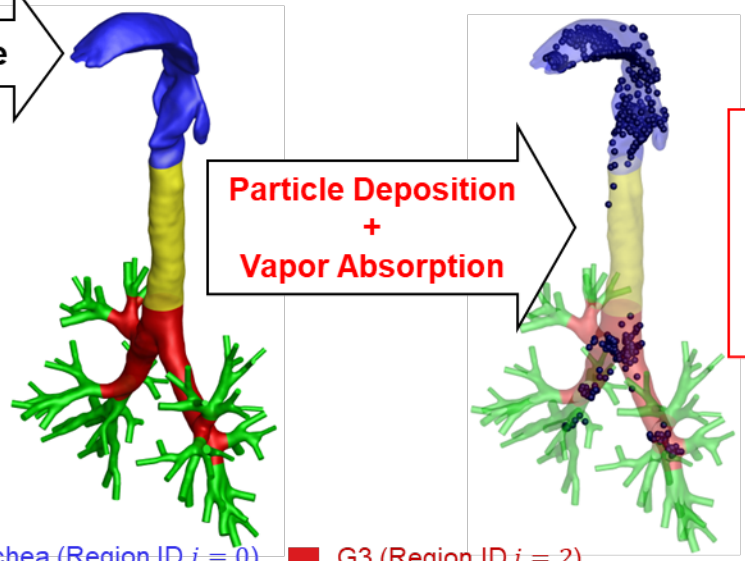
Step 1: Delivered Dose Prediction to the Respiratory System

Step 2: Plasma Concentration $C_{THC,Blood}$ Prediction

Computational Fluid Particle Dynamics (CFPD) Model

Inhaled Dose

Airflow
+
Particles
+
Vapor



Particle Deposition
+
Vapor Absorption

Mouth to Trachea (Region ID $i = 0$)
G1 to G2 (Region ID $i = 1$)
G3 (Region ID $i = 2$)
G4 and Beyond (Region ID $i = 3$)

Lung Absorption Rate

$q_{in} = \sum_{i=0}^{3} q_{in,i} BA_i$

Pharmacokinetic (PK) Model

Delivered dose enters via total absorption rate q_{in} scaled by regional bioavailability BA_i

A_1
Central Compartment

THC Concentration Over Time

$C_{THC,Blood} = A_1/V_1$

k_{21}
k_{12}
Peripheral A_2 Compartment 1

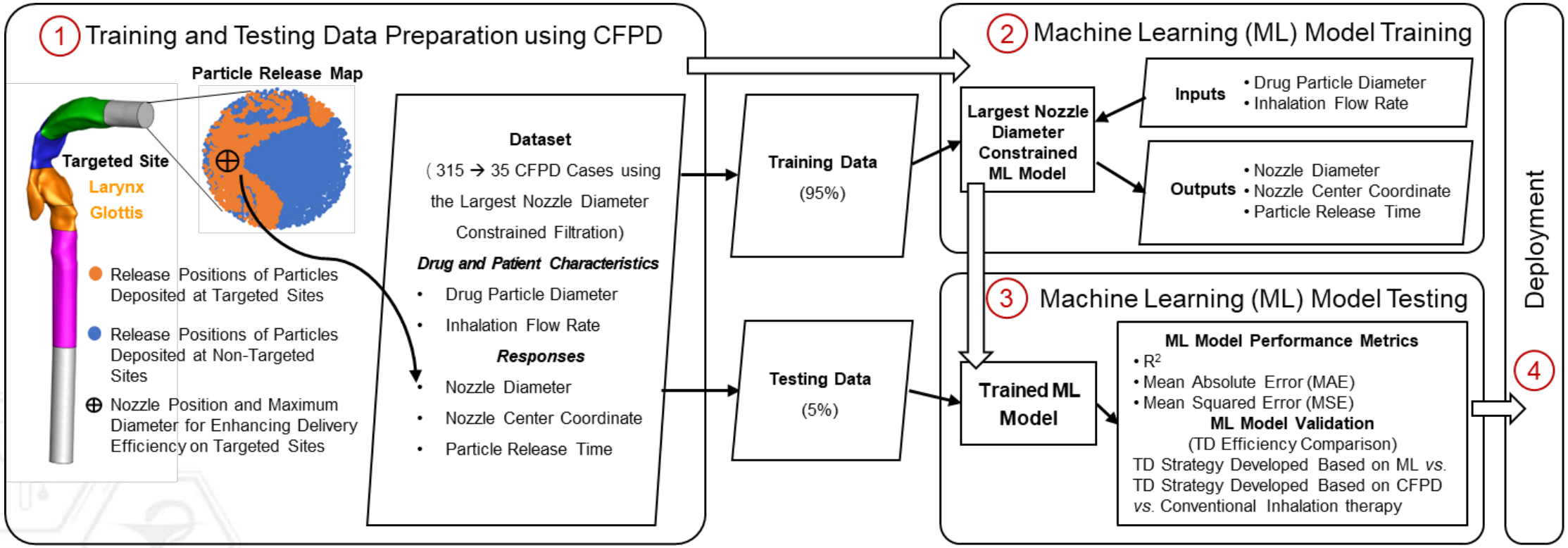
k_{31}
k_{13}
Peripheral A_3 Compartment 2

k_{10} (Elimination)

Objective: Provide Quantitative Evidence for Therapeutic Effectiveness Evaluation, Overdose Risk Control, and Satisfaction Optimization

- Zhao, J., Feng, Y., Tian, G., Taylor, C., Arden, S. N. (2021). Influences of Puff Protocols and Upper Airway Anatomy on Cannabis Pharmacokinetics: A CFPD-PK Study. Computers in Biology and Medicine, 132, 104333
- Sperry, T., Feng, Y., Song, C., Shi, Z. (2024). CFPD-PK Simulation of Inhaled Delta-9-tetrahydrocannabinol Aerosol Dynamics: Transport, Deposition, and Translocation in a Subject-Specific Mouth-to-G10 Airway. Journal of Aerosol Science, 177, 106334

Example 2: AI-Empowered Smart Inhaler for Patient-Specific Targeted Drug Delivery



