Fiscal Year 2024
Generic Drug Science & Research Initiatives
Public Workshop

For more information, please visit:

WELCOME!

We will begin promptly at 8:00 A.M Eastern Time (GMT -4)

Session Introduction
Public Comments

Dr. Sam Raney

Associate Director for Science &

Chief Scientific Advisor

Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration

Session 3 Faculty
Bold Italics Denotes Presenter

Moderator

Dr. Sam Raney, MS, PhD, Associate Director for Science & Chief Scientific Advisor
ORS, OGD, CDER, FDA

Public Panelists

- Tausif Ahmed, MS, PhD, VP & Head, Biopharmaceutics & Bioequivalence, GCM, Dr. Reddy's Laboratories Ltd.
- Pradeep Dabhi, PhD, Co-Founder and Chief Scientific Officer, Cutyx Research
- William Ganley, PhD, Sr. Specialist, Nanopharm, an Aptar Pharma company
- Andrew Graves, MS, Director, Immunogenicity Assessment, Specialty Bioanalytics, Teva
- Ripen Misri, PhD, Sr. Director, Liquids & Specialty Dosage Forms, Global R&D, Apotex Inc.
- ***Prabhakar Reddy, PhD, Director, Pharmaceutical Sciences, United States Pharmacopeia***
- ***Anna Schwendeman, PhD, Co-Director, CRCG and Prof., Univ. of Michigan***
- Thomas Tice, PhD, Sr. Director, Global Strategic and Technical Marketing, Health Care, Evonik Corp

FDA Panelists

- Meng Hu, PhD, Team Lead, DQMM, ORS, OGD, CDER, FDA
- Yan Wang, PhD Acting Deputy Director, DTP I, ORS, OGD, CDER, FDA
- Eric Pang, PhD, Senior Chemist, DTP I, ORS, OGD, CDER, FDA
- Cameron Smith, PhD, Supervisory Chemist, DPQA-IV, OPQA-I, OPQ, CDER, FDA
- Daniela Verthelyi, PhD, Supervisory Biologist, DPQR-IV, OPQR, OPQ, CDER, FDA
- Deyi Zhang, PhD, Senior Chemist, DTP I, ORS, OGD, CDER, FDA
- Lei Zhang, PhD, Deputy Director, ORS, OGD, CDER, FDA

Public Comments for Session 3

In Person Comments:

- ***Alexander Shekhtman, PhD, Professor and Chair, Department of Chemistry, University at Albany, State University of New York***
- ***Marco Guerrini, MS Director Istituto di Ricerche Chimiche e Biochimiche***
- ***Jace Jones, PhD Assistant Professor University of Maryland***
- ***Andrew Graves, MS, SCYM Director, Immunogenicity Assessment Teva***
- ***David Borhani Senior Director, Business Development Ginkgo Bioworks***
- ***Ravishankara MN, PhD Senior General Manager (R & D) Sun Pharma***
- ***Marina Juretić, PhD Senior Analytical Scientist, R&D, IVR/IVIVC PLIVA Hrvatska***
- ***Itay Speicher, BSc, MBA Sr. Director of Business Development DigiM Solution***
- ***Jon Lenn, PhD Chief Scientific Officer MedPharm***
- Marc Taraban, PhD Associate Research Professor University of Maryland Baltimore
- Grzegorz Garbacz, PhD Co-Founder & CEO Physiolution Polska
- Laura Philips, PhD President & CEO Spheryx, Inc
- Katherine M. Harris, PhD Principal Scientist Carelon Research
- James K. Ferri, PhD Professor Virginia Commonwealth University

Virtual Comments:

- Conor L. Evans, PhD Associate Professor Harvard Medical School
- Matthias Wacker, PhD Associate Professor National University of Singapore
- Tao Zhang, PhD Assistant Professor, Pharmaceutical Sciences SUNY Binghamton University
- Hannah Batchelor Professor University of Strathclyde
- Jozef Al-Gousous, PhD Adjunct Assistant Professor University of Michigan
- Panos Macheras, PhD Professor Emeritus National and Kapodistrian University of Athens
- Hala Fadda, PhD Professor of Pharmaceutics Butler College
- Kathleen Walsh, MSc, MD Director, Patient Safety Research Center Boston Children's Hospital, Harvard University
- Alexa Simon Meara, MD Associate Professor The Ohio State University Wexner Medical Center
- Jacqueline Griffin Associate Professor Northeastern University
- Molly Moore Jeffery, PhD Robert D. and Patricia E. Kern Honored Investigator in the Science of Health Care Delivery | Scientific Director of Emergency Medicine Research and Platform Knowledge Solutions | Associate Professor Emergency Medicine Mayo Clinic
- Ozlem Ergun, PhD; Daniel Kosmas, PhD Professor Northeastern University
- Fang Yu, PhD Computational Modeling Scientist CONTINUUS Pharmaceuticals, Inc.
- Dongmei Li, PhD Professor, Clinical and Translational Research, Obstetrics and Gynecology and Public Health Sciences University of Rochester School of Medicine and Dentistry
- James Hasty CEO/Founder BHEC
- Peter Gompper Co-Founder, Rubitel

Generic RNA based drugs: challenges in analytical characterization

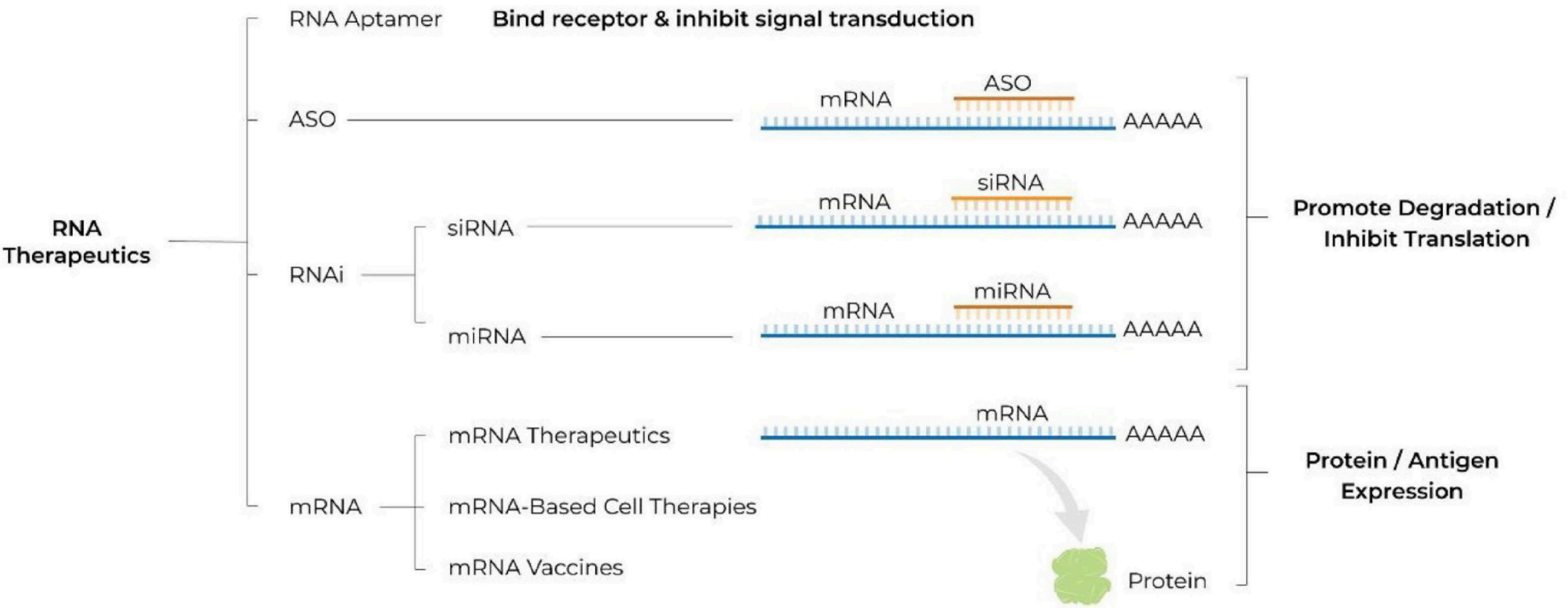
Alexander Shekhtman

Department of Chemistry

University at Albany, State University of New York

FY24 GDUFA Public Workshop

RNA Therapeutics– Different Modalities

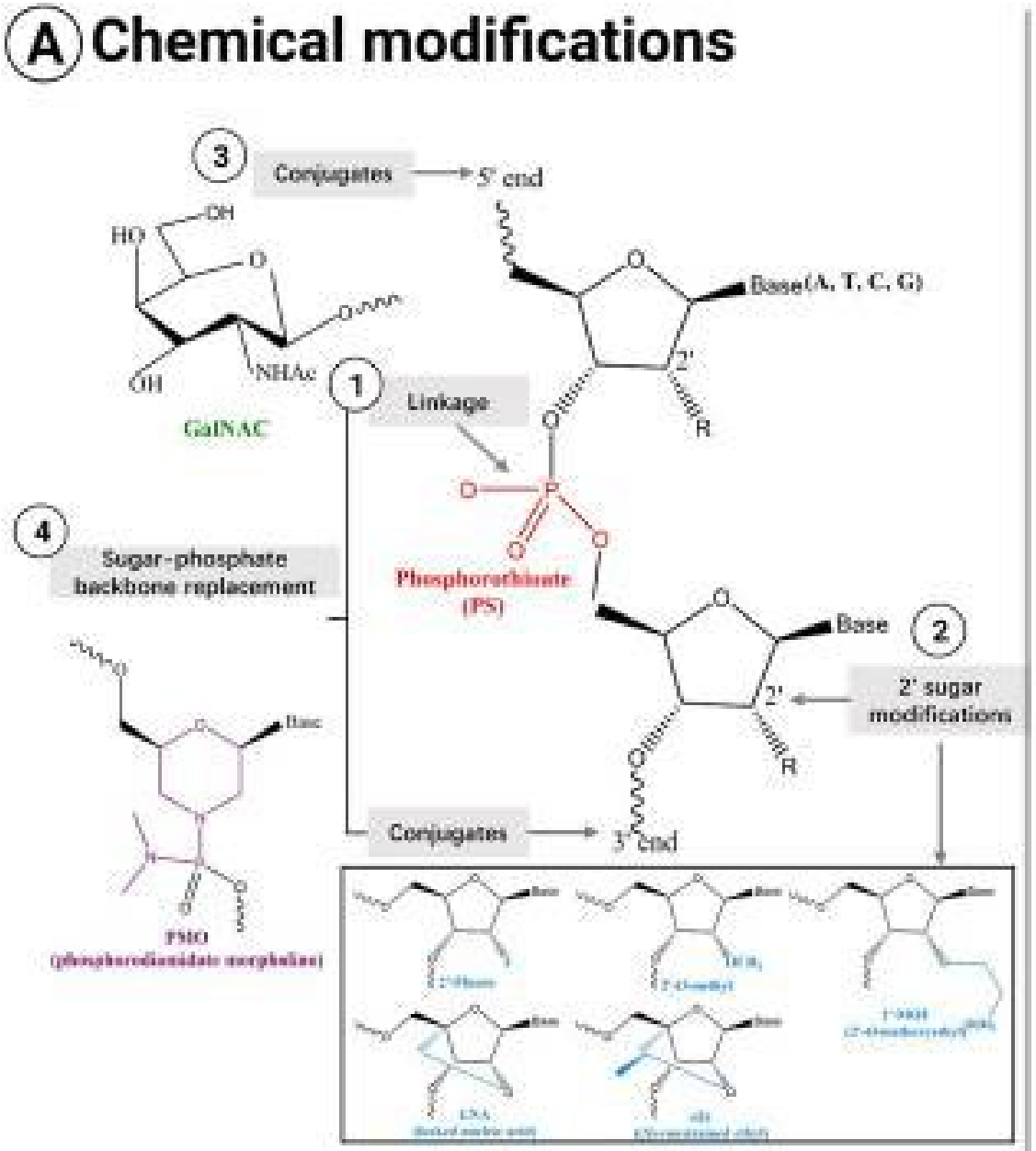


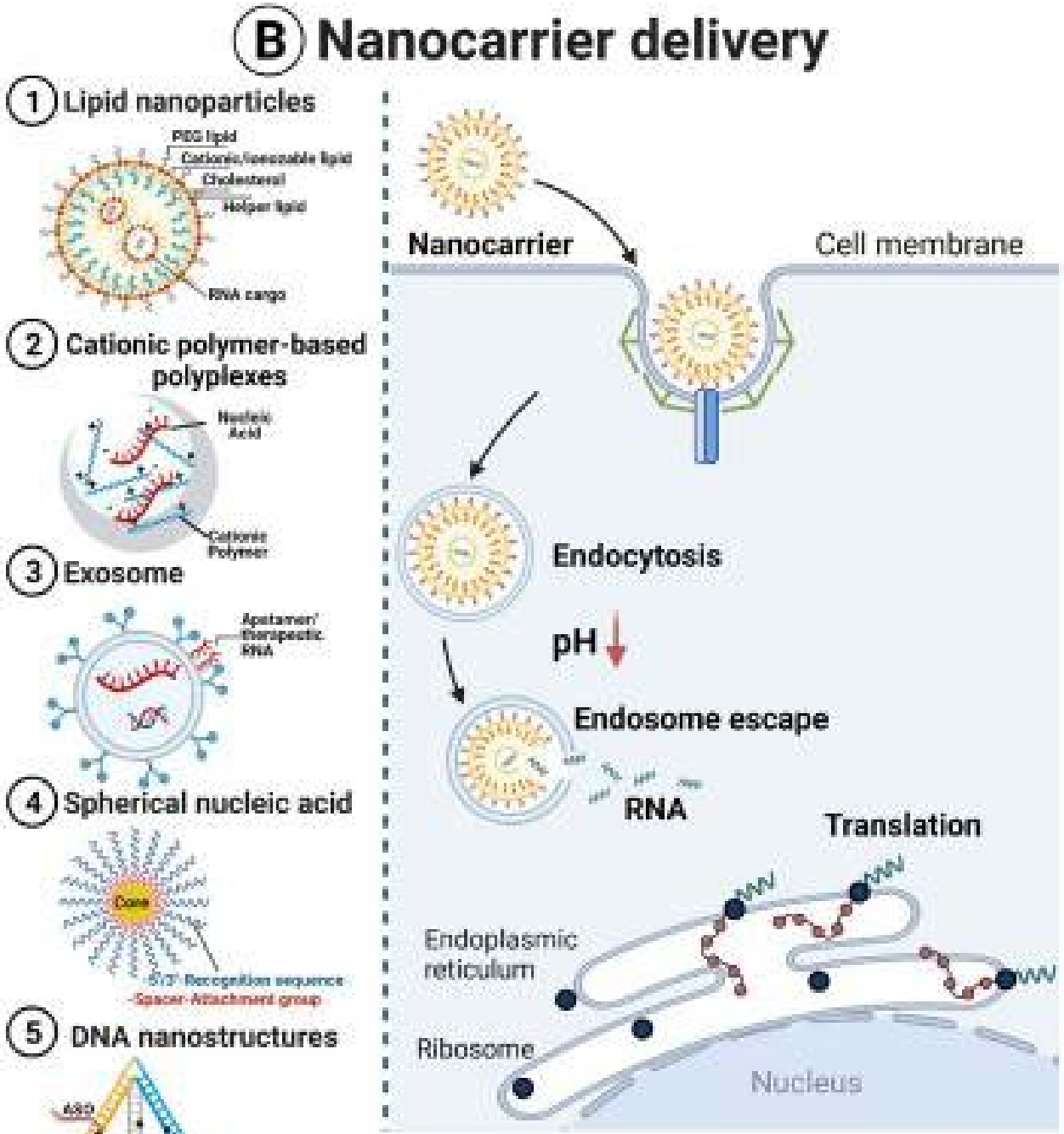
35 RNA Drugs—FDA Approved and in clinical trials

Drug	Type of RNA	Company	Route of delivery	Condition/Disease	Status
Nusinersen (Spinraza)	ASO	Ionis	Intrathecal	Spinal muscular atrophy	FDA approval in 2016
Eteplirsen (Exondys 51)	ASO	Sarepta	Intravenous	Duchenne muscular dystrophy	FDA approval in 2016
Inotersen (Tegsedi)	ASO	Ionis	Subcutaneous	Familial amyloid polyneuropathy	FDA approval in 2018
Volanesorsen (Waylivra)	ASO	Ionis	Subcutaneous	Familial chylomicronemia syndrome	EU approval in 2019
Patisiran (Onpattro)	siRNA	Alnylam	Intravenous	Polyneuropathy	FDA approval in 2018
Givosiran (Givlaari)	siRNA	Alnylam	Subcutaneous	Acute hepatic porphyria	FDA approval in 2019
Cobomarsen (MRG-106)	miRNA	miRagen (Viridian)	Intravenous/subcutaneous	Blood cancers	Phase II
Remlarsen (MRG-201)	miRNA	miRagen (Viridian)	Intradermal	Keloids	Phase II
MRG-110	miRNA	miRagen (Viridian)	Intradermal	Tissue Repair	Phase I
Pegaptanib (Macugen)	Aptamer(RNA)	Bausch + Lomb	Intravitreal	Macular Degeneration	FDA approval in 2014
Emapticap pegol (NOX-E36)	Aptamer(RNA)	NOXXON	Intravenous/Subcutaneous	Diabetic nephropathy, lung and pancreatic cancer	Phase II
Olaptesed pegol (NOX-A12)	Aptamer(RNA)	NOXXON	Intravenous	Brain cancer	Phase I/II
BNT162b2	mRNA	BioNTech and Pfizer	Intramuscular	COVID-19	FDA authorization for emergency use in 2020
mRNA-1273	mRNA	Moderna	Intramuscular	COVID-19	FDA authorization for emergency use in 2020
CVnCoV	mRNA	CureVac	Intramuscular	COVID-19	Phase III
AZD8601	mRNA	Moderna/Astrazeneca	Epicardial	Ischemic heart disease	Phase II
mRNA-1647	mRNA	Moderna	Intramuscular	Cytomegalovirus infection	Phase II
P-BCMA-101	mRNA	Poseida	Intravenous	Multiple myeloma	Phase II
mRNA-4157	mRNA	Moderna	Intramuscular	Cancer	Phase II
mRNA-3704	mRNA	Moderna	Intravenous	Methylmalonic aciduria	Phase I/II
MRT5005	mRNA	Translate Bio	Inhalation	Cystic Fibrosis	Phase I/II
mRNA-2416	mRNA	Moderna	Intratumoral	Solid tumors/ lymphoma/advanced ovarian carcinoma	Phase I/II
BNT131 (SAR441000)	mRNA	BioNTech/ Sanofi/Genmab	Intratumoral	Advanced melanoma	Phase I/II
Descartes-08	mRNA	Cartesian	Intravenous	Generalized myasthenia gravis	Phase I/II
BNT122	mRNA	BioNTech	Intravenous	Solid tumors	Phase I/II
mRNA-2752	mRNA	Moderna	Intratumoral	Solid tumors	Phase I
MEDI1191	mRNA	Moderna	Intratumoral	Solid tumors	Phase I
mRNA-1944	mRNA	Moderna	Intravenous	Chikungunya infection	Phase I
CV8102	mRNA	CureVac	Intratumoral	Solid tumors	Phase I
ARCT-810	mRNA	Arcturus	Intravenously	Urea disorder	Phase I
CV7202	mRNA	CureVac	Intramuscular	Rabies	Phase I
mRNA-1893	mRNA	Moderna	Intramuscular	Zika	Phase I
CV9202	mRNA	CureVac	Intradermal	Non-small cell lung cancer	Phase I
mRNA-5671	mRNA	Moderna	Intravenous	Cancer	Phase I
BNT111	mRNA	BioNTech	Intravenous	Advanced Melanoma	Phase I

The table summarizes information available at ClinicalTrials.gov (https://clinicaltrials.gov/) as of January 26, 2021. ASO, antisense oligonucleotide; siRNA, small interfering RNA; miRNA, microRNA; RNA, ribonucleic acid; mRNA, messenger RNA.

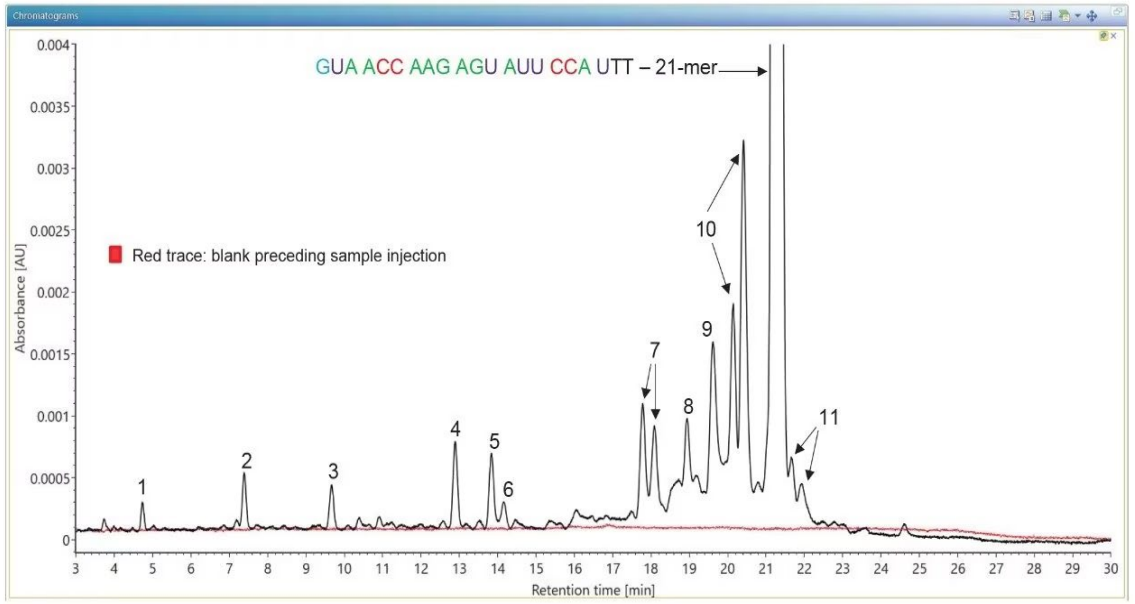
Damase et al, Frontiers in Bioengineering, 2022

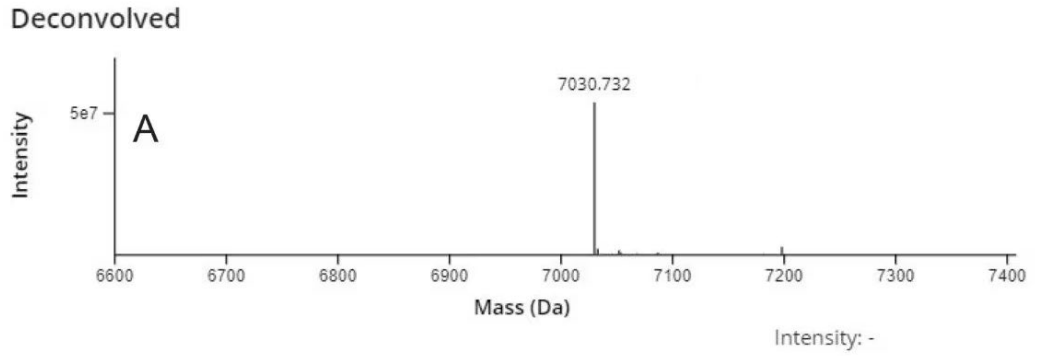


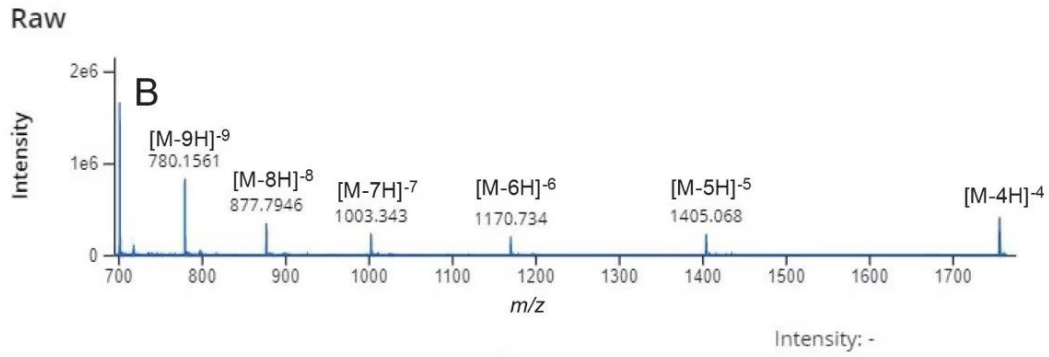


Yiran Zhu et al *Cell Death & Disease* **13**, 644 (2022)

LC-MS Characterization of RNA oligonucleotides







NMR and Vibration Spectroscopy based characterization of RNA pharmaceuticals

- Solution based
- Minimal preparation
- Tunable to functional groups
- Amenable to characterizing impurities
- Fast and non-destructive
- Can be used at POS.

Thank you!

FY 2024 GDUFA Public Workshop

Silver Spring, May 20-21

RONZONI·INSTITUTE
CHEMICAL AND BIOCHEMICAL RESEARCH
NONPROFIT RESEARCH FOUNDATION

Marco Guerrini

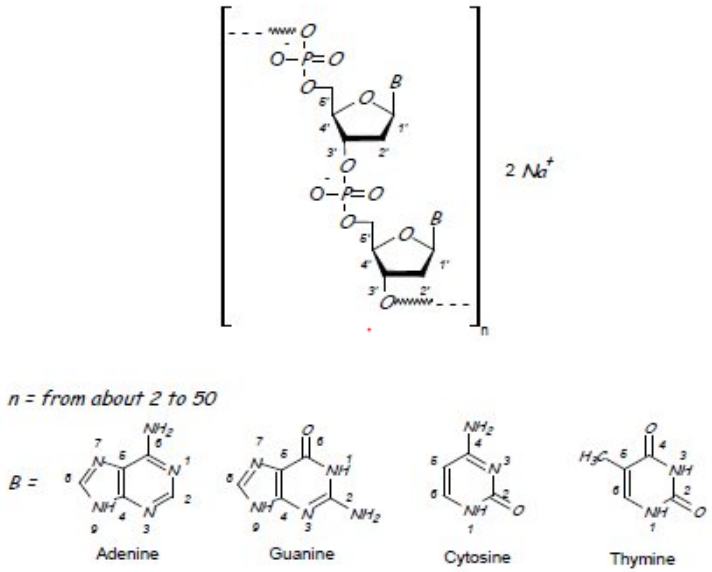
Director of
Institute for Chemical and Biochemical Research **G. Ronzoni** Milan, Italy

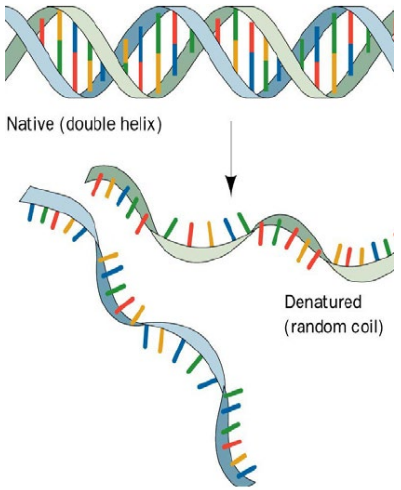
Research area 2A: Developing novel analytical methods, as well as improving and standardizing existing methods, to characterize components (including impurities) that can support a demonstration of sameness for oligonucleotide APIs.

Defibrotide

- ✓ Defibrotide is a “multi-targets compound” indicated for treatment of hepatic veno-occlusive disease (VOD).

- ✓ It is a mixture of 90% single-stranded phosphodiester oligonucleotides (length, 9-80mer; average, 50mer with an average molecular mass of 16.5 ± 2.5 KDa) and 10% double stranded phosphodiester oligonucleotides, derived from the controlled depolymerization of porcine intestinal mucosal DNA.





Draft Guidance on Defibrotide Sodium May 2023

1. ***Source of the starting material*** The starting material (animal source and organ tissue) used to manufacture the test active ingredient should be equivalent to that used to manufacture the active ingredient for the RLD.
2. ***Mode of depolymerization*** Depolymerization method used in the test active ingredient manufacturing process should be equivalent to that used in the RLD active ingredient manufacturing process.
3. ***Chemical structure, molecular weight distribution and composition*** Evaluation of test active ingredient and the active ingredient from the RLD should be performed to demonstrate comparable chemical structure, molecular weight distribution and composition. These could include but not be limited to the following:

    a. Elemental composition

    b. Nucleic base composition including purines/pyrimidines ratio

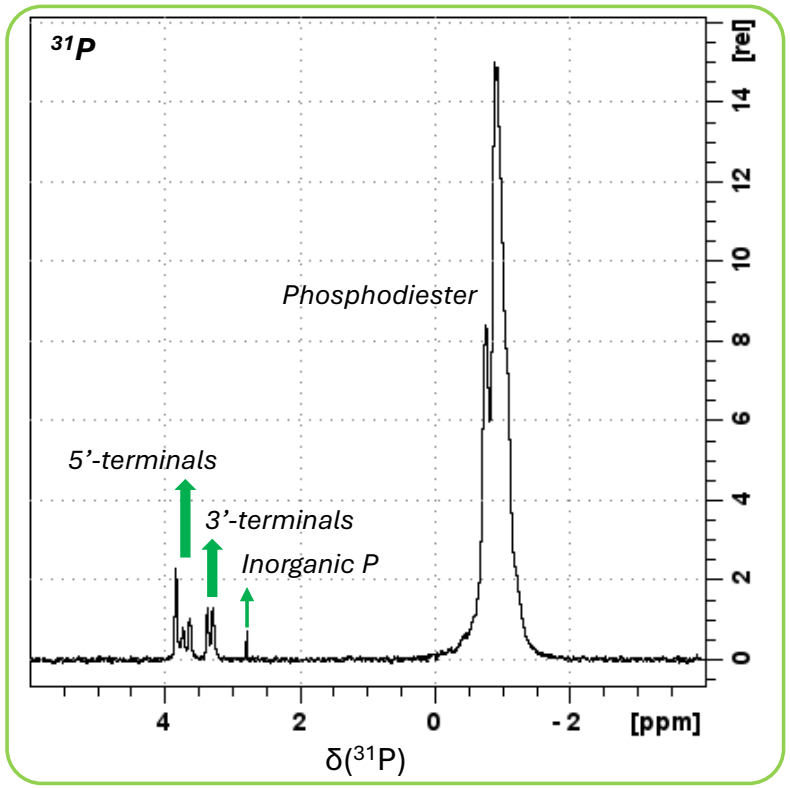
    c. Nucleic phosphorus content including sodium/phosphorus and phosphorus/base ratios

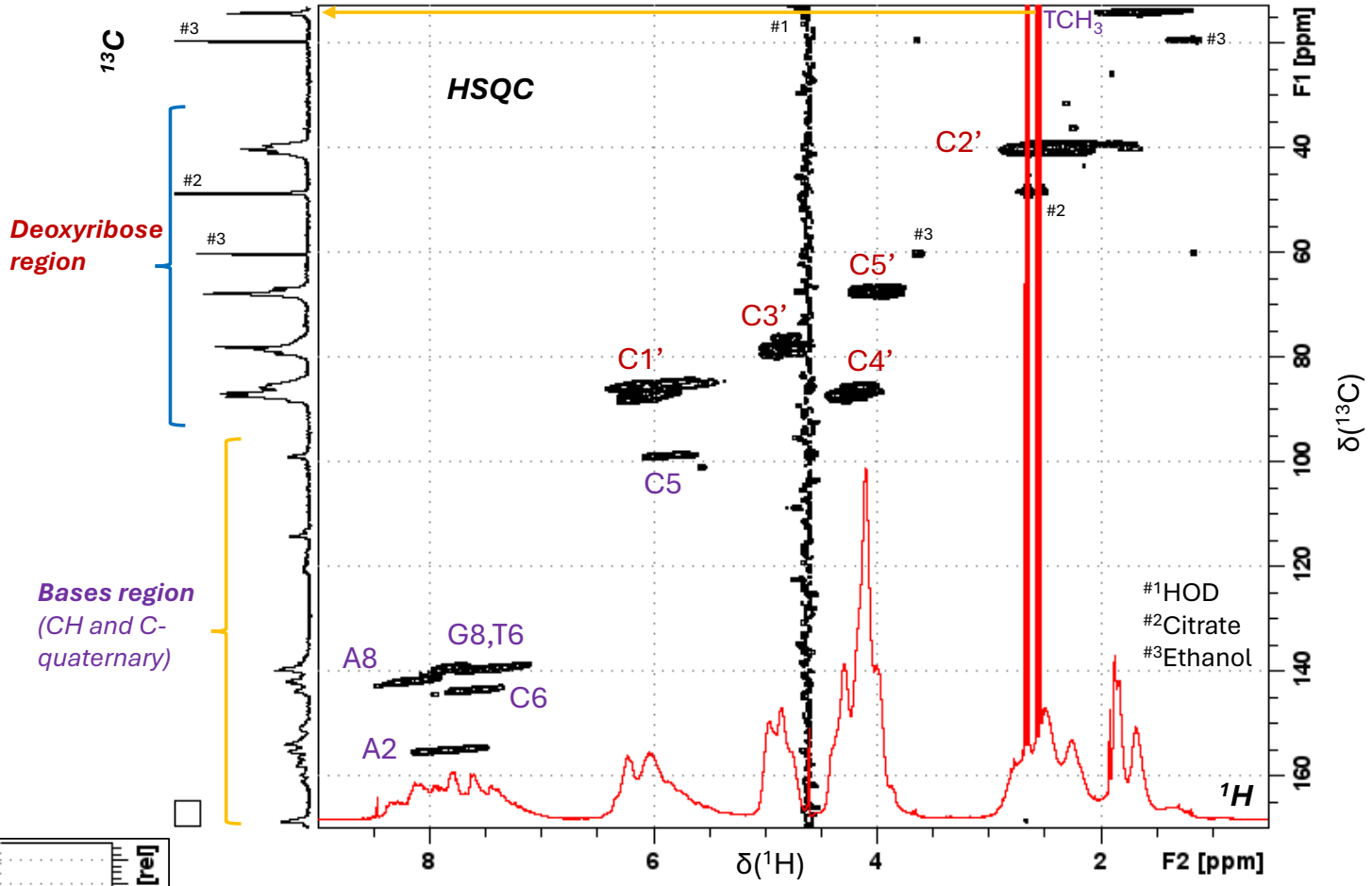
    d. **Fingerprint structural features using diverse spectroscopic technologies**

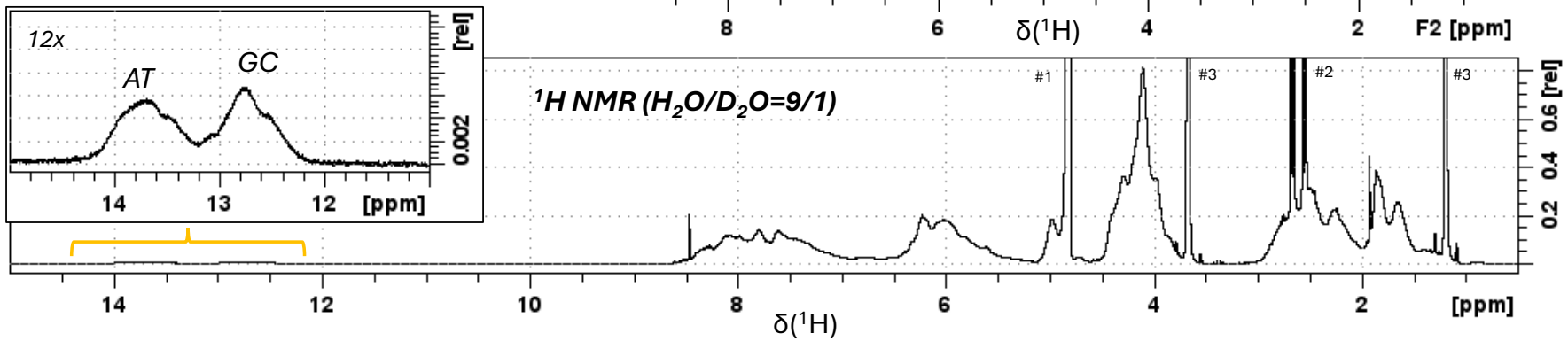
    e. Molecular weight and distribution, including mean molecular weight and polydispersity, point-to-point comparison and multiple fractions comparison (e.g., 3 – 6 kDa, 6 – 12 kDa, > 12 kDa, and > 41 kDa) of the molecular weight distribution curve

4. ***Physicochemical properties*** Side-by-side comparative physicochemical characterizations of the test and RLD products should be performed to include high order structures (e.g., through CD, melting temperature) and aggregation of the active ingredient in the drug product
5. ***Biological activity***

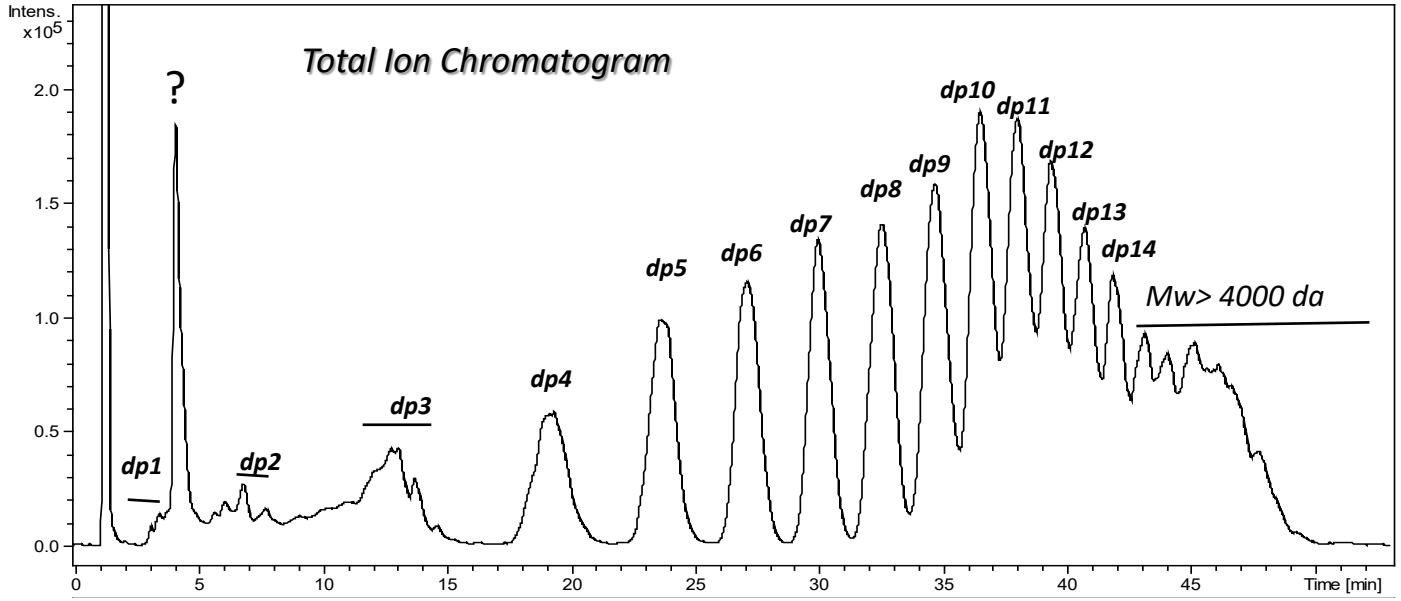
Defibrotide : NMR characterization

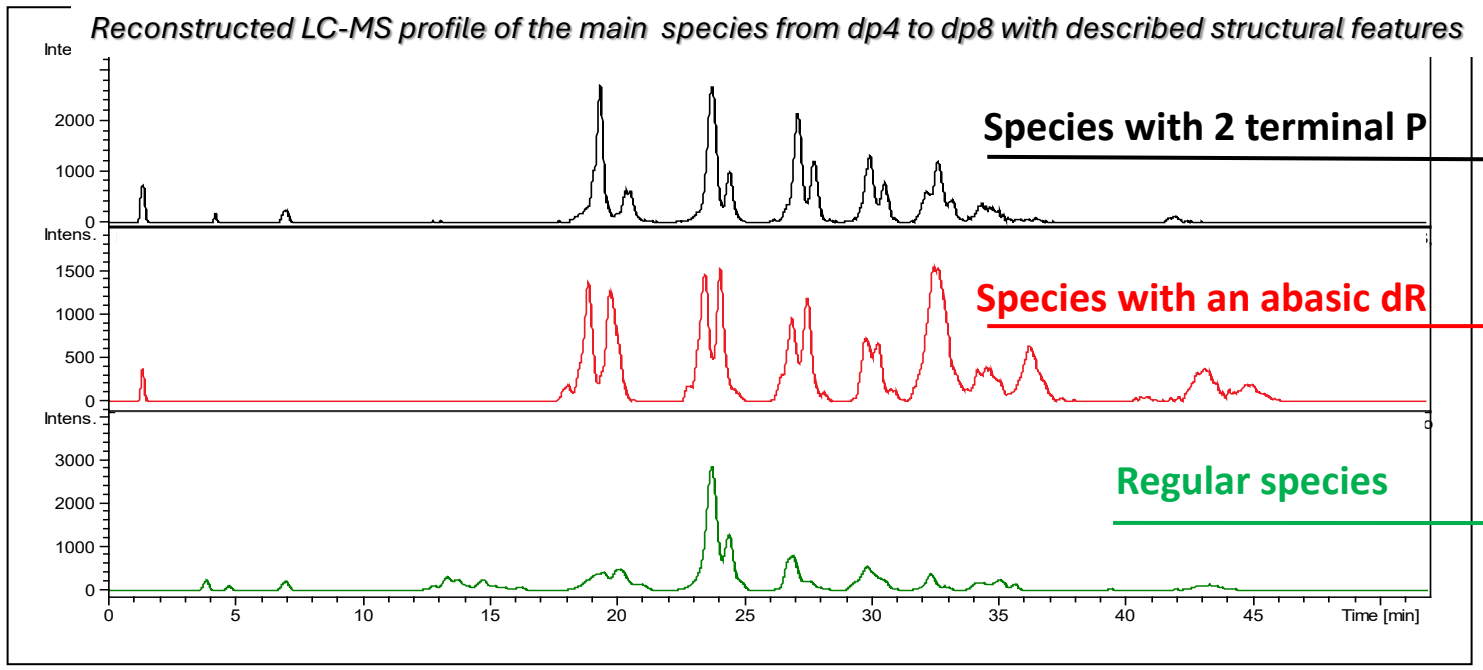


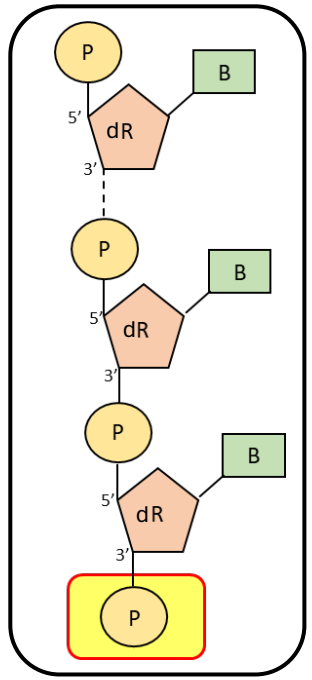


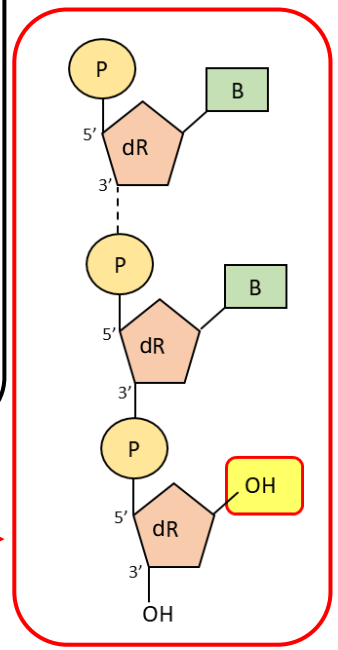


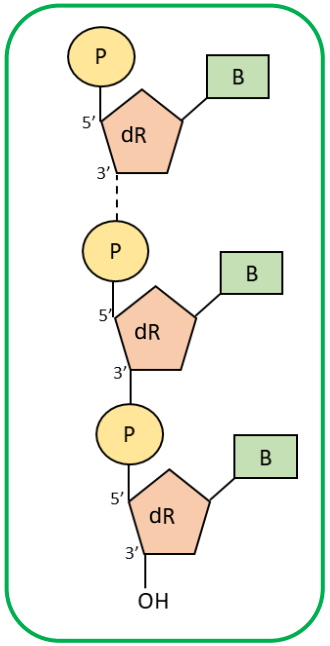
LC-MS characterization of whole Defibrotide











Present situation and future developments

Structural details detected and identified:

- ✓ Regular single stranded oligonucleotides
- ✓ Single stranded oligonucleotides with 2 terminal phosphates (P)
- ✓ Single stranded oligonucleotides with an abasic deoxyribose (*R*)

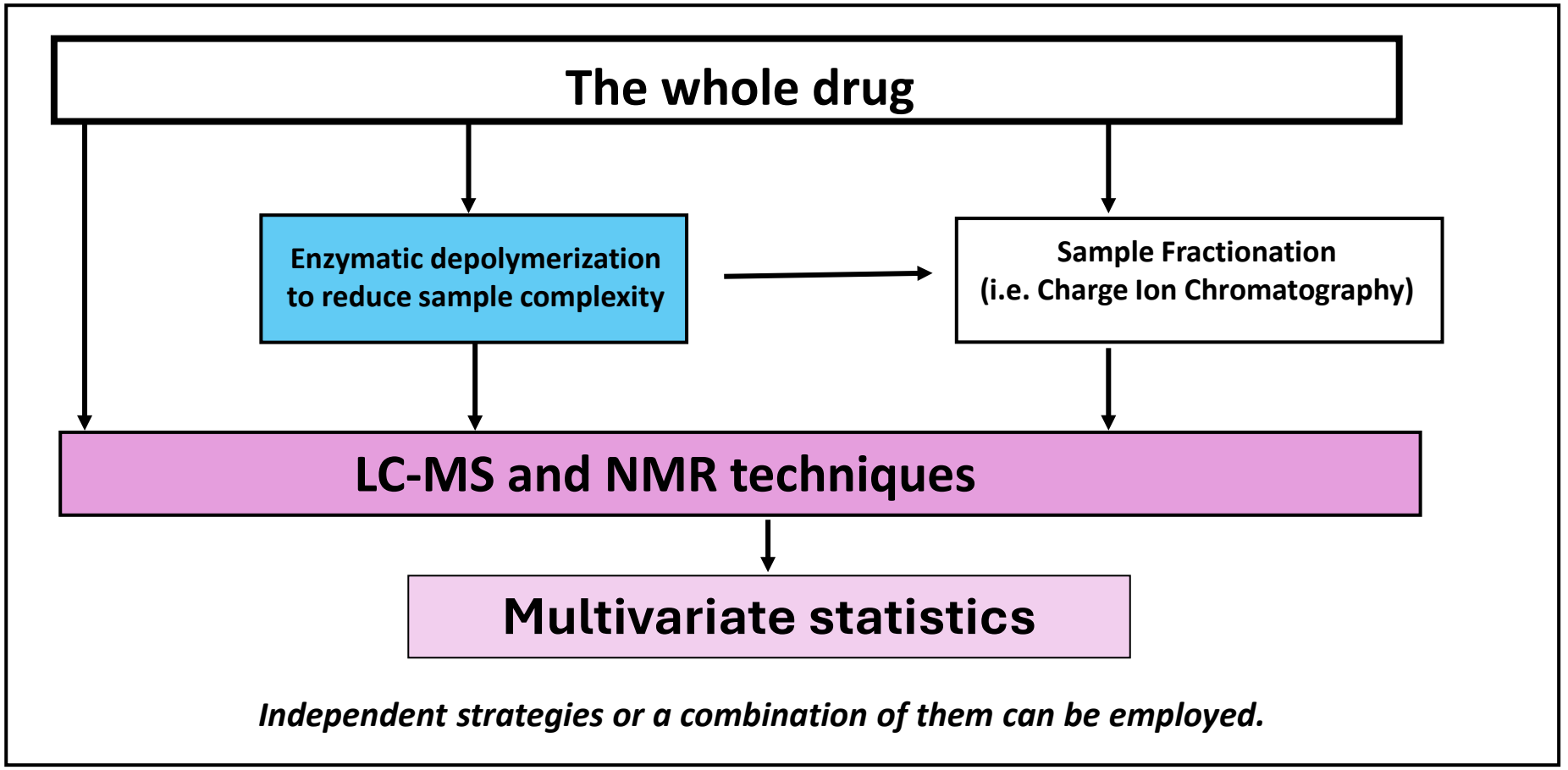
Possible oxidative damage of terminal abasic deoxyribose and its removal

Very likely depurination

MANUFACTURING PROCESS SIGNATURES

Structural modifications arising from oxidative damage and further chemical derivatives must be investigated

Possible strategies ….