- Islam, M.R., Liu, C., Shah, J., Cai, C., Feng, Y. (2024). A User-Centered Smart Inhaler Algorithm for Targeted Drug Delivery in Juvenile Onset Recurrent Respiratory Papillomatosis Treatment Integrating Computational Fluid Particle Dynamics and Machine Learning. *Physics of Fluids, 36,* 021912 (Editor's Pick and AIP Scilight Article https://doi.org/10.1063/10.0025061

Suggestions

Avicenna Alliance
Association for Data Driven Medicine

- **More Special Grant Opportunities**
  - Research and development of **AI-empowered smart inhaler technology**, not only for patient data communication, but for the **improvement in inhalation therapy effectiveness**.
  - Support the development of **international standards** for simulation-based testing for inhaler innovation with **new computational techniques and resources**.
  - Encourage the funding of **educational and training programs** focused on the intersection of CFPD-PBPK, AI, and inhaler technology. A well-informed workforce is crucial for sustained innovation and regulation in this field.
- **Extended Funding Cycles**
  - Longer funding periods (**3-5 years instead of 2 years**), as the integration of CFPD-PBPK and AI technologies requires sustained research and development beyond typical grant cycles.

Avicenna Alliance
Association for Data Driven Medicine

Enhancing Inhaler Development: Leveraging Machine Learning and Deep Learning with Multiscale CFPD-PBPK Models for Accelerated Innovation

Thank you!

Yu Feng, Ph.D.
Associate Professor, School of Chemical Engineering, Oklahoma State University, Stillwater, OK, USA
Academic Co-Chair, Pharmaceutical (Pharma) Strategy Task Force, Avicenna Alliance

CBBL@OSU

Inhalation Sciences

Dissolution and absorption testing of size-fractionated aerosols

Per Gerde, Assoc Prof, CSO

Maria Malmlöf PhD, Director of Projects

Complex relation between aerosol particle size and lung disposition

- For slowly dissolving substances with fast permeation – a strong relation exists between particle size and lung disposition
- This relation gradually disappears towards fast dissolving substances with slow permeation
- For **polydisperse** aerosols these relations are difficult to study, because of overlapping kinetics from the different aerosol size classes
- Separation of such aerosols into **narrow-disperse** size fractions may allow the critical effect of particle size to be better elucidated

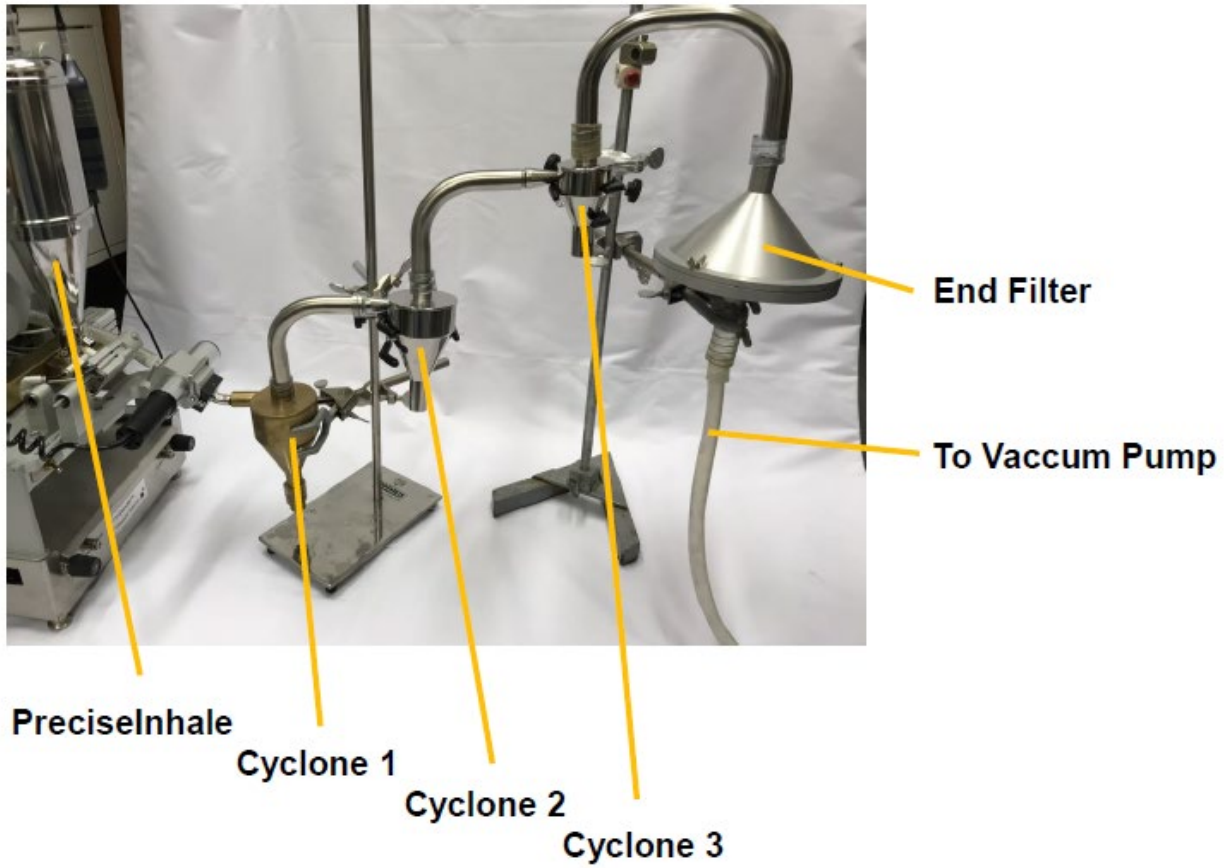
Inhalation Sciences

The case for study dissolution and permeation of size-fractionated aerosols

- In cascade impactors, high velocity impaction of separated size fractions precludes study of undisturbed kinetics from separated particles
- Aerodynamic (softer) separation of aerosols in cyclones into narrow size fractions, may allow their release kinetics to be studied following successive re-aerosolization of the different size fractions
- The powder generator of the PreciseInhale system can be used to re-aerosolize cyclone-separated size fractions

Inhalation Sciences

Size separation of polydisperse aerosols in a three-stage cyclone battery plus end filter



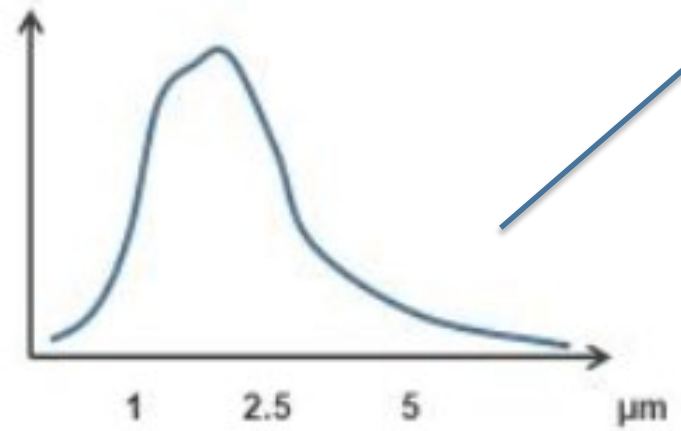
Cascade Impactors: Hard separation of particles destroying their integrity

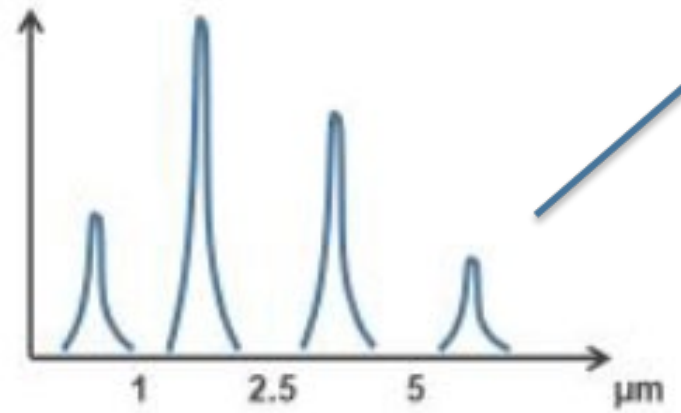
Cyclone Battery: Soft separation maintaining particle integrity

Cutoff Sizes at 25 L/min: 5 µm, 2.5 µm and 1 µm → four size categories

Inhalation Sciences

Tentative scheme for investigating size-separated aerosols





I) Primary Aerosolization of polydisperse powder

II) Separation on cyclone battery

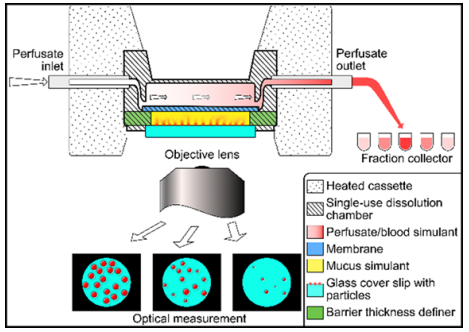
III) Re-aerosolization of size fractions into narrow-disperse aerosol fractions

IV) Dissolution/Permeability experiments on narrow-disperse aerosol fractions

Inhalation Sciences

Two suitable systems for evaluating the dissolution/permeability of size separated aerosols

I. The Dissolv*it* system with an artificial air/blood barrier



Primarily for evaluating the dissolution/permeablity kinetics of lipophilic substances

II. The Isolated, ventilated and perfused rat lung

Adding the physiological permeability barriers for hydrophilic substances of the intact lung; cell membranes and tight junctions

Inhalation Sciences

Enhancing Bioequivalence Assessment for Combination Nasal Products with In Vitro Anatomically-Similar Nasal Models Accounting for Intersubject Variability

Laleh Golshahi, Ph.D.[1,2,*]

Associate Professor

Virginia Commonwealth University (VCU)

Richmond, VA, United States

[1] Mechanical and Nuclear Engineering

[2] Pharmaceutical Engineering

*LGOLSHAHI@VCU.EDU

Need for Effective Testing Tools and Methods for Assessment of Regional Nasal Drug Delivery

- *In vitro* methods demonstrating equivalent performance are generally recommended, either alone or in combination with other *in vivo* methods, by the U.S. Food and Drug Administration (FDA) to establish bioequivalence (BE) for generic locally-acting nasal suspension spray drug products with the reference product.

- Both *in vitro* and *in vivo* BE studies provide indirect assessments of the drug deposition at the nasal sites of action, which limits their ability to provide direct measurements of the drug concentration following nasal deposition.

- Regional nasal deposition *in vitro* studies offer a new potential way to evaluate performance differences between nasal spray products that may support the BE evaluation of these products across different patient populations.

Key Questions in Evaluating Drug Delivery for Local Action in Human Subjects

- How does intersubject variability affect the performance of nasal sprays?

- Can we utilize a pre-clinical product evaluation platform, which allows consideration of intersubject variability while also considering time and cost constraints?

- If we can have representative nasal anatomies, how could they be used in assessing bioequivalence (BE) of nasal products in terms of their drug delivery efficiency to the target regions?

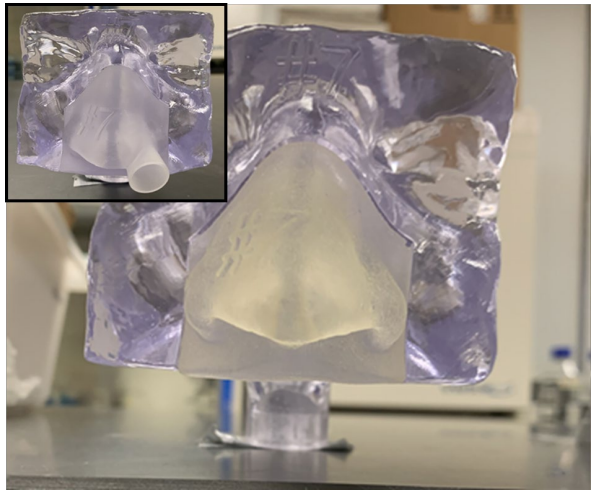
Objectives

- Our primary objective was to capture the range of variability for regional deposition following administration of locally-acting suspension nasal drug products in adults and children.