…. for the development of methods:

- To monitor and possible quantify specific modifications reflecting the manufacturing process;
- To support active ingredient sameness.

Thank you!

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Jones Lab

Untangling the compositional complexity of oligonucleotide therapeutics for advancing drug development

Fiscal Year 2024 Generic Drug Science and Research Initiatives Public Workshop

21-May-2024

Jace W. Jones, Ph.D.
Department of Pharmaceutical Sciences
School of Pharmacy, University of Maryland

Untangling the compositional complexity of oligonucleotide therapeutics for advancing drug development

Scientific Problem:

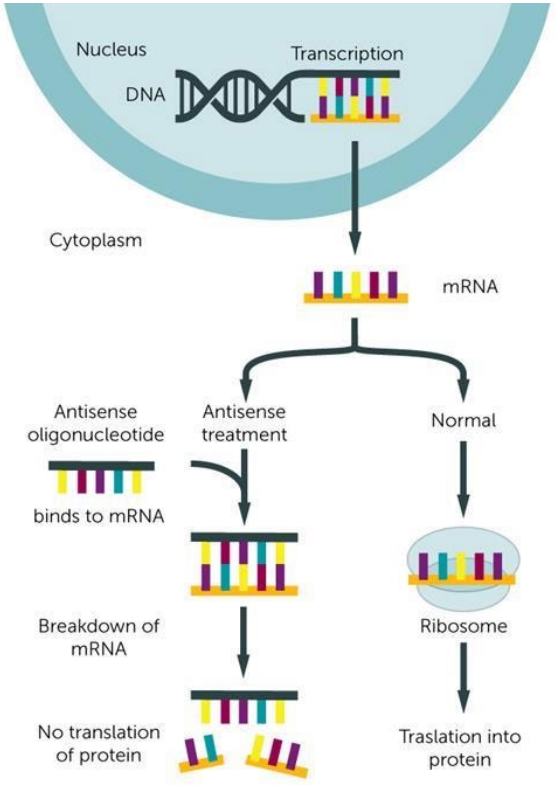
- ***How to support active ingredient sameness for generic drug development of phosphorothioate (PS) oligonucleotide therapeutics***

GDUFA Research Priority Areas :

- **Enhance the Efficiency of Equivalence Approaches for Complex Active Ingredients**
  - ***Developing novel analytical methods***, as well as improving and standardizing existing methods, to characterize components that can support a ***demonstration of sameness for oligonucleotide APIs***

Oligonucleotide (OGN) Drug Development

OGN Therapeutics

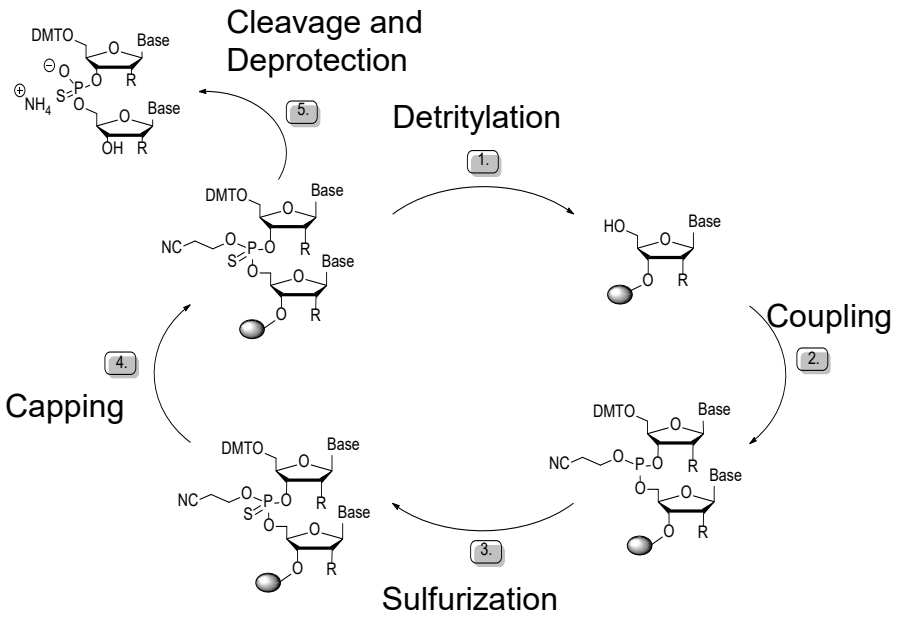


OGNs:

- Antisense Oligonucleotide (ASO)
- siRNA
- Regulate gene expression

https://www.chemistryworld.com/features/oligonucleotide-drugs-step-up/8968.article

Chemical Synthesis



Chemical Modifications:

- Sugar modifications
  - O-Me, MOE, F
- Base modifications
  - 5-methylcytosine
- Conjugates (GalNAc)
- Backbone modifications
  - Phosphorthioate (PS)

Impurities:

- Acetylation byproducts
- Truncations/Failed Sequences
- Incomplete deprotection
- Incomplete thiolation
- Deamination, Depurination

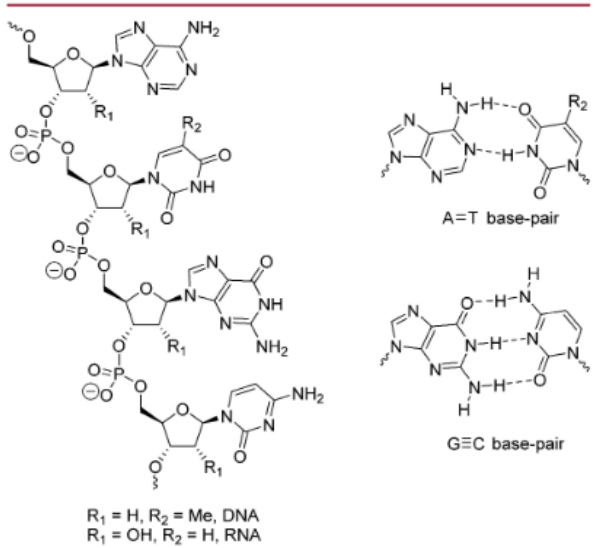


Figure 1. Structure of DNA and RNA and Watson–Crick base pairing.

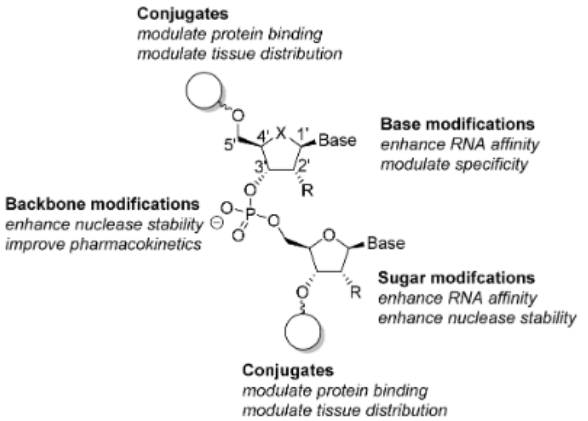


Figure 2. Sites for modification on a dinucleotide subunit.

Wan and Seth. J Med Chem. 2016 Nov 10;59(21):9645-9667.

OGN Therapeutics Consist of a Complex Mixture of Diastereomers

Phosphorothioate (PS) Linkages

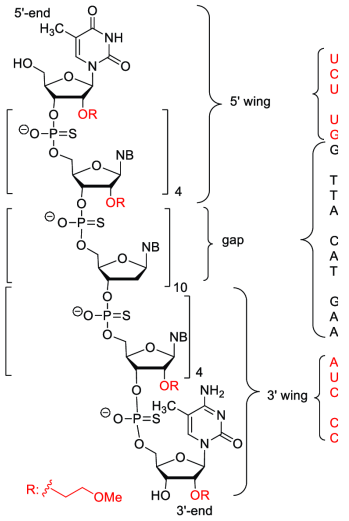
Considerations for API Sameness:

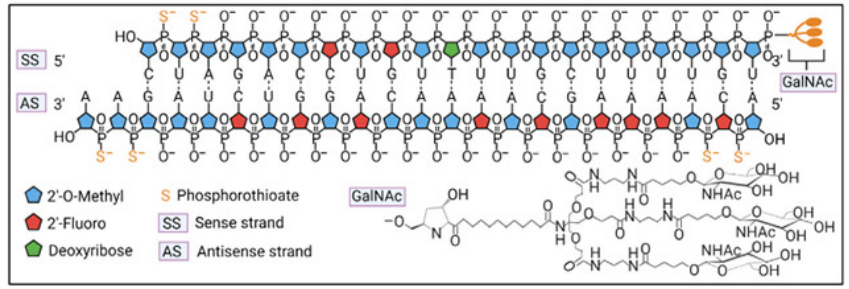
- Equivalence in primary sequence, chemical structure, and **diastereomeric composition**

PSG for Inotersen (Nov 2022)

"To ensure the diastereomeric sameness of test API and the API from the RLD, reagents and reaction conditions that can impact the diastereomeric composition outcomes should be appropriately selected and adequately controlled. The R/S configuration ratio at each phosphorothioate nucleotide linkage following each elongation cycle should be measured using appropriate methods. The test API sequence, chemical structure and diastereomeric composition should be compared to that of the API from the RLD using a broad range of orthogonal analytical methods..."

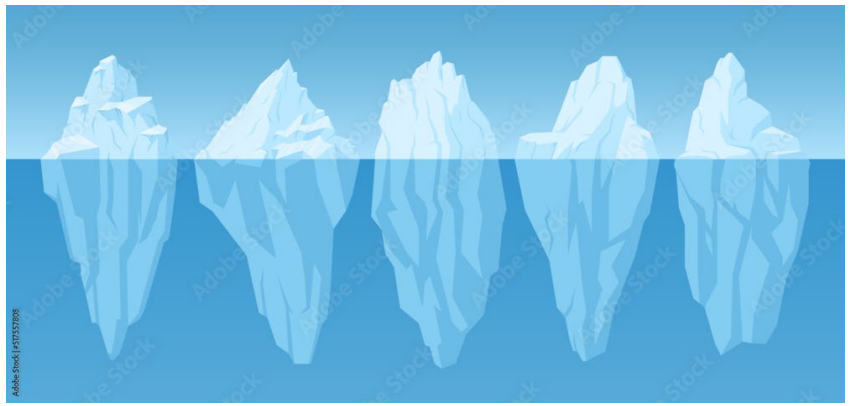
- 20-mer yields 2^{19} (524,288) stereoisomers
- PS stereochemistry affects pharmacologic properties
- Synthesis conditions (e.g., choice of activator) affect PS stereochemistry
- **Adversely impact active ingredient sameness**





ASO: TEGSEDI (Inotersen)
20-mer, 19 PS linkages
>500k diastereomers

siRNA: LEQVIO (Inclisiran)
Duplex: SS, 2 PS linkages (4);
AS, 4 PS linkages (16)



https://stock.adobe.com/search?k=tip+of+the+iceberg

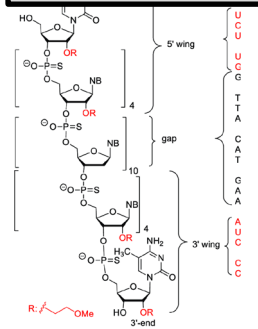
Multidimensional Approach to Characterize Diastereomer Composition

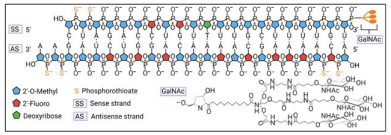
Research Proposal, Key Objective:

- Computationally integrate high-resolution analytical data for sensitive and robust determination of diastereomer composition in PS OGNs

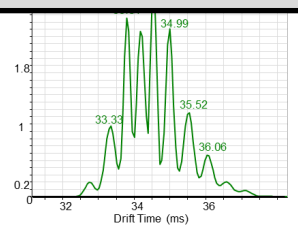
Outcome

- Establish PS diastereomer composition as a well-defined quality control attribute

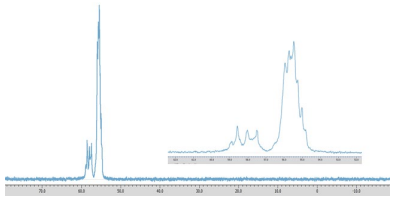




- **Full Product**
  - *Top-Down App*
  - Intact analysis
  - Enzymatic (sele digestion
  - Duplex Formation/Degradation
- **Shorter –mers**
  - *Bottom-Up Approach*
  - Sequential sampling during synthesis elongation
  - Synthesis of shorter –mers to build a model



NMR: ^{1}H, ^{13}C, ^{31}P



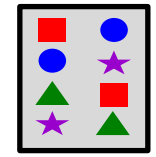
Data Analysis/ Visualization

Machine Learning

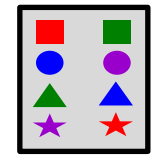
- Integrate and Visualize Data
- Determine Diastereomer Composition
- Predict Outcomes

API Sameness: Equivalent Diastereomeric Composition

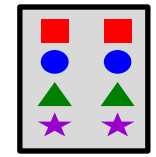
RLD Test



Correct Color, Wrong Order



Correct Order, Wrong Color



Exact Match

Knowledge Gaps

- Already approved RLD: R/S configuration ratio at each PS linkage unknown
- Assumption: shorter –mers are representative of full-length product
- Longer sequences

Knowledge Gaps

- How many and which analytical methods are appropriate?
- How to establish baseline methodology?
- How to integrate multidimensional data?
- How to establish diastereomer composition as a quality control attribute?

Acknowledgements

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Yulemni Morel, PhD
Padmapriya Sridhar, MS
Mayur Shete, MS

www.jacewjoneslab.com

UNIVERSITY of MARYLAND
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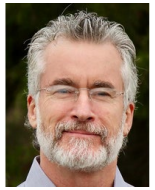
Fletcher Lab (UMB PSC)
Brinson Lab (IBBR, NIST)
Agilent Inc.



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- Agilent Research Gift #4520
- MassTech Research Contract
- ASMS Research Award

Assessing innate immunogenicity risk via *in vitro* assays

Generic Drug Science and Research Initiatives Public Workshop
May 2024

Andrew Graves
Director, Immunogenicity Assessment, Teva Pharmaceutical Industries, Ltd.

Disclaimer

The opinions expressed in this presentation are those of the presenter and not necessarily those of Teva Pharmaceuticals, Inc. or its affiliates (collectively “Teva”).

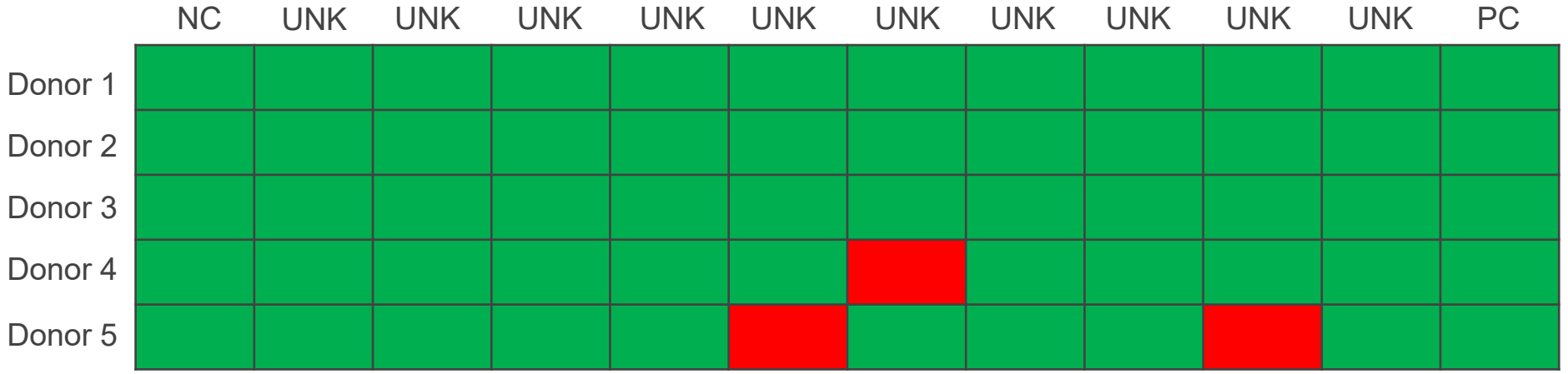
Background

- The FDA finalized guidance for ANDAs for synthetic peptides in May 2021, and as part of that document established expectations for immunogenicity assessment of proposed generics.
- While this guidance served as a launchpad for *in vitro* immunogenicity assays supporting ANDA submissions, the maturation of the science behind these assessments presents a timely opportunity to streamline and harmonize the approaches.
- Further research would aid both industry and the Agency by establishing best-practice approaches and perhaps broadening the utility of these assays.

 Guidance for Industry- Synthetic Peptides (fda.gov)

Establishing Sensitivity Limits of Innate Immunogenicity Assays

- Holley et. al. (2021) outlines the use of 10 example IIRMIs to establish the assay sensitivity of an innate cytokine release assay with teriparatide.
- We previously posited that a blinded validation experiment using a mixture of IIRMI-spiked (at sensitivity level) and unspiked samples can further establish the reliability and sensitivity of a platform.



When results are unblinded, we see 2 false positives out of 25 expected negatives and one false negative out of 25 expected positives

Sensitivity = 96% Specificity = 92%

- While the most sensitive assay is desirable, each drug is formulated at a different concentration (e.g., teriparatide at 250 µg/mL, liraglutide at 6 mg/mL), likely impacting the dilutions needed for the assay, and perhaps the assay sensitivity.

Research opportunity:

Establish the lowest acceptable sensitivity limits for innate immunogenicity assays supporting ANDA submissions

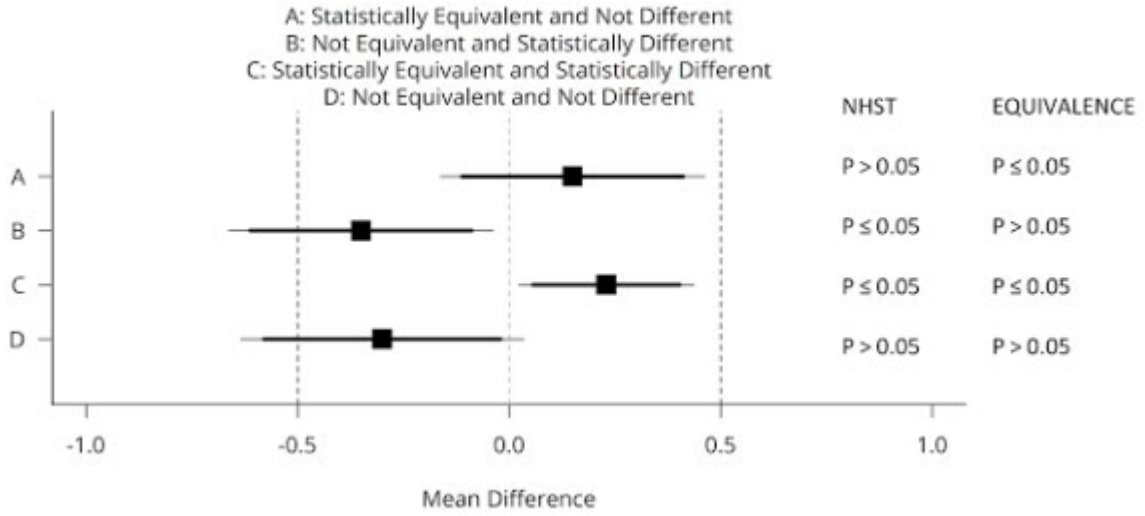
Holley: https://doi.org/10.3390/molecules26247461

Streamlining Statistical Approaches for *In Vitro* Immunogenicity Assays

- *In vitro* immunogenicity assays have the potential to generate many data points which must be analyzed statistically to justify an outcome.
- A standardized or preferred statistical approach would aid in the analysis and understanding of the results.
- However, while *in vitro* assays are a good surrogate for clinical immunogenicity, there is no established link between the results observed in the lab compared to the correlative results that should be observed clinically.
  - Example 1: If the results of an immunogenicity assay comparing RLD to proposed generic indicates a statistically significant difference, is that statistical difference biologically meaningful?
  - Example 2: If the results are compared for equivalence (i.e. TOST), how should the equivalence margin be set?
  - Example 3: How best to factor statistical testing in multi-factor assays (i.e. cytokine release)?

Research opportunity:

Establish standardized or preferred statistical approaches for analysis of *in vitro* comparative immunogenicity results



Adapted from Lakens (2017)

https://doi.org/10.1177/1948550617697177

Innate Immunogenicity Assays for Recombinant Generic Peptides

- The ANDA guidance from May 2021 specifically states the guidance is for the development of synthetic generic peptides.
- While analytical assays may provide descriptive results for the presence of contaminants such as host cell proteins in recombinant peptide candidates, a fair lingering question regarding the safety and immunogenicity of a recombinant generic compared to the RLD must be addressed.
- With the advancement of innate immunogenicity assay platforms e.g., reporter cell lines and multi-factor human PBMC cytokine release, DC activation, and so forth, would these innate *in vitro* assays appropriately and sufficiently characterize the safety and immunogenicity concerns of a recombinant peptide candidate?

Research opportunity:

Examine the utility of innate immunogenicity assays for supporting recombinant peptide ANDA submissions

RLD: reference listed drug; PBMC: peripheral blood mononuclear cells


teva

Immunogenicity Testing using Human Spleen Organoids, Enabled by High-Throughput Reconfigurable Automation Cart (RAC)-based Automated Workflows

Priority Initiatives Topic 2:
Enhance the Efficiency of Equivalence Approaches for Complex Active Ingredients

FDA FY24 GDUFA Public Workshop
May 21, 2024

David Borhani
Senior Director, Business Development
Ginkgo Bioworks, Inc.
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Director, Stanford Institute for Immunity, Transplantation and Infection and the Burt and Marion Avery Family Professor
Stanford University School of Medicine
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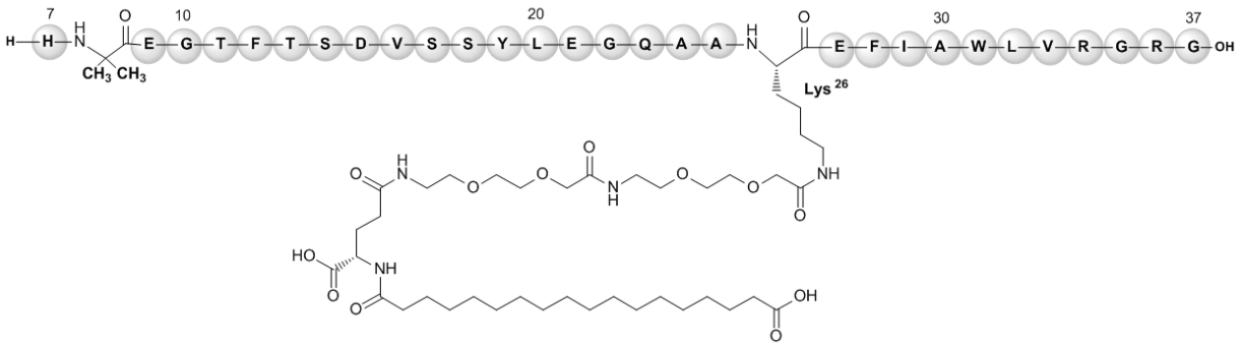
Problem Statement

How to demonstrate that the immunogenicity of a generic peptide or oligo-nucleotide product is substantially equivalent to that of the innovator product?

"The Process is the Product"

Semaglutide



Semaglutide Manufacturing is an at least 6-Step Hybrid Biological/Chemical Process:
Fermentation; solid-phase peptide synthesis; ≥2 chemical modifications; ≥2 purifications

The manufacturing process for semaglutide active substance consists of a fermentation process in yeast cells, recovery and purification of semaglutide precursor. The semaglutide precursor is subjected to a synthetic modification process and purified. …

In addition to the active substance itself three other intermediates are isolated and storage conditions and shelf life are defined. …

The construction of the expression plasmid and the source and history of S cerevisiae strain ([Arg34]GLP-1-(9-37)) producing semaglutide precursor are described in detail. …

Product-related impurities are structurally related to semaglutide. They are generated as by-products in fermentation by the host organism as well as in the recovery and purification process of semaglutide precursor, in the modification steps and in the purification process of semaglutide.

Assessment report: "Ozempic." International non-proprietary name: semaglutide (EMA, 2017) https://www.ema.europa.eu/en/documents/assessment-report/ozempic-epar-public-assessment-report_en.pdf

Should we…

- Measure an ever-expanding list of critical quality attributes (CQAs)?
- Perform extensive animal testing?

OR…

Proposed Solution

*Immunogenicity testing using **human spleen organoids**, enabled by high-throughput Reconfigurable Automation Cart-based **automated workflows***

Human spleen organoids

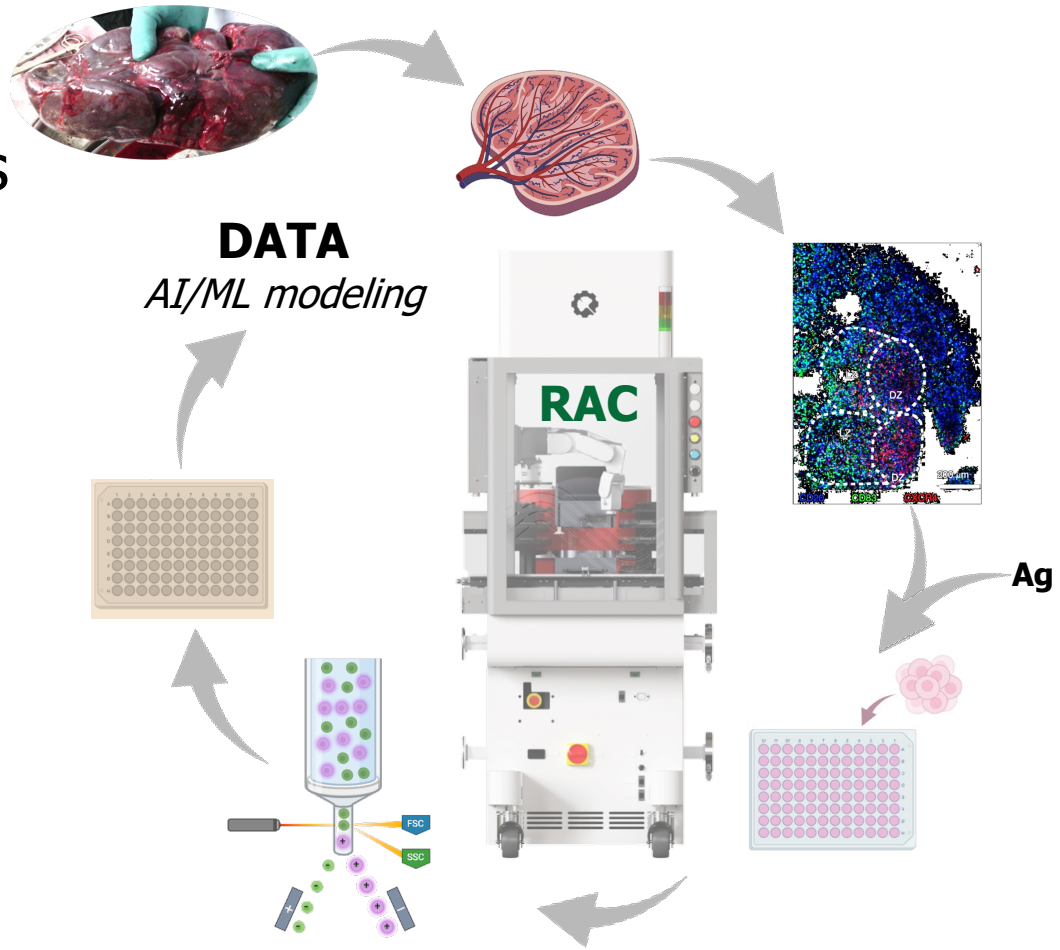
- Holistic naïve and recall immune responses from an immunologically complete tissue
  - (SOTA: poorly predictive, reductive computational models, MHC-binding, or other assays)

Immunological diversity

- Ability to test many genetically diverse "individuals" against many complex APIs

RAC-based HT automated workflows

- Organoid/API "immunization"
- Complete immune response assessment
  - B and T cell responses, cytokines, etc.



Wagar, LE … Davis, MM. "Modeling human adaptive immune responses with tonsil organoids." *Nat Med* (2021) 27(1):125–135. doi: 10.1038/s41591-020-01145-0
Zymergen [now Ginkgo] Technology Team. "The Case for Modular Lab Automation." (2019) https://medium.com/@ZymergenTechBlog/the-case-for-modular-lab-automation-c34f214e1276

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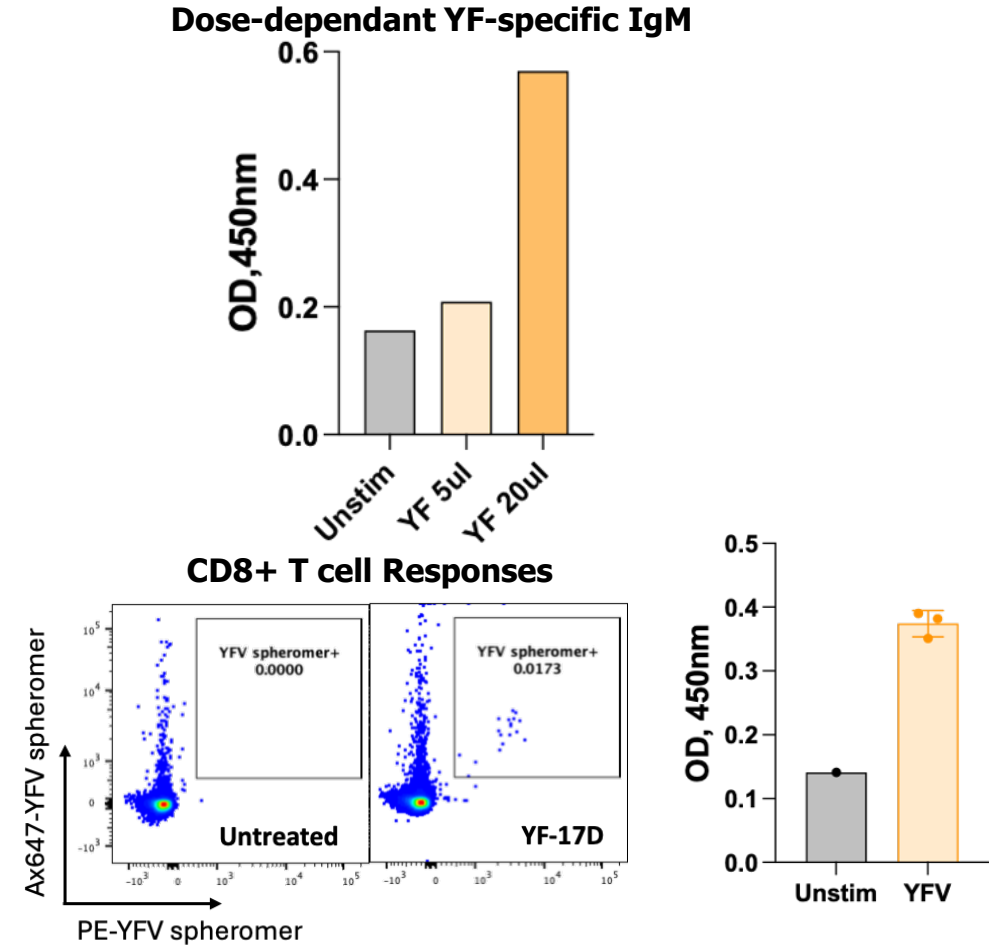
Naïve Responses — Yellow Fever Vaccine



Sola, E … Davis, MM. *unpublished results*

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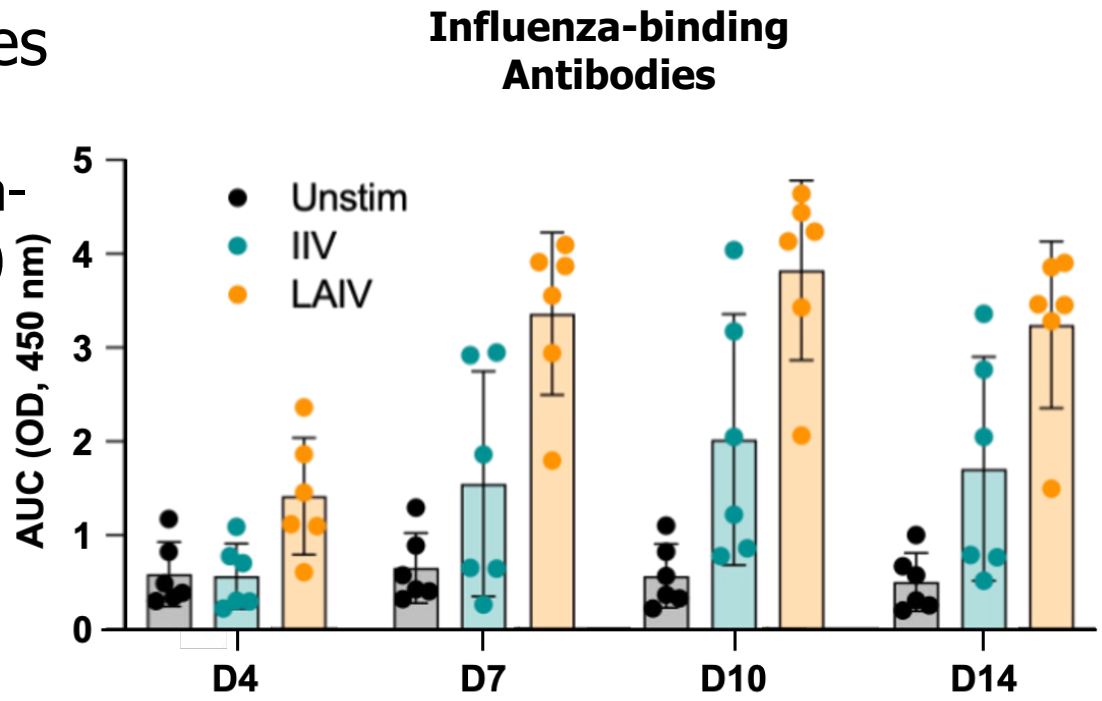
Recall Responses — Influenza Vaccine



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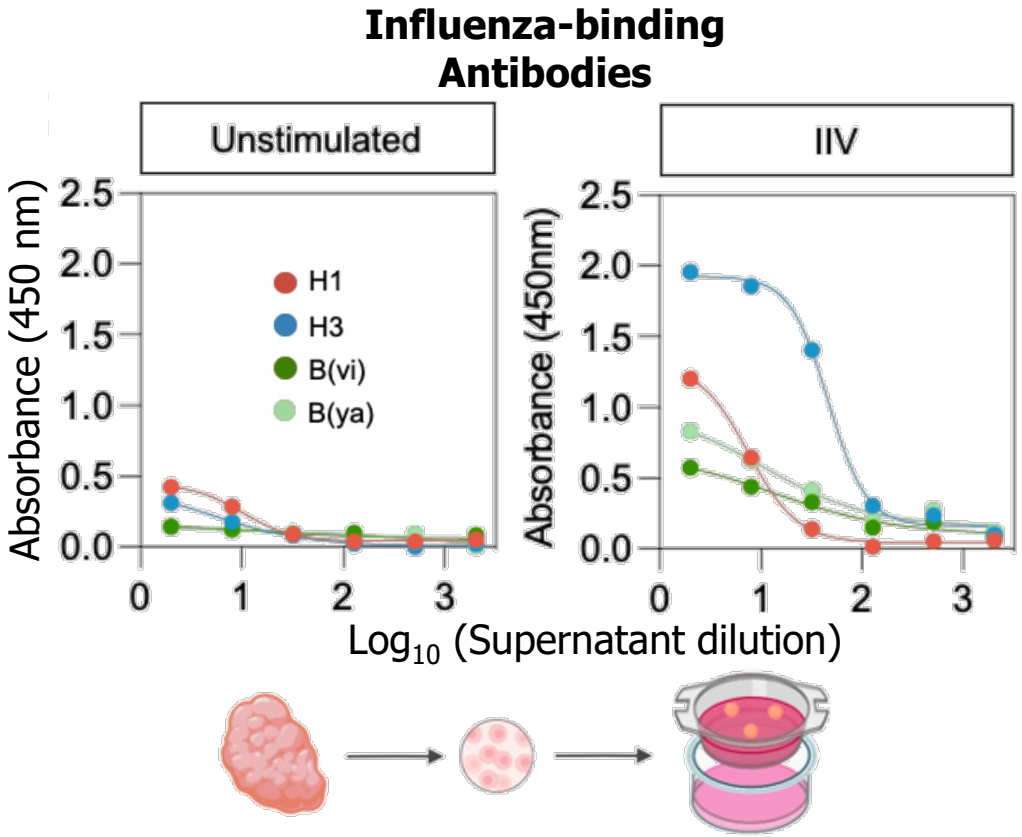


Tissue ⇒ single-cell suspension ⇒ transwell-supported organoid

Mallajosyula V … Davis, MM. *under review*

A Natural Extension

Assess the immune function impact of drugs or other substances by quantifying responses of human organoids against a diverse panel of reference vaccines

Adjuvant screening

- Quantify impact on immune responses relative to standard benchmarks

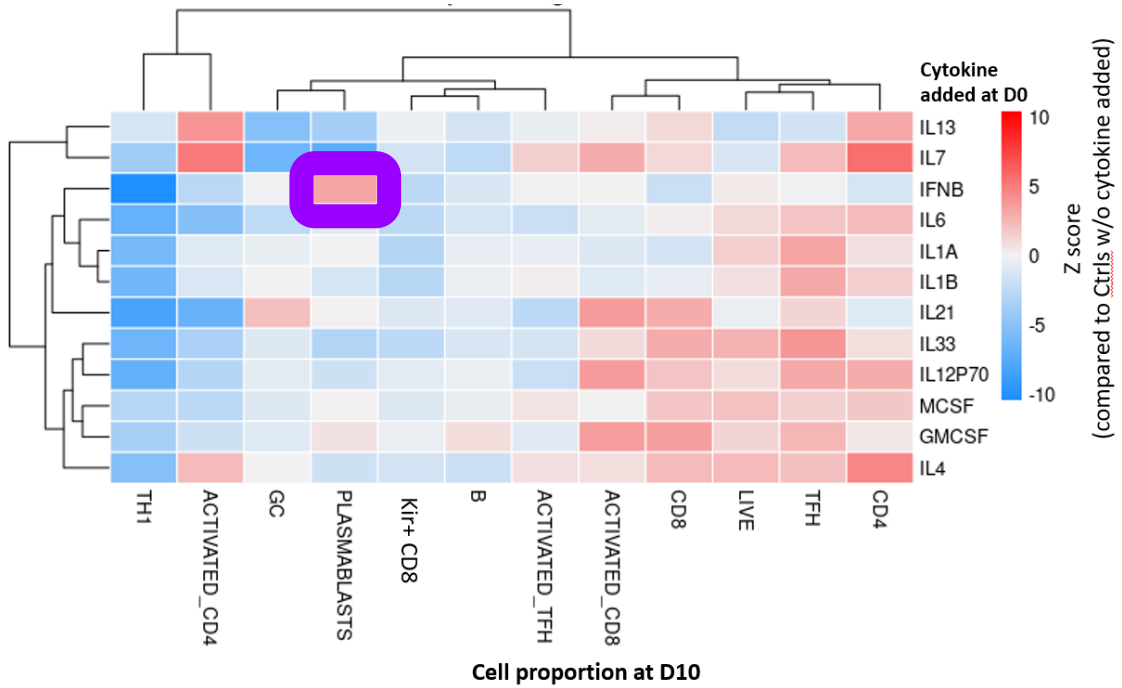
SM or biological drug screening

- Characterize and quantify any impacts (expected or not) on immune function
  - Immunosilent, -suppressive, or -stimulatory

Standards setting

- Coordinate with, e.g., FDA, NIST, & USP to enable claims of defined, categorical immunomodulatory effects

Systematic evaluation of the immunomodulatory effect of cytokines upon vaccine responses



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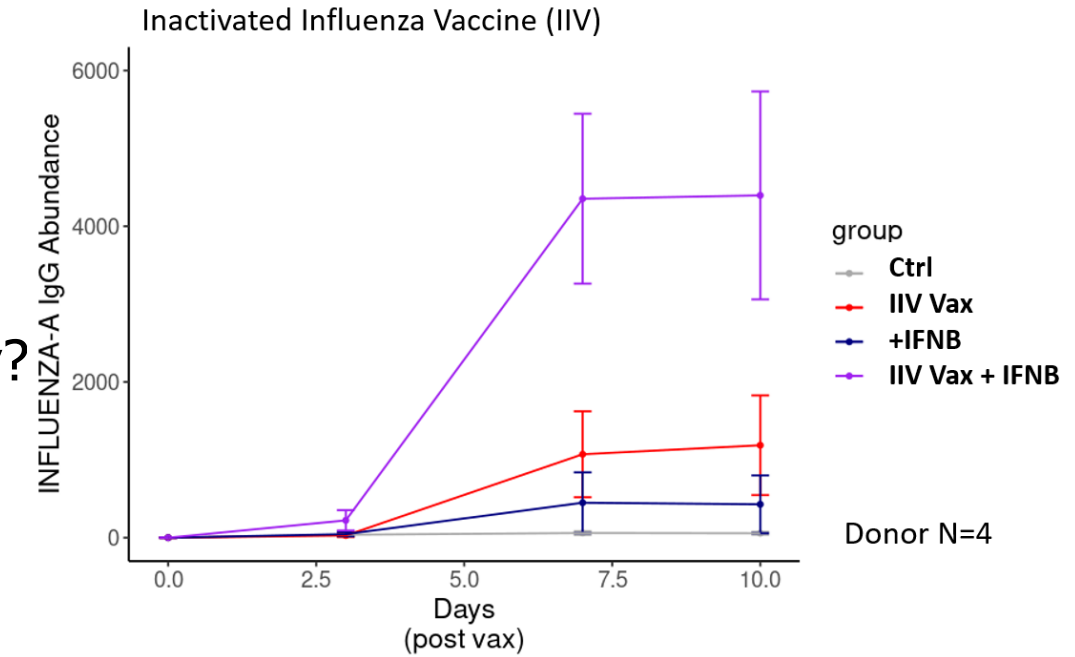

Davis Lab
Stanford University/HHMI


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Let's grow the world we want to see

Ginkgo’s Platform Spans Pharma Modalities

Commercial and USG R&D Innovation Partner
Our horizontal platform enables partners working in diverse therapeutic modalities

Since 2008, building integrated automation, software, and biological tools

In 2021, began trading publicly on the NYSE ($DNA) after raising $1.6 billion

Board members include Arie Belldegrun and Reshma Kewalramani

GINKGO BIOWORKS

Accelerating health solutions with the leading cell programming platform

Improve cell therapies on our end-to-end optimization platform

Discover & optimize the next generation of gene therapies

Use circular RNA to achieve impactful and tissue-specific expression

Create new solutions using novel microbiome therapy approaches

Harness enzyme services to advance their activity, expression, and production

Unlock the biological "black box" using our databases and AI/ML

The basics…
What is a biological "Foundry"?