- To achieve this goal, we first identified and processed sinonasal CT scans of 20 adults (50% female and 50%≥50 years, age range 21-75 years old) to develop our anatomically-correct 3D models of adult nasal airways that would incorporate a measure of intersubject variability.

- A similar approach was taken and high-resolution computed tomography scans of the sinonasal region of 20 healthy pediatric human subjects (2-11 years old, 50% 2-6 years old and 50% female) were used to develop 20 three-dimensional (3D) replicas of the nasal airways, capturing 40 different nasal cavity geometries.

Anatomically-Similar Nasal Models to Understand the Impact of Intersubject Variability on Nasal Spray Performance



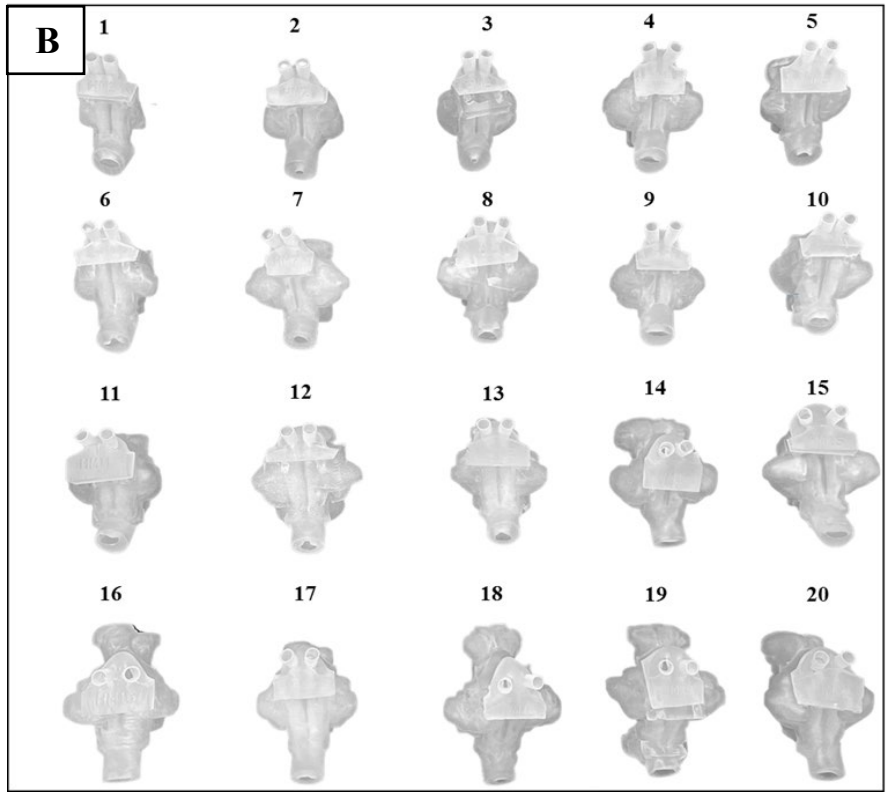


Figure 1 - Twenty 3D printed nasal airway models of the studied (A) adult subjects, showing the region posterior to internal nasal valve, and middle panel is an enlarged view of one of the adult models with the flexible anterior piece attached. Later a nozzle holder was included for administration consistency. Panel (B) shows the nasal models of the pediatric subjects.

- Two nasal sprays, Flonase and Flonase Sensimist, with different nozzle designs, formulation, and plume characteristics were used for deposition studies within the adult nasal models.
- Similarly, two different products, Nasacort and Flonase Sensimist, were used for deposition studies within the pediatric nasal models.