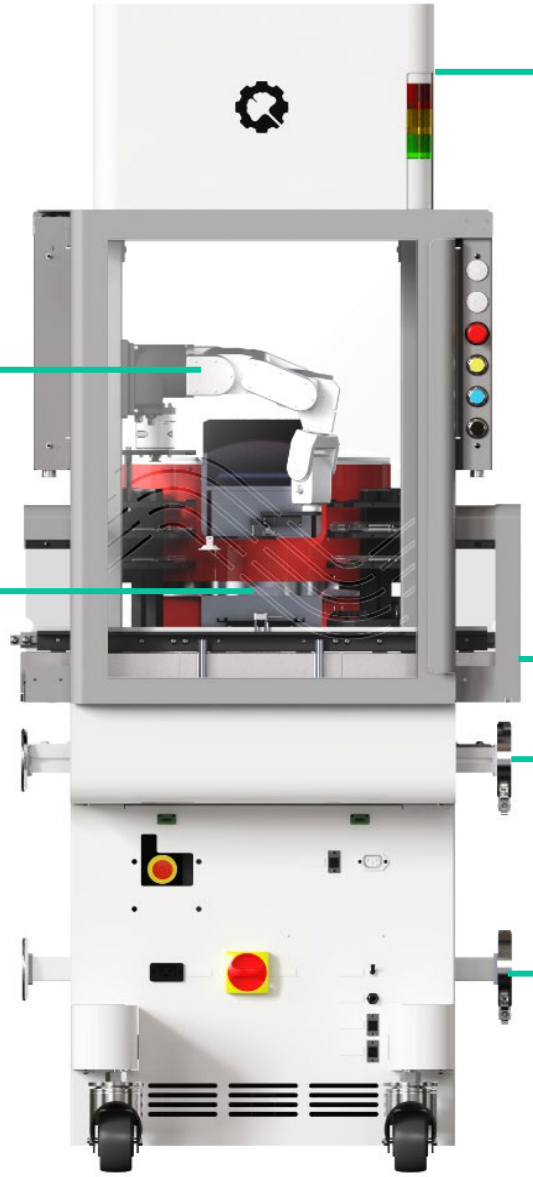
Learn more about our platform

Reconfigurable Automation Carts (RACs)

Hardware building blocks for the automated lab

A **RAC** is a **standardized enclosure** for integrating scientific instrumentation.

Rigorously engineered hardware designed with industrial components improves the reliability of integrated lab equipment and allows for unparalleled scalability and flexibility.



Optional **HEPA Filter**

Dedicated **robotic arm** improves reliability and throughput

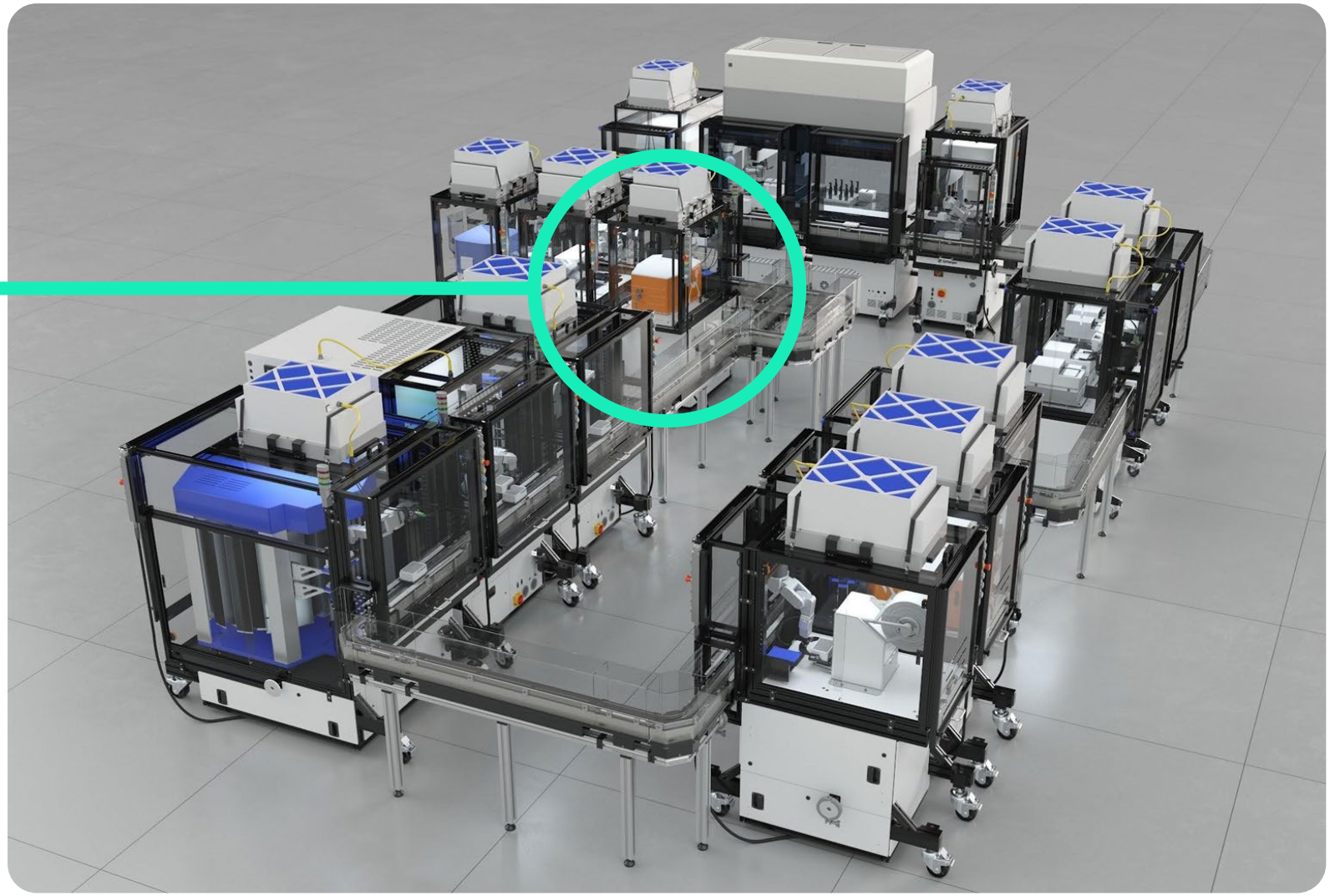
Lab device of choice, from any application or vendor

Plate **transport track**

Quick connection points enable system reassembly in minutes, not days

Utility routing (electrical, air, and data)

Combine RACs to create RAC Systems = Complete workflows



RACs in crates to a RAC System running protocols in an afternoon

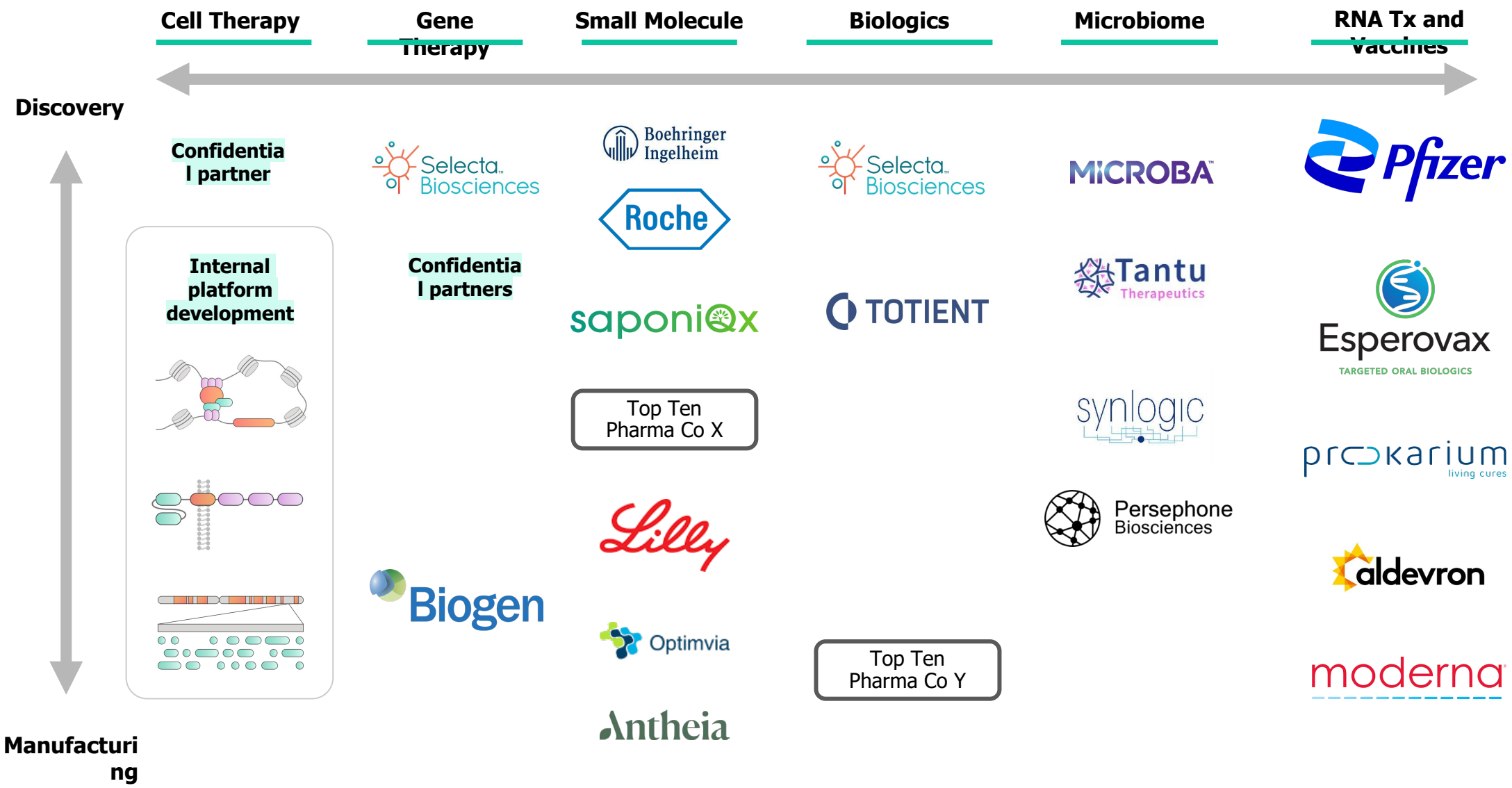
Ginkgo's cell programming platform enables diverse industries & companies…

Non-exhaustive

	PHARMA	WELLNESS / FOOD / AGRICULTURE	INDUSTRIAL BIOTECHNOLOGY
LARGE COMPANIES	Boehringer Ingelheim, Pfizer, GSK, Lilly, Roche, Top Ten Pharma Co X, moderna, Biogen, Top Ten Pharma Co Y	syngenta, BAYER, SOLVAY, CORTEVA agriscience, ADM, CRONOS GROUP, Cargill	SUMITOMO CHEMICAL, Givaudan, geno., ROBERTET GROUPE
STARTUPS	Selecta Biosciences, aldevron, synlogic, Antheia, TOTIENT, prokarium living cures, Tantu Therapeutics, Optimvia, MICROBA, Esperovax TARGETED ORAL BIOLOGICS, SENSIBLE BIOTECHNOLOGIES, saponiQx, Persephone	KERRY, motif FOODWORKS, BIOMEDIT, NAMUH, ARCAEA, AYANA BIO, verb biotics, Phytolon	BOLT THREADS, CAMBIUM, huue., allonnia, light bio, Humble Bee Bio, BIOWEG, zymtronix, LYGOS, FREDsense

Ginkgo's platform spans Pharma modalities and technologies, from therapeutics and vaccine discovery to manufacturing

Non-exhaustive

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Immunogenicity Assessment of Peptide Products – Current Challenges and Recommendations

Dr. Ravishankara MN

Functional Head: Biologics and Peptide Analytics

Sun Pharmaceutical Industries Limited, India

Disclaimer

The views, thoughts and opinions expressed in this presentation are solely of presenter and should not be construed to represent Sun Pharma's official views.

Immunogenicity Assessment requirement of Peptides

- **Immunogenicity** is generally defined as an unexpected or **undesirable immune response** to a protein or peptide biologic.
- Immunogenicity is generally **associated with T cell (cellular) and B cell (humoral) immune responses.** Measurement of antidrug antibodies (ADA) is usually one of the key methods that is used to assess the immunogenicity of biologics prior to approval.
- The **link** between **T-cell response to T-cell epitopes** that are present in biologics and the development of ADA responses was **well recognized**
- This is because T cells, responding to **linear amino acid sequences** within the peptide in the context of Human Leukocyte Antigen (**HLA**), provide '**help' to B cells, driving ADA contribution** of linear T-cell epitopes presented by HLA to the generation of ADA by B cells.
- Because human **ADA** are generally **measured** in Phase I, II and III trials of **biologics**, and **no clinical** trials are conducted in the **ANDA** process for Peptides, ADA measurements are not available to assess the immunogenicity risk for generic peptides.

Regulatory Expectation on Peptide related Impurities

- Any new impurity which is **not present** in the RLD, it should **not exceed 0.50%.**
- Any new impurities **present at 0.10%** or greater should be **identified** and **Characterized**
- Provide **Justification** – New I**mpurity would not affect the safety** of the proposed generic synthetic peptide or its **effectiveness**
- **Any differences in impurities wrt to RLD - do not modify physicochemical properties, biological activity, or immunogenicity risk** of the product.
- Each new impurity **does not contain sequences** that have an **increased affinity** for major histocompatibility complex (MHC), known as ***T-cell epitopes.***
- Proposed generic synthetic peptide **does not increase the aggregation propensity** or the nature of the aggregates formed, especially under **stress conditions.**
- For the **impurities** that are **common** between DS/DP (Generic) and the RLD, the acceptance criteria **should be not more** than those observed in the **RLD** (at the end of the shelf-life).

Reference-2

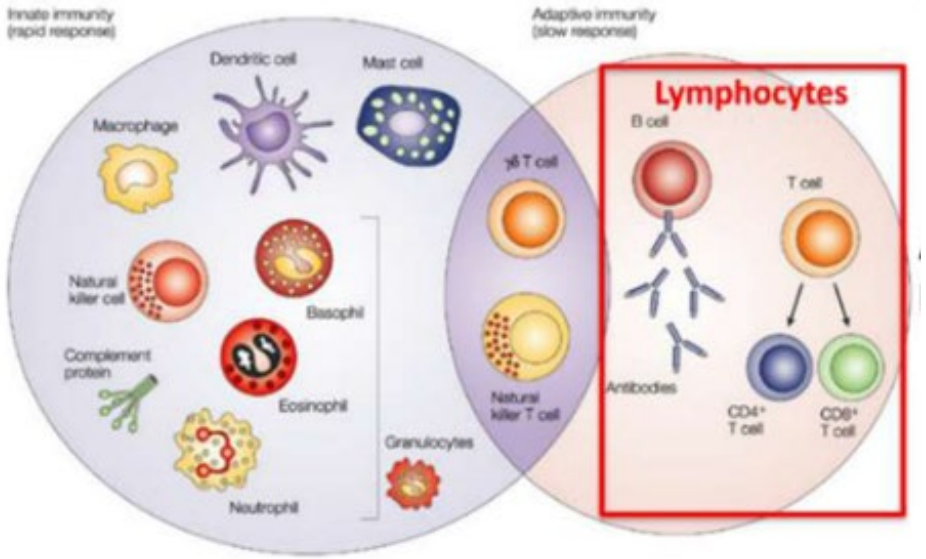
Regulatory recommendation of Immunogenicity Studies for Impurities

Innate Immunity

All Process related impurities shall be evaluated which includes contaminants, Leachables

Recommend to Test the Whole Drug Product independent of presence of impurities

Innate immunogenic potential of impurities will evaluated through Innate Immune Response Modulating Impurities (IIRMI) Assays



Adaptive Immunity

All Peptide Related Impurities shall be evaluated

Testing on Each Isolated Impurity

in silico	Epitope Prediction
in vitro	HLA Binding
in vitro	T cell Activity

Challenges/Recommendations related to Adaptive Immunogenicity Assessment

- Clear Guidance Document is not available for Immunogenicity assessment for Peptide products.

- Length peptide is an important factor for immunogenicity – No clear document is available to state that what length of Peptide molecules shall be considered for Immunogenic assessment.

- Guidance document recommends In-silico assessment of peptide related impurities to assess the Immunogenic potential of an impurity. However, as per the Agency, In-silico assessment alone is not sufficient and mandatorily, T-cell proliferation assay to be performed to demonstrate the non-immunogenic potential of peptide impurities. In such cases, does In-silico assessment have any value addition?

- For the immunogenicity evolution, concentration of Impurities were not specified. Based on the communication with agency, *0.5% level of impurities is not acceptable for immunogenic evaluation and individual impurities shall be assessed at concentration that ensure adequate presentation by Antigen presenting cells (generally more than 0.5 uM).* This corresponds to 10 to 20% level of the target product.
    - How do we evaluate the concentration that ensure adequate presentation by Antigen presenting cells
    - There is also a suggestion to conduct study at 100% level for impurities. Is this realistic?

- As per the recent recommendation, two markers should be evaluated for immunogenicity assessment instead of one Marker. Proper guidance shall be provided for selection of second marker for evaluation.

Challenges/Recommendations related to Adaptive Immunogenicity Assessment

- If particular Impurity is observed to be higher in Generic Formulation when compared to RLD, then Immunogenicity assessment shall be done for that impurity. Since, same impurity is also present in Innovator product, how do we assess the differences in immunogenicity response with minor change in level of impurity.

Hypothetical Case-1

Impurity-A in Innovator product : 0.15%
Impurity-A in Generic Product: 0.20%
Difference in content is 0.05%

Hypothetical Case-2

Impurity-B in Innovator Product – 0.47%
Impurity-B in Generic Product – 0.52%
Difference in content is 0.05% (>0.50% level in Generic product is a matter of concern?)

- Guidance document differentiating the Immunogenicity requirements for Peptide Drug Products is required taking in to consideration Short Term Treatment vs Long term Treatment, Dose Content, Route of Administration, Duration of the treatment and dosing frequency as these are important factors that would determine the immunogenicity Risk of a therapeutic peptide.

- If the set of impurities are observed to be non-immunogenic by In-silico assessment, whether Cocktail approach (combining all impurities at particular concentration) can be used for T-cell proliferation Assay?

- Clarity/Guidance shall be provided for consideration of T-Cell numbers during T-cell proliferation Assay

- Can we consider minimum number of Donors to cover >90% HLA Allele (Eg: 30 Donors with >90% HLA Allele (general practice) vs 15 Donors with > 90% HLA Allele) ?

Challenges/Recommendations related to Innate Immunogenicity Assessment

- Currently no clarity is available on selection criteria of Donors and number of Donors for the Innate Immunity Study.
- Guidance shall be provided for Cell viability (Pre and Post Drug exposure) in Innate immunogenicity study in terms of Total PBMC viability vs Subtype Population viability
- If the Cytokine response observed is at low level for RLD vs Generic Product (Eg.: 1 pg vs 3 pg) but statistically significant, is such low level of response is clinical significant/relevant? What should be the way forward in such cases?
- Since excipients might cause significant interference in Innate immunogenicity assay in terms of reducing/nullifying the response of positive control, would processing of both DP and RLD samples are allowed using suitable molecular weight cut off filters or Dialysis to remove the excipients and keeping Drug and Impurities Intact in Formulation?
- For generic peptide where Innovator product is also of Synthetic origin, do we need immunogenicity assessment.
- Can agency look for harmonization of guidance document for immunogenicity assessment across different regulatory agency.

Recommendations for Collaborative Studies/Projects

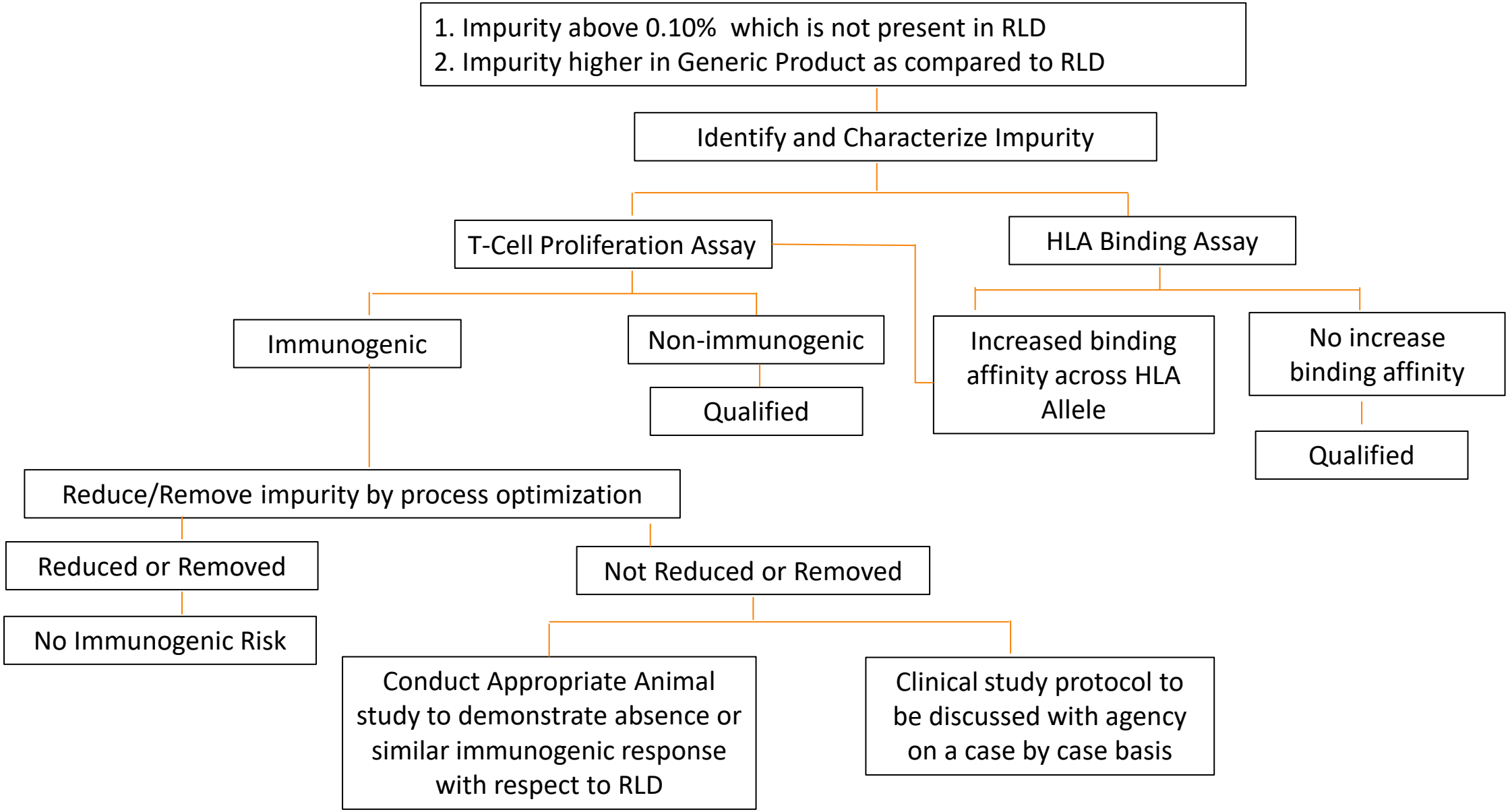
- In-silico immunogenicity assessment of potential impurities for Peptide Products needs to be evaluated and considered for waiver of immunogenicity study assuming they are under 0.5%.

- T-Cell Proliferation Assay for commercially available Impurity Standards should be assessed to waive off T-cell study requirement for those impurities which are non-immunogenic. This will lessen the burden of T-cell study for such impurities.

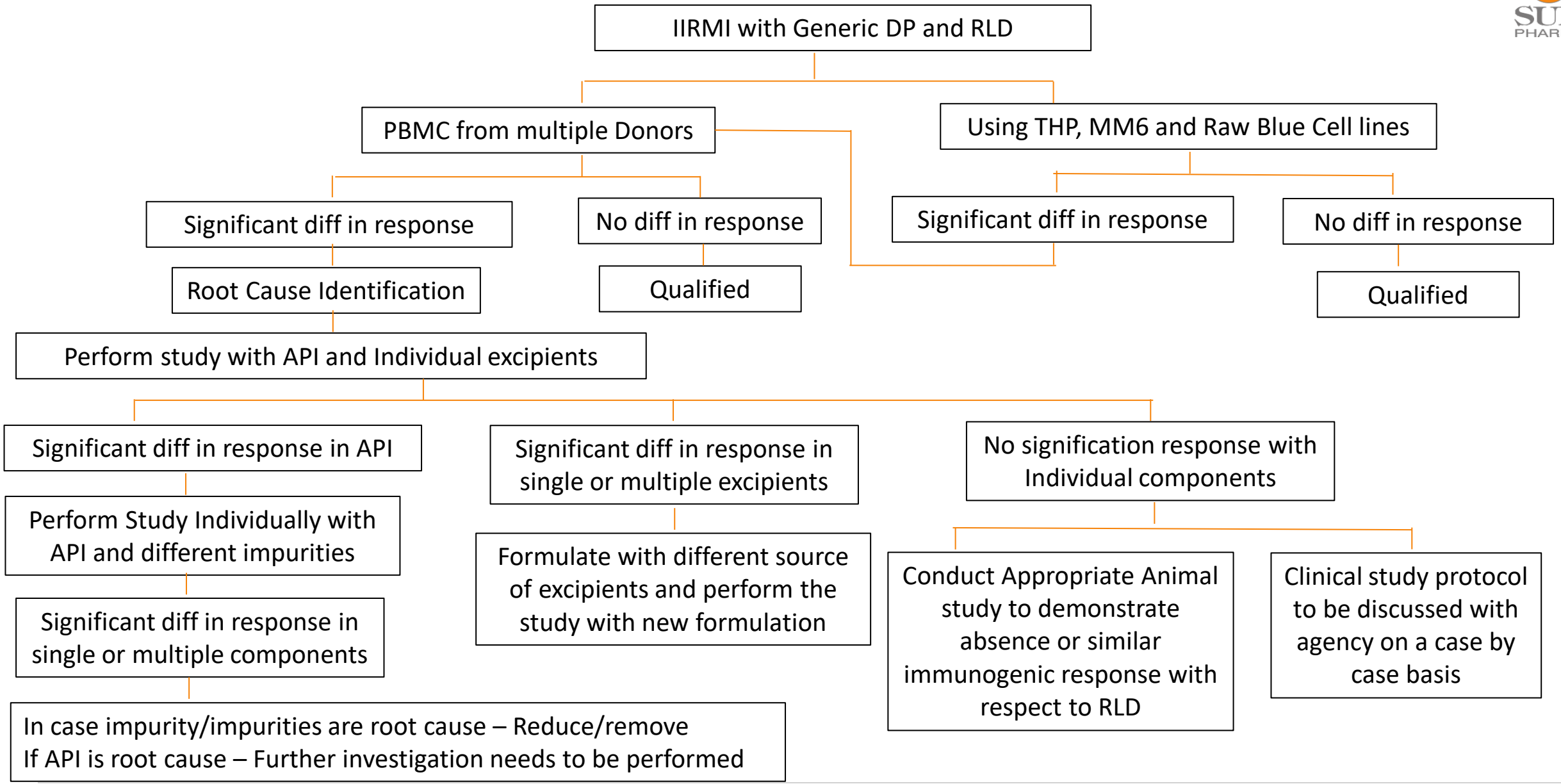
- The risk behind every impurity and its clinical relevance with respect to immunogenicity is less understood for Peptide products whose Dosage, dosing frequency and duration of treatment are widely varied. It would be ideal to study clinical relevance for products that vary significantly on Per Day Human Exposure of each of the product related impurities.

- The agency should study the best method of removal/minimization of excipients during the immunogenicity assessment of drug product and provide this information in the Immunogenicity guidance document so as to bring all the sponsors on a single reliable platform.

Proposed Decision Tree for Adaptive immunogenicity Study



Proposed Decision Tree for Innate immunogenicity Study



References

Reference-1: Immunogenicity risk assessment of synthetic peptide drugs and their impurities –Groot et al

Reference-2: FDA Guidance Document - ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin

Reference-3: Dranoff, G., Nature Rev. Cancer, 2004


Thank You

Biorelevant and biopredictive in vitro release tool to accelerate development of generic long acting injectables for intramuscular and subcutaneous administration

Marina Juretić, PhD

Senior Analytical Scientist, Research and development, IVR/IVIVC

Teva Pharmaceuticals Ltd.

Introduction

- The scope of this presentation are **generic long acting injectables (LAIs) for intramuscular (IM) or subcutaneous (SC) administration intended for systemic action**
- One of the challenges in generic LAIs development is **long duration (months to years) of bioequivalence (BE) studies**
  - Often >1 BE study is needed which increases patient burden in BE studies and prolongs LAI development limiting patient's access to generic LAIs
  - Reasons for failed BE study:
    - a lack of knowledge of the critical bioavailability attributes (CBA) of the LAI
    - small or insignificant differences between the test and reference product observed in vitro may become critical at the IM/SC injection site resulting in the difference in drug release rate and performance in vivo
    - the overall effect of the observed small in vitro differences between the test and reference product on the LAI performance in vivo becomes apparent only after the IM/SC injection of drug product

Biorelevant in vitro release (IVR) assay mimicking IM/SC injection site with the ability to predict in vivo performance of LAI would enable a successful selection of a test formulation for BE study and thus accelerate the overall generic LAI development

Physiological and anatomical aspects of SC and IM injection site influencing in vivo drug release and performance of LAIs

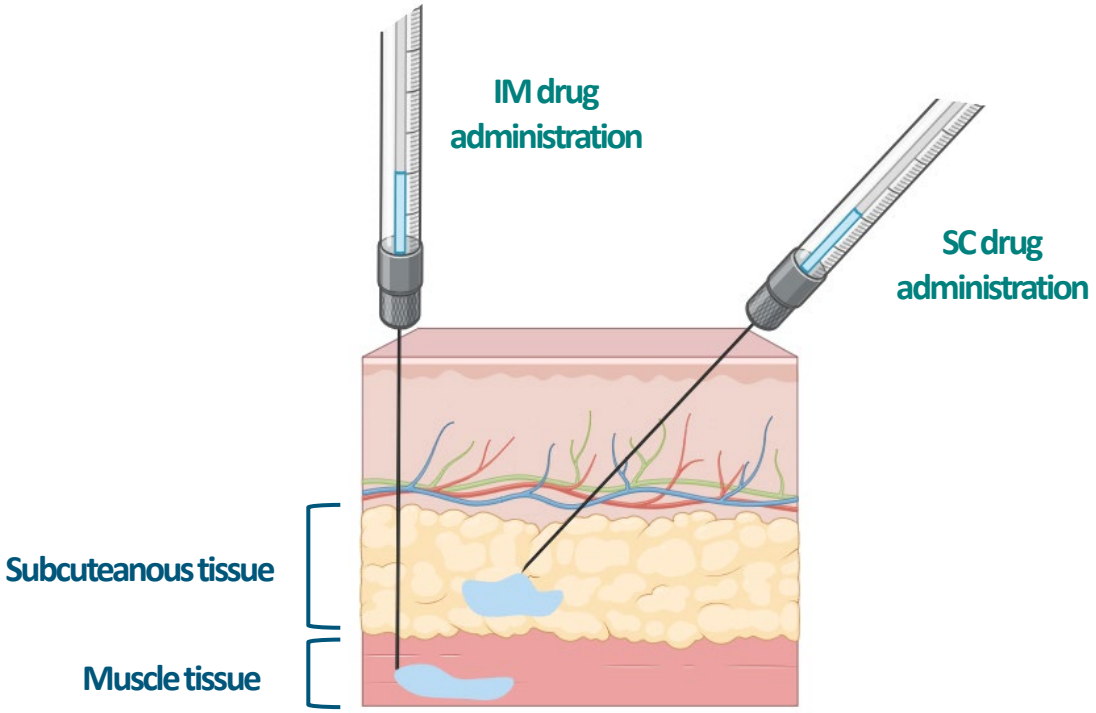


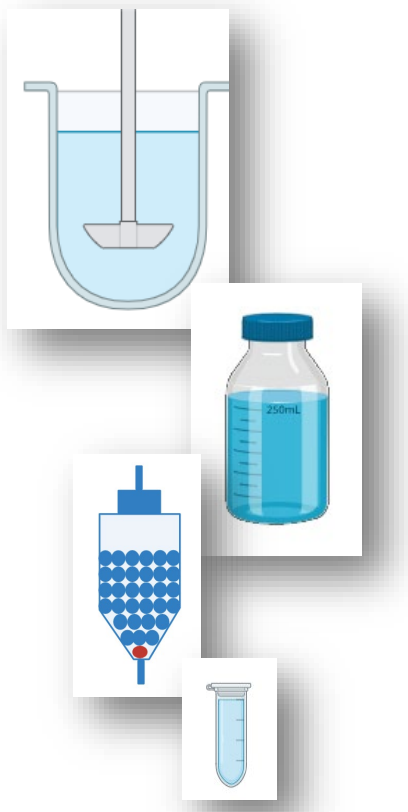
Figure created in Biorender.com

- Extracellular matrix (collagen and glycosaminoglycans (hyaluronic acid))
- Temperature = 34-37°C and pH=7.2-7.4
- Limited volume of SC/IM fluid
- Presence of different ions, proteins in SC/IM fluid
- Inflammation response

Outcomes of previous GDUFA research projects with respect to IVR method development for LAI

Some of the papers with conducted IVR analysis of LAIs, published as part of the previous GDUFA research projects:

- *International Journal of Pharmaceutics, 610, (2021) 121265.* ***Effect of polymer source variation on the properties and performance of risperidone microspheres.*** *Bo Wan, Quanying Bao , Yuan Zou, Yan Wang, Diane J. Burges.*
- *International Journal of Pharmaceutics, 592 (2021) 120105.* ***Effect of implant formation on drug release kinetics of in situ forming implants.*** *Min Sung Suh, Michail Kastellorizios, Namita Tipnis, Yuan Zou, Yan Wang, Stephanie Choi, Diane J Burgess.*
- *AAPS J. 2021, 23(2): 42.* ***Impact of Formulation Parameters on In Vitro Release from Long-Acting Injectable Suspensions****. Quanying Bao, Yuan Zou, Yan Wang, Stephanie Choi, Diane J Burgess.*
- *Journal of Controlled Release, 314 (2019) 25–37.* ***In vitro-in vivo correlation of parenteral PLGA microspheres: Effect of variable burst release****. Janki V Andhariya, Rajan Jog, Jie Shen, Stephanie Choi, Yan Wang, Yuan Zou, Diane J Burgess.*
- *Journal of Controlled Release, 308 (2019) 1-13.* ***Development of Level A In Vitro-In Vivo Correlations for Peptide Loaded PLGA Microspheres****. Janki V. Andhariya, Rajan Jog, Jie Shen, Stephanie Choi, Yan Wang, Yuan Zou, Diane J. Burgess.*
- *Journal of Controlled Release, 218 (2015) 2–12.* ***In vitro-in vivo correlation of parenteral risperidone polymeric microspheres****. Jie Shen, Stephanie Choi, Wen Qu, Yan Wang, Diane J Burgess.*



All figures created in Biorender.com

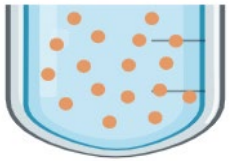
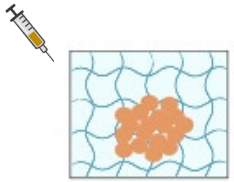
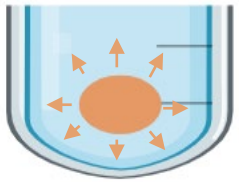
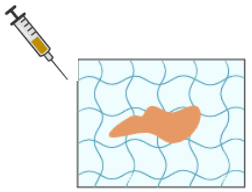
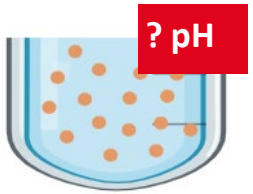
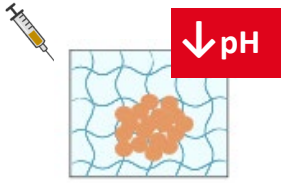
In the published papers, IVR analyses were conducted using compendial and non-compendial IVR apparatuses which applied:

- non-physiological large medium volume
- non-physiological medium composition (surfactants, high buffer capacity)
- non-physiological hydrodynamics
- temperature 34-37°C and pH=7.4 → the only physiological aspects of the IM/SC injection site that were mimicked

→ For some of the developed IVR methods, biopredictivness was demonstrated using animal data, despite the lack of biorelevance. However, the established biopredictivness may be valid exclusively for this specific formulation type and API and thus, the developed method cannot be universally applied to all other LAIs for the prediction of in vivo performance.

Why we need to incorporate biorelevance to establish biopredictivness of the IVR assay

The examples of phenomena critical for drug release taking place in IM/SC injection site, but missing in standard IVR setups

	Typical in vitro setup		IM/SC injection site	
AQUEOUS SUSPENSION		• Both drug particles and excipients freely dispersed in the medium		• Aggregation of drug particles • Retention/diffusion of excipients?
IN SITU FORMING DEPOT		• Uniform depot shape • Free depot swelling		• More irregular and variable depot shape • Limited depot swelling
POLYMERIC MICROSPHERES		• Acidification of the microsphere microenvironment due to acidic polymer degradants is attenuated by high volume and high buffer capacity of the IVR medium?		• Pronounced acidification of the microsphere microenvironment as a result of accumulation of acidic polymer degradants due to low volume and lower buffer capacity of IM/SC fluid

All figures created in Biorender.com

Research to be implemented in future GDUFA program

- **Development of a biorelevant and biopredictive in vitro release assay which mimics physiological and anatomical aspects of the IM/SC injection site critical for drug release and is thus able to predict in vivo performance of LAI** → the application of this tool:
    - elucidation of drug product properties critical for in vivo drug performance which would contribute to faster and more successful development of the test product
    - a selection of the test product for BE study
- The developed assay is not expected to be used for quality control (QC purpose) given its higher complexity, however, it could contribute to a more successful development of QC IVR method based on the understanding of drug product CBAs gained from this assay
- Inflammation response in the IM/SC tissue is not expected to be included in this biorelevant assay → development of other cell-based/tissue-based tools evaluating potential of LAI for immunological response for this purpose?