Intersubject Variability in Adult Nasal Drug Delivery via Nasal Sprays

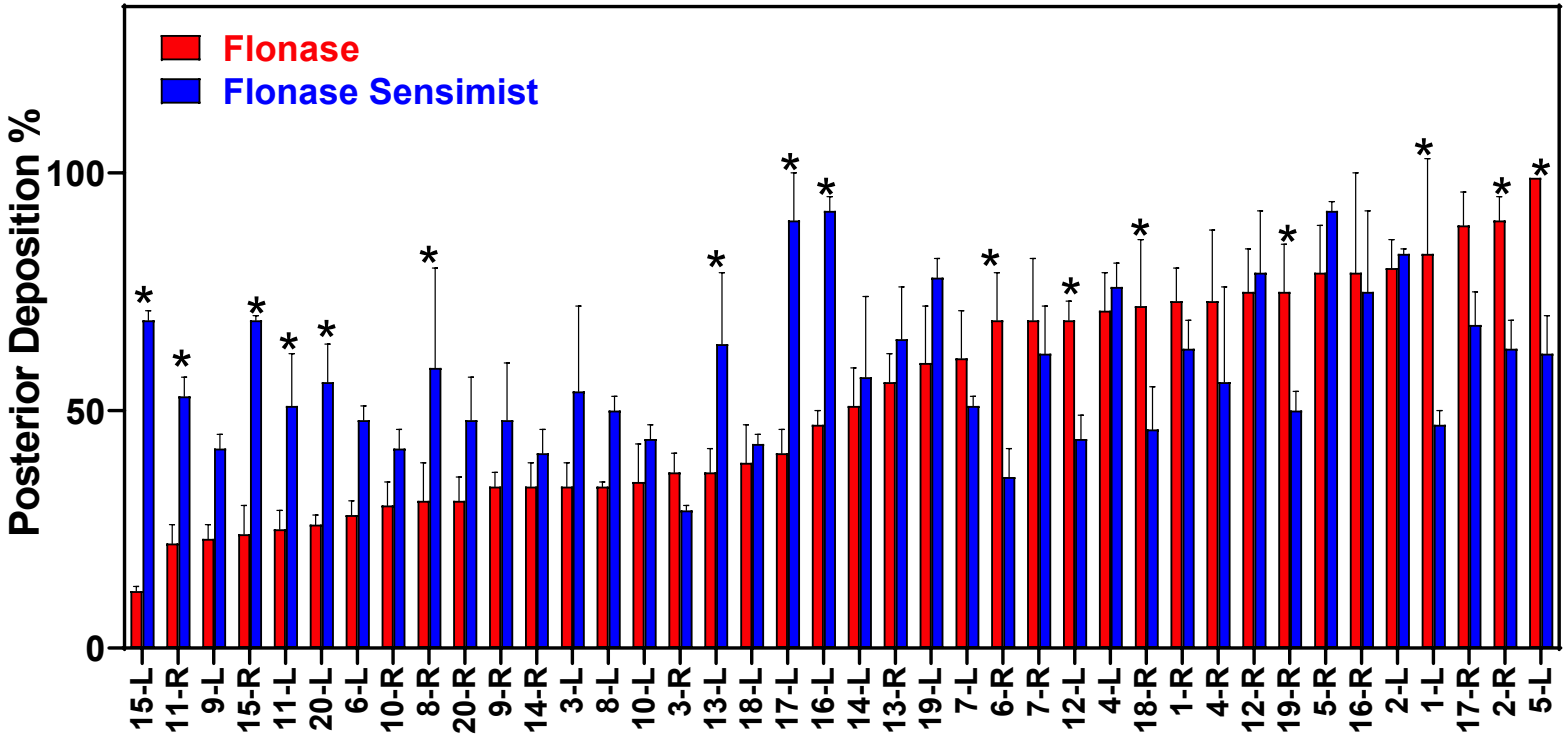


Figure 2 - Posterior deposition (PD) for Flonase (API: Fluticasone Propionate, FP) and Flonase Sensimist (API: Fluticasone Furoate, FF), sorted by ascending values of Flonase PD. Numbers show the model number; L and R stand for left and right nostril, respectively. The star (*) sign indicates a significant difference between the two devices in the same nasal geometry.

Posterior region (circled)

Range of FP: 12-99% of dose in target regions **Range of FF:** 29-92% of dose in target regions

** = significant difference between the 2 groups (observed in 16 of 40 nasal cavities).

Predictive Tools for Generic Product Development & Assessment

Rodrigo Cristofoletti, Ph.D.

Assistant Professor & Associate Director

Center for Pharmacometrics & Systems Pharmacology

UF | College of Pharmacy
UNIVERSITY of FLORIDA

Predicting food-formulation interaction

- **Generic drugs:**

- **FACT:** co-administration of food with oral drug products can impact drug bioavailability on a formulation-dependent way.

- **CONSEQUENCE:** FDA recommends that applicants conduct a fed BE study, in addition to a fasting BE study, except when the RLD labeling states that the product should be taken on an empty stomach

- **ALTERNATIVE:** generating Model Integrated Evidence for waiving fed BE studies
  - Integrating in vitro biopharmaceutics data under fasting and fed state conditions, PBPK modeling and fasting BE study

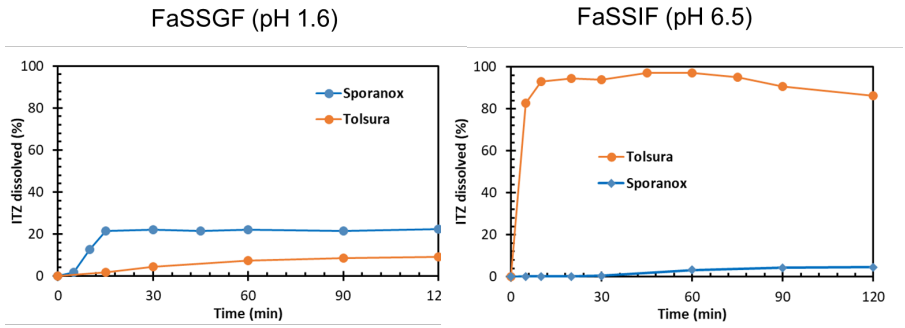
Manuscript in preparation

UF College of Pharmacy UNIVERSITY of FLORIDA

Predicting food-formulation interaction

- A tale of 2 amorphous solid dispersions (ASD) containing itraconazole:
  - Tolsura® contains hypromellose phthalate (pH-dependent)
  - Sporanox® contains hypromellose (pH-independent)

Notice of Award
FAIN# U01FD007352
Federal Award Date
07/20/2021



More research in oral IVIVE-PBPK modeling is needed to access the generalizability of these findings, which may streamline the development of complex oral generic formulations (*e.g.* ASD)

- Fasted PBPK model recapitulated Sporanox® and Tolsura® PK and fasted BE

- Fed PBPK model recapitulated:
  - Positive food effect on Sporanox®
  - Slightly negative food effect on Tolsura®

Manuscript in preparation

Lung PBPK modeling

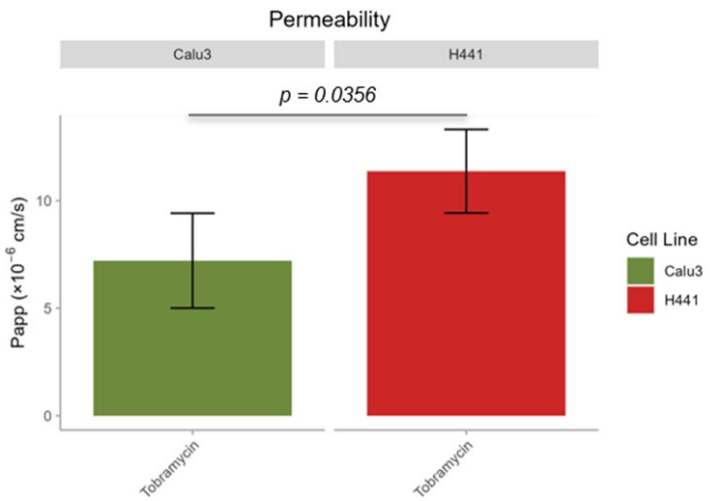
FDA U.S. FOOD & DRUG ADMINISTRATION

AWARD/CONTRACT

2. CONTRACT (Proc. Inst. Ident.) NO.
75F40122C00182

- In lung PBPK models we generally assume the same permeability across bronchial and alveolar epitheliums

- However, in vitro permeability studies across Calu-3 (representing bronchial epithelium) and NCI-H441 (representing alveolar epithelium) monolayers showed statistically significant differences:



Manuscript in preparation

UF College of Pharmacy UNIVERSITY of FLORIDA

Lung PBPK modeling

U.S. FOOD & DRUG ADMINISTRATION
AWARD/CONTRACT
2. CONTRACT *(Proc. Inst. Ident.)* NO.
75F40122C00182

- We also investigated tobramycin permeability across an organotypic model generated with primary human lung cells (MucilAir™, Epithelix):

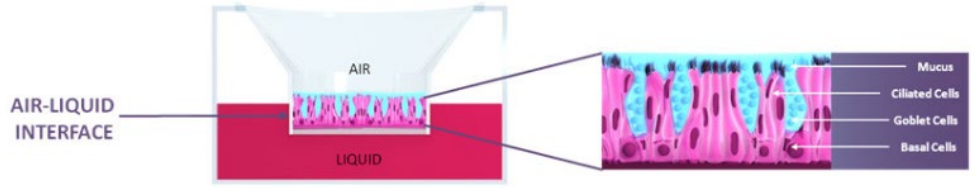
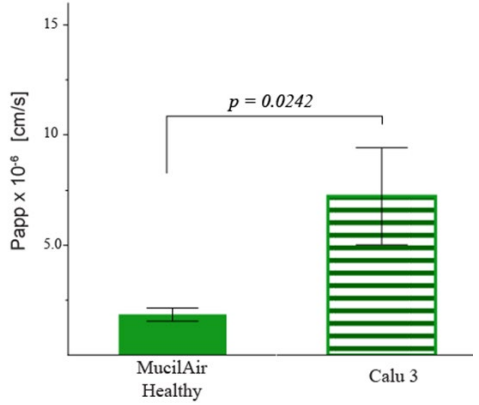


Figure representing the three cell types in MucilAir™ : basal, ciliated and goblet cells

- Apparent permeability measurements differ between 2D *in vitro* monolayers formed by immortalized Calu-3 cells and the 3D organotypic bronchial model



More research assessing segment-dependent absorption across lung epithelium is needed to support the development of lung PBPK models

Manuscript in preparation

UF College of Pharmacy UNIVERSITY of FLORIDA

Thank you

UF College of Pharmacy
UNIVERSITY of FLORIDA

Intersubject Variability in Pediatric Nasal Drug Delivery via Nasal Sprays

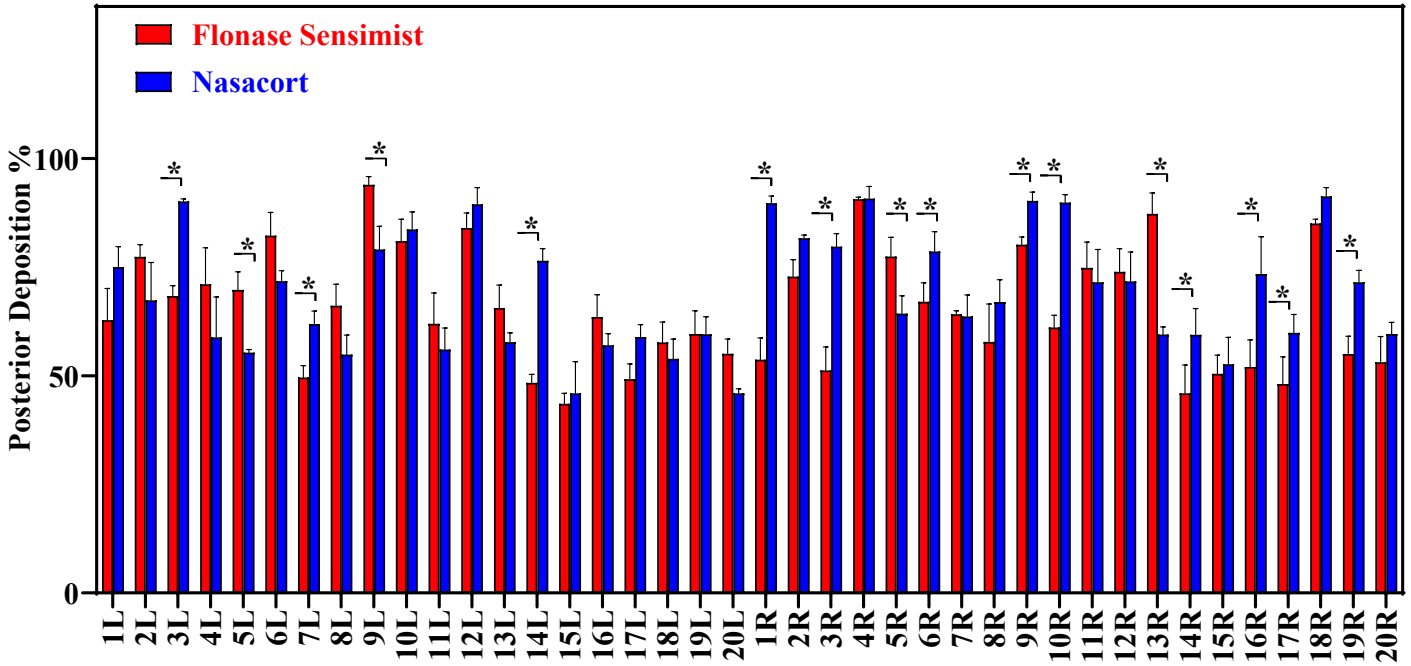


Figure 3 - Statistical analysis to identify models with significantly different PD between Flonase Sensimist and Nasacort. The star (*) sign shows the models with significantly different PD comparing the two devices.

Table 1- Maximum, average and minimum PD of Flonase Sensimist and Nasacort, across all 40 nasal cavities.

	Average PD (%)	
	Nasacort	Flonase Sensimist
Minimum	45.94±1.07	43.53±2.42
Mean	69.14±13.34	65.32±13.45
Maximum	91.31±1.99	93.99±1.87

Nasal Models Representing the Range of Drug Delivery in Adults and Children 2-11 years old

- By choosing nasal models that represent the entire population, we can account for intersubject variability while also considering time and cost constraints.
- Three nasal geometries, for each age group, were selected to represent three levels of posterior deposition: low (L), mean (M), and high (H) posterior deposition. Further details are provided below.

Table 2 - Final selected low (L), mean (M), and high (H) adult models.