References

- *Journal of Controlled Release 336 (2021) 322–335. Evaluating parameters affecting drug fate at the intramuscular injection site. Adam J.S. McCartan, David W. Curran, Randall J. Mrsny.*
- *International Journal of Pharmaceutics 610 (2021) 121257. Prediction of subcutaneous drug absorption - do we have reliable data to design a simulated interstitial fluid? Iria Torres-Ter´an, M´arta Venczel, Sandra Klein.*
- *Journal of Pharmaceutical Sciences 112 (2023) 1492−1508. Simulate SubQ: The Methods and the Media. David Li, Poh Yee Chow, Tzu Ping Lin, Celine Cheow, Zhuoxuan Li, Matthias G. Wacker.*
- *International Journal of Pharmaceutics 594 (2021) 120142. In-vitro drug release testing of parenteral formulations via an agarose gel envelope to closer mimic tissue firmness. Jan Kozak, Miloslava Rabiskova, Alf Lamprecht.*
- *Expert Opinion On Drug Delivery 2022, Vol. 19, No. 6, 671–684. Biopredictive tools for the development of injectable drug products. Mônica Villa Nova, Kennard Gan & Matthias G. Wacker.*

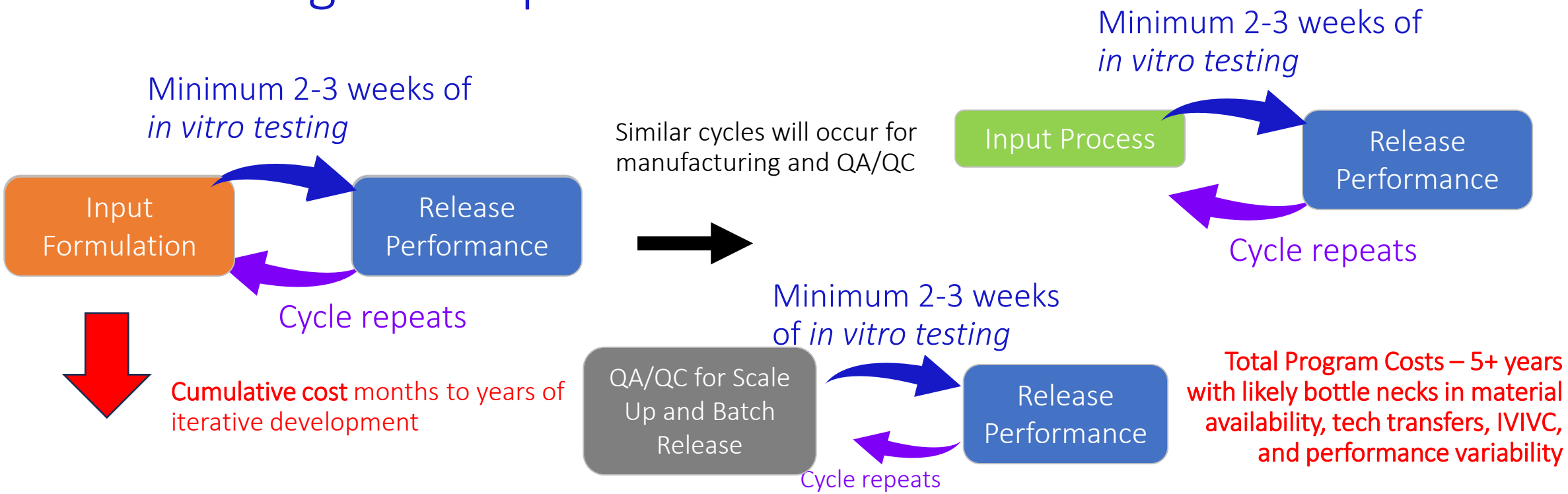

teva

Microstructure Science to Accelerate Generic Development

2024 Generic Drug Science and Research Initiatives Public Workshop
May 1-2, 2024

Itay Speicher
Sr. Director of Business Development
digiM solution LLC
Itay.Speicher@digimsolution.com

The Challenge with Traditional Approaches to Controlled Release Drug Development

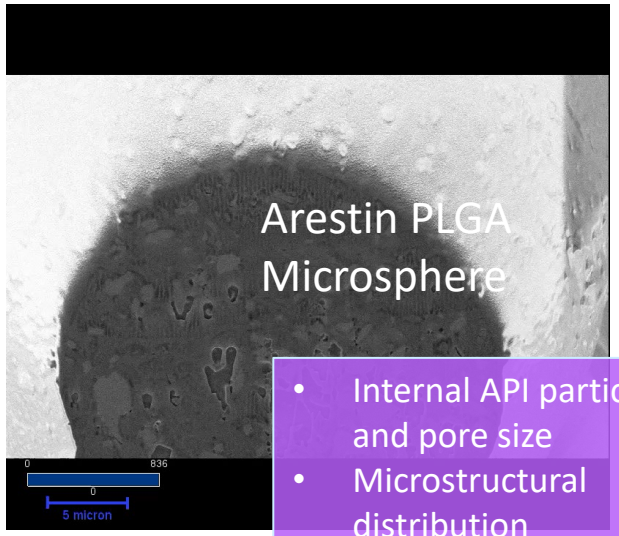


What about Generic Development? The situation is similar, with the added consideration of getting the product first time right to match RLD → guessing the RLD structure and performance and hoping your product will match is *costly and time consuming*

digiM
digimsolution.com

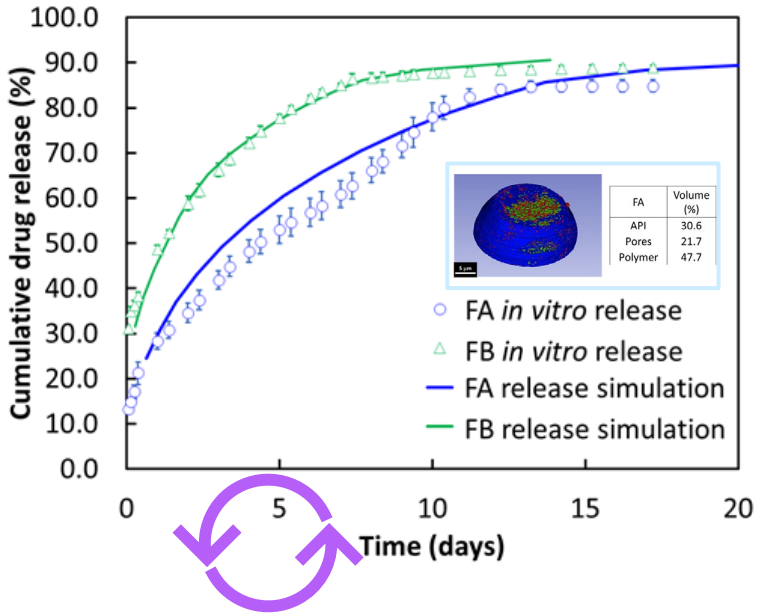
digiMAP for Successful Generic Product Approval

1. Quantify the **RLD** Critical Quality Attributes as a Benchmark



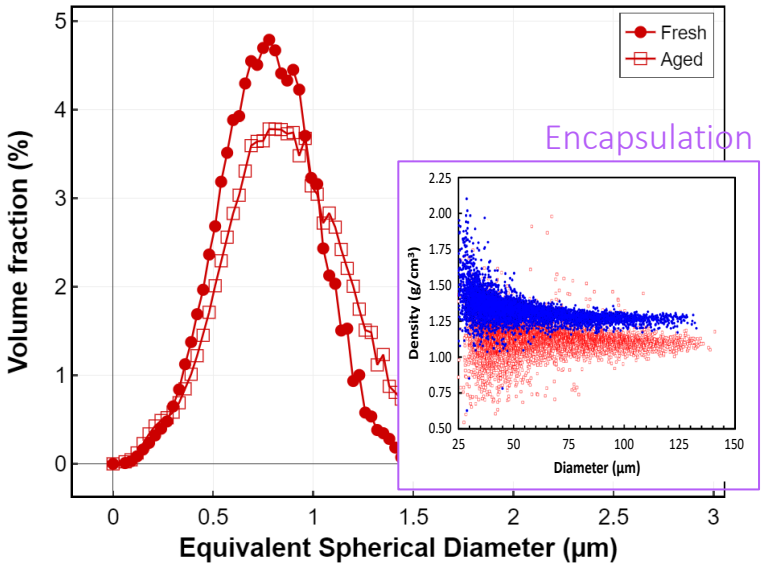
- Internal API particle and pore size
- Microstructural distribution
- Batch homogeneity

2. Compare **In House** Formulations and Evaluate Performance *In Silico*



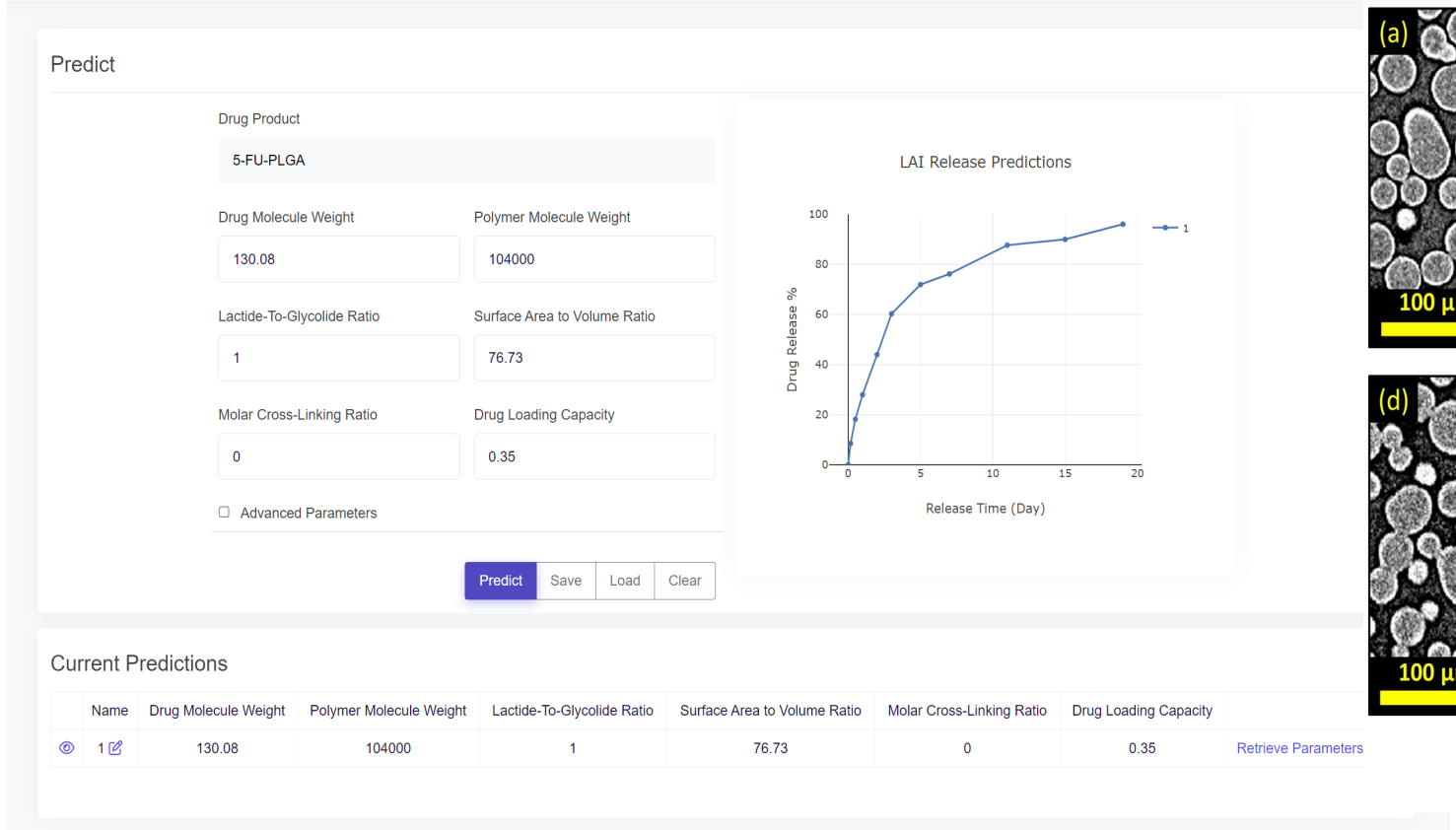
Rapid Feedback Loop to Evaluate Manufacturing Space

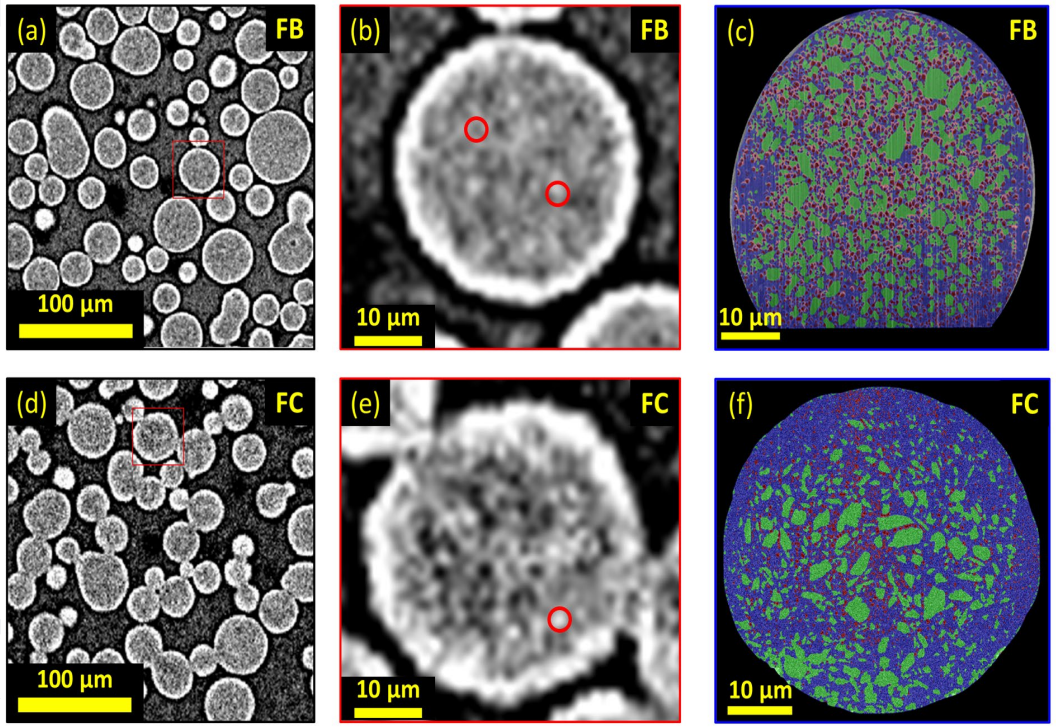
3. Demonstrate **Microstructure Equivalence** and Support ANDA Data Package



Encapsulation

Democratization of Data and Prediction for Future Programs





Batch characterization
MicroCT/XRM/Synchrotron

Intra-particle characterization
FIB-SEM/EDX/Tof-SIMS

Integration of digiM microstructure data, literature data, and existing data to build design space models for formulation, manufacturing, and performance

digiM
digimsolution.com

digiM

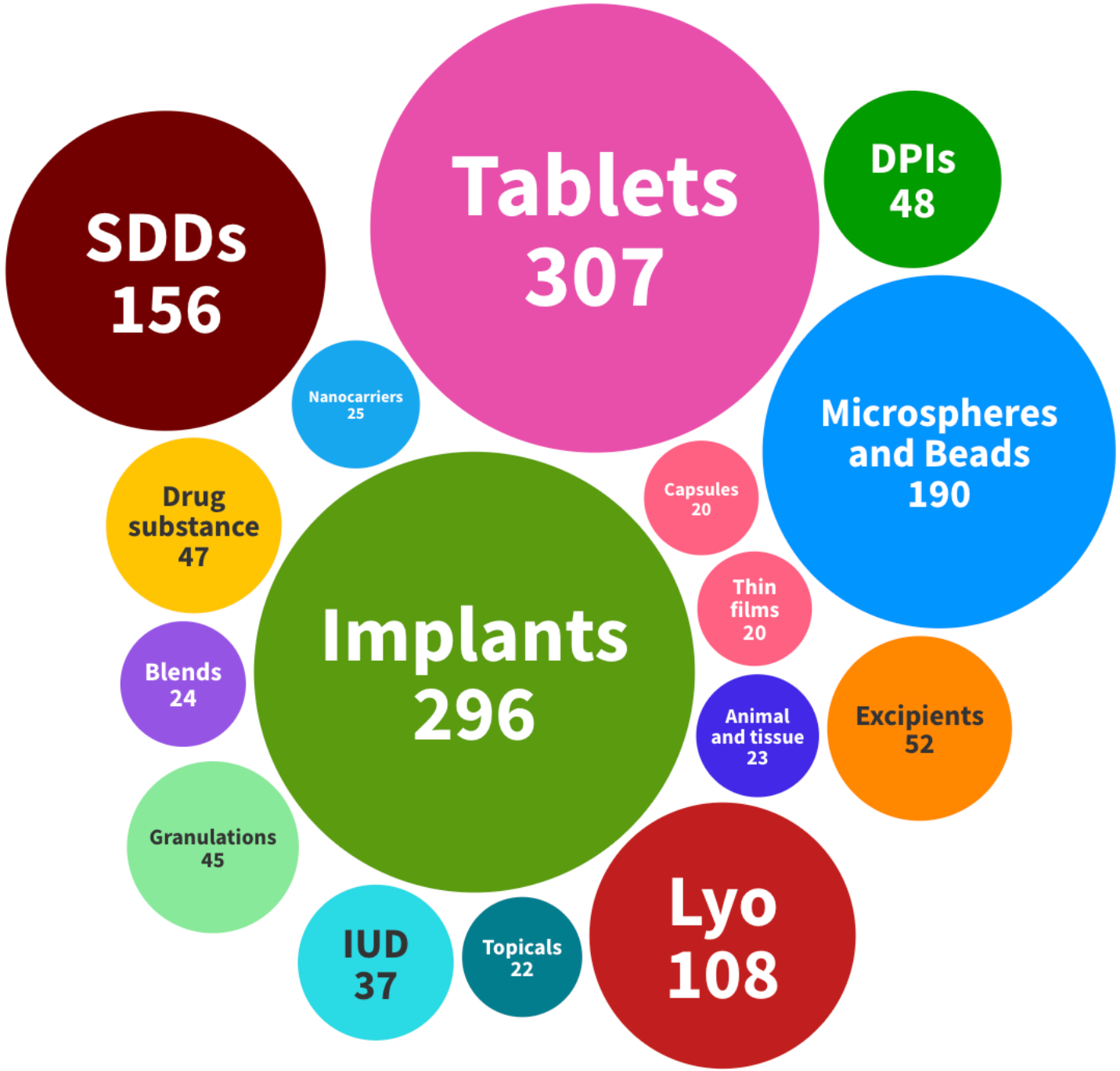
Pharmaceutical development support

1,511 formulations studied

104 partners

202 programs

28 generic programs



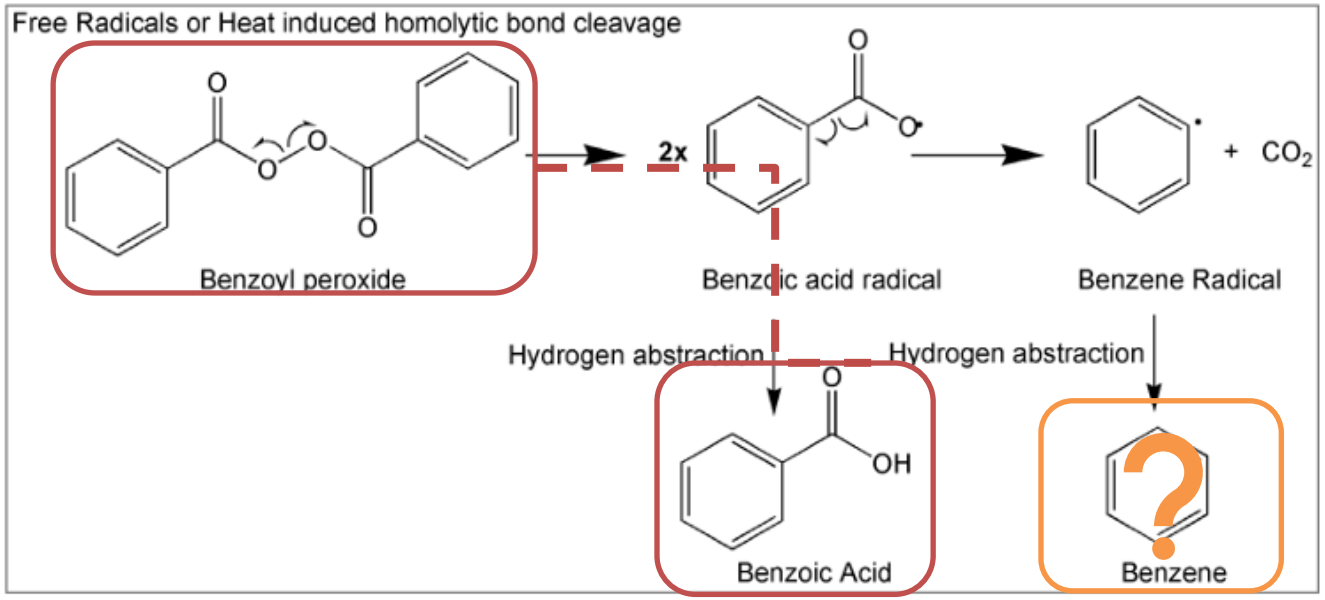
MedPharm
Breaking through boundaries

21 | May | 2024

Chemical stability of benzoyl peroxide and the formation of benzene in topical products

2024 FDA GDUFA Public Workshop
Jon Lenn, PhD
Chief Scientific Officer
MedPharm, Ltd
21st May, 2024

Benzoyl Peroxide – Inherently Unstable Molecule



Critical Factors for BPO Products

- Formulation to stabilize BPO
- Physical stability
- Solution vs suspension
- Packaging for shelf-life
- Storage conditions (temp & duration)
- Accelerated temperature – recommend 40°C
- In Use vs storage
- Duac (4C), Benzacline (4ms compounded, Monographs (room temp)

Scientific Problem – Stability of BPO

MedPharm

- Benzoyl Peroxide (BPO)
  - Bactericidal, widely used standalone or in combination for the treatment of acne vulgaris
  - Used by children, teens, and adults
  - Developed as a prescription (Rx) and over-the-counter (OTC)
- Valisure Citizen Petition on BPO Drug Products (5 March, 2024)
  - Data suggests that on-market BPO products could produce substantial amounts of benzene when stored at above-ambient temperatures - 37°C (98.6°F), 50°C (122°F) and 70°C (158°F).
  - Detected high levels of benzene in a wide range of BPO products (>800 times the limit benzene), Benzene Class 1 solvent (carcinogen) to be avoided at levels above 2ppm
  - Benzene causes cancer in human - *Centers for Disease Control and Prevention*
- The social media effect – *AAD, ABC News, Bloomberg, CBS, CNN, Fox News, Fortune, Instagram, NewsNation, People, Time, Newsweek, New York Post, TikTok, USA Today, etc*
- As a result, consumers, physicians, patients, and product development companies are concerned

Proposed Areas of Focus – Guidance for Industry

MedPharm

- What are the acceptable levels for benzene?
- Benzene Analysis - parameters to consider
  - Analytical Instruments
    - GC-FID, GC-PID, GC-MS, LC-UV, etc
    - Standards and Validation
    - Current monographs - benzoyl peroxide, benzoic acid, ethyl benzoate, and benzaldehyde
  - Extraction procedures for topicals (e.g. DMSO)
  - Temperature and humidity
    - Accelerated - 40°C vs 50°C
    - Gels very different than Creams
    - Shelf-life vs consumer conditions
    - Exposing BPO outside of formulation
  - Duration
    - Package labels vs excessive conditions - can’t control everything
  - Products
    - Prescription vs OTC
    - Standards & Controls
  - Modify USP BPO monographs (e.g. hydrous, lotion, gel, etc)

Proposed Areas of Focus - Consumers

MedPharm

- Does the use of BPO products increase a person's risk of cancer?
- Safe use and storage conditions
  - Education, PR, packaging
- Increased exposure to benzene
  - IVRT – 'worst case' - release as a max risk to skin
  - IVPT – 'best case' - utilize functional barrier
  - Animal PK
    - Tissue and blood levels of benzene
  - Human PK
    - Blood levels of benzene (mirror benzene and sunscreens)
  - Temperature and humidity outside packaging recommendations
    - cars/excessive storage conditions
- Health Literacy - How to control human behavior and packaging neglect?

Questions

MedPharm

- MedPharm is an international CDMO that works exclusively on topical and transdermal product development (Rx, OTC, Devices, and cosmetics).
  - Over 25 yrs of experience
  - Extensive *in vitro* BE experience
  - 300+ peer-reviewed publications
  - 85+ commercial products working with MedPharm
  - Extensive BPO experience – formulation and testing
  - Current programs to extend shelf life for marketed BPO products

MedPharm

BREAKING THROUGH BOUNDARIES

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USA

Panel Questions

Public Comments for Session 3

In Person Comments:

- Alexander Shekhtman, PhD, Professor and Chair, Department of Chemistry, University at Albany, State University of New York
- Marco Guerrini, MS Director Istituto di Ricerche Chimiche e Biochimiche
- Jace Jones, PhD Assistant Professor University of Maryland
- Andrew Graves, MS, SCYM Director, Immunogenicity Assessment Teva
- David Borhani Senior Director, Business Development Ginkgo Bioworks
- Ravishankara MN, PhD Senior General Manager (R & D) Sun Pharma
- Marina Juretić, PhD Senior Analytical Scientist, R&D, IVR/IVIVC PLIVA Hrvatska
- Itay Speicher, BSc, MBA Sr. Director of Business Development DigiM Solution
- Jon Lenn, PhD Chief Scientific Officer MedPharm
- Marc Taraban, PhD Associate Research Professor University of Maryland Baltimore
- Grzegorz Garbacz, PhD Co-Founder & CEO Physiolution Polska
- Laura Philips, PhD President & CEO Spheryx, Inc
- Katherine M. Harris, PhD Principal Scientist Carelon Research
- James K. Ferri, PhD Professor Virginia Commonwealth University

Virtual Comments:

- ***Conor L. Evans, PhD Associate Professor Harvard Medical School***
- ***Matthias Wacker, PhD Associate Professor National University of Singapore***
- Tao Zhang, PhD Assistant Professor, Pharmaceutical Sciences SUNY Binghamton University
- Hannah Batchelor Professor University of Strathclyde
- Jozef Al-Gousous, PhD Adjunct Assistant Professor University of Michigan
- Panos Macheras, PhD Professor Emeritus National and Kapodistrian University of Athens
- Hala Fadda, PhD Professor of Pharmaceutics Butler College
- Kathleen Walsh, MSc, MD Director, Patient Safety Research Center Boston Children's Hospital, Harvard University
- Alexa Simon Meara, MD Associate Professor The Ohio State University Wexner Medical Center
- Jacqueline Griffin Associate Professor Northeastern University
- Molly Moore Jeffery, PhD Robert D. and Patricia E. Kern Honored Investigator in the Science of Health Care Delivery | Scientific Director of Emergency Medicine Research and Platform Knowledge Solutions | Associate Professor Emergency Medicine Mayo Clinic
- Ozlem Ergun, PhD; Daniel Kosmas, PhD Professor Northeastern University
- Fang Yu, PhD Computational Modeling Scientist CONTINUUS Pharmaceuticals, Inc.
- Dongmei Li, PhD Professor, Clinical and Translational Research, Obstetrics and Gynecology and Public Health Sciences University of Rochester School of Medicine and Dentistry
- James Hasty CEO/Founder BHEC
- Peter Gompper Co-Founder, Rubitel

Pharmacokinetic Tomography for Topical Product Bioequivalence

Conor L. Evans

Wellman Center for Photomedicine
Massachusetts General Hospital
Harvard Medical School

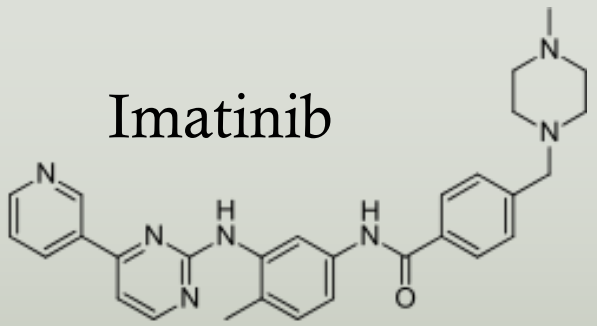
Challenges in Measuring Topical Product Bioequivalence

- A central concern in drug development is that a drug reaches its intended target
- Challenging for topical product administration due to lack of methods to follow flow and flux of APIs on the microscale
- Radiographic methods (e.g. MARG) give uptake, but not dynamics
- Modifications to drugs for tracking (e.g. fluorescence) often fundamentally alter pharmacokinetics
- Sampling method (IVPT, tape stripping, dMD, dOFM) do not provide microscale information

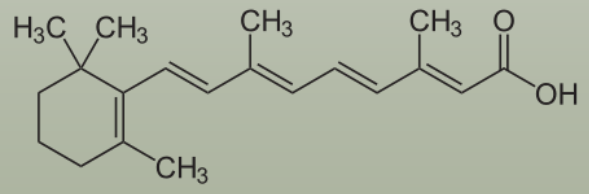
Pharmacokinetic Tomography

A paradigm for the microscopic imaging and quantification of drugs based on *intrinsic* sources of contrast:

Imatinib



Retinoic Acid

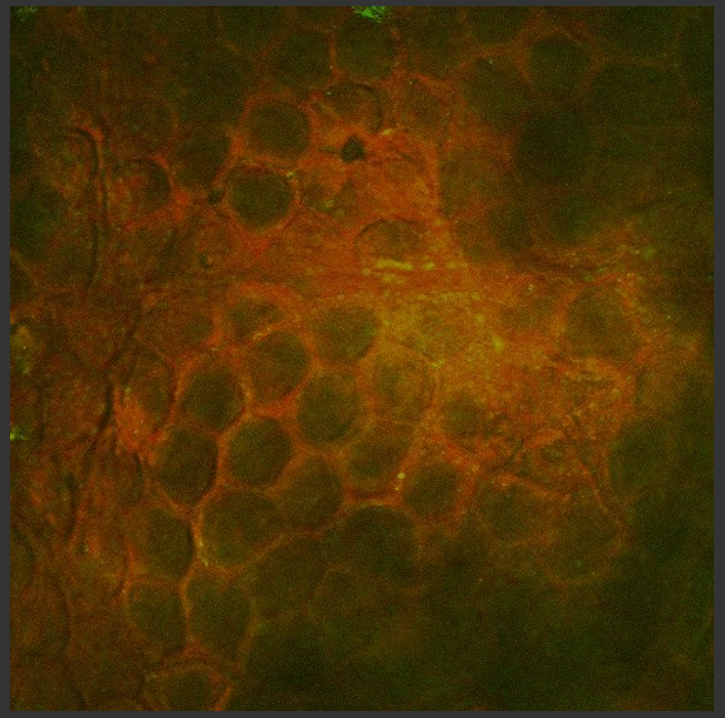


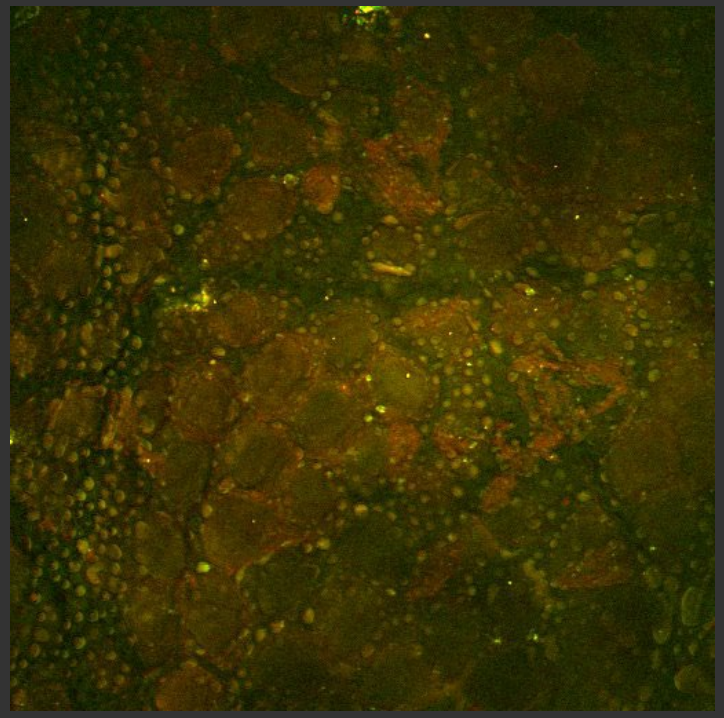
Stimulated Raman scattering (SRS) methods enable *direct* imaging and quantification of APIs in skin via their Molecular vibrations

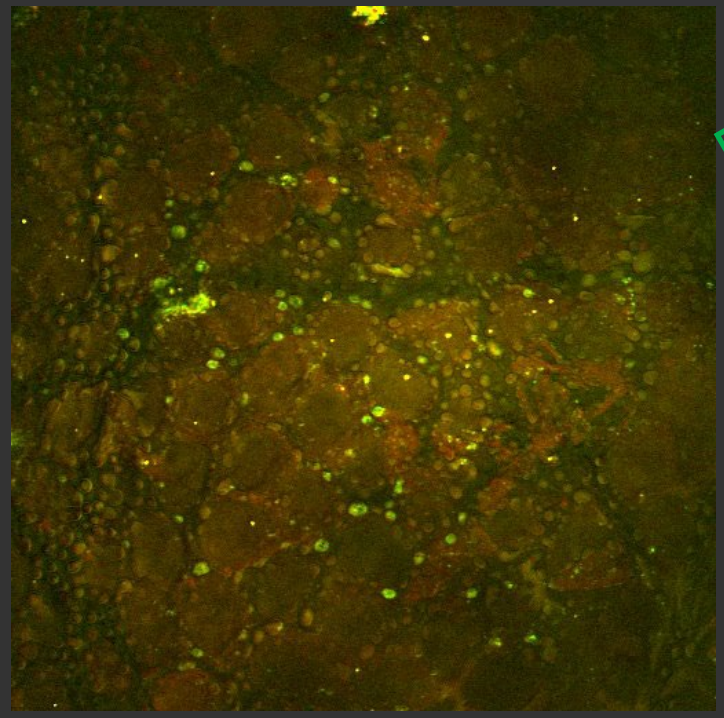
API Epidermal Pharmacokinetics

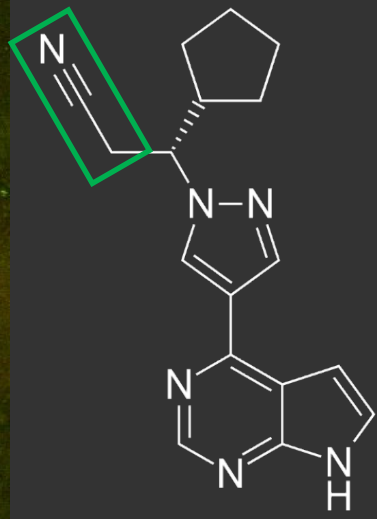
Red: Lipid 2845 cm^{-1}

Green: Nitrile 2250 cm^{-1}







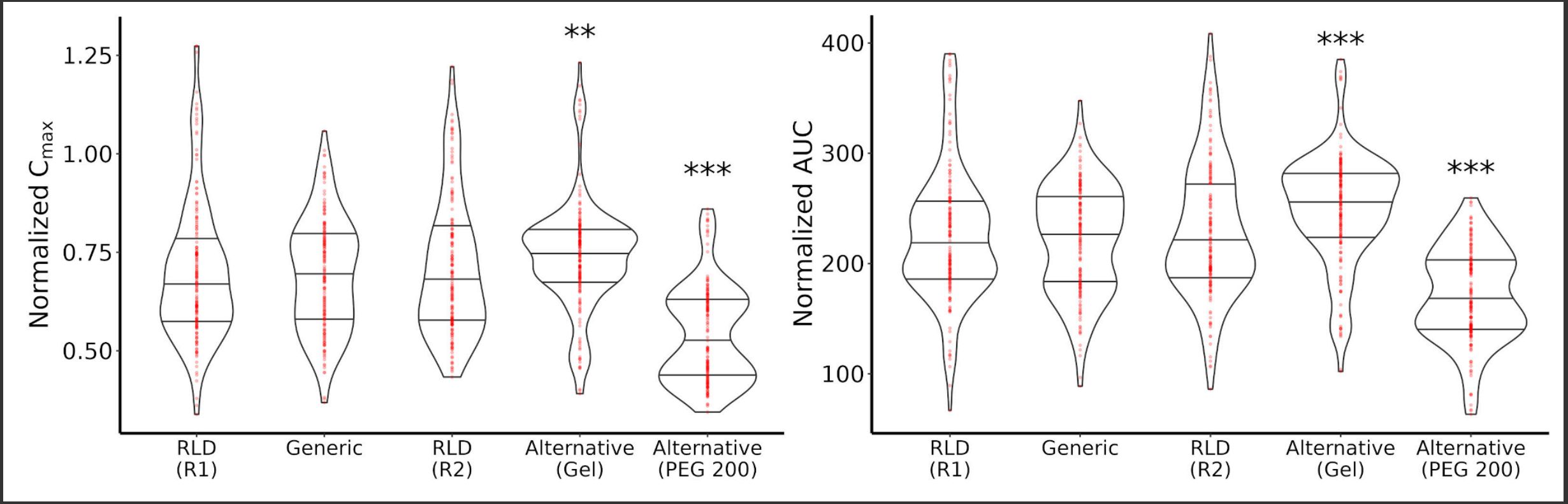


15 min **70 min** **120 min**

Direct visualization of Ruxolitinib forming depots within the epidermis within the lipid-rich interlamellar spaces

Quantifying Imaging Data

Using machine learning and image analysis, SRS images can be analyzed to extract *local* PK parameters including Tmax, Cmax, and AUC for comparison of APIs across different formulations and products



Comparison of PK parameters for different Brand, Generic, and lab-made Tazarotene products in *ex vivo* human skin

Measuring Bioequivalance

Product 1	Product 2	90% Confidence interval for the mean difference of the C_{max} values (Product 2 – Product 1)		90% Confidence interval for the mean difference of the AUC values (Product 2 – Product 1)	
		Lipid-rich intralamellar region	Lipid-poor corneocytes region	Lipid-rich intralamellar region	Lipid-poor corneocytes region
RLD(R1)	RLD(R2)	(0.94,1.07)	(0.94,1.06)	(0.94,1.08)	(0.94,1.06)
RLD(R1)	Generic	(0.94,1.05)	(0.94,1.05)	(0.94,1.06)	(0.94,1.04)
RLD(R1)	Alternative (Gel)	(1.01,1.14)	(1.01,1.14)	(1.05,1.19)	(1.04,1.17)
RLD(R1)	Alternative (PEG 200)	(0.72,0.82)	(0.71,0.81)	(0.70,0.80)	(0.73,0.83)

If a topical product is within the 90% confidence intervals of 0.8 and 1.25, it is considered bioequivalent

Complex Injectables:
Understanding Drug Delivery

Generic Drug Science and Research Initiatives Workshop, May 2024

Associate Professor Matthias G. Wacker, PhD
Department of Pharmacy and Pharmaceutical Sciences
matthias.g.wacker@nus.edu.sg

NUS National University of Singapore

TheWackerLab
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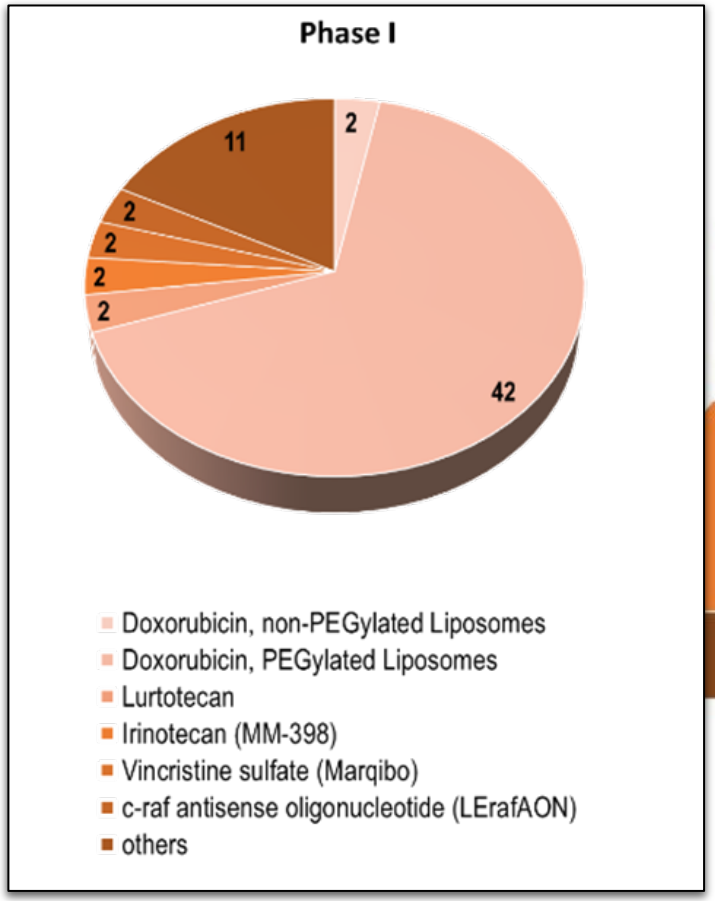
Matthias G. Wacker

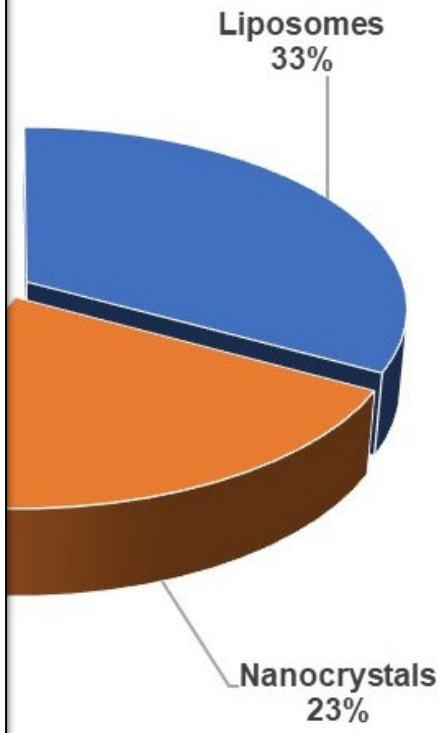
"The physical and biological realms converge in clinical applications. Our discipline, pharmaceutical science, leverages a deeper understanding of molecular interactions. This is the essence of bioprediction: Creating safer medicines by learning of their complex mechanics."

www.thewackerlab.com

Safety-by-Design
Stealth Liposomes and Beyond

- IVIVC of liposomal doxorubicin is difficult yet achievable.
- Most injectable nanosimilars are based on the Doxil® Stealth liposome platform.