	Model	Age	Gender	Race	Average PD (%)	
					Flonase	Flonase Sensimist
L	3-Right	63	F	White	39.3±8.5	26.6±7.4
M	7-Left	35	M	Middle Eastern	54.7±8.8	48.4±1.8
H	2-Left	22	F	African American	88.9±2.3	87.1±1.5

Table 3 - Final selected low (L), mean (M), and high (H) pediatric models.

	Model	Age	Gender	Race	Average PD (%)	
					Nasacort	Flonase Sensimist
L	15-Left	9	F	African American	45.96±7.29	43.54±2.42
M	7-Right	5	F	White	63.67±4.93	64.21±0.73
H	4-Right	3	F	Hispanic	90.81±2.79	90.65±0.48

Regionally Sectioned Representative Nasal Models for Bioequivalence Studies

- The posterior region of the selected nasal cavities was sectioned into subregions: front, superior, middle, inferior turbinate regions, and nasopharynx.
- The *in vitro* regional drug deposition in each nasal model was studied using a controlled method for reference and test products.
- The population BE (PBE) of test products in comparison to reference product was performed for each model and its regions.

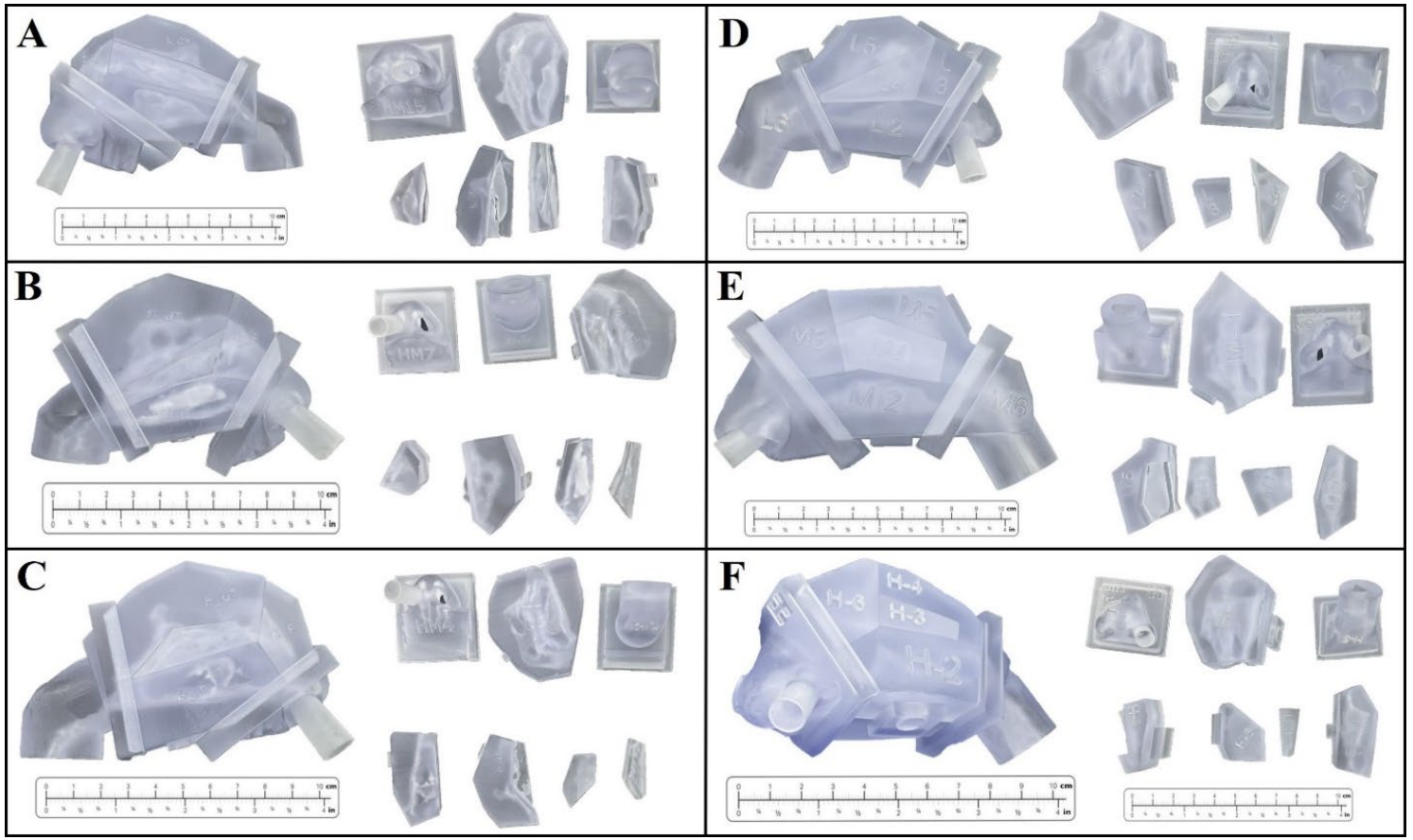


Figure 4. Representative pediatric (panels A, B and C) and adult (panels D, E and F) sectioned nasal models.

Evaluation of Population Bioequivalence (PBE)

- The PBE method, provided in Draft Guidance on Fluticasone Propionate by the FDA, was assessed in all regions of 6 models for two generic products of triamcinolone acetonide in comparison to Nasacort.

- The regulatory constants used were: BE limit = 1.11 (in vitro) and 1.25 (in vivo), $\varepsilon_p = 0.01$, $\sigma_{T0} = 0.1$.

- Complicated geometry of nasal airways can cause significant differences in regional deposition and by testing with these models as assessment tools early in the development process failure in in vivo studies may be avoided.

- Recommendations on an appropriate BE limit and analysis seems to be warranted.

BE Limit = 1.11

	Anterior	Front	Inferior	Middle	Superior	Nasopharynx
L - Leader						
L - Perrigo						
M - Leader						
M - Perrigo						
H - Leader						
H - Perrigo						

BE Limit = 1.25

	Anterior	Front	Inferior	Middle	Superior	Nasopharynx
L - Leader						
L - Perrigo						
M - Leader						
M - Perrigo						
H - Leader						
H - Perrigo						

Age group in which PBE was established: Both | Just Child | Just Adult | Neither

Other Key Questions Explored with the Developed Tools

- How does disease affect regional drug deposition? Are representative models based on healthy airways relevant to diseased airways?