Mast et al. 2021, Adv Drug Del Rev (https://www.doi.org/10.1016/j.addr.2021.113829)
Marques et al. 2019, Adv Drug Del Rev (https://www.doi.org/10.1016/j.addr.2019.06.003)

Bioequivalence Assessment
Stealth Liposomes

European Journal of Pharmaceutics and Biopharmaceutics 153 (2020) 257–272

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

A physiologically-based nanocarrier biopharmaceutics model to reverse-engineer the *in vivo* drug release

Shakti Nagpal[a,1], Svenja Braner[a,1], Harshvardhan Modh[a], Ada Xi Xin Tan[a], Marc-Phillip Mast[b,c], Karim Chichakly[d], Volker Albrecht[e], Matthias G. Wacker[a,*]

[a] National University of Singapore, Department of Pharmacy, Faculty of Science, Singapore
[b] Fraunhofer-Institute for Molecular Biology and Applied Ecology IME, Branch for Translational Medicine and Pharmacology, Frankfurt, Germany
[c] Goethe University, Institute of Pharmaceutical Technology, Frankfurt, Germany
[d] isee Systems Inc., Lebanon, NH, USA
[e] Biolitec Research GmbH, Jena, Germany

Nagpal et al. 2020, Eur J Pharm Biopharm (https://www.doi.org/10.1016/j.ejpb.2020.06.004)
Li and Gan et al. 2024, Int J Pharm (https://www.doi.org/10.1016/j.ijpharm.2024.123942)

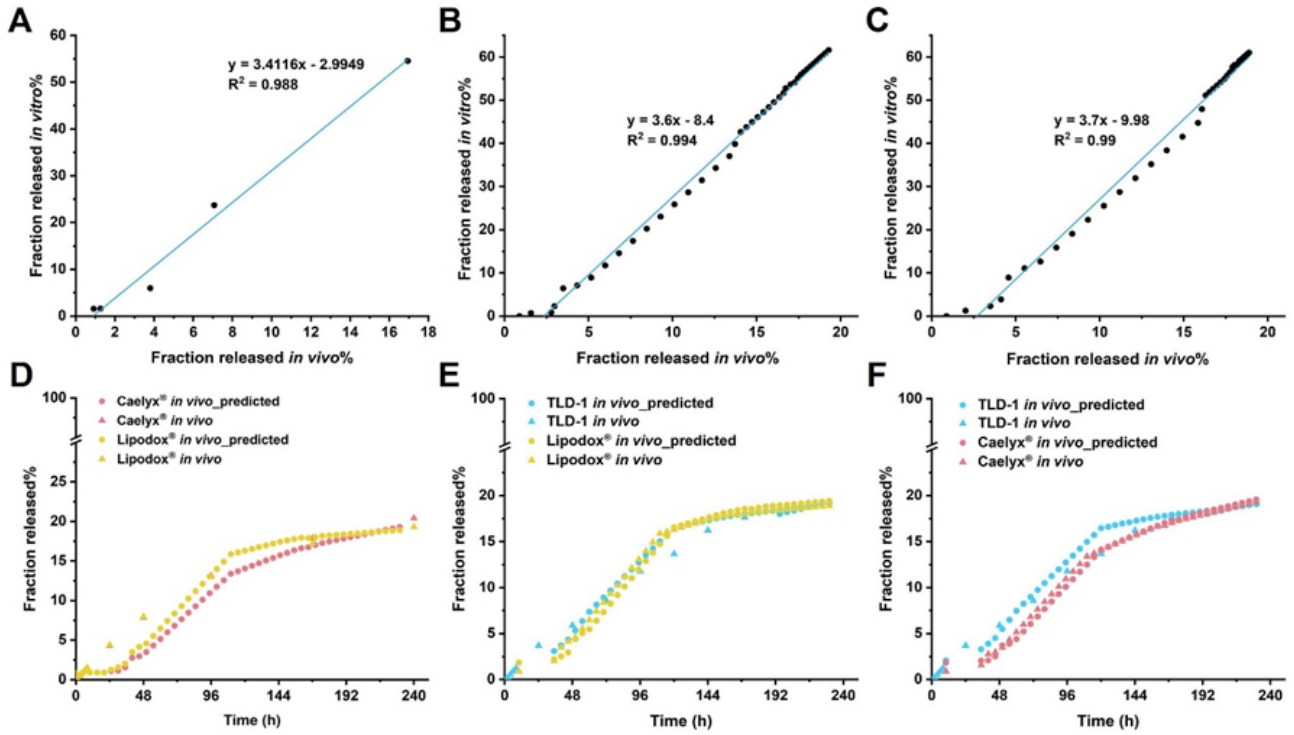
RELEASE TESTING IN SERUM USING THE DISPERSION RELEASER

- Confirm Physiological Relevance
- Understand Mechanisms
- Setting Standards

More on our validation procedures is reported in Mast et al. 2021, Pharmaceutics (https://www.doi.org/10.3390/pharmaceutics13122007)

IVIVC
Caelyx® vs. Lipodox® vs. Talidox ®

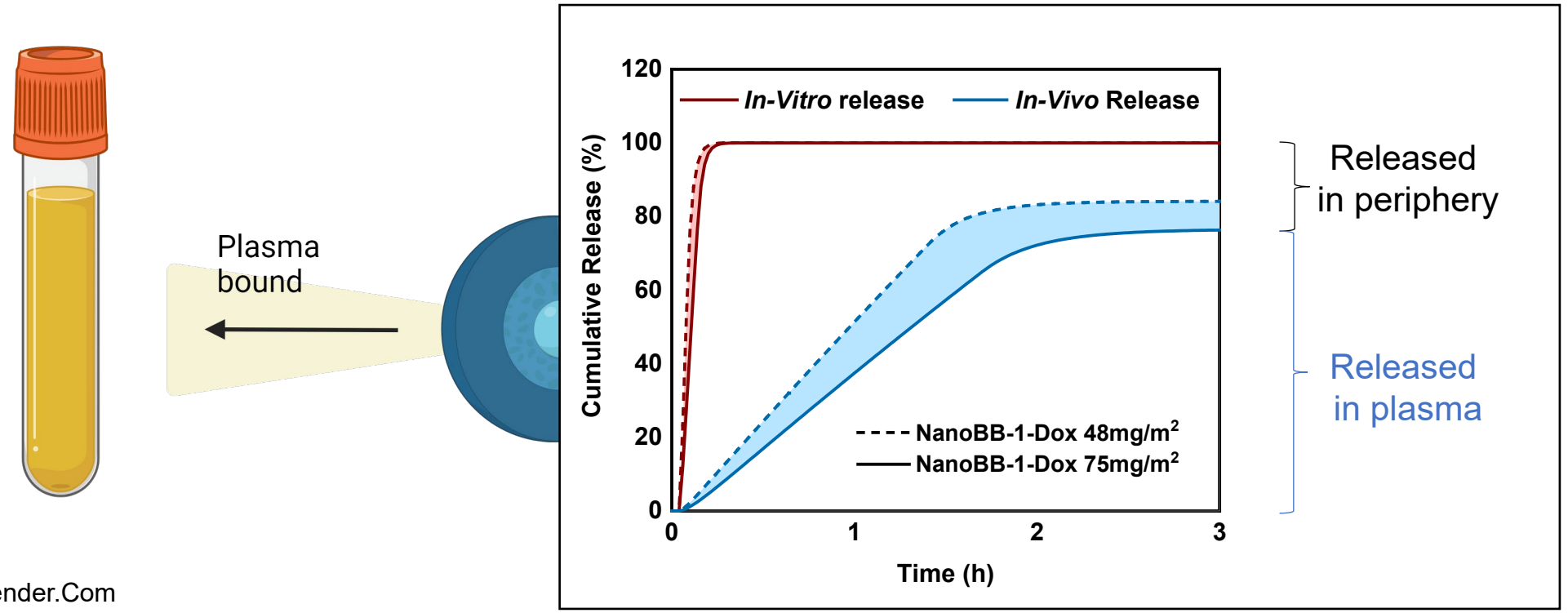
- Rodent studies are inherently limited in the assessment of human safety.
- IVIVC based on human data improves risk estimations.
- Validation against a continuously growing generics database.



Li and Gan et al. 2024, Int J Pharm (https://www.doi.org/10.1016/j.ijpharm.2024.123942)

PBB Modeling in Risk Estimation

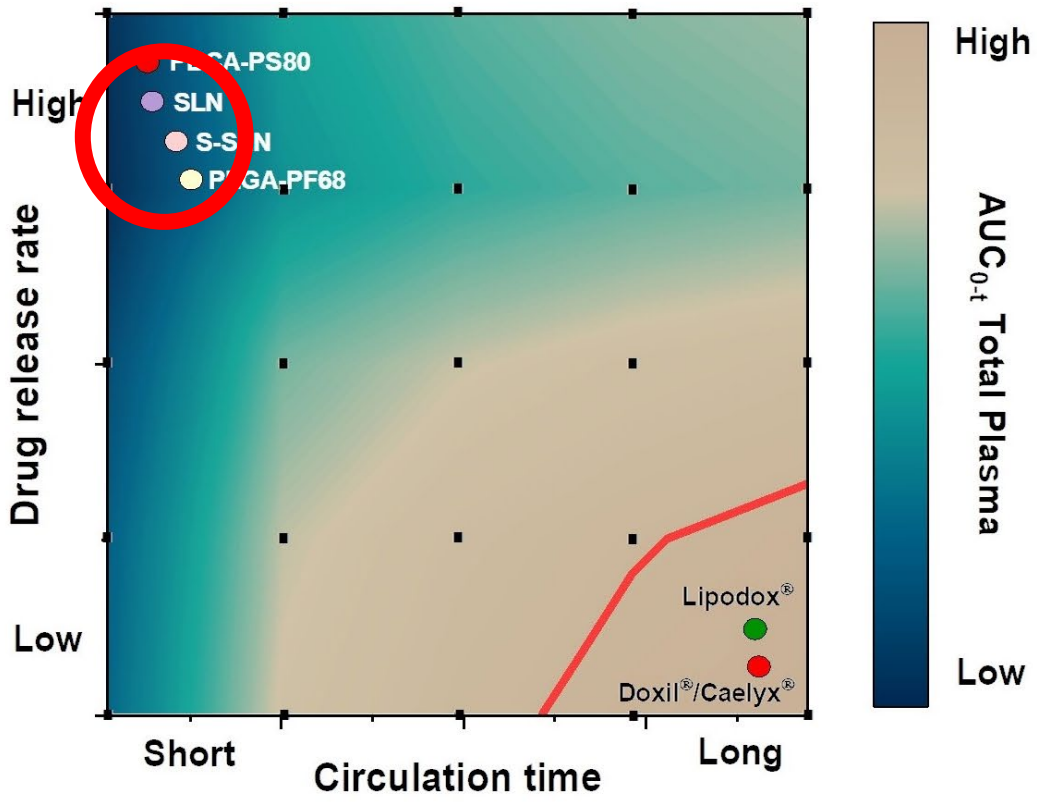
- Pre-classification of liposomal generics based on two parameters obtained by our model are **carrier halflife** and **in vivo release (absorption) rate**.

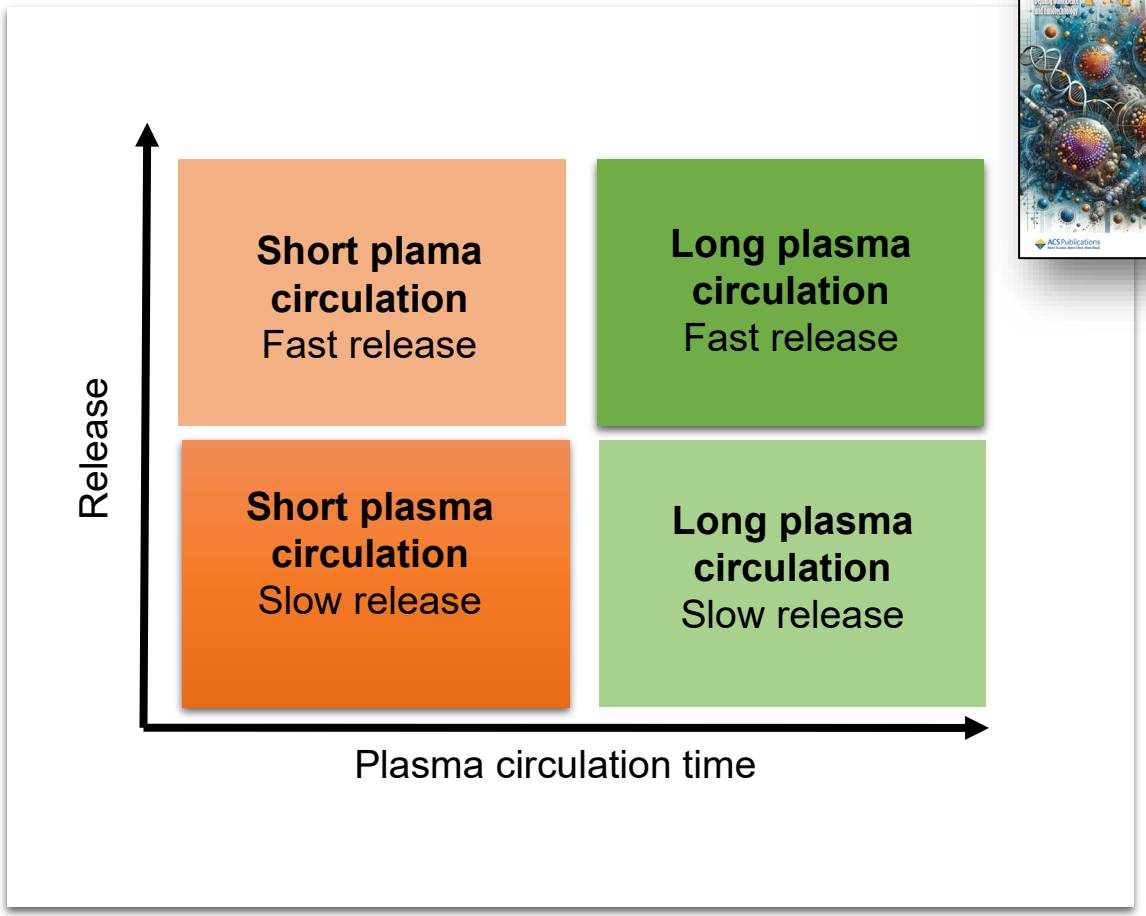


Created with BioRender.Com

Nagpal et al. 2020, Eur J Pharm Biopharm (https://www.doi.org/10.1016/j.ejpb.2020.06.004)

Low Risk vs. High Risk





Nagpal et al. 2024, ACS Nano (https://www.doi.org/10.1021/acsnano.3c08290)

NUS
National University of Singapore

FUTURE RESEARCH NEEDS

- **Advancing PBB Modeling** to Enhance Predictive Accuracy & Replace Animal Testing.
- **Developing Data-Driven Risk Assessment** Tools That Leverage Existing Data Pools (e.g., LAIs, LNPs, SLNs, Exosomes, Iron Complexes).
- **Establishing Robust Testing Protocols** for Performance Validation.

Public Comments for Session 3

In Person Comments:

- Alexander Shekhtman, PhD, Professor and Chair, Department of Chemistry, University at Albany, State University of New York
- Marco Guerrini, MS Director Istituto di Ricerche Chimiche e Biochimiche
- Jace Jones, PhD Assistant Professor University of Maryland
- Andrew Graves, MS, SCYM Director, Immunogenicity Assessment Teva
- David Borhani Senior Director, Business Development Ginkgo Bioworks
- Ravishankara MN, PhD Senior General Manager (R & D) Sun Pharma
- Marina Juretić, PhD Senior Analytical Scientist, R&D, IVR/IVIVC PLIVA Hrvatska
- Itay Speicher, BSc, MBA Sr. Director of Business Development DigiM Solution
- Jon Lenn, PhD Chief Scientific Officer MedPharm
- ***Marc Taraban, PhD Associate Research Professor University of Maryland Baltimore***
- ***Grzegorz Garbacz, PhD Co-Founder & CEO Physiolution Polska***
- Laura Philips, PhD President & CEO Spheryx, Inc
- Katherine M. Harris, PhD Principal Scientist Carelon Research
- James K. Ferri, PhD Professor Virginia Commonwealth University

Virtual Comments:

- Conor L. Evans, PhD Associate Professor Harvard Medical School
- Matthias Wacker, PhD Associate Professor National University of Singapore
- Tao Zhang, PhD Assistant Professor, Pharmaceutical Sciences SUNY Binghamton University
- Hannah Batchelor Professor University of Strathclyde
- Jozef Al-Gousous, PhD Adjunct Assistant Professor University of Michigan
- Panos Macheras, PhD Professor Emeritus National and Kapodistrian University of Athens
- Hala Fadda, PhD Professor of Pharmaceutics Butler College
- Kathleen Walsh, MSc, MD Director, Patient Safety Research Center Boston Children's Hospital, Harvard University
- Alexa Simon Meara, MD Associate Professor The Ohio State University Wexner Medical Center
- Jacqueline Griffin Associate Professor Northeastern University
- Molly Moore Jeffery, PhD Robert D. and Patricia E. Kern Honored Investigator in the Science of Health Care Delivery | Scientific Director of Emergency Medicine Research and Platform Knowledge Solutions | Associate Professor Emergency Medicine Mayo Clinic
- Ozlem Ergun, PhD; Daniel Kosmas, PhD Professor Northeastern University
- Fang Yu, PhD Computational Modeling Scientist CONTINUUS Pharmaceuticals, Inc.
- Dongmei Li, PhD Professor, Clinical and Translational Research, Obstetrics and Gynecology and Public Health Sciences University of Rochester School of Medicine and Dentistry
- James Hasty CEO/Founder BHEC
- Peter Gompper Co-Founder, Rubitel

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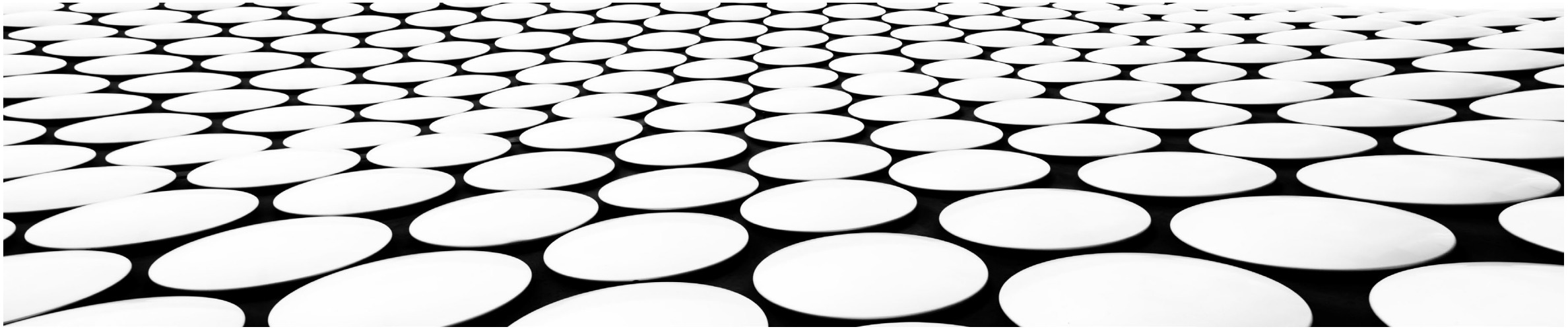
& BIOTECHNOLOGY RESEARCH

BENCHTOP NMR

NON-INVASIVE AND FAST ANALYSIS OF DRUG PRODUCTS

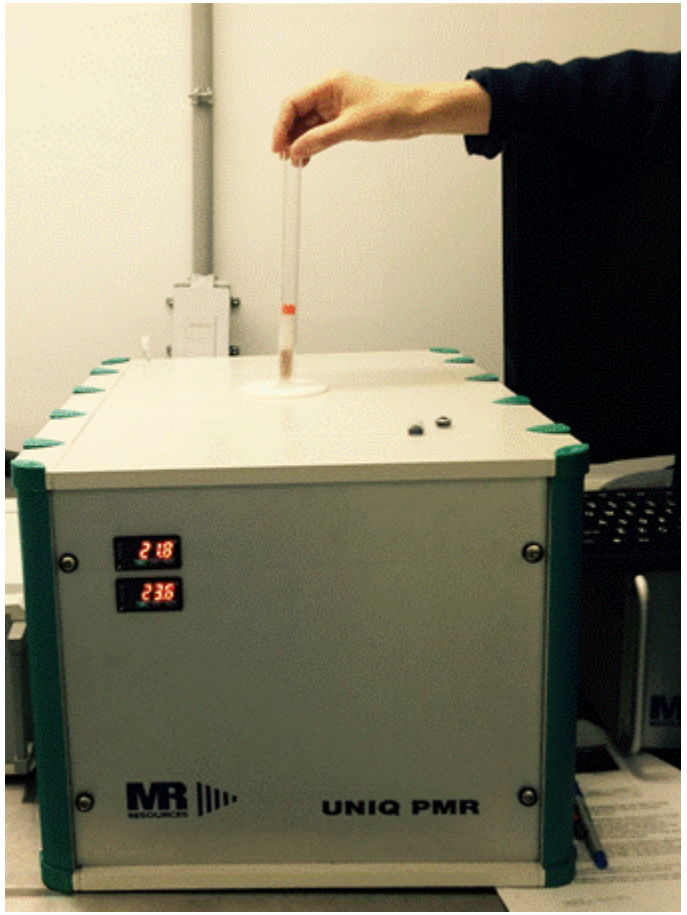
MARC TARABAN



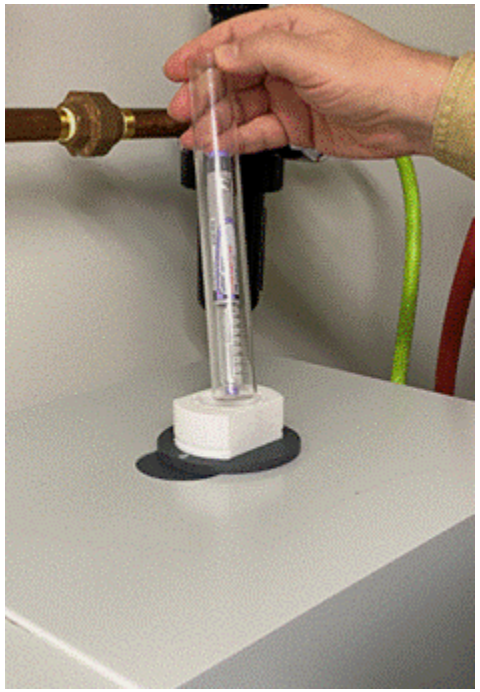
FY24 FDA GDUFA PUBLIC WORKSHOP

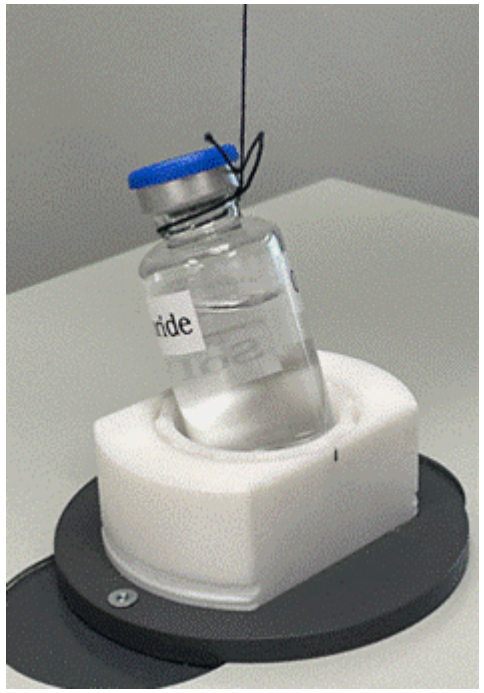
MAY 20-21, 2024

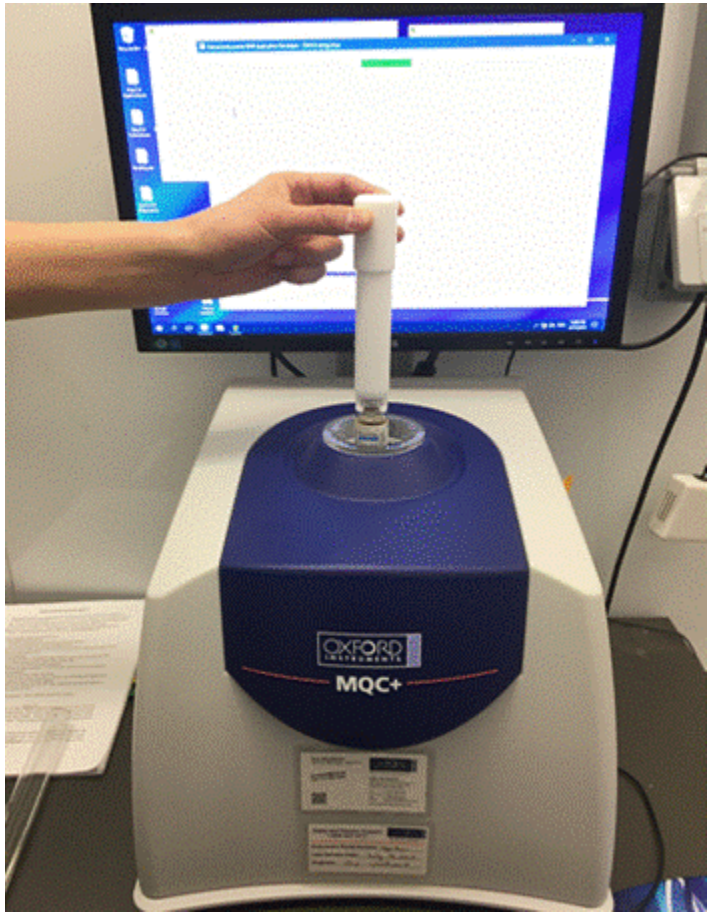
ANALYSIS OF DRUGS IN THE ORIGINAL CONTAINERS



WIDE-BORE ACCOMODATES VIALS, SYRINGES, INJECTION PENS







Measurements are fast and allow to characterize drug products non-destructively, the content is not compromised, and is safe for further use (administration).

UMB BENCHTOP NMR SUITE AT IBBR (ROCKVILLE, MD)

APPLICATIONS OF BENCHTOP NMR FOR GENERIC DRUG PRODUCTS

VARIABILITY BRAND vs. GENERIC

- ***For liquid formulations***—Reveals differences between brand and generic drugs, compares variability between brand and generic
  —*Demonstrated for insulin innovator and follow-on products in the prefilled injection pens and biotherapeutics in a vial (filgrastim brand and generics)*
- ***For solid formulations***—Provides highly accurate quantitative estimates of the formulation content and morphology, e.g., amorphous, crystalline, allows to compare brand vs. generic variability

DISSOLUTION KINETICS BRAND vs. GENERIC

- ***For tablets***—Comparison of dissolution kinetics between brand and generic drug products, provides the values of dissolution rates/rate constants
  —*Could be performed at different temperatures, different media and volumes, with data collection increment from seconds to minutes to hours*
- ***For lyophilized powders***—Comparison of dissolution kinetics of brand vs. generic of the lyophilized powder formulations; could be performed directly in the drug product container (vial)

QUESTIONS?

CONTACT INFORMATION

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Bio- and Nanotechnology Center Director
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Institute for Bioscience and Biotechnology Research
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Biopredictive testing of oral drugs in physiological design space

Physiolution

Marcela Staniszewska, Dorota Danielak, Oksana Laptieva, Anne Deuter, Daria Myslitska, Justyna Dobosz, Michał Smoleński, Michał Romański, Jaroslaw Sczodrok, Jadwiga Paszkowska, Grzegorz Garbacz

Our goals:

- to develop methodology for the reflection of the *in vivo* variability of the fasted stomach conditions in *in vitro* test protocols.
- to generate neration of dissolution profiles for the individual simulated gastric conditions within the physiological test space.

Same drug - different PK

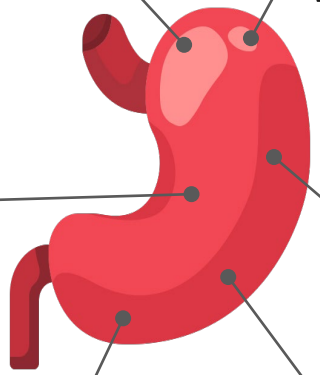
CAPSULES WITH PELLETS	vs	BARE PELLETS
↑ 3-fold greater variability		↑ 75% higher $AUC_{0\text{-}inf}$
↑ 25% longer T_{max}		↑ 86% higher C_{max}

Are the variable gastric motility patterns the reason?

Physiological parameters of interest

Gradient of temperature
22 → 37◦C in 15 min

Gastric pH
HCl pH 1.2 - 4.0



Gastric emptying rate
Variable flow rate

Timing of intragastric stresses (IST)
5 - 41 min

Pressure magnitude of intragastric stresses (ISP)
150 mbar

Timing of gastric emptying event (GET)
1 - 60 min

3D physiological test space designed with DoE

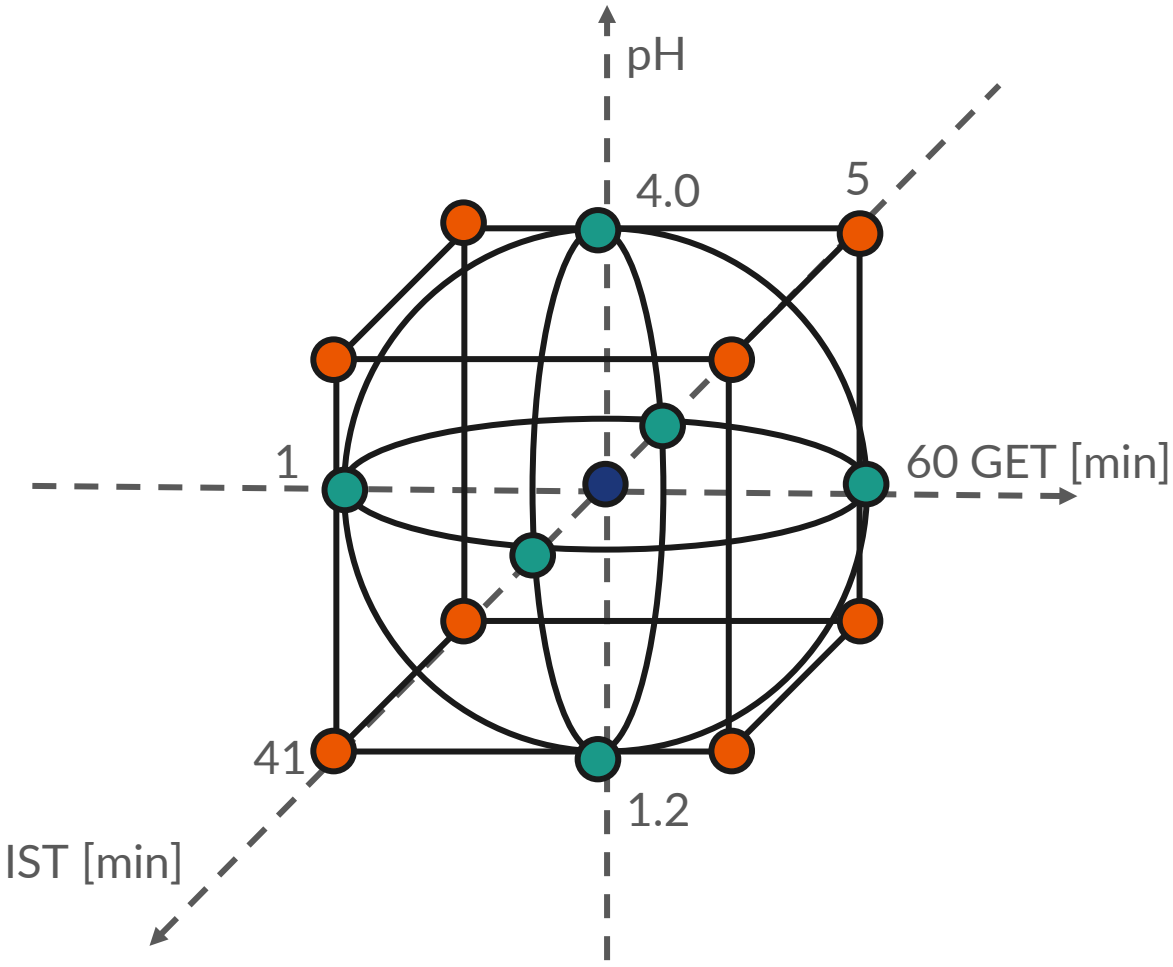
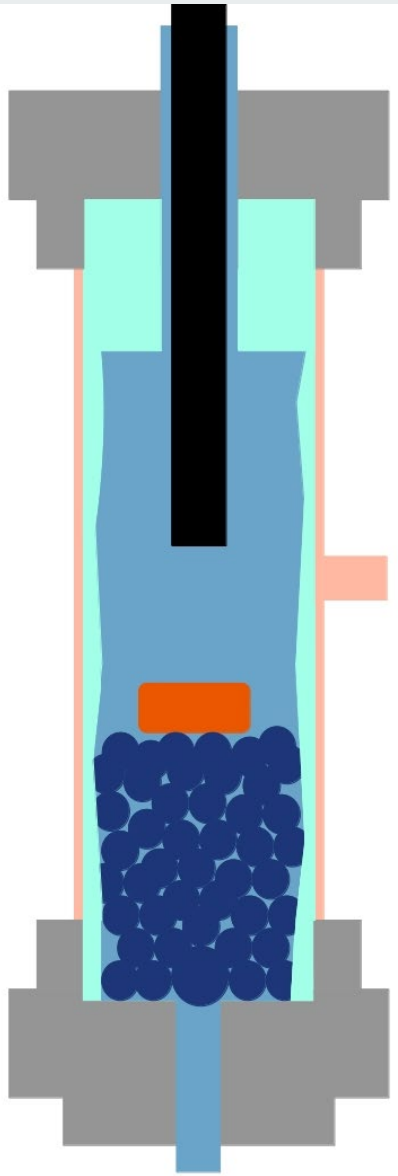


image: Flaticon.com

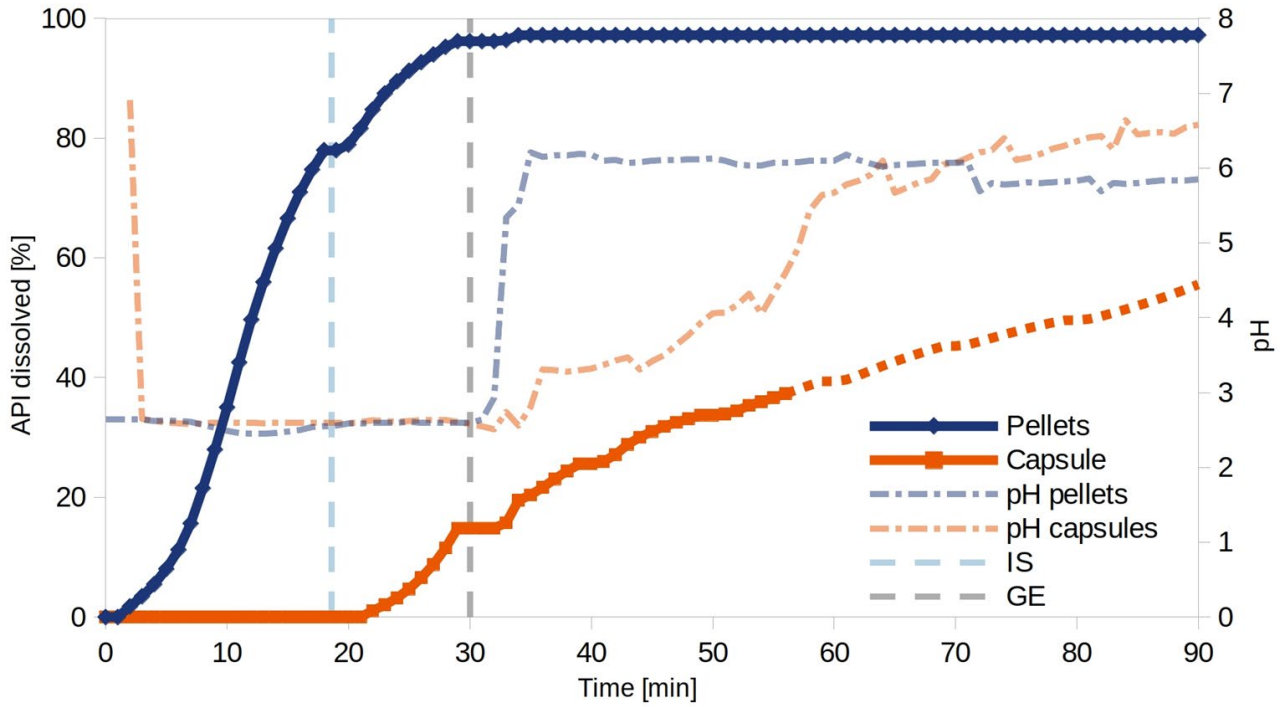
Our tool

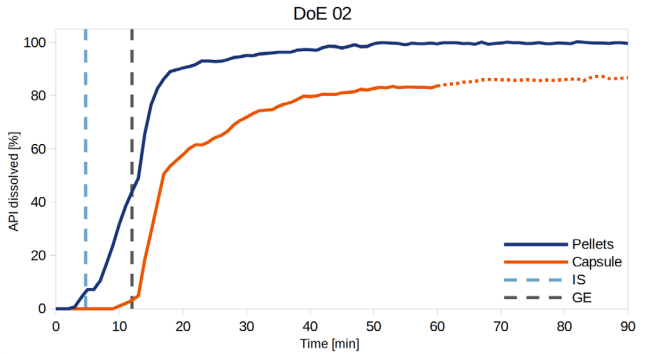
PhysioCell

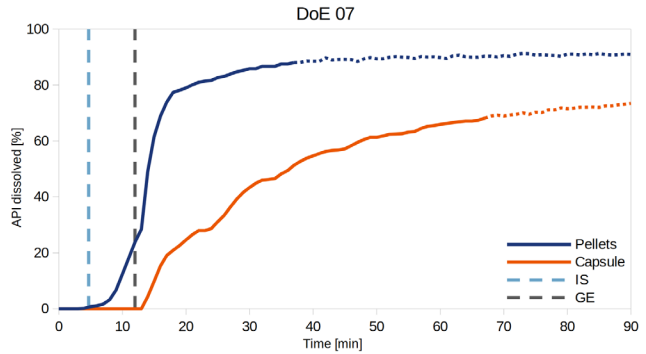
- **Flow-through cell**
- **Small volume** (ca. 25 mL) of the dissolution media in the probe chamber
- Simulation of **motility forces**
- pH and temperature measurement
- **Temperature gradients**: temperature increase from about 25 up to 37 °C within 10 – 15 min
- **Variable kinetics of gastric emptying** of non caloric liquids

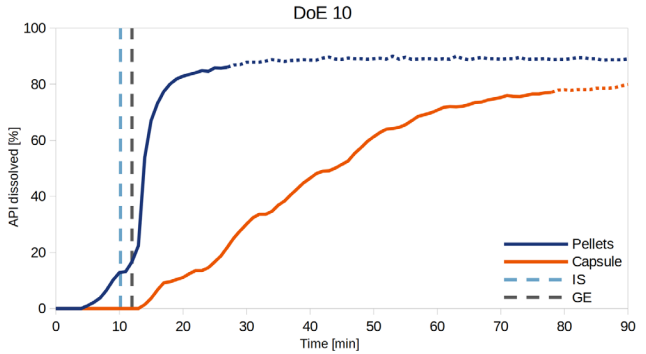


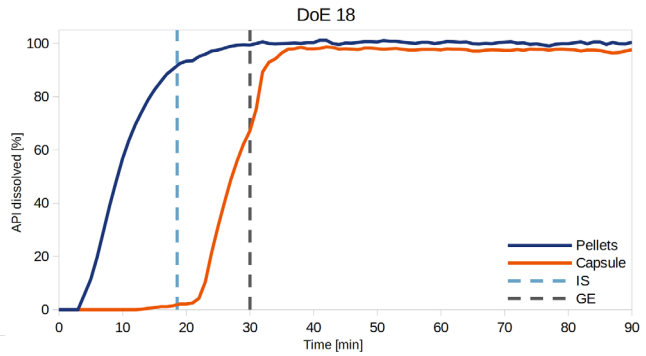
Dissolution of capsules with pellets vs loose pellets







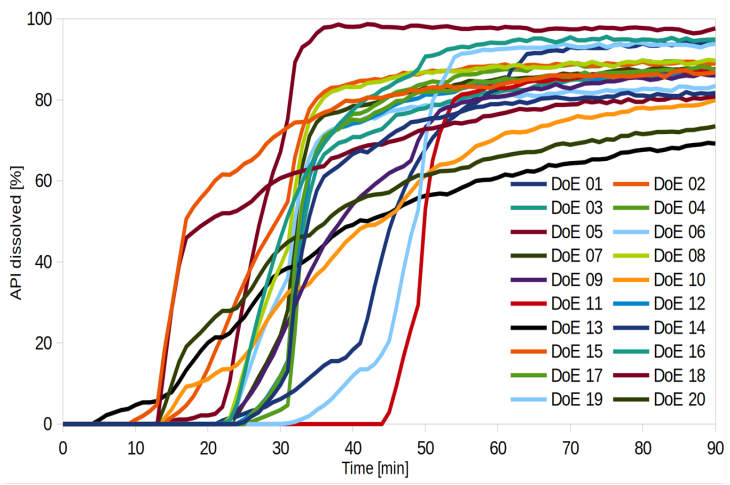




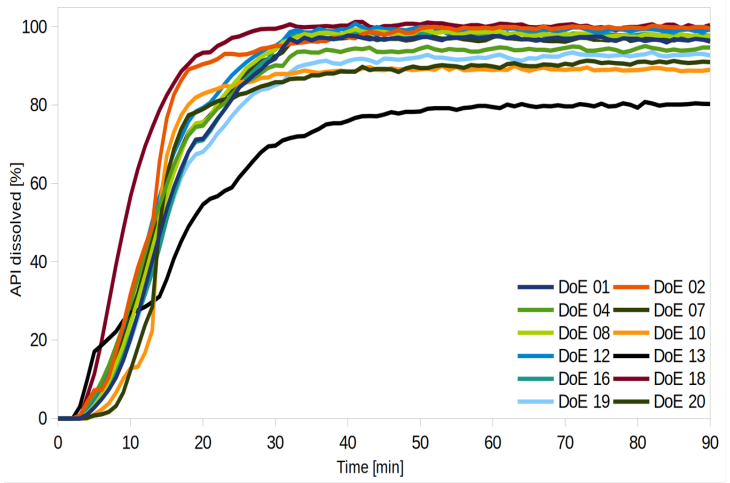
CAPSULES WITH PELLETS	VS	BARE PELLETS
↑ 3-fold greater variability		↑ 75% higher $AUC_{0\text{-}inf}$
↑ 25% longer T_{max}		↑ 86% higher C_{max}

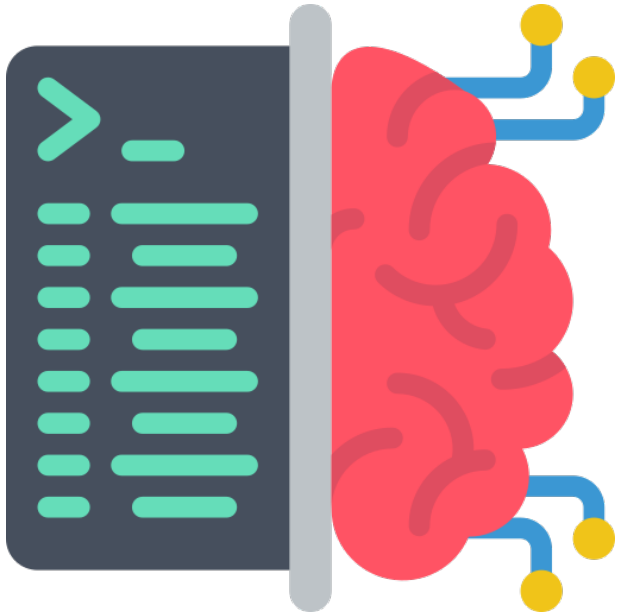
Modeling by machine learning

Capsules



Pellets



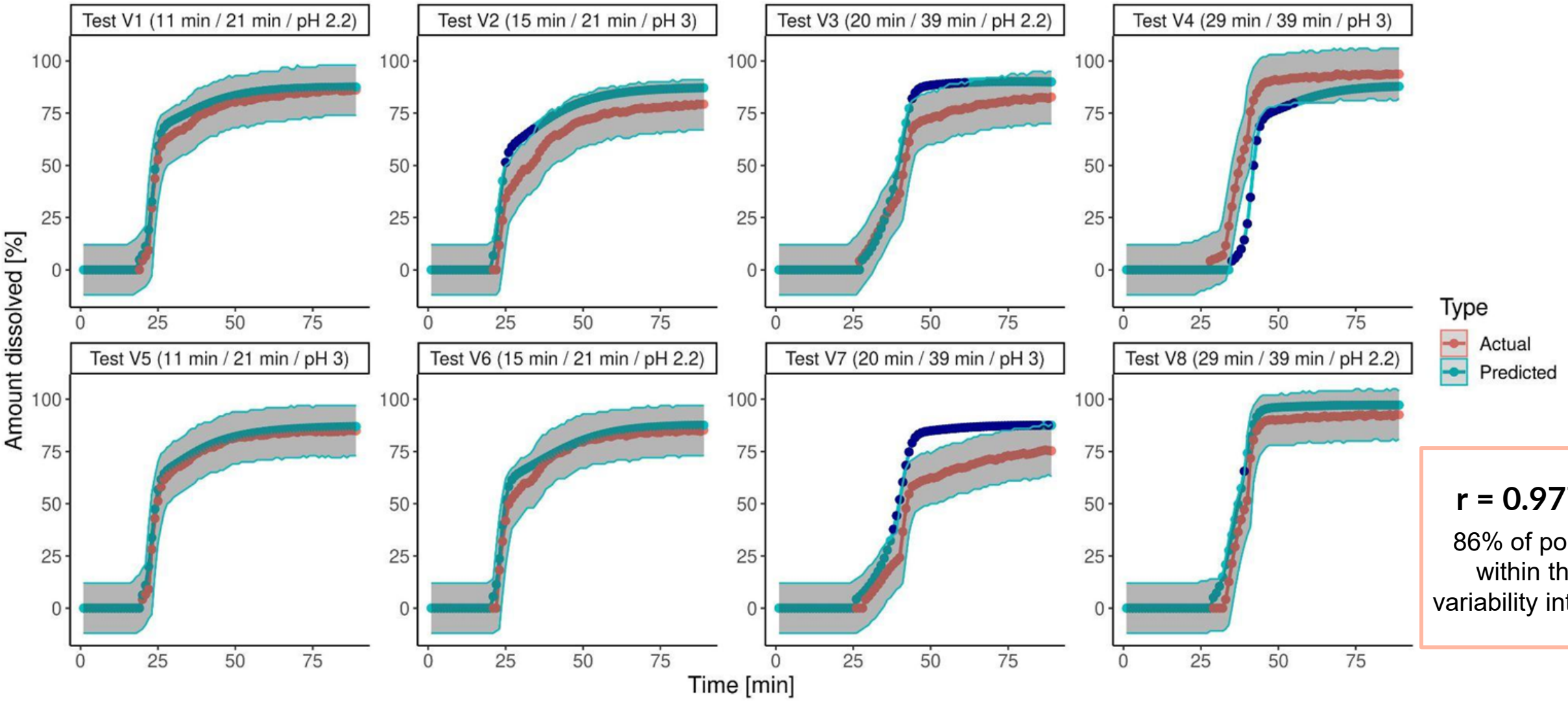


Neural Networks / Random Forest algorithms
implemented in WEKA Environment

Bio-predictive dissolution models

image: Flaticon.com

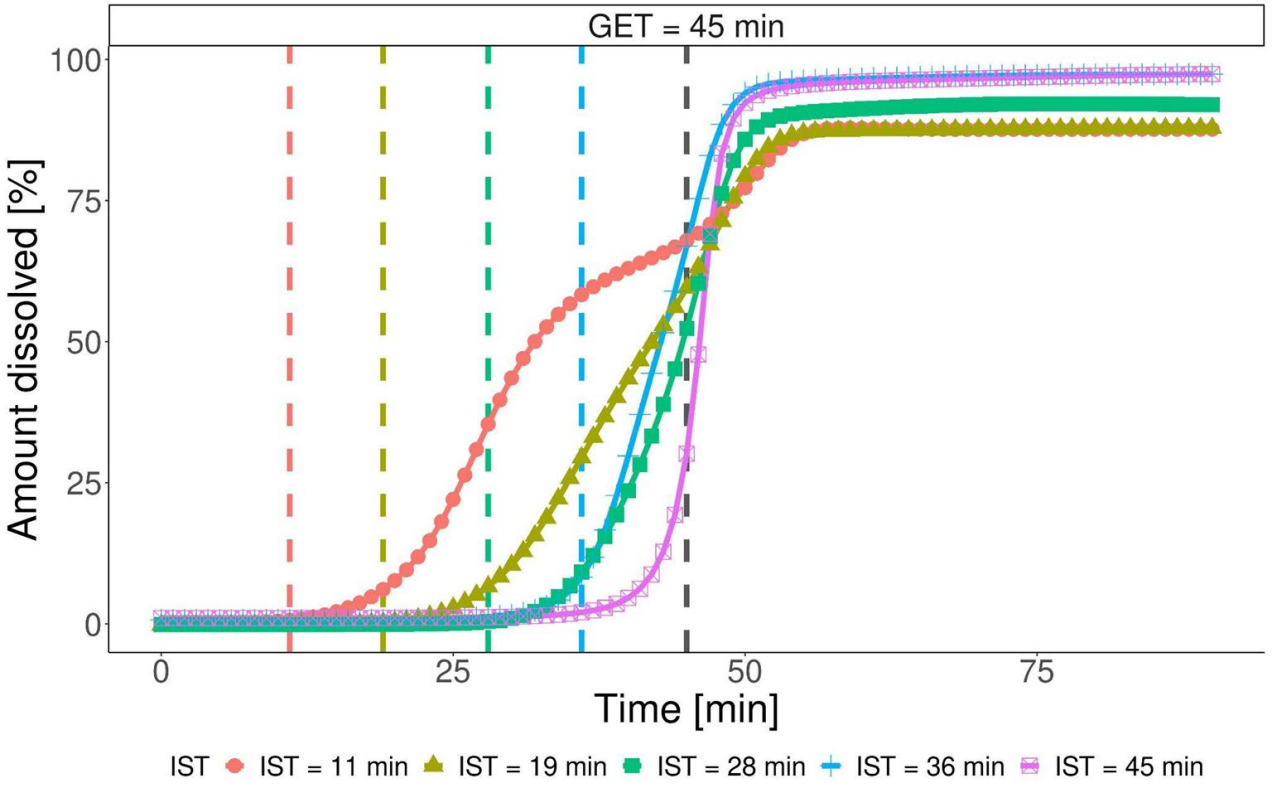
Model verification

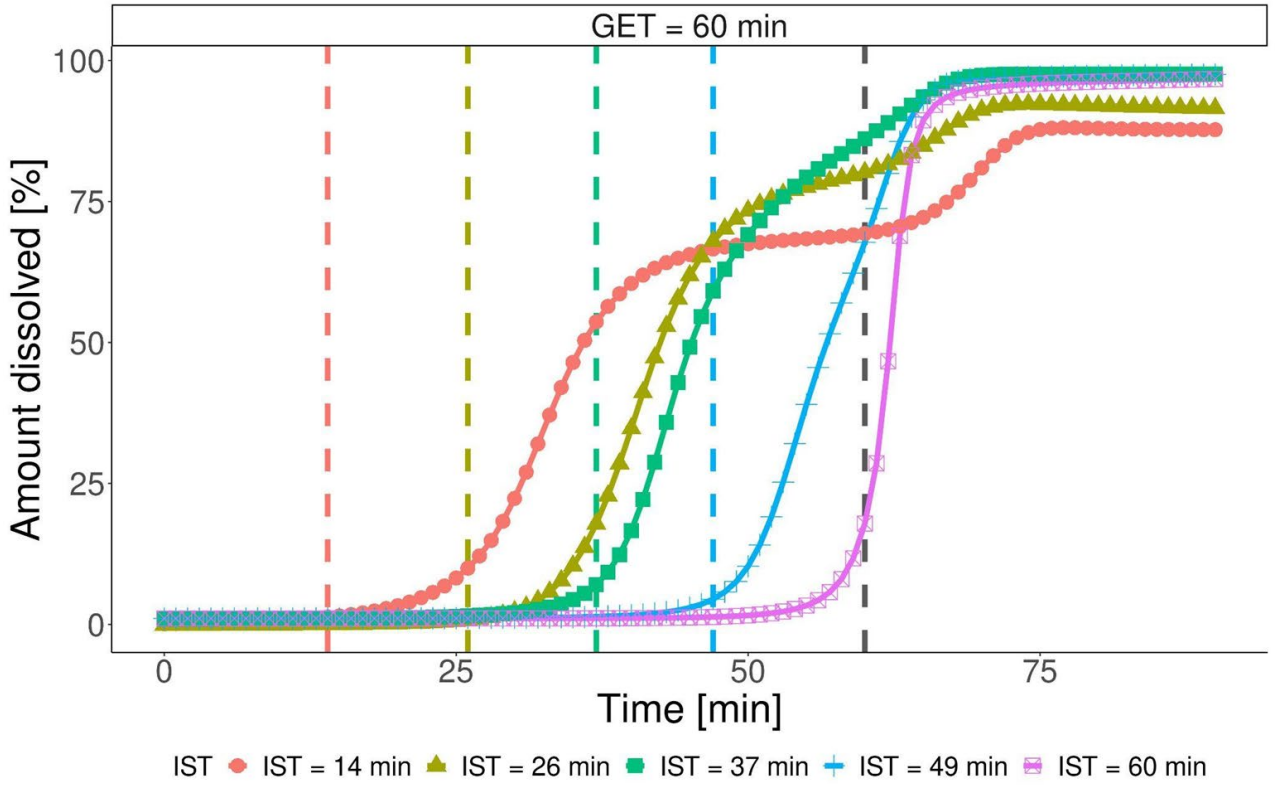


r = 0.9778

86% of points within the variability interval

ML-generated dissolution profiles of capsules





Add on value of the DoE and ML

Experimental design:

- simultaneous determination of **dissolution, local pH effects and precipitation**
- evaluation of the **gastric motility** influence on the dosage form performance
- understanding of physiological parameters' impact on the dissolution

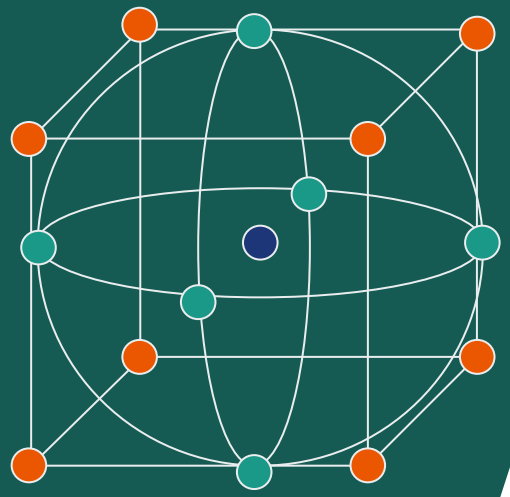
ML modeling:

- investigation of multiple "what if" scenarios: simulations using **conditions unmet in the experiments**
- full coverage of relevant physiological factors
- capturing full **interindividual and interocassion variability** of GIT parameters at the dissolution stage

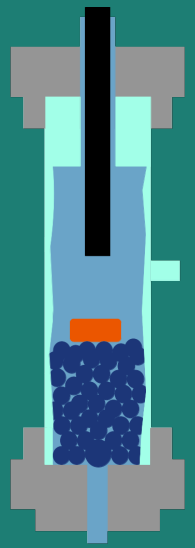
Future perspectives

Application of the ML-generated dissolution profiles to PK simulations of the plasma profiles and virtual bioequivalence study.

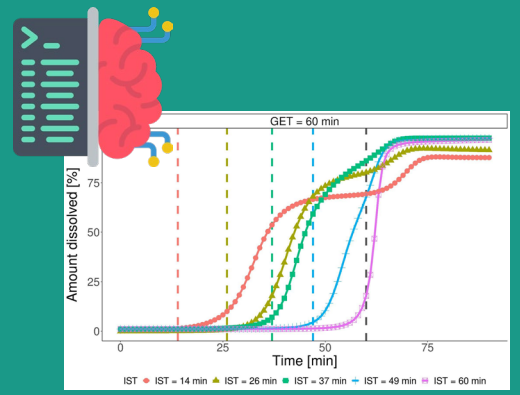
Physiological test space



Bio-predictive dissolution tests



Dissolution modeling with machine learning



Model-predicted dissolution profiles translated to PK profiles

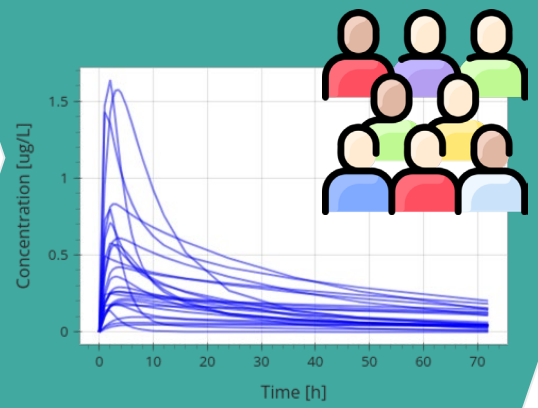


image: Flaticon.com


PHYSIOLUTION
Predictive Dissolution Testing
www.physiolution.eu
Thank you very much for your attention.
Any questions?
[Stress your formulation, not yourself]

Public Comments for Session 3

In Person Comments:

- Alexander Shekhtman, PhD, Professor and Chair, Department of Chemistry, University at Albany, State University of New York
- Marco Guerrini, MS Director Istituto di Ricerche Chimiche e Biochimiche
- Jace Jones, PhD Assistant Professor University of Maryland
- Andrew Graves, MS, SCYM Director, Immunogenicity Assessment Teva
- David Borhani Senior Director, Business Development Ginkgo Bioworks
- Ravishankara MN, PhD Senior General Manager (R & D) Sun Pharma
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- Grzegorz Garbacz, PhD Co-Founder & CEO Physiolution Polska
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BINGHAMTON UNIVERSITY | SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

Assessing Food Effect of Oral Extended-Release Products to Support Biowaivers

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Background

Approximately one quarter of the oral drugs approved by the FDA between 1998 and 2021 were MR formulations

Orally administered modified-release (MR) formulations:

- Delayed release (DR) formulations
- Orally disintegrating tablets/films (ODT)

- Extended release (ER) formulations: extended drug release over 6-24 hours through diffusion-controlled, dissolution-controlled, osmotic-controlled, ion-exchange, or other mechanisms.

- ER/IR combined formulations

Clinical food effect (FE) study

- **Current FDA Recommendation**
  - Clinical food effect (FE) study may be waived for oral IR formulations of BCS class I drugs based on case-by-case discussions between the FDA and sponsors.
  - A dedicated FE study should be conducted using the to-be-marketed formulation for all oral MR drug products regardless of BCS class.
- More than half of ER drug products do not show any food effect under fed conditions (Zou, 2023 AAPS J.)

Physiological changes upon food intake

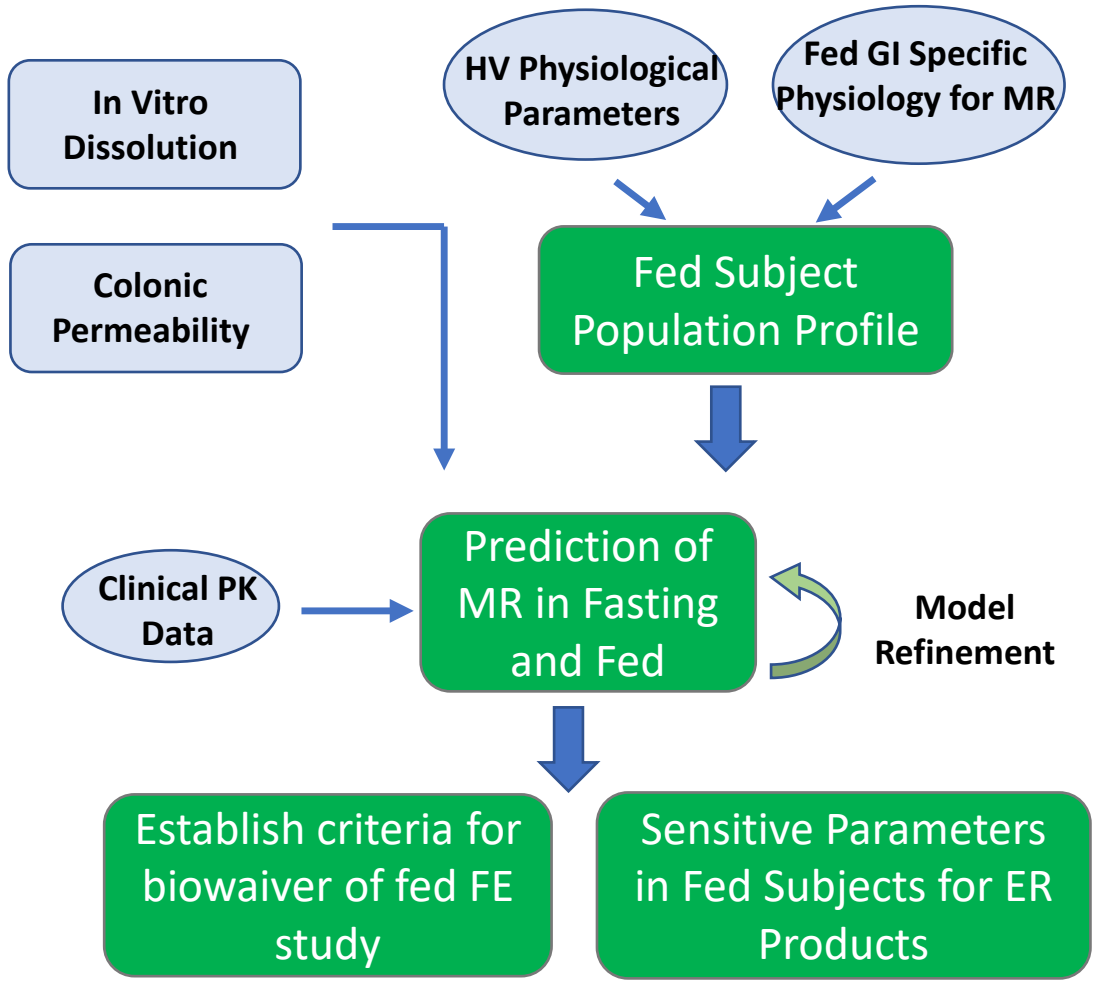
- **Postprandial physiological changes:**
  - Delayed gastric emptying
  - Prolonged intestinal transit
  - Increased intestinal and liver blood flow
  - Increased bile flow
  - Increased bile acid concentrations in gastrointestinal (GI) tract
  - Changes in GI pH

- For most ER products, in vivo drug release is limited (< 20%) within 4 hours post dose.
- **Fasting state:**
  - An ER tablet arrives at ascending colon as early as 3.5 hours post oral administration.
  - ER drug absorption under fasting state may mainly occur in colon and rectum.
- **Fed state:**
  - It takes > 6.5 hours for an ER tablet to arrive at ascending colon.
  - Drug absorption occurs both in small and large intestines.

Limitations and Challenges

- The knowledge of drug absorption in **human large intestine** is critical for the prediction of food effects (presence or absence) for ER products.
  - The development and validation of reliable tools to predict colonic absorption of ER drug products have been very limited over the years.
- The use of **mechanistic PBPK modeling and simulation** to support regulatory decisions and expedite generic drug development has been supported by FDA's Office of Generic Drugs.
  - Many of the models for food effect prediction were developed for specific drug products or dosing scenarios with optimized parameters only working for those products.
- More research is warranted to develop consistent and reproducible in vitro assays and improved extrapolation to PBPK models to fill the knowledge gap, and to facilitate the implementation of risk-based approaches to support FE study biowaivers for MR products.

In Vitro Methods and PBPK Modeling Approach to Assess Food Effect of Oral Extended-Release Products



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Proposal: Improving predictability of generic product bioequivalence in pediatric populations by using advanced dissolution apparatus in conjunction with PBPK modelling for high risk oral products

Aligned to : Improve the Efficiency of BE Approaches for Oral and Parenteral Generic Products

Professor Hannah Batchelor

University of Strathclyde, Glasgow, Scotland

CMAC

Overview

- Previous work has identified bio*in*equivalence in pediatric populations compared to adults and identified **a need for better predictions of equivalence for generic products in vulnerable populations**.
- The goal is to develop and validate advanced dissolution apparatus to demonstrate an IVIVR for pediatric products and then use this to provide further understanding of the impact of composition or processing changes on the performance of these products in a pediatric population.
- The output in vitro and in silico methodology will help to define the types of in vivo bioequivalence studies needed for high-risk generic products that will be used in pediatric populations.

The AAPS Journal (2021) 23: 57
DOI: 10.1208/s12248-021-00592-y

Research Article

Development of a Pediatric Relative Bioavailability/Bioequivalence Database and Identification of Putative Risk Factors Associated With Evaluation of Pediatric Oral Products

Gopal Pawar,[1,5] Fang Wu,[2,5] Liang Zhao,[2] Lanyan Fang,[2] Gilbert J. Burckart,[3] Kairui Feng,[2] Youssef M. Mousa,[2] Franci Naumann,[1] and Hannah K. Batchelor[4,5]

Received 6 January 2021; accepted 6 April 2021; published online 21 April2021

Abstract. Generally, bioequivalence (BE) studies of drug products for pediatric patients are conducted in adults due to ethical reasons. Given the lack of direct BE assessment in pediatric populations, the aim of this work is to develop a database of BE and relative bioavailability (relative BA) studies conducted in pediatric populations and to enable the identification of risk factors associated with certain drug substances or products that may lead to failed BE or different pharmacokinetic (PK) parameters in relative BA studies in pediatrics. A literature search from 1965 to 2020 was conducted in PubMed, Cochrane Library, and Google Scholar to identify BE studies conducted in pediatric populations and relative BA studies conducted in pediatric populations. Overall, 79 studies covering 37 active pharmaceutical ingredients (APIs) were included in the database: 4 bioequivalence studies with data that passed BE evaluations; 2 studies showed bioequivalence results; 34 relative BA studies showing comparable PK parameters, and 39 relative BA studies showing differences in PK parameters between test and reference products. Based on the above studies, common putative risk factors associated with differences in relative bioavailability (DRBA) in pediatric populations include age-related absorption effects, high inter-individual variability, and poor study design. A database containing 79 clinical studies on BE or relative BA in pediatrics has been developed. Putative risk factors associated with DRBA in pediatric populations are summarized.

KEY WORDS: bioequivalence; oral product; pediatric relative bioavailability; risk factors.

INTRODUCTION

To ensure therapeutic equivalency, the rate and extent of drug absorption should not be significantly different between generic products and their corresponding reference products when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses (1, 2). BE studies form an integral part in generic and new drug products approval process. For assessing BE, PK endpoints such as peak plasma concentration (Cmax) and area under the plasma concentration time curve (AUC), which reflect the rate and extent of drug absorption, are used. According to the U.S. Food and Drug Administration (U.S. FDA), the test and reference products are considered BE when the 90% confidence interval of the geometric mean ratio of Cmax, AUC_{0-t}, and $AUC_{0-\infty}$ between the test and reference formulations are within the BE acceptance region of 80–125% (3). Because the purpose of a BE study is to draw a generalizable conclusion about the test and reference products, BE studies are most often conducted in healthy adult populations. BE studies are designed to compare the test and reference products with the same dosage form in the most sensitive, accurate, and reproducible way. From this evidence, regulators then conclude that the test and reference products can be substituted for all patient populations described in the product label.

Due to the need for age-appropriate medicines with flexible dosing options, pediatric formulations can differ from the product used in adults (e.g., use of a suspension rather than a tablet); thus, a change in relative BA may be possible. Indeed, the pediatric formulation is designed to achieve the target systemic exposure in the population of interest thus a change in PK exposure may be attributable to formulation design. The purpose of relative BA studies, as distinct from BE studies, is to compare the rate and extent of drug absorption between two pharmaceutical dosage forms (e.g., a novel pediatric formulation) and a reference product (e.g., adult formulation); they are usually conducted in healthy adults (4). Moreover, there is no formal statistical assessment associated with relative BA studies to demonstrate whether they "pass" or "fail" yet sometimes BE acceptance limits are applied to these studies (5). Because relative BA studies are often designed to be descriptive and intended to inform instructions for product use, it is more common to find a

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https://doi.org/10.1208/s12248-023-00826-1

RESEARCH ARTICLE

Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict *In Vivo* Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study

Gopal Pawar[1] · Fang Wu[2] · Liang Zhao[2] · Lanyan Fang[2] · Gilbert J. Burckart[3] · Kairui Feng[2] · Youssef M. Mousa[2] · Abdullah Al Shoyaib[2] · Marie-Christine Jones[1] · Hannah K. Batchelor[4]

Received: 5 January 2023 / Accepted: 25 May 2023 / Published online: 29 June 2023
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Abstract
This study investigated the impact of gastro-intestinal fluid volume and bile salt (BS) concentration on the dissolution of carbamazepine (CBZ) immediate release (IR) 100 mg tablets and to integrate these *in vitro* biorelevant dissolution profiles into physiologically based pharmacokinetic modelling (PBPK) in pediatric and adult populations to determine the biopredictive dissolution profile. Dissolution profiles of CBZ IR tablets (100 mg) were generated in 50–900 mL biorelevant adult fasted state simulated gastric and intestinal fluid (Ad-FaSSGF and Ad-FaSSIF), also in three alternative compositions of biorelevant pediatric FaSSGF and FaSSIF medias at 200 mL. This study found that CBZ dissolution was poorly sensitive to changes in the composition of the biorelevant media, where dissimilar dissolution ($f2 = 46.2$) was only observed when the BS concentration was changed from 3000 to 89 µM (Ad-FaSSIF or Ped-FaSSIF 50% 14 BS). PBPK modeling demonstrated the most predictive dissolution volume and media composition to forecast the PK was 500 mL of Ad-FaSSGF/Ad-FaSSIF media for adults and 200 mL Ped-FaSSGF/FaSSIF media for pediatrics. A virtual bioequivalence simulation was conducted by using Ad-FaSSGF and/or Ad-FaSSIF 500 mL or Ped-FaSSGF and/or Ped-FaSSIF 200 mL dissolution data for CBZ 100 mg (reference and generic test) IR product. The CBZ PBPK models showed bioequivalence of the product. This study demonstrates that the integration of biorelevant dissolution data can predict the PK profile of a poorly soluble drug in both populations. Further work using more pediatric drug products is needed to verify biorelevant dissolution data to predict the *in vivo* performance in pediatrics.

Keywords carbamazepine tablets · *in vitro* dissolution · PBPK · pediatric biorelevant dissolution media · virtual bioequivalence

Introduction

Dissolution is commonly used as an *in vitro* testing method for orally administered drug products, such as tablets. Typically, biopredictive dissolution methods can use biorelevant media that is designed to simulate the composition of gastrointestinal (GI) fluids, such as fasted state simulated gastric fluid (FaSSGF) and fasted state simulated intestinal fluid (FaSSIF) which are both derived from the characterization of healthy adults GI media

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- Pawar, G., Wu, F., Zhao, L., Fang, L., Burckart, G.J., Feng, K., Mousa, Y.M., Al Shoyaib, A., Jones, M.-C., Batchelor, H.K. Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study (2023) AAPS Journal, 25 (4), art. no. 67. DOI: 10.1208/s12248-023-00826-1
- Pawar, G., Wu, F., Zhao, L., Fang, L., Burckart, G.J., Feng, K., Mousa, Y.M., Naumann, F., Batchelor, H.K. Development of a Pediatric Relative Bioavailability/Bioequivalence Database and Identification of Putative Risk Factors Associated With Evaluation of Pediatric Oral Products (2021) AAPS Journal, 23 (3), art. no. 57. DOI: 10.1208/s12248-021-00592-y

Proposed Research Activity

Existing PBPK models are widely used in pediatric product development BUT they do not incorporate sufficient formulation parameters to enable evaluation of formulation adjustments or bridging during development

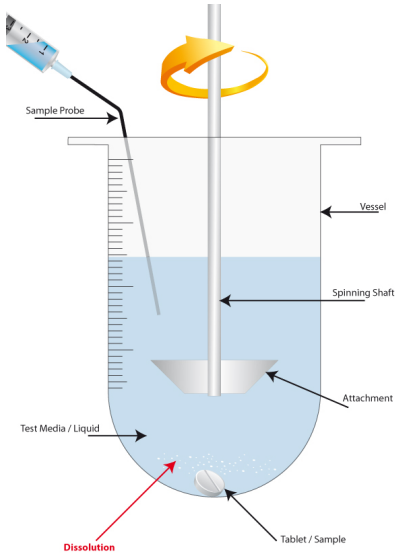
The identification of a biopredictive dissolution method for pediatric populations and subsequent integration of the generated dissolution data into PBPK modeling would aid in de-risking pediatric clinical programs, specifically with reference to relative bioavailability studies or bioequivalence (BE) studies for generic drug products.

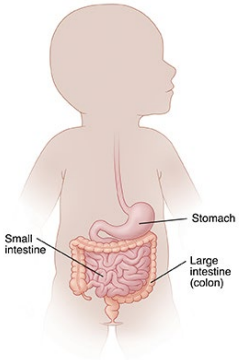
Furthermore, virtual bioequivalence (VBE) trials using PBPK modeling could provide a powerful tool to predict and compare the *in vivo* performance of test drug products and reference listed drug (RLD) products by integrating the dissolution data generated by using the biorelevant medias and the inclusion of inter-subject variabilities.

Dissolution and risks of bioinequivalence

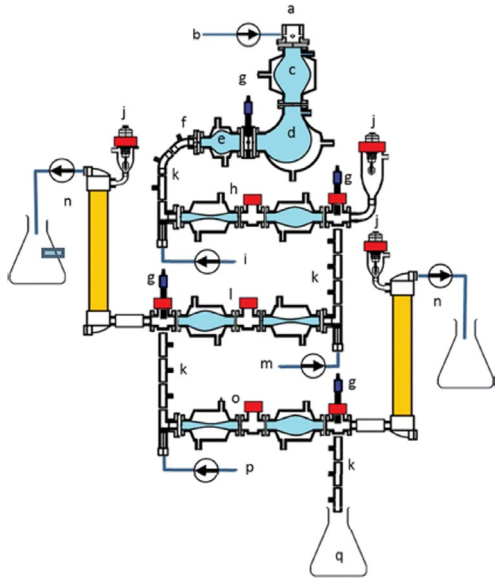
There is known variability in GI fluids in children compared to adults

There is a known difference in fluid volume in children compared to adults



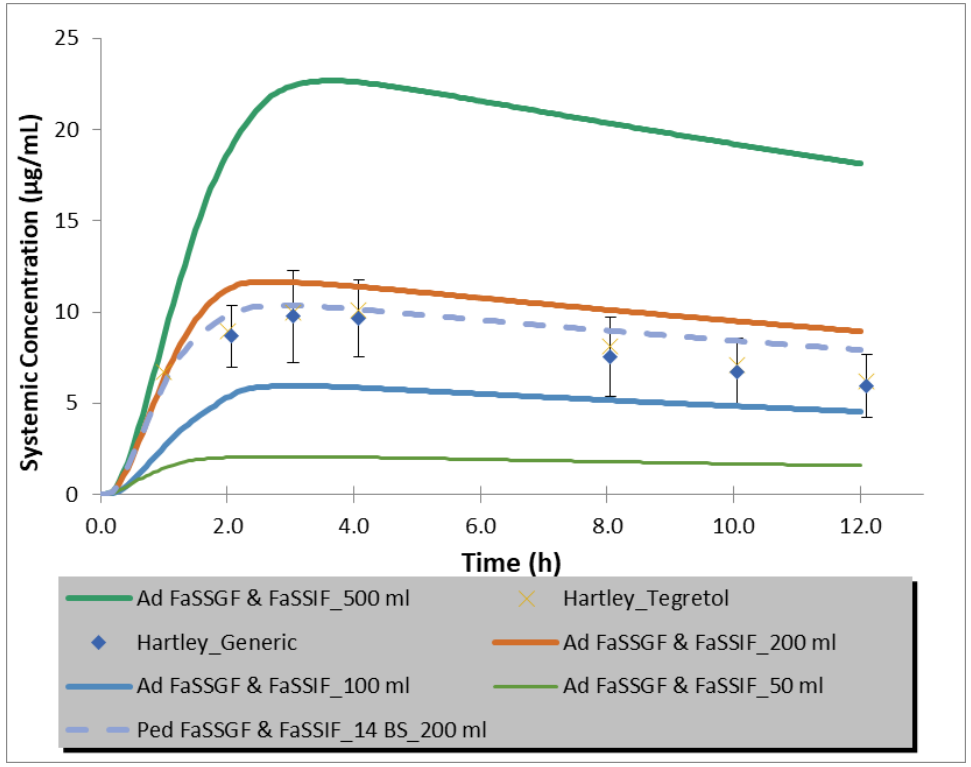


Can we use dissolution testing integrated into PBPK modelling to mimic these differences and better predict a risk of bio*in*equvialence?



Build on conventional dissolution data sets
Eg for a case study on carbamazepine

Pawar, G., Wu, F., Zhao, L., Fang, L., Burckart, G.J., Feng, K., Mousa, Y.M., Al Shoyaib, A., Jones, M.-C., Batchelor, H.K. Integration of Biorelevant Pediatric Dissolution Methodology into PBPK Modeling to Predict In Vivo Performance and Bioequivalence of Generic Drugs in Pediatric Populations: a Carbamazepine Case Study (2023) AAPS Journal, 25 (4), art. no. 67. DOI: 10.1208/s12248-023-00826-1



Dissolution data from 200mL Ped FaSSGF/FaSSIF Na TCA media was closest to the clinical data although a slightly lower volume may have provided a more accurate prediction

Input dissolution datasets	PK parameter	Mean Predicted	Mean observed	PPE
Ad-FaSSGF/FaSSIF 500 mL	AUC (µg/mL.h)	224	99	126.3
	Cmax (µg/mL)	23	8.2	180.5
Ad-FaSSGF/FaSSIF 200 mL	AUC (µg/mL.h)	116	99	17.2
	Cmax (µg/mL)	12	8.2	46.3
Ad-FaSSGF/FaSSIF 100 mL	AUC (µg/mL.h)	58.2	99	-41.2
	Cmax (µg/mL)	6.0	8.2	-26.8
Ad-FaSSGF/FaSSIF 50 mL	AUC (µg/mL.h)	21	99	-78.8
	Cmax (µg/mL)	2.1	8.2	-74.4
Ped-FaSSGF/FaSSIF NaTCA 200 mL	AUC (µg/mL.h)	103.25	99	-4.34
	Cmax (µg/mL)	10.35	8.2	16.92

Target is PPE<20%

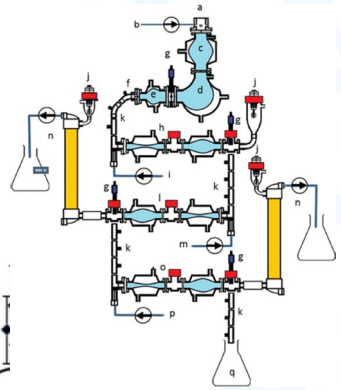
Clinical data from Hartley 1991
(n=12 children aged 6.5-15 years taking CBZ as either 100 or 200mg tablets twice daily).

Hartley R, Aleksandrowicz J, Bowmer CJ, Cawood A, Forsythe WI. Dissolution and relative bioavailability of two carbamazepine preparations for children with epilepsy. Journal of Pharmacy and Pharmacology. 1991;43(2):117-9. doi: https://doi.org/10.1111/j.2042-7158.1991.tb06644.x.

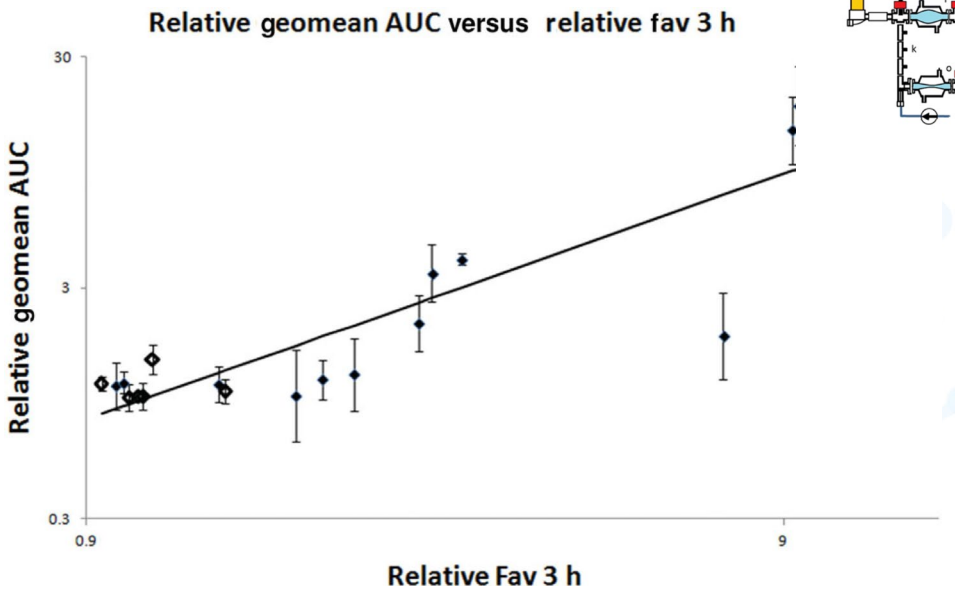
RESEARCH ARTICLE – *Pharmaceutics, Drug Delivery and Pharmaceutical Technology*

Application and Validation of an Advanced Gastrointestinal *In Vitro* Model for the Evaluation of Drug Product Performance in Pharmaceutical Development

RICHARD BARKER,[1] BERTIL ABRAHAMSSON,[2] MARTIN KRUUSMÄGI[1]



- Methods to understand and predict the oral bioavailability of drug products are a prioritized research area within the pharmaceutical industry.
- Models to predict oral bioavailability have the potential to reduce risk, time, and cost in development as well as decrease the need for animal studies.
- 19 unique comparisons between different formulations evaluated in both TIM-1 and *in vivo* studies among the nine identified compounds
- The TIM-1 correctly predicted *in vivo* rank order in 84% and 79% of cases for AUC and C_{max}, respectively. There was only one case for C_{max} in which TIM-1 did not predict an *in vivo* difference.
- The correlation coefficient (R^2) between relative (test vs. reference formulations) fraction available in TIM-1 after 3 h and AUC was 0.78.
- Thus, this study suggests that the TIM-1 system can be used to assess the risk for significant differences in exposure between formulations and compound modifications.



Linear regression for the logarithm of relative geomean AUC (with 90% CI) and Fav at 3 h for all comparisons in the study.

https://doi.org/10.1002/jps.24177

International Journal of Pharmaceutics 457 (2013) 327–332

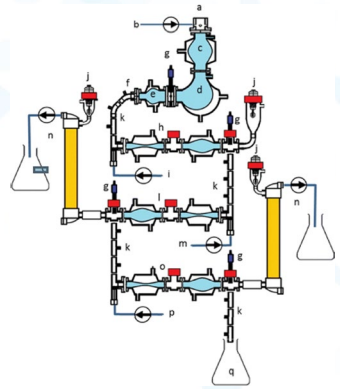
Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

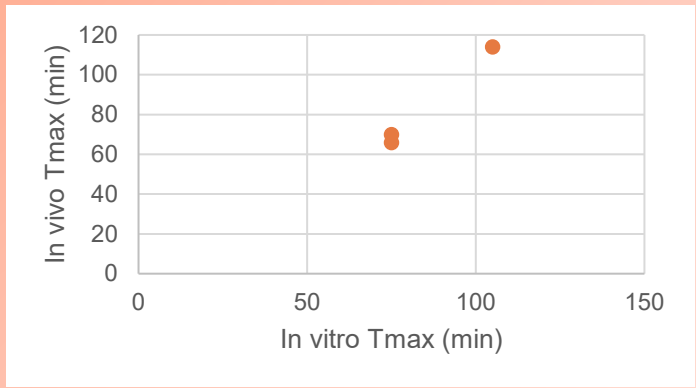
In vitro gastrointestinal model (TIM) with predictive power, even for infants and children?

Robert Havenaar[a,*], Bart Anneveld[a], Lidwien M. Hanff[b,1], Saskia N. de Wildt[b,1], Barbara A.E. de Koning[b,1], Miriam G. Mooij[b,1], Jan P.A. Lelieveld[a], Mans Minekus[a]



- For neonates (0-1 month), infants (1-6 months) and toddlers (6m – 2y)
- Results showed rank order trends but not a detailed correlation

Paracetamol



Correlation with Tmax
Bioaccessibility was similar which matched equivalent Cmax values for all ages

Diclofenac

Data showed:
Lower Cmax for neonates vs infants
Lower overall bioaccessible dose for neonates
Higher bioaccessible dose for a crushed tablet with a food matrix

Esomeprazole

Data showed that the bioaccessibility of esomeprazole after a first dose of a crushed tablet to infants is low, but increases after repeated dosing due to a higher gastric pH by the PPI

Correlations for TIM have been shown under relevant physiological conditions

Journal of Pharmaceutical Sciences 000 (2024) 1–11

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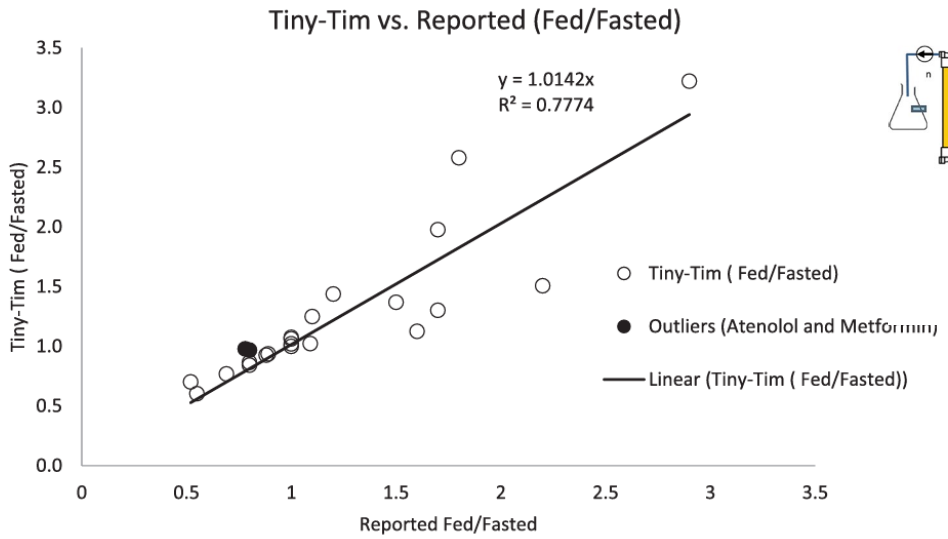
journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Evaluating Utilization of Tiny-TIM to Assess the Effect of Food on the Absorptions of Oral Drugs and Its Application on Biopharmaceutical Modeling

Jia Liu*, Karthik Nagapudi, Po-Chang Chiang



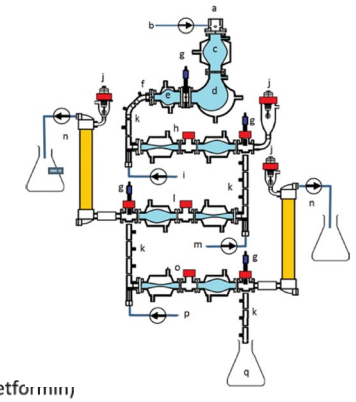


Figure 1. Plot of reported food effect ratios versus predicted food effect ratios from Tiny-TIM (open circles: compounds with correct prediction of food effect; black dots: outliers with incorrect prediction of food effect).

Journal of Pharmaceutical Sciences 110 (2021) 3020–3026

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Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Utilizing Tiny-TIM to Assess the Effect of Acid-Reducing Agents on the Absorption of Orally Administered Drugs

Check for updates

Jia Liu[a,*], Karthik Nagapudi[a], Michael J Dolton[b], Po-Chang Chiang[a]

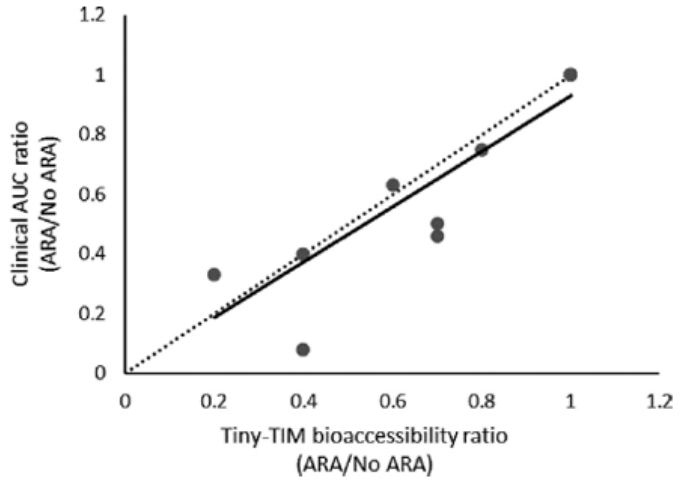


Fig. 2. Ratio of bio-accessibility (ARA/Non-ARA) obtained from Tiny-TIM compared with the ratio of AUC_{0-24} (ARA/Non-ARA) obtained from clinical studies. Solid line represents a simple linear regression, dashed line is the line of identity.

Dissolution and PBPK modelling

Typical inputs for PBPK software packages capture the physicochemical properties of the API and limited aspects of the dosed formulation (eg drug particle size).

PBPK cannot currently assess the impact of
Formulation process change (e.g. switching from direct compression to a wet-granulated process for an oral tablet)
Compositional variation (e.g. switching a tablet filler from lactose to dicalcium phosphate)

There needs to be integration of dissolution data into the PBPK software to capture such changes

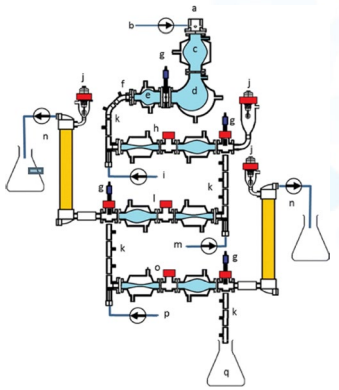
Using data from biorelevant dissolution testing of drug product would improve model prediction performance, as a biorelevant test would be expected to capture the in vivo impact of compositional and process changes.