- Is consideration of variation in breathing patterns critical in evaluation of nasal sprays?

- How sensitive is the regional drug deposition to the user-related parameters or administration parameters of nasal sprays, i.e. administration angles, insertion depth?

Examples of Other Remaining Considerations for Evaluating Drug Delivery with Nasal Drug Delivery Products

- Protective aspects of nasal cavity such as mucociliary clearance and the interaction of formulations in different forms, e.g. powder, with mucosa and cells should be considered by including biorelevant features.

- Given the growing interest in intranasal vaccines, understanding the intersubject variability in intranasal delivery in infants (<2 years old) would be beneficial.

- Other nasal drug delivery products and applications beyond locally-acting drugs, e.g. nose to brain, call for similar evaluation approach to provide product developers with pre-clinical assessment tools.

Acknowledgements

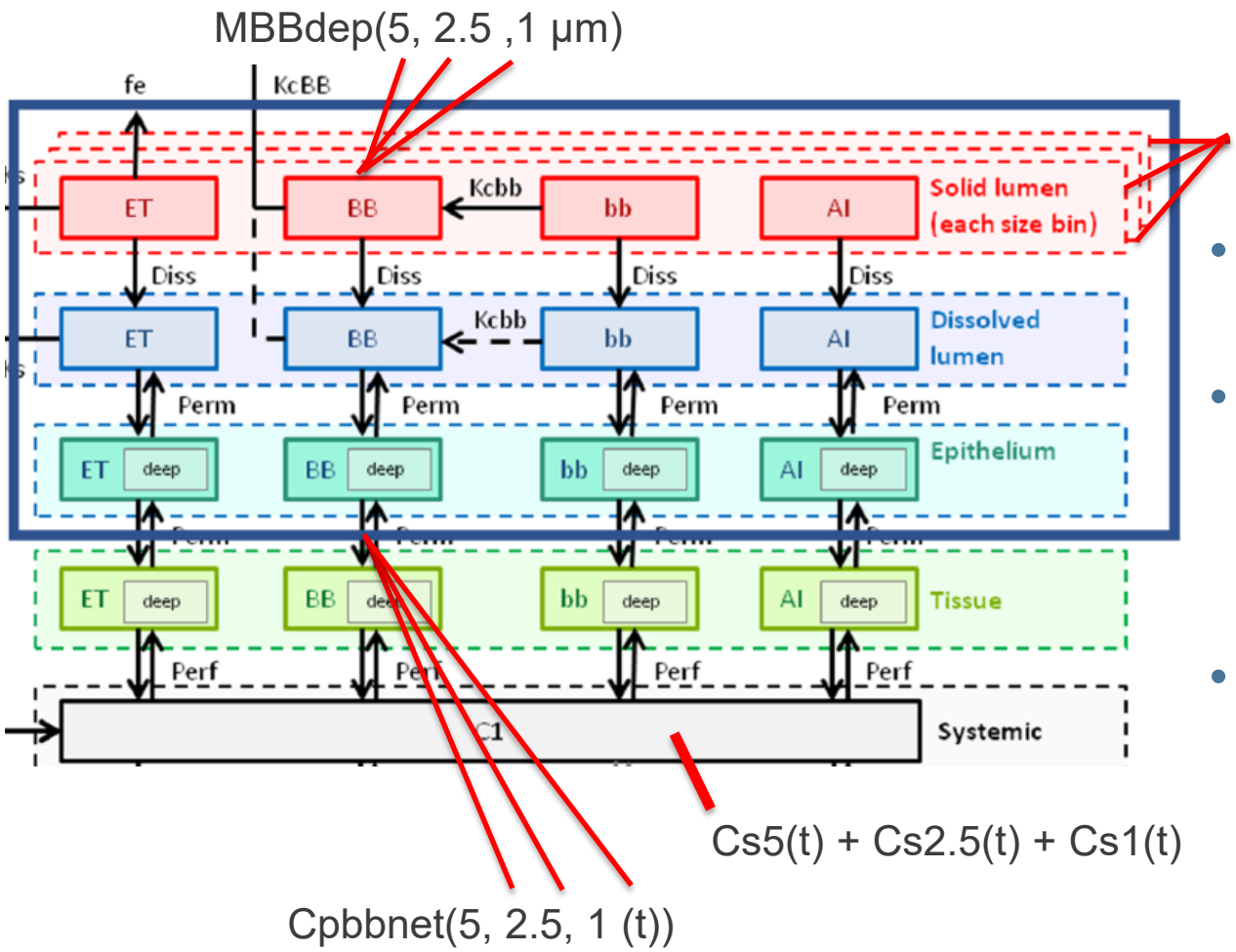
VCU Collaborators: Dr. David Edwards , Dr. Mike Hindle, Dr. P. Worth Longest, Dr. Theodore Schuman
FDA Collaborators: Dr. Andrew Babiskin, Dr. Sneha Dhapare, Dr. Anubhav Kaviratna, Dr. Bryan Newman, Dr. Ross Walenga
RARE Lab Contributors: Dr. Ali Alfaifi, Dr. Amir Reza Esmaeili, Mohammad Hejazi, MSc, Dr. Sana Hosseini, Dr. Prakash Khadka, Dr. Michele Manniello, Xiomara (Maria) Owen, Dr. John Wilkins

Funding: Department of Health and Human Services, U.S. Food and Drug Administration(2 Awards).

Views expressed in this talk do not necessarily reflect the official policies of the U.S. Food and Drug Administration, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

* All last names are listed in alphabetical order and the order does not necessarily reflect the order of contributions.

Advancing kinetic data from size-separated aerosols towards human systemic data using PBPK models



- Preludium is prepared for modelling of size separated aerosols
- Data will be derived from both typical- (Noyes-Whitney), as well as atypical dissolution processes of for example engineered particles
- Broader understanding of the link between particle size and lung disposition

Bäckman et al. 2022

Inhalation Sciences

Thank You