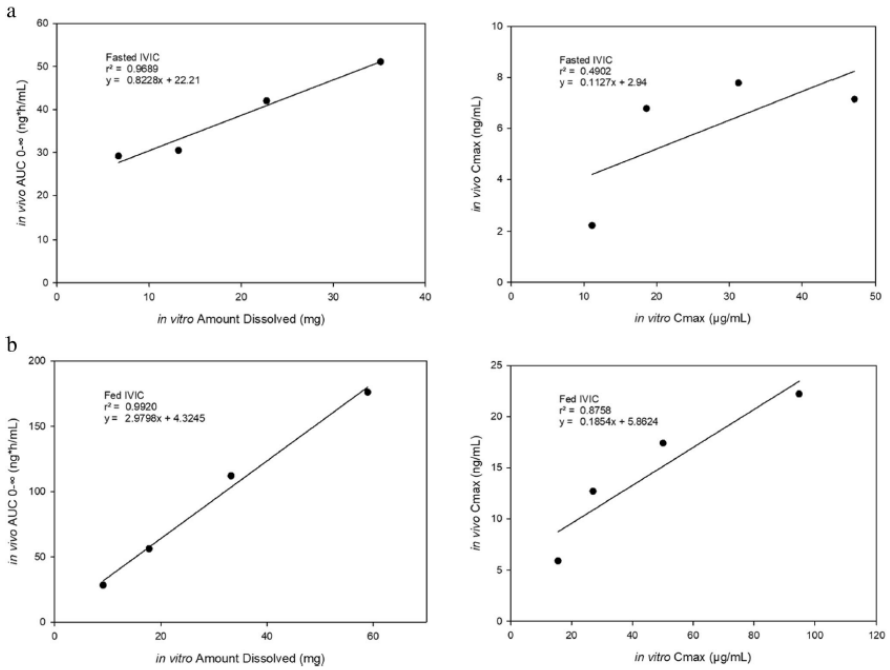
AAPS PharmSciTech (2022) 23: 185
https://doi.org/10.1208/s12249-022-02343-4

RESEARCH ARTICLE

Using Tiny-TIM Dissolution and In Silico Simulation to Accelerate Oral Product Development of a BCS Class II Compound

Laibin Luo[1] · Naveen K. Thakral[1] · Robert Schwabe[1] · Li Li[1,2] · Shirlynn Chen[1]





Simple IVIVR was demonstrated for AUC BUT was not as good for Cmax

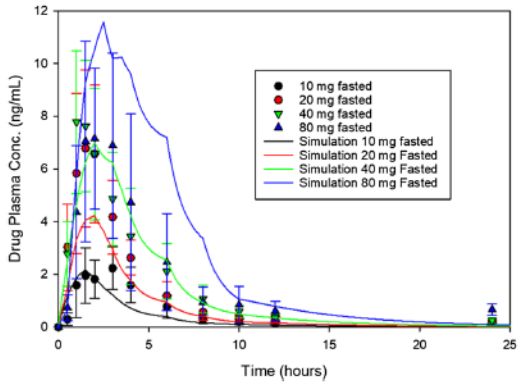


Fig. 6 PBPK simulation (the mean of plasma concentration versus time) for 10 to 80 mg doses at fasted state (solid line). The clinical data is overlaid (dotted) with the simulated profile

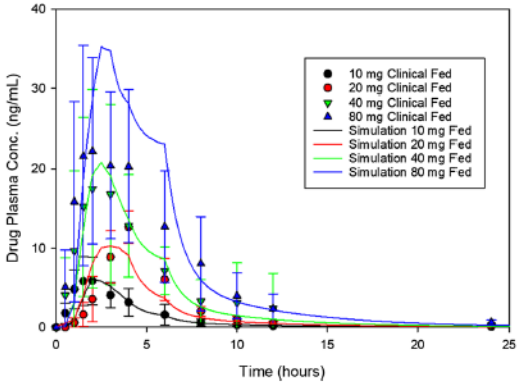


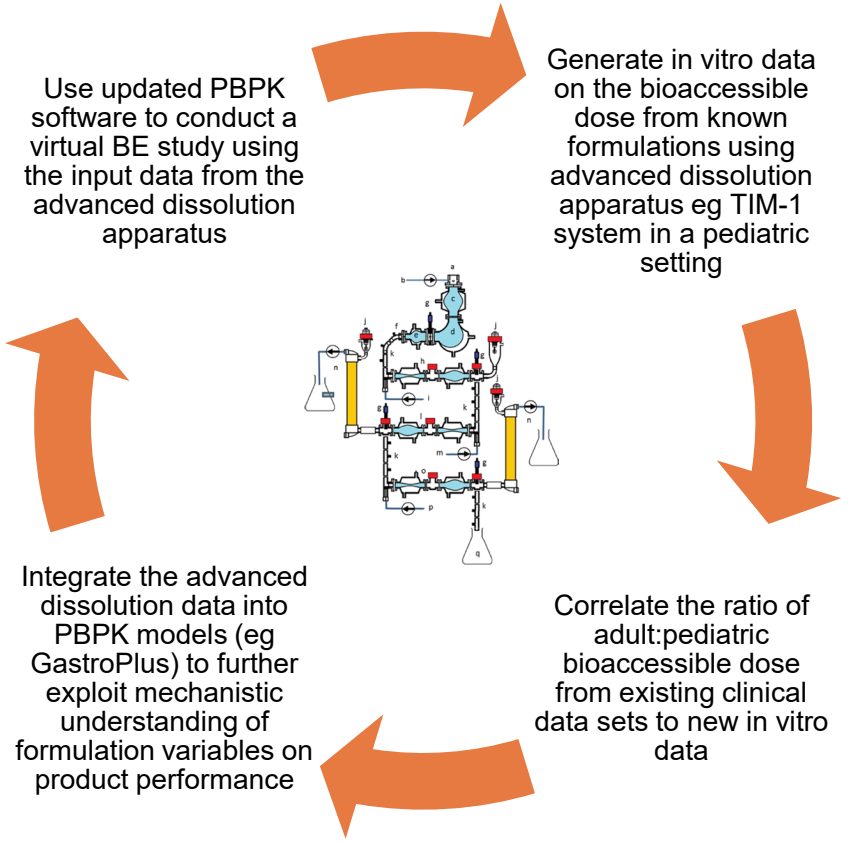
Fig. 8 PBPK simulation (the mean of plasma concentration versus time) for 10 to 80 mg doses in fed state (solid line). The clinical data is overlaid (dotted) with the simulated profile

Integration of Tiny-TIM data gave superior predictions

Proposed Research

Develop and validate advanced dissolution apparatus to demonstrate an IVIVR for pediatric products and then use this to provide further understanding of the impact of composition or processing changes on the performance of these products in a pediatric population

Based on existing literature this is most likely to be achieved by coupling advanced dynamic dissolution apparatus to PBPK software



Thanks for your attention and the opportunity to present

The Finite Absorption Time (F.A.T.) Concept Signifies the Dawn of a New Era in Drug-Generics Development, Clinical/Regulatory Assessment and Relevant Software

Panos Macheras,

Emeritus Professor
National & Kapodistrian University of Athens
PharmaInformatics Unit, Research Center ATHENA, Greece

Presentation at the GDUFA Public Workshop, May 21, 2024

OUTLINE

1. The false assumption that breaks pharmacokinetics of oral drug absorption

2. The Development of Finite Absorption Time (F.A.T) Concept

3. Development of Physiologically Based Finite Time Pharmacokinetic (PBFTPK) Models

4. Applications: Development of Drugs

5. Applications: Development of Generics

6. Applications: Bioequivalence assessment

7. Bibliograpy

OUTLINE

1. The false assumption that breaks pharmacokinetics of oral drug absorption

The Bateman equation is a mathematical model describing abundances and activities in a decay chain as a function of time, based on the decay rates and initial abundances. The model was formulated by Ernest Rutherford in 1905 and the analytical solution was provided by Harry Bateman in 1910 . For the simple case of a chain of three isotopes (mother, daughter, grand-daughter),

The model of a chain of three isotopes. The transition rates are only allowed from one species to the next but never in the reverse sense.

the corresponding Bateman equation reduces to an equation with two exponentials for the abundance of the daughter species $N_{daugther}$:

$$N_{daughter}=\frac{\lambda_m N_{m0}}{\lambda_m-\lambda_d}\left(e^{-\lambda_d t}-e^{-\lambda_m t}\right) \qquad (1)$$

where λ_m and λ_d are first-order rate constants for the transition of the mother to daughter species and the transition from the daughter to grand-daughter species, respectively; N_{m0} is the initial abundance of the mother species.

H. Bateman, The solution of a system of differential equations occurring in the theory of radioactive transformations. *Proc. Cambridge Philos. Soc. Math. Phys. Sci.* **15**, 423-427 (1910)

Friedrich Hartmut Dost: First-order *ABSORPTION* kinetics (1953)

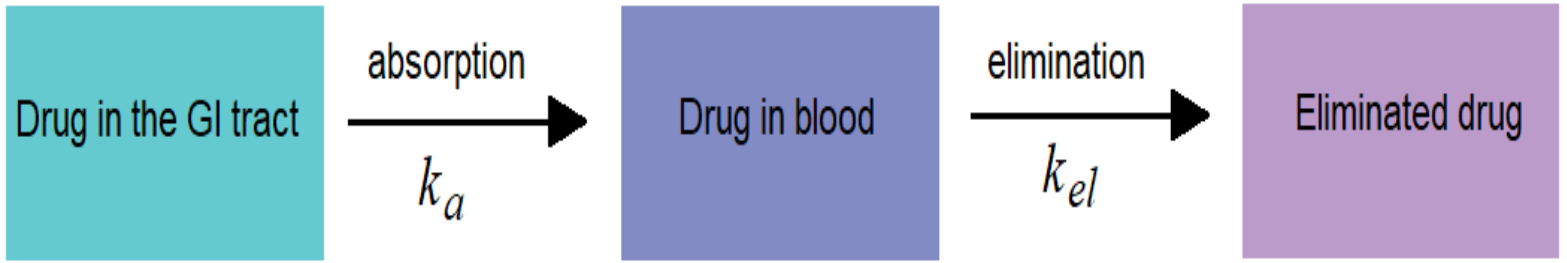
Friedrich Hartmut Dost, who introduced the term Pharmacokinetics, adopted in 1953 the Bateman equation to describe the concentration of drug in plasma, $C_b(t)$ assuming first-order absorption (input) and first-order elimination

$$C_b(t) = \frac{FDk_a}{V_d(k_a - k_{el})}\left(e^{-k_{el}t} - e^{-k_a t}\right) \qquad (2)$$

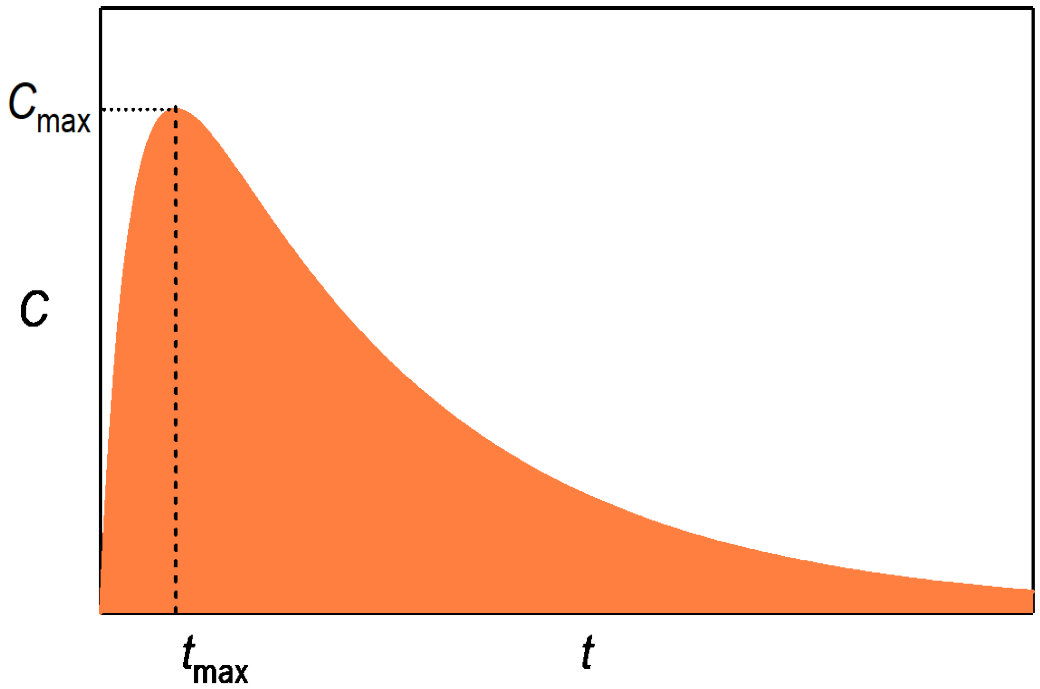
where F is the bioavailable fraction of dose (D), V_d is the volume of distribution and k_a, k_{el} are the absorption and elimination first-order rate constants, respectively.

Bateman's decay chain of isotopes

Dost's drug kinetics:



Harry Bateman's vis a vis Friedrich Harmut Dost's kinetic considerations



A concentration-time curve showing bioavailability parameters. The shaded area depicts $[AUC]_0^\infty$.

AUC is the ***infinite*** integral of Eq. 2

$$\text{AUC}=\int_0^\infty C_b\,dt = \int_0^\infty \frac{FDk_a}{V_d(k_a-k_{el})}\left(e^{-k_{el}t}-e^{-k_a t}\right)\text{dt}=\frac{FD}{V_d k_{el}}=\frac{FD}{CL} \quad (7)$$

Pharm Res (2019) 36: 94
https://doi.org/10.1007/s11095-019-2633-4

COMMENTARY

On an Unphysical Hypothesis of Bateman Equation and its Implications for Pharmacokinetics

Panos Macheras [1,2,3]

Received: 18 March 2019 / Accepted: 25 April 2019 / Published online: 8 May 2019

KEY WORDS bateman equation · oral absorption · pharmacokinetics

The classical pharmacokinetic analysis of oral drug-absorption data relies on Bateman equation (Eq. 1) assuming a one compartment model disposition with first-order absorption and elimination rate (1):

$$C = \frac{F \cdot D \cdot ka}{V \cdot (ka - kel)} \cdot \left(e^{-k_{el} \cdot t} - e^{-k_a \cdot t}\right) \quad (1)$$

where C is the drug concentration in the body (compartment) at time t, F is the bioavailable fraction of dose (D), V is the

of the parent-daughter-granddaughter chain. Almost half a century later the German Professor of paediatrics *Friedrich* Hartmut Dost (3) adopted this equation for the pharmacokinetic analysis of blood data following a one compartment model disposition with first-order absorption and elimination rate. The similarity of drug processes is obvious with the isotopes chain, namely, drug in the gastrointestinal tract-drug in the blood-drug eliminated via the renal and hepatic routes. Dost was the first to coin the term "pharmacokinetics" in his 1953 monograph 'Der Blutspiegel" (Blood levels) (3) wherein Eq. 1 was quoted. Although Eq. 1 has been used in thousands of oral drug absorption research articles, the unrecognized assumption of infinite absorption time associated with Eqs. 1 and 2 is not

OUTLINE

2. The Development of Finite Absorption Time (F.A.T.) Concept

Pharm Res (2020) 37:187
https://doi.org/10.1007/s11095-020-02894-w

RESEARCH PAPER

Revising Pharmacokinetics of Oral Drug Absorption: I Models Based on Biopharmaceutical/Physiological and Finite Absorption Time Concepts

Panos Macheras[1,2,3] • Pavlos Chryssafidis[1,3]

Received: 1 June 2020 / Accepted: 24 July 2020

ABSRACT

Purpose To demonstrate that oral drug absorption is terminated in finite time. To develop models based on biopharmaceutical/physiological and finite absorption time concepts.

Methods The models are based on i) the passive drug diffusion mechanism under the sink conditions principle ii) the rate limiting role of the drug's properties solubility and permeability and iii) the relevant restrictions associated with the gastrointestinal transit times of drug in the stomach, the small intestines and the colon. Two input functions of constant rate are considered for the absorption of drug from i) the stomach/small intestines with an upper limit of 5 h and ii) the colon with an upper limit of 30 h. Branched differential equations were written for the time course of drug in the body.

Results Simulations were performed using different scenarios, assuming a variety of drug properties and limited or non-existent absorption from the colon. Literature oral data of cephradine, ibuprofen, flurbiprofen and itraconazole were analyzed. For all drugs examined, nice fittings of the branched differential equations to the experimental data were observed.

Conclusions For all drugs the absorption process was terminated in the small intestine. The meaning of partial AUCs,

KEY WORDS oral drug absorption · finite absorption time · pharmacokinetics, BCS, BDDCS

ABBREVIATIONS

BCS	Biopharmaceutic classification system
BDDCS	Biopharmaceutic drug disposition classification System
GI	Gastrointestinal
IVIVC	*In vitro in vivo* correlations
PBFTPK	Physiologically based finite time pharmacokinetic
PBPK	Physiologically based pharmacokinetic

INTRODUCTION

The oral route is the most common for drug administration. Extensive work in this field of research revealed that two basic drug properties, namely, solubility and permeability of gastrointestinal membrane determine the extent of oral drug absorption [1, 2]. These scientific advances lead to the development of

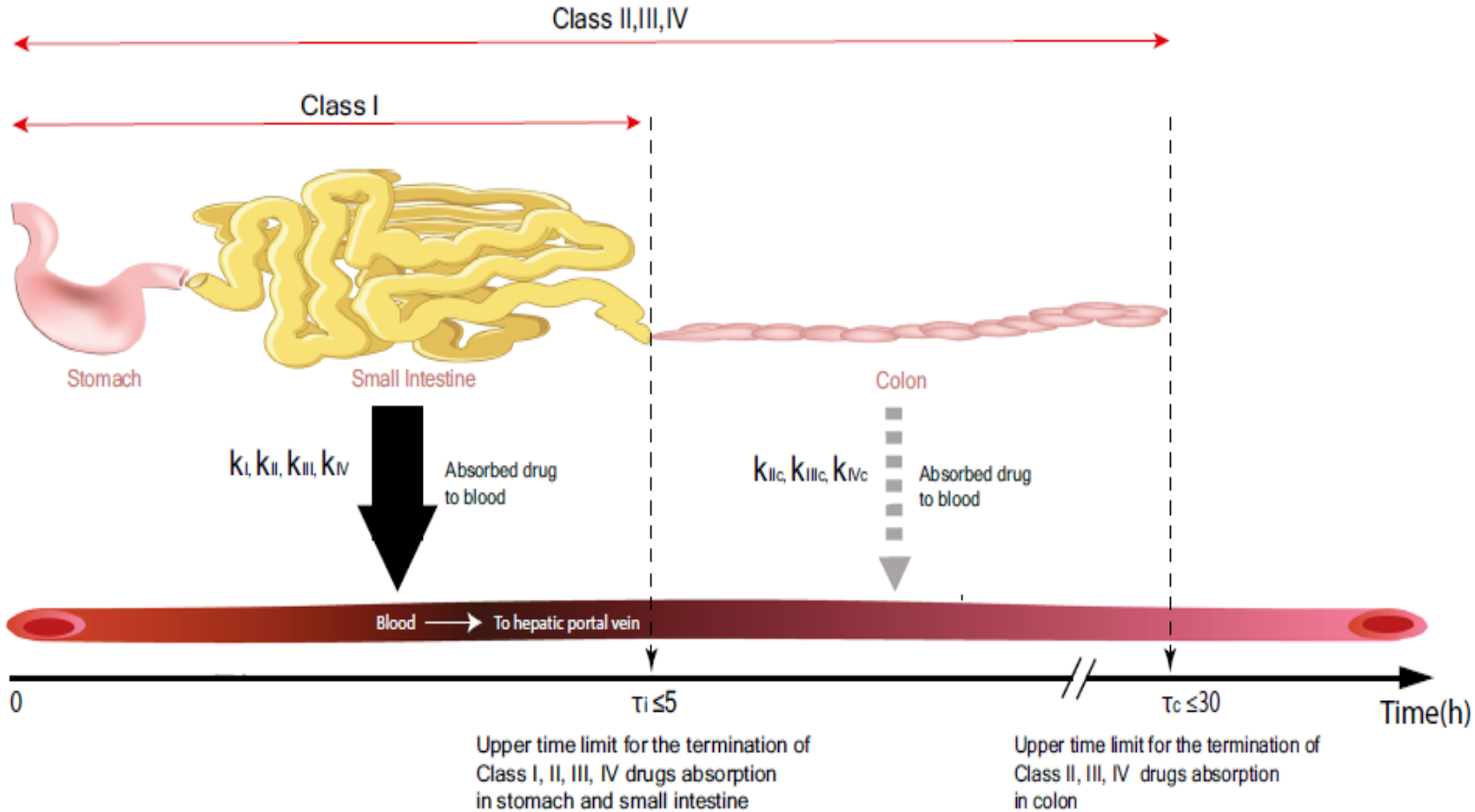


Fig. 2 A schematic of the biopharmaceutical/physiological drug absorption model, which relies on the transit times of the drug along the gastrointestinal tract. For Class I drugs, the completion of absorption ($F > 0.90$) ceases in a shorter time than the duration of the stomach and small intestine transit 4.86 h (21). For Class II, III and IV drugs, the limited overall absorption ($F < 0.90$) can be continued beyond the ileocecal valve and lasts not more than the whole gut transit time e.g. 29.81 h (21). The absorbed drug reaches the hepatic portal vein; the blood flow (20–40 cm/s) impose sink conditions on drug transfer. The thick black arrow denotes the major site of drug absorption, namely, the small intestine. The dashed arrow indicates the potentially limited drug absorption from the colon.

OUTLINE

3. Development of Physiologically Based Finite Time Pharmacokinetic (PBFTPK) Models

Pharmaceutical Research (2022) 39:691–701
https://doi.org/10.1007/s11095-022-03230-0

RESEARCH PAPER

Re-writing Oral Pharmacokinetics Using Physiologically Based Finite Time Pharmacokinetic (PBFTPK) Models

Pavlos Chryssafidis[1,2] · Athanasios A. Tsekouras[1,3] · Panos Macheras[1,2]

Received: 23 January 2022 / Accepted: 9 March 2022 / Published online: 4 April 2022

Abstract

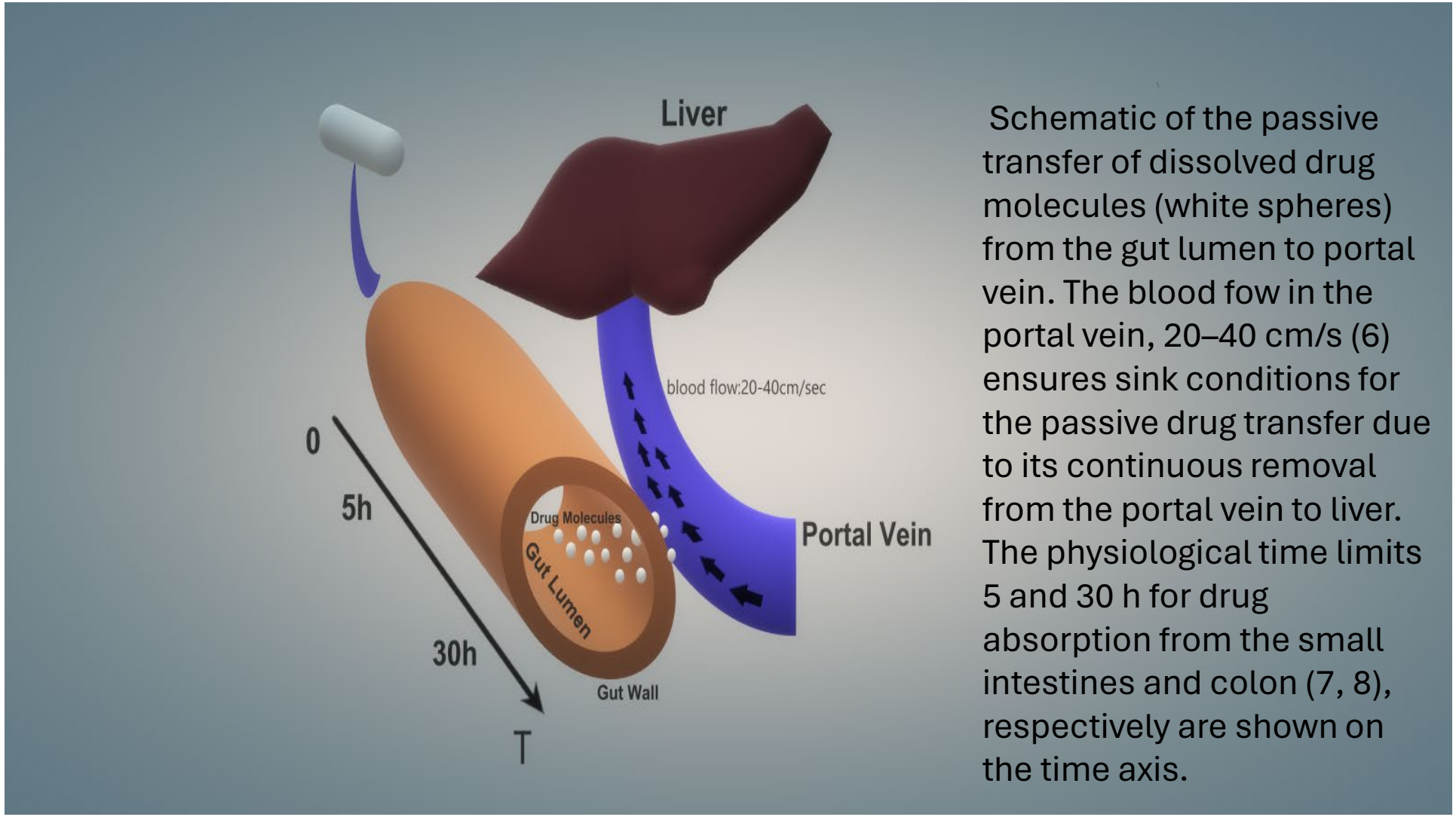
Purpose To develop physiologically based finite time pharmacokinetic (PBFTPK) models for the analysis of oral pharmacokinetic data.

Methods The models are based on the passive drug diffusion mechanism under the sink conditions principle. Up to three drug successive input functions of constant rate operating for a total time τ are considered. Differential equations were written for all these models assuming linear one- or two-compartment-model disposition. The differential equations were solved and functions describing the concentration of drug as a function of time for the central and the peripheral compartment were derived. The equations were used to generate simulated data and they were also fitted to a variety of experimental literature oral pharmacokinetic data.

Results The simulated curves resemble real life data. The end of the absorption processes τ is either equal to t_{max} or longer than t_{max} at the descending portion of the concentration time curve. Literature oral pharmacokinetic data of paracetamol, ibuprofen, almotriptan, cyclosporine (a total of four sets of data), and niraparib were analyzed using the PBFTPK models. Estimates for τ corresponding to a single or two or three different in magnitude input rates were derived along with the other model parameters for all data analyzed.

Conclusions The PBFTPK models are a powerful tool for the analysis of oral pharmacokinetic data since they rely on the physiologically sound concept of finite absorption time.

KEY WORDS almotriptan · cyclosporine · finite absorption time · ibuprofen · niraparib · oral drug absorption · oral



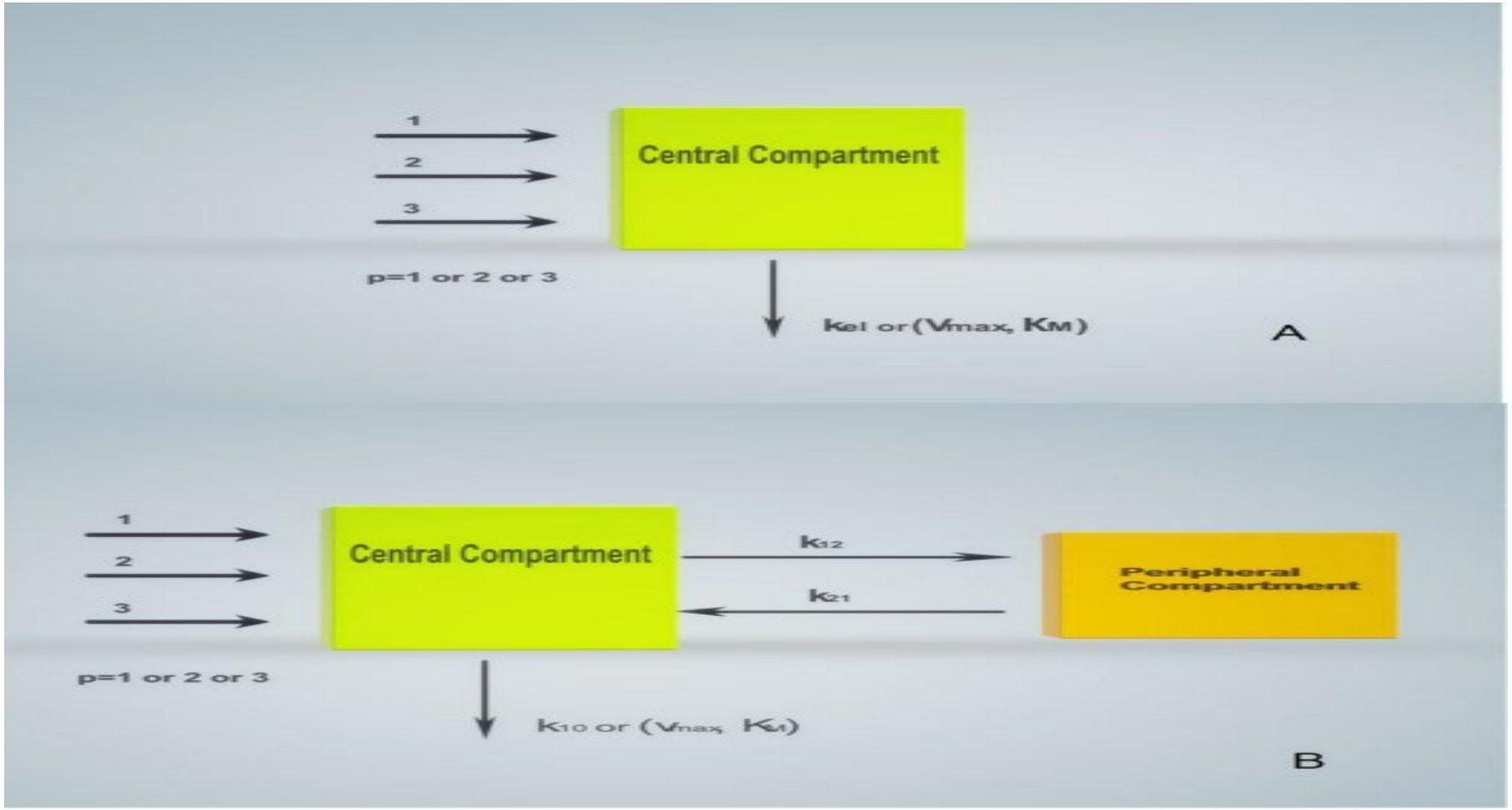
Schematic of the passive transfer of dissolved drug molecules (white spheres) from the gut lumen to portal vein. The blood fow in the portal vein, 20–40 cm/s (6) ensures sink conditions for the passive drug transfer due to its continuous removal from the portal vein to liver. The physiological time limits 5 and 30 h for drug absorption from the small intestines and colon (7, 8), respectively are shown on the time axis.

p- PBFTPK- m

Number of inputs

Number of compartments

- **Solubility**
- **Permeability**
- **Ionization**



Chryssafidis, P., Tsekouras, A.A. & Macheras, P. Re-writing Oral Pharmacokinetics Using Physiologically Based Finite Time Pharmacokinetic (PBFTPK) Models. *Pharm Res* **39**, 691–701 (2022)

One-compartment model equations

p	m	Kinetic (differential) equations	$t_1 < t \leq t_2$	
1	1	$\frac{dC}{dt} = \frac{FD}{\tau V_d} - k_{el}C$	0	τ
		$\frac{dC}{dt} = -k_{el}C$	τ	∞
2	1	$\frac{dC}{dt} = \frac{F_1 D}{\tau_1 V_d} - k_{el}C$	0	τ_1
		$\frac{dC}{dt} = \frac{F_2 D}{\tau_2 V_d} - k_{el}C$	τ_1	$\tau_1 + \tau_2$
		$\frac{dC}{dt} = -k_{el}C$	$\tau_1 + \tau_2$	∞
3	1	$\frac{dC}{dt} = \frac{F_1 D}{\tau_1 V_d} - k_{el}C$	0	τ_1
		$\frac{dC}{dt} = \frac{F_2 D}{\tau_2 V_d} - k_{el}C$	τ_1	$\tau_1 + \tau_2$
		$\frac{dC}{dt} = \frac{F_3 D}{\tau_3 V_d} - k_{el}C$	$\tau_1 + \tau_2$	$\tau_1 + \tau_2 + \tau_3$
		$\frac{dC}{dt} = -k_{el}C$	$\tau_1 + \tau_2 + \tau_3$	∞

Chryssafidis, P., Tsekouras, A.A. & Macheras, P. Re-writing Oral Pharmacokinetics Using Physiologically Based Finite Time Pharmacokinetic (PBFTPK) Models. *Pharm Res* **39**, 691–701 (2022)

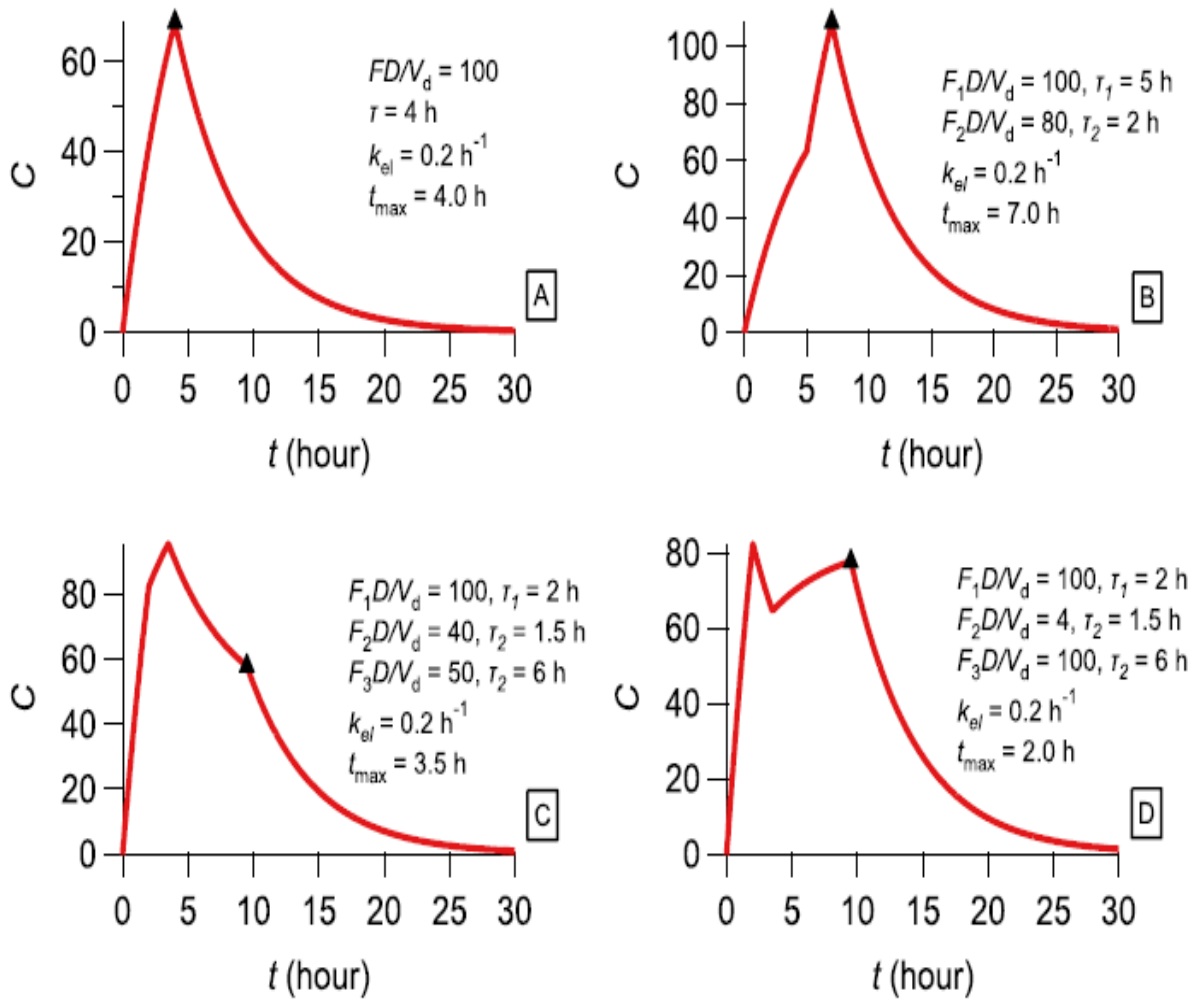
Solutions of one compartment model equations

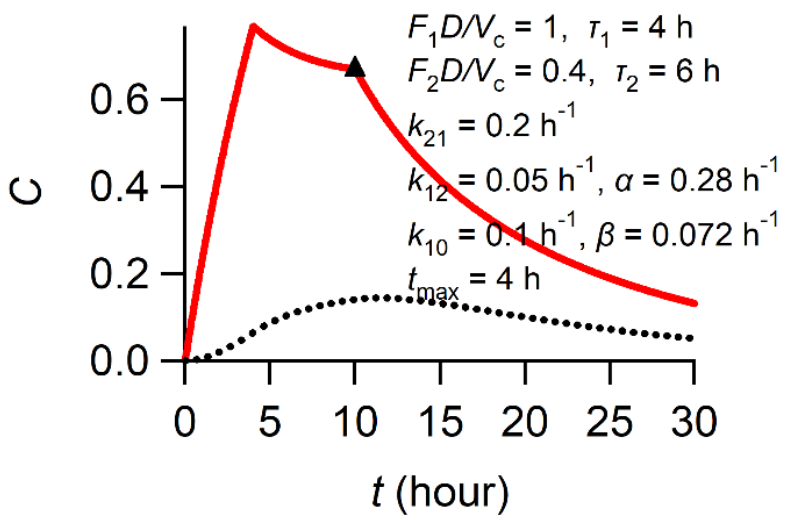
p	m	$C(t)$	$t_1 < t \leq t_2$	
1	1	$\frac{FD}{\tau V_d k_{el}}\left(1-e^{-k_{el}t}\right)$	0	τ
		$C(\tau)e^{-k_{el}(t-\tau)}$	τ	∞
2	1	$\frac{F_1 D}{\tau_1 V_d k_{el}}\left(1-e^{-k_{el}t}\right)$	0	τ_1
		$C(\tau_1)e^{-k_{el}(t-\tau_1)} + \frac{F_2 D}{\tau_2 V_d k_{el}}\left(1-e^{-k_{el}(t-\tau_1)}\right)$	τ_1	$\tau_1+\tau_2$
		$C(\tau_1+\tau_2)e^{-k_{el}(t-\tau_1-\tau_2)}$	$\tau_1+\tau_2$	∞
3	1	$\frac{F_1 D}{\tau_1 V_d k_{el}}\left(1-e^{-k_{el}t}\right)$	0	τ_1
		$C(\tau_1)e^{-k_{el}(t-\tau_1)} + \frac{F_2 D}{\tau_2 V_d k_{el}}\left(1-e^{-k_{el}(t-\tau_1)}\right)$	τ_1	$\tau_1+\tau_2$
		$C(\tau_1+\tau_2)e^{-k_{el}(t-\tau_1-\tau_2)} + \frac{F_3 D}{\tau_3 V_d k_{el}}\left(1-e^{-k_{el}(t-\tau_1-\tau_2)}\right)$	$\tau_1+\tau_2$	$\tau_1+\tau_2+\tau_3$
		$C(\tau_1+\tau_2+\tau_3)e^{-k_{el}(t-\tau_1-\tau_2-\tau_3)}$	$\tau_1+\tau_2+\tau_3$	∞

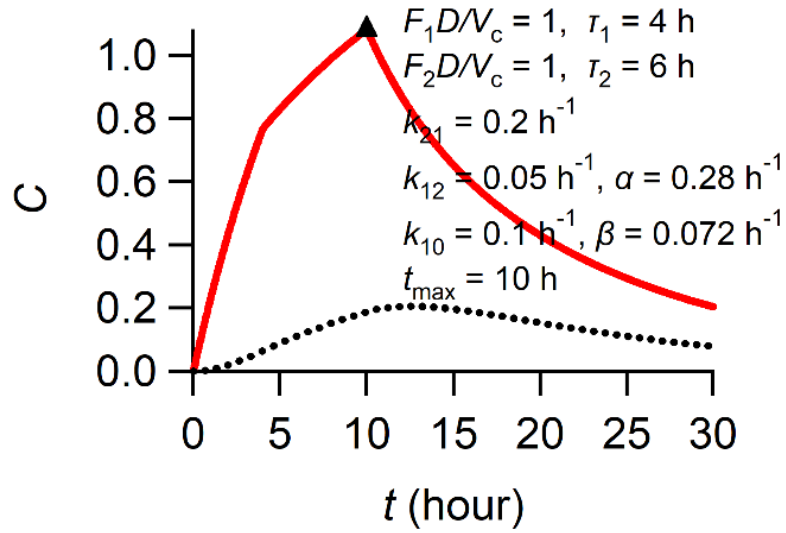
Chryssafidis, P., Tsekouras, A.A. & Macheras, P. Re-writing Oral Pharmacokinetics Using Physiologically Based Finite Time Pharmacokinetic (PBFTPK) Models. *Pharm Res* **39**, 691–701 (2022)

Simulations

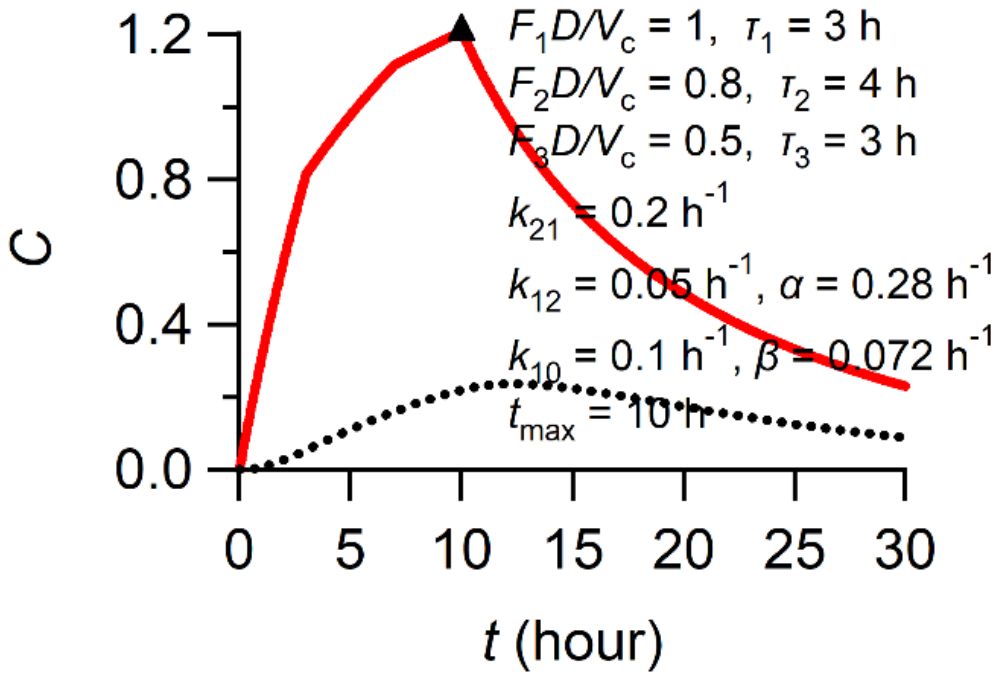
Fig. 3 Simulated curves for one compartment model drugs ($m=1$) following linear disposition kinetics with $p=1$ (Eqs. 29–30, panel (**A**)), $p=2$ (Eqs. 31–33, panel (**B**)), $p=3$ (Eqs. 34–37, panels (**C**) and (**D**)). Model parameter values are shown in each panel. The symbol ▲ denotes termination of all absorption stages.

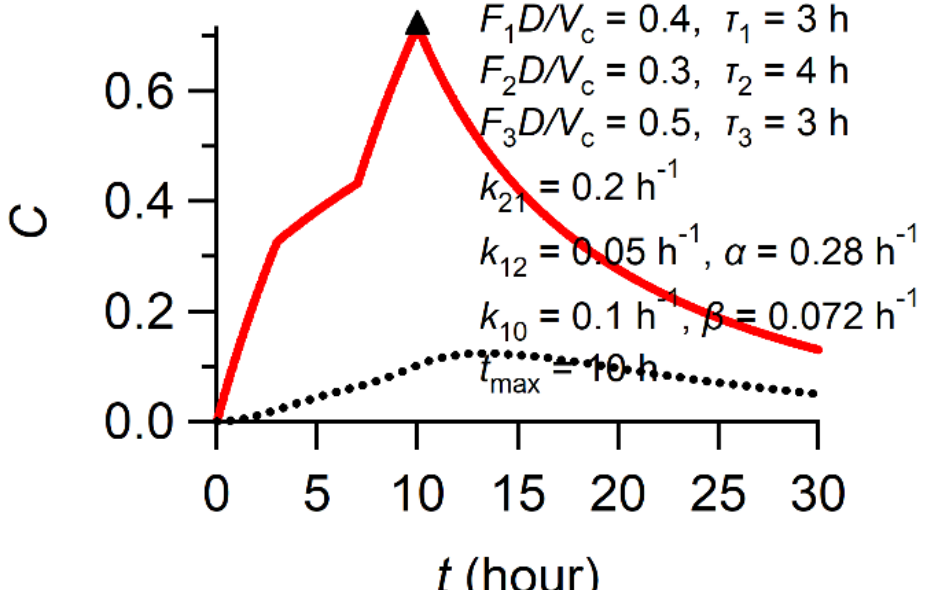


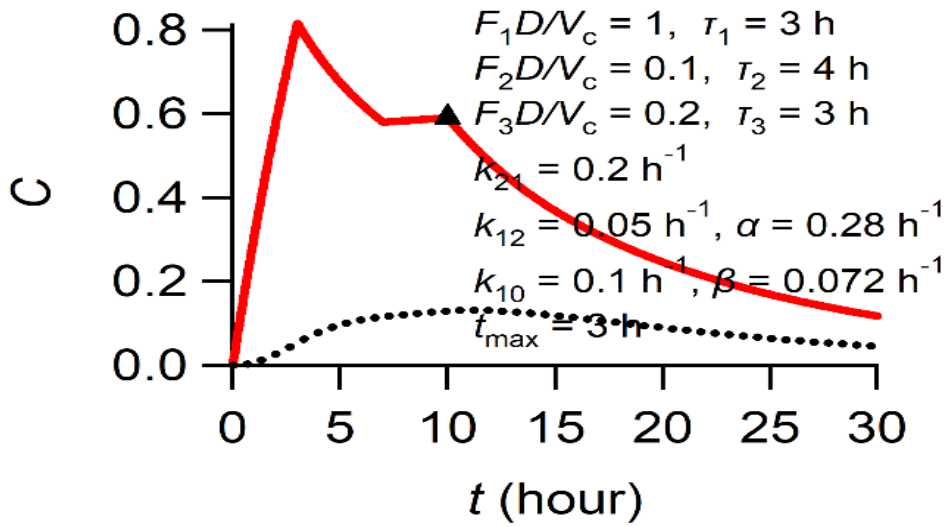


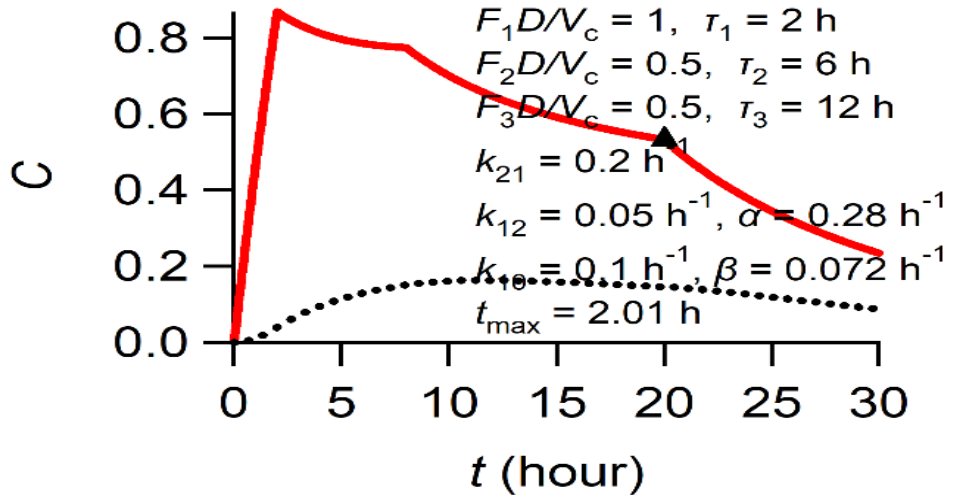


Simulated drug concentration in the blood (red solid) and in the peripheral (black dotted) compartment for an orally administered formulation that follows zero-order absorption processes in a two-compartment model, see Eqs. 4.70-4.75. Maximum concentration is reached at the end of either the first or the second absorption stage. Model parameter values can be seen next to the curve









Simulated drug concentration in the blood (red solid) and in the peripheral (black dotted) compartment for orally administered formulations that follow zero-order absorption processes in a two-compartment model. Maximum concentration is observed at tmax (upper panel) or not (tmax<τ , lower panel).

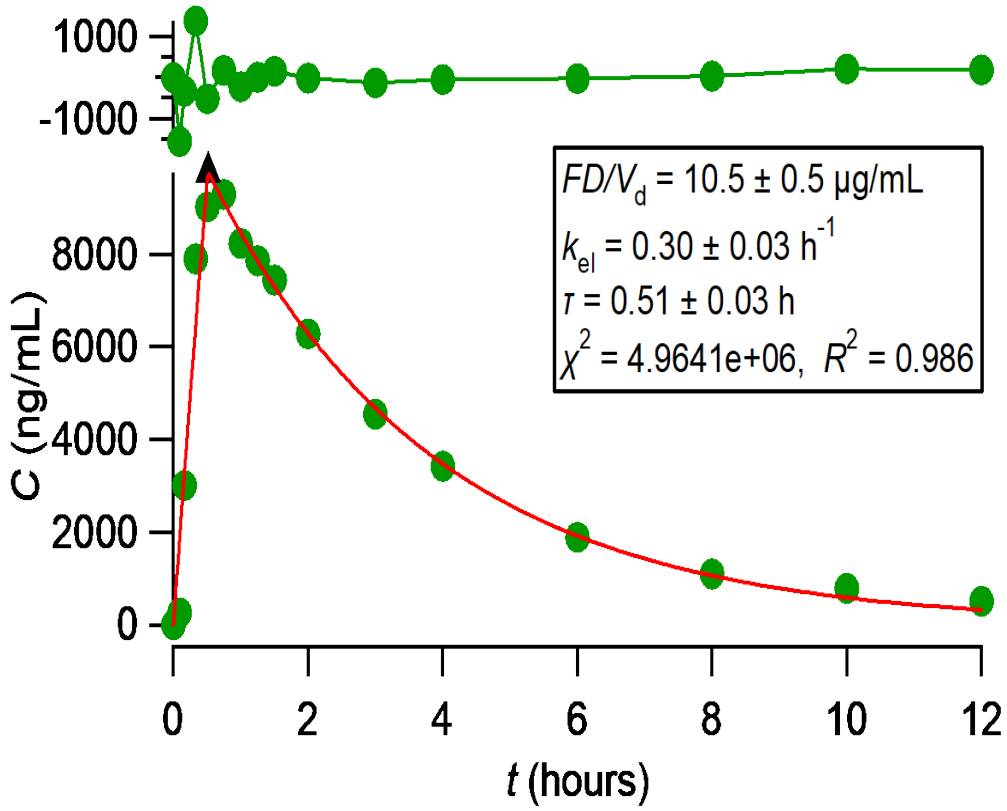


Fig. 6 Best fIt results of Eqs. 29, 30 to paracetamol experimental data (12). The symbol ▲ denotes the end of the absorption process. The top panel depicts the fit residuals.

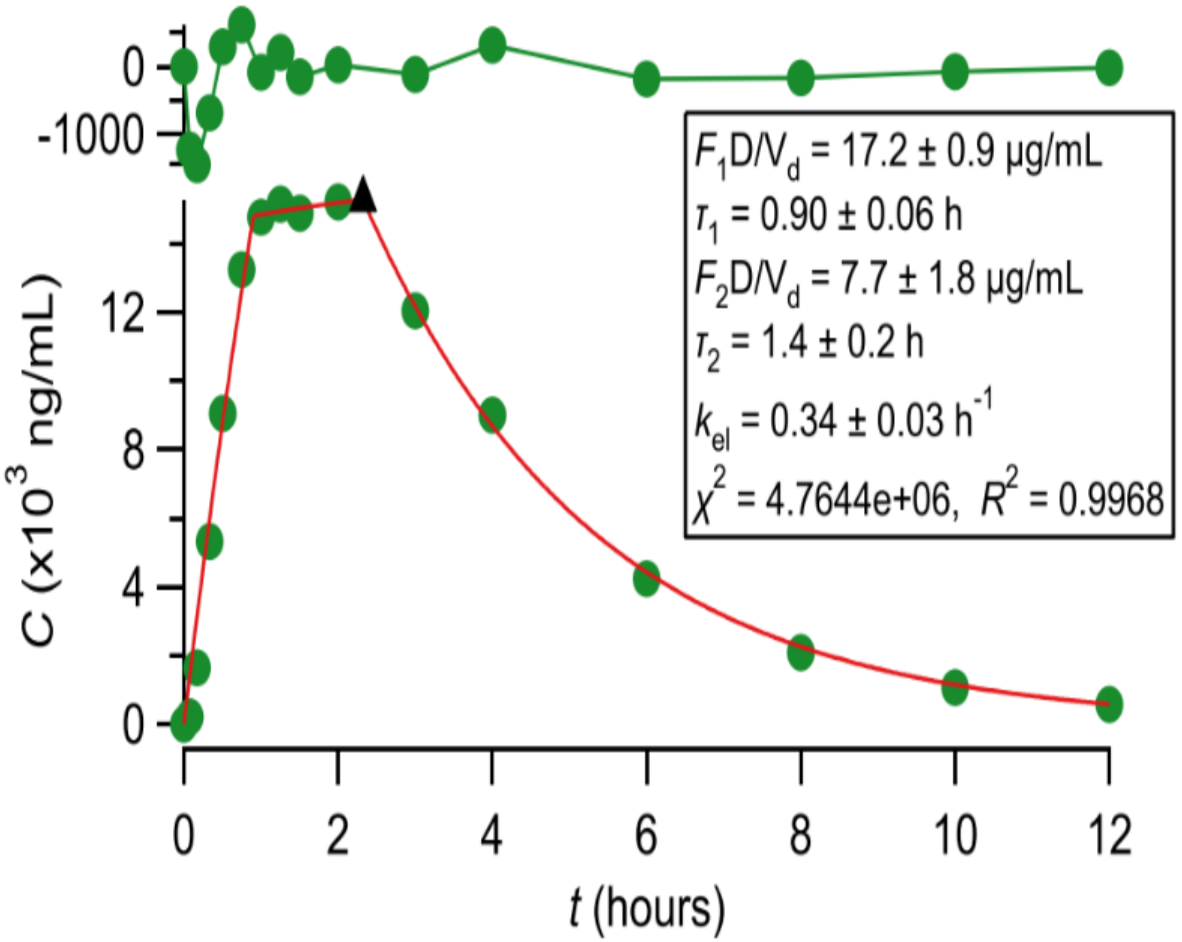


Fig. 7 Best fit results of Eqs. 31–33 to ibuprofen experimental data (12). The symbol ▲ denotes the end of the absorption processes.

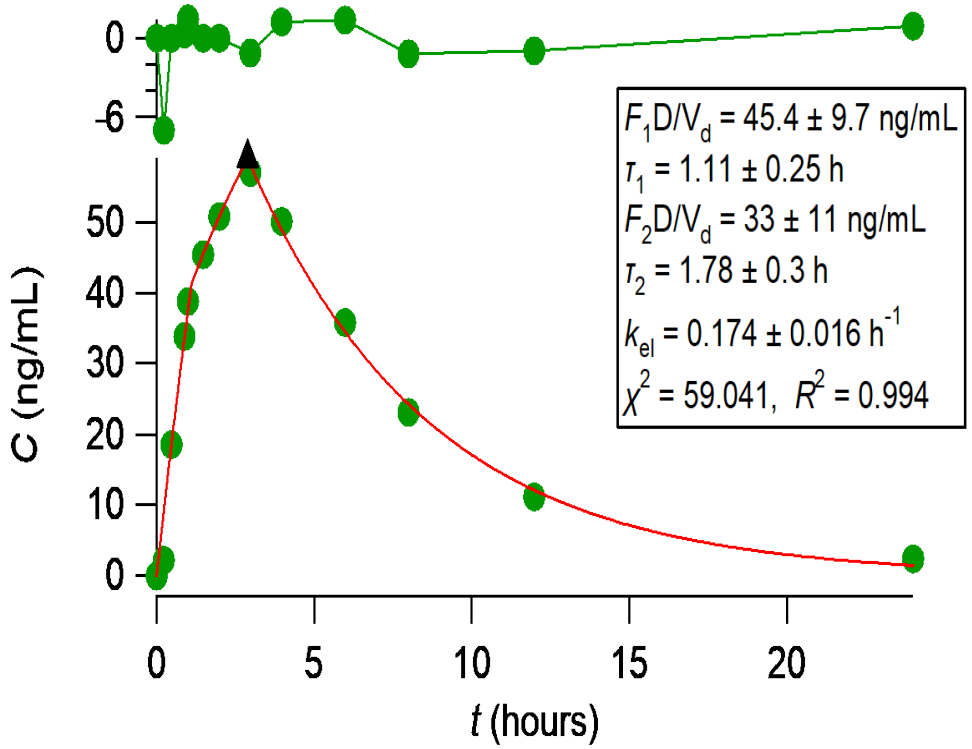


Fig. 8 Best fIt results of Eqs. 31–33 to almotriptan experimental data (13). The symbol ▲ denotes the end of the absorption processes

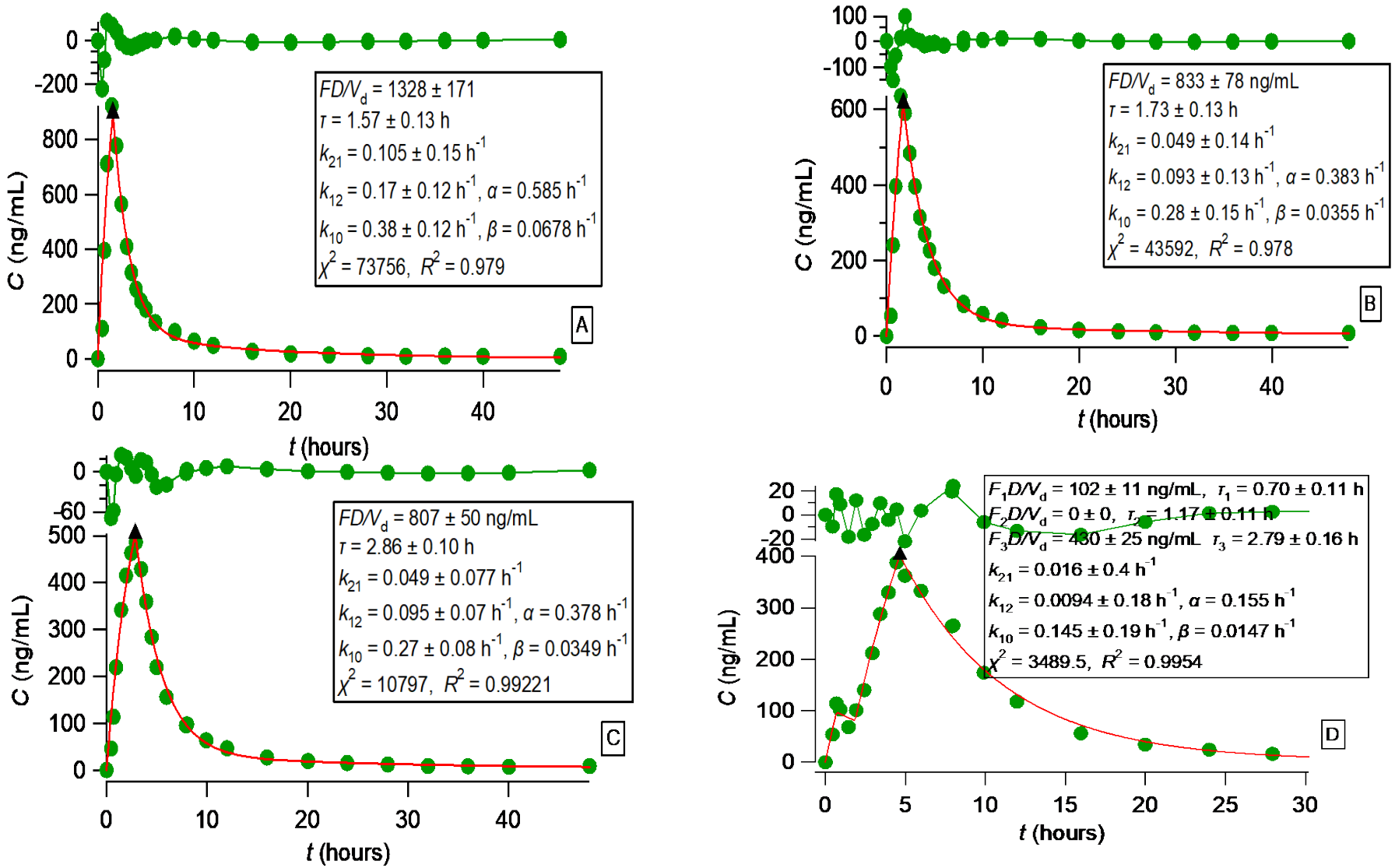


Fig. 9 Cyclosporin. Best fIt results of Eqs. 29, 30 to test formulation under fasted (A), fed (B) conditions and reference formulation under fasted (C) conditions (15). Best ft results of Eqs. 48–55 to reference formulation under fed (D) conditions. The symbol ▲ denotes the end of the absorption processes

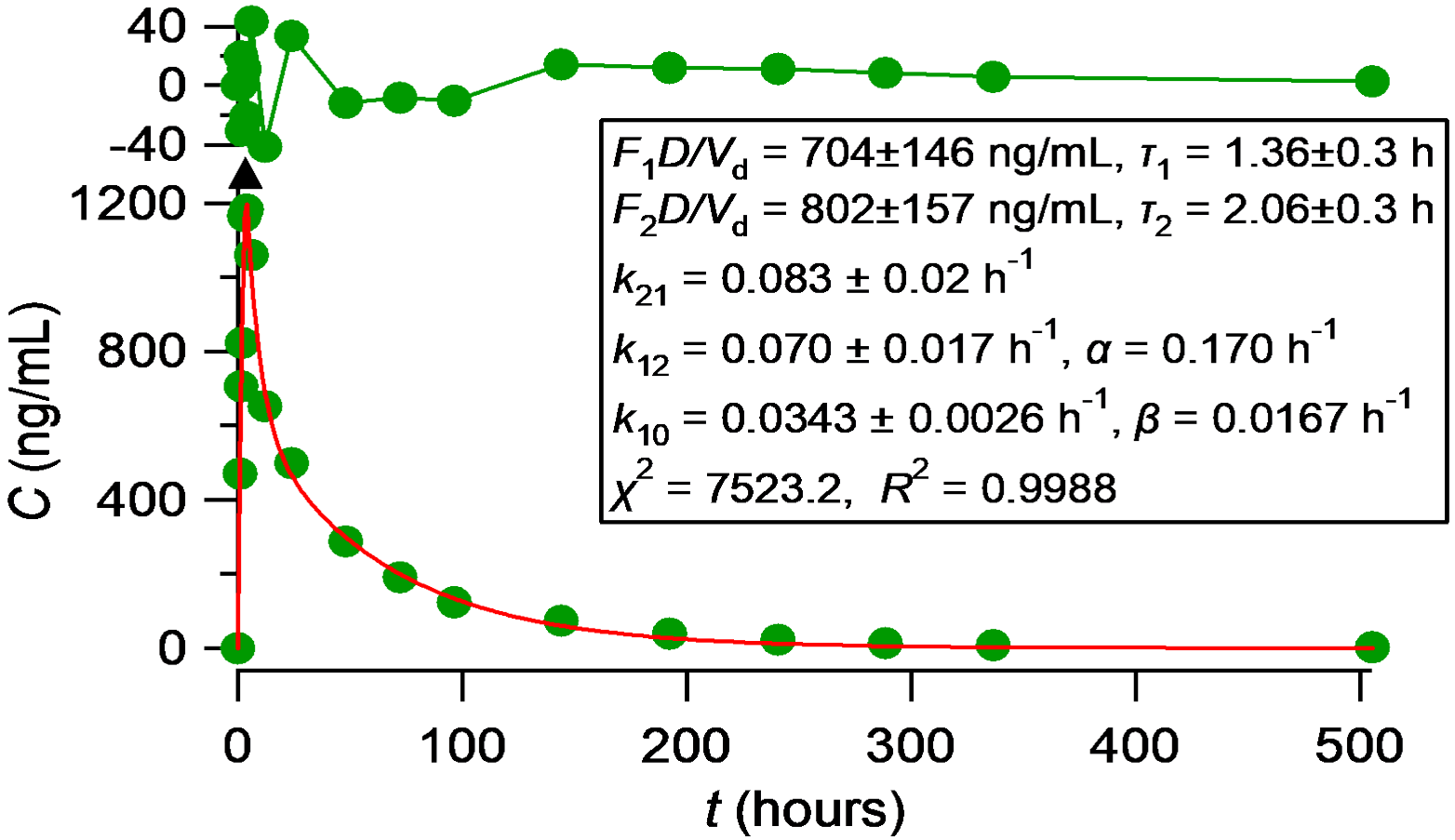


Fig. 10 Best fit results of Eqs. 42–48 to experimental data of niraparib (16). The symbol ▲ denotes the end of the absorption processes.

OUTLINE

4. Applications: Development of Drugs

A software for the estimation of absolute bioavailability from oral data exclusively: Towards the abolishment of microdosing studies in big pharma

- To be presented in Population Approach Group in Europe (PAGE), Rome, June 25-28, 2024

For one compartment model drugs, the estimation of absolute biovailability, F relies on Eq.1.

$$F = \sqrt{\frac{[(AUC)]_{0\ oral}^{\infty}}{[(AUC)]_{0\ hyp.\ I.V.}^{\infty}}} \qquad (1)$$

where $[(AUC)]_{0\ oral}^{\infty}$ is the area under the curve of the oral data from zero until infinity and $[(AUC)]_{0\ hyp.\ I.V.}^{\infty}$ is the area under the hypothetical curve of an equivalent I.V. administration of the same exact dose. It should be noted that the $[\mathrm{AUC}]_{0,\mathrm{hyp.\ I.V.}}^{\infty}$ was calculated with two distinct methods, one theoretical, which utilizes the ratio $e^{y-intercept}/k_{\mathrm{el}}$ from the semi-logarithmic plots of Fig. 2, and one that utilizes the classical trapezoidal rule for calculating the area under the blood concentration time curve.

P. CHRYSSAFIDIS, A. A. TSEKOURAS, P. MACHERAS. Revising Pharmacokinetics of Oral Drug Absorption: II Bioavailability-Bioequivalence Considerations, *Pharmaceutical Research* 38, 1345–1356 (2021) [DOI: 10.1007/s11095-021-03078-w]

OUTLINE

5. Applications: Development of Generics

Pharmaceutical Research (2023) 40:2167–2175
https://doi.org/10.1007/s11095-023-03578-x

ORIGINAL RESEARCH ARTICLE

Revamping Biopharmaceutics-Pharmacokinetics with Scientific and Regulatory Implications for Oral Drug Absorption

Nikolaos Alimpertis[1,2] · Athanasios A. Tsekouras[2,3] · Panos Macheras[1,2]

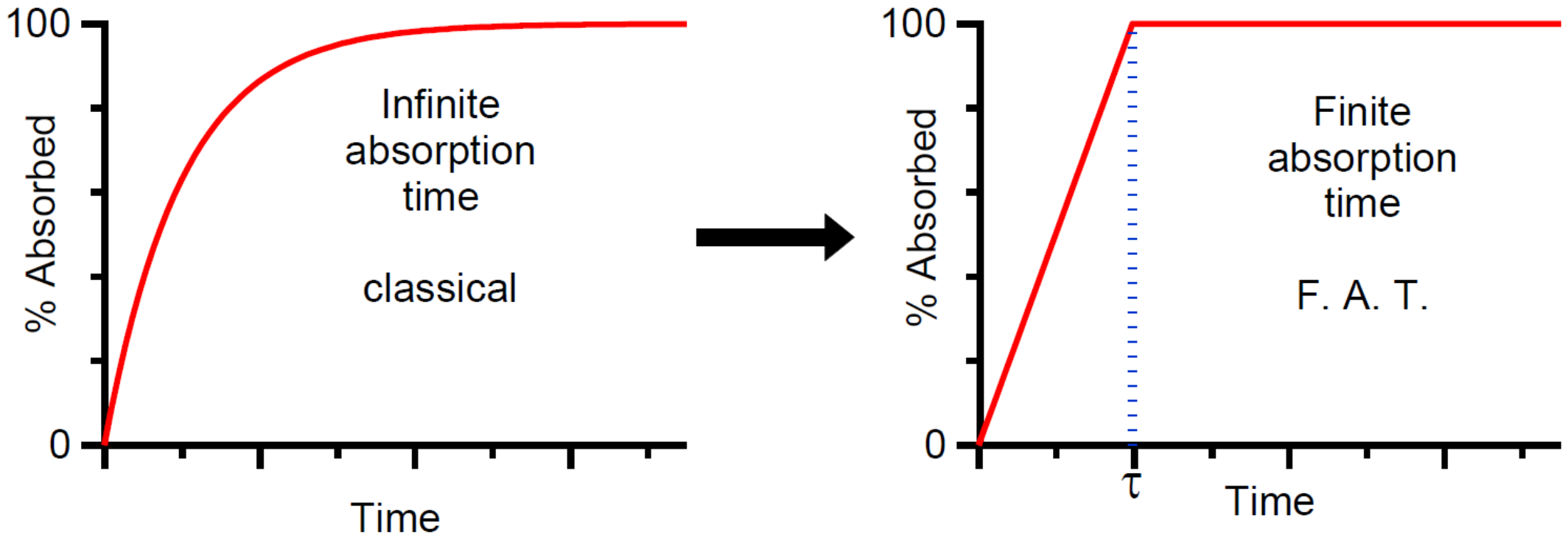
Received: 11 May 2023 / Accepted: 25 July 2023 / Published online: 3 August 2023

Abstract

Purpose The Wagner-Nelson and Loo-Riegelman methods developed in the 1960s and used since for the construction of percent of drug absorbed as a function of time as well as in *in vitro in vivo* correlations are re-considered in the light of the physiologically sound Finite Absorption Time (F.A.T.) concept developed recently.

Methods The classical equations for the percentage of drug absorption as a function of time were modified by taking into account the termination of drug absorption at F.A.T., replacing the parameters associated with the assumption of infinite drug absorption.

Graphical abstract



Wagner - Nelson

- Classic (1963)

$$\frac{A_t}{A_\infty} = \frac{C_t + k_{el}\int_0^t C dt}{k_{el}\int_0^\infty C dt} = \frac{C_t + k_{el}[AUC]_0^t}{k_{el}[AUC]_0^\infty}$$

- F.A.T.

$$\frac{A_t}{A_\tau} = \frac{C_t + k_{el}\int_0^t C dt}{C_\tau + k_{el}\int_0^\tau C dt} = \frac{C_t + k_{el}[AUC]_0^t}{C_\tau + k_{el}[AUC]_0^\tau} \qquad \text{for } t \leq \tau$$

Loo - Riegelman

- Classic (1968)

$$\frac{A_{t_n}}{A_\infty} = \frac{C_{1_{t_n}} + C_{2_{t_n}} + k_{el}\int_0^{t_n} C_1 dt}{k_{el}\int_0^{\infty} C_1 dt} = \frac{C_{1_{t_n}} + C_{2_{t_n}} + k_{el}[AUC]_0^{t_n}}{k_{el}[AUC]_0^{\infty}}$$

- F.A.T.

$$\frac{A_{t_n}}{A_\tau} = \frac{C_{1_{t_n}} + C_{2_{t_n}} + k_{el}[AUC]_0^{t_n}}{C_{1\tau} + C_{2\tau} + k_{el}[AUC]_0^{\tau}} \qquad \text{for } t \leq \tau$$

***

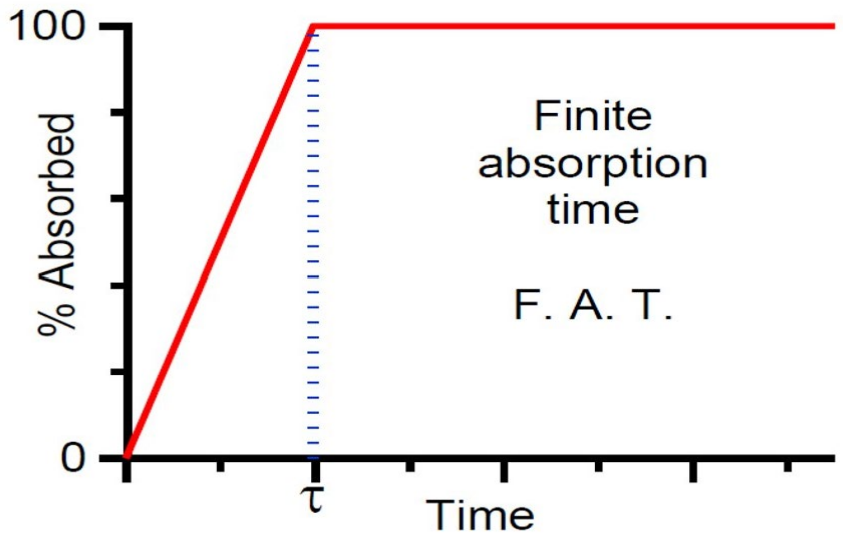
$$C_{2_{t_n}} = \frac{k_{12}}{k_{21}} C_{1_{t_{n-1}}}[1 - e^{-k_{21}\Delta t}] + \frac{k_{12}\Delta C_1 \Delta t}{2} + C_{2_{t_{n-1}}} e^{-k_{21}\Delta t}$$

We mathematically proved for one- and two-compartment model drugs:

$$\frac{A_t}{A_\tau} = \frac{t}{\tau} \quad \text{for } t \leq \tau$$

$$\frac{A_t}{A_\tau} = 1 \quad \text{for } t > \tau$$

F.A.T. for a single input stage:



Pharmaceutical Research (2024) 41:235–246
https://doi.org/10.1007/s11095-024-03653-x

ORIGINAL RESEARCH ARTICLE

IVIVC Revised

Nikolaos Alimpertis[1,2] · Antony Simitopoulos[1] · Athanasios A. Tsekouras[3,2] · Panos Macheras[1,2]

Received: 16 October 2023 / Accepted: 29 December 2023 / Published online: 8 January 2024

Abstract

Purpose To revise the IVIVC considering the physiologically sound Finite Absorption Time (F.A.T.) and Finite Dissolution Time (F.D.T.) concepts.

Methods The estimates τ and τ_d for F.A.T. and F.D.T., respectively are constrained by the inequality $\tau_d \leq \tau$; their relative magnitude is dependent on drug's BCS classification. A modified Levy plot, which includes the time estimates for τ and τ_d was developed. IVIVC were also considered in the light of τ and τ_d estimates. The modified Levy plot of theophylline, a class I drug, coupled with the rapid (30 min) and very rapid (15 min) dissolution time limits showed that drug dissolution/absorption of Class I drugs takes place in less than an hour. We reanalyzed a carbamazepine (Tegretol) bioequivalence study using PBFTPK models to reveal its complex absorption kinetics with two or three stages.

Results The modified Levy plot unveiled the short time span (~2 h) of the *in vitro* dissolution data in comparison with the duration of *in vivo* dissolution/absorption processes (~17 h). Similar results were observed with the modified IVIVC plots. Analysis of another set of carbamazepine data, using PBFTPK models, confirmed a three stages absorption process. Analysis of steady-state (Tegretol) data from a paediatric study using PBFTPK models, revealed a single input stage of duration 3.3 h. The corresponding modified Levy and IVIVC plots were found to be nonlinear.

Conclusions The consideration of Levy plots and IVIVC in the light of the F.A.T. and F.D.T. concepts allows a better physiological insight of the *in vitro* and *in vivo* drug dissolution/absorption processes.

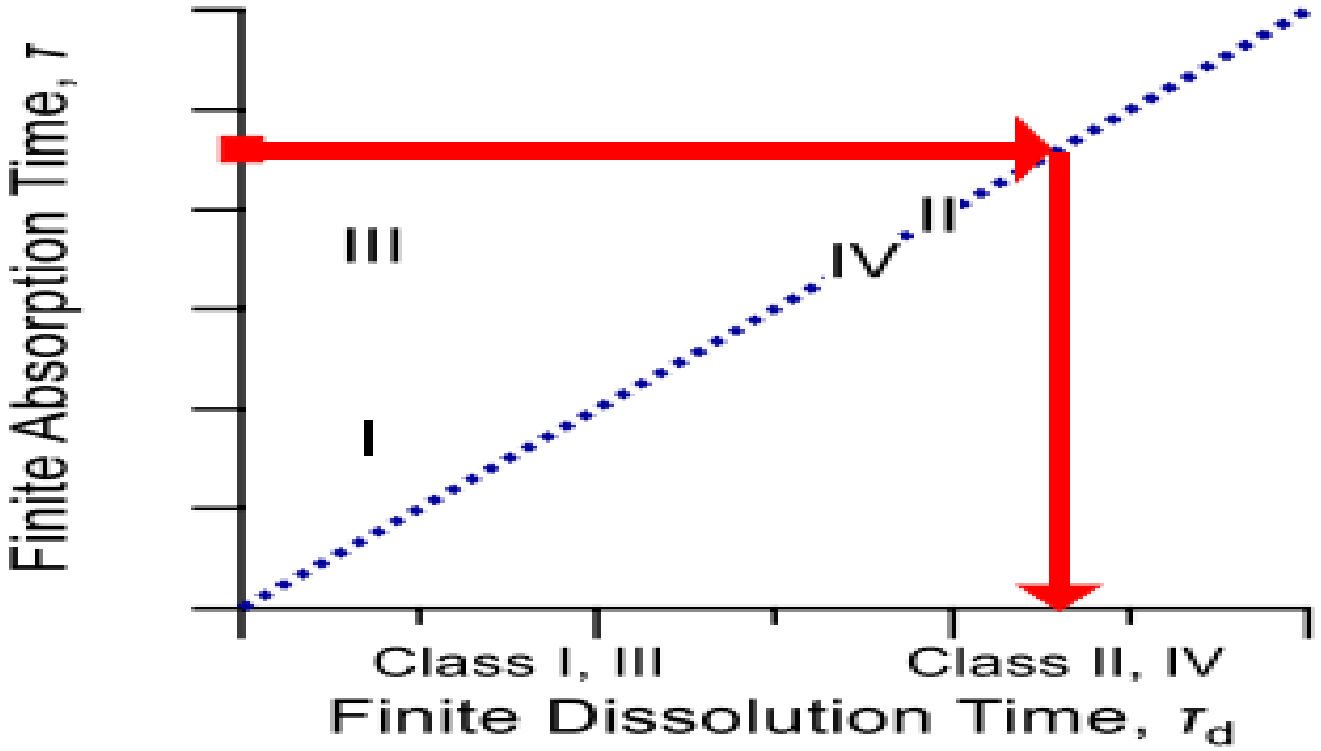


Fig. 2 The Levy-Macheras plot. The estimate for F.A.T., τ, defines the value of equal duration F.D.T., τ_d. In principle, for class I drugs $\tau_d \leq \tau$, for class III drugs $\tau_d << \tau$, while for class II and IV drugs $\tau_d = \tau$. The approximate positions of class I and III drugs is indicated by the respective symbols. The dotted line is the line of identity where class II and IV drugs are always located. The values of τ_d increase in the following order: (biowaivers), (Class I, III drugs), (Class II, IV drugs).

OUTLINE

6. Applications: Bioequivalence Assessment

The Holy Grail of Bioequivalence: The Finite Absorption Time (F.A.T.) Concept

Athanasios A. Tsekouras[1,3], Panos Macheras[2,3]

[1]Department of Chemistry, National and Kapodistrian University of Athens, Athens, Greece

[2]Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece

[3]PharmaInformatics Unit, ATHENA Research Center, Athens, Greece

ABSTRACT

Purpose. To formulate a methodology for the assessment of bioequivalence using metrics, which are based on the physiologically sound F.A.T. concept.

Pharmaceutical Research: Under revision

Understanding the gastrointestinal absorption of drugs using Physiologically Based Finite Time Pharmacokinetic (PBFTPK) Models: Focus on Biowaivers

Antony Simitopoulos[1], Athanasios Tsekouras[2,3], and Panos Macheras[1,3,*]

[1] Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece; antonsim@pharm.uoa.gr

[2] Department of Chemistry, National and Kapodistrian University of Athens, Athens, Greece; thanost@chem.uoa.gr

[3] PharmaInformatics Unit, ATHENA Research Center, Athens, Greece; macheras@pharm.uoa.gr

Purpose To apply the PBFTPK models for the analysis of Class I drugs and explore if the estimates for the bioavailable fraction, F, and the duration of absorption, τ are in accord with the rapid and complete absorption, e.g., F>0.90 of Class I drugs.

Pharmaceutical Research, submitted

OUTLINE

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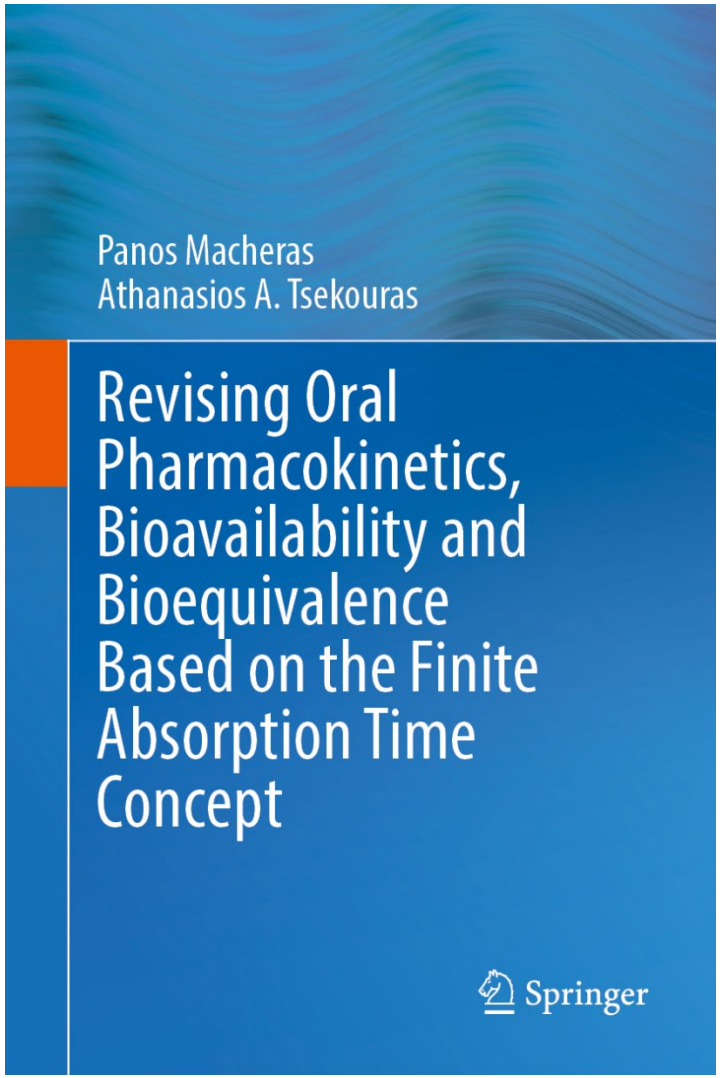
Panos Macheras
Athanasios A. Tsekouras
Revising Oral Pharmacokinetics, Bioavailability and Bioequivalence Based on the Finite Absorption Time Concept
Springer

Scheduled presentations

1. **AAPS WEBINAR**

4th Talk: June 4th, 2024, 12.30pm EAST.

Panos Macheras . Scientific and regulatory applications of F.A.T. concept and PBFTK models: II Dissolution, IVIVC, biowaivers.

Contact: "Stacey Royston" <roystons@aaps.org>

2. Satellite workshop. Population Approach Group in Europe (PAGE), Rome, Italy, 25 June, 2024

Physiology and/or topology dictate Biopharmaceutic, Pharmacokinetic, Pharmacodynamic processes and PBPK models, Pharmacometric structural models to follow Classical, Finite Time, and Fractal-Fractional kinetics.

Contact: "Panos Macheras" <macheras@pharm.uoa.gr>

In vitro testing and biopharmaceutics classification of pediatric drugs and formulations

Hala Fadda, PhD

Professor of Pharmaceutics

Pediatric Formulations Chair

International Pharmaceutical Federation (FIP)

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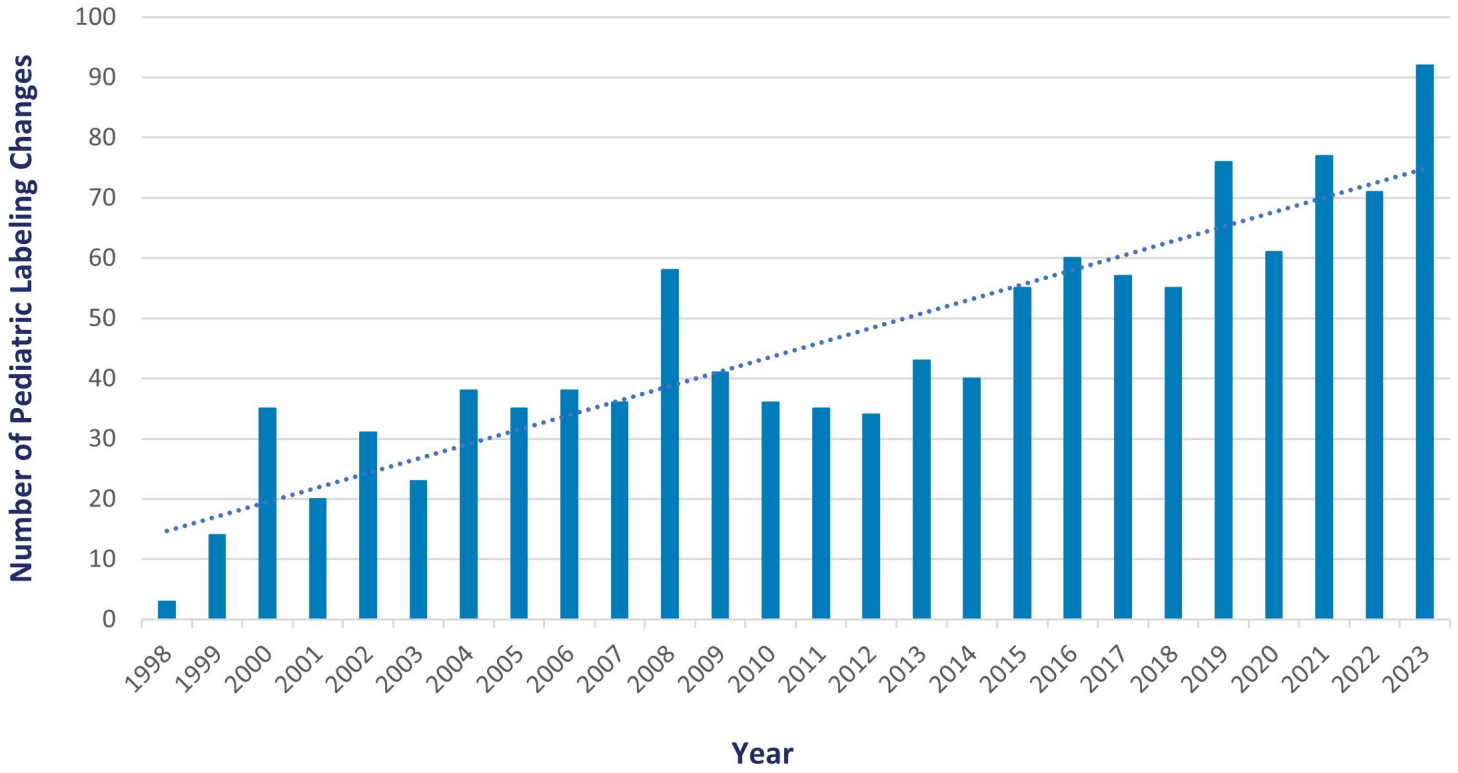
Success of pediatric labelling changes

Increase in number of pediatric labeling changes for drugs and biologics pursuant to the Best Pharmaceuticals for Children Act (BPCA), Pediatric Research Equity Act (PREA) and Pediatric Rule



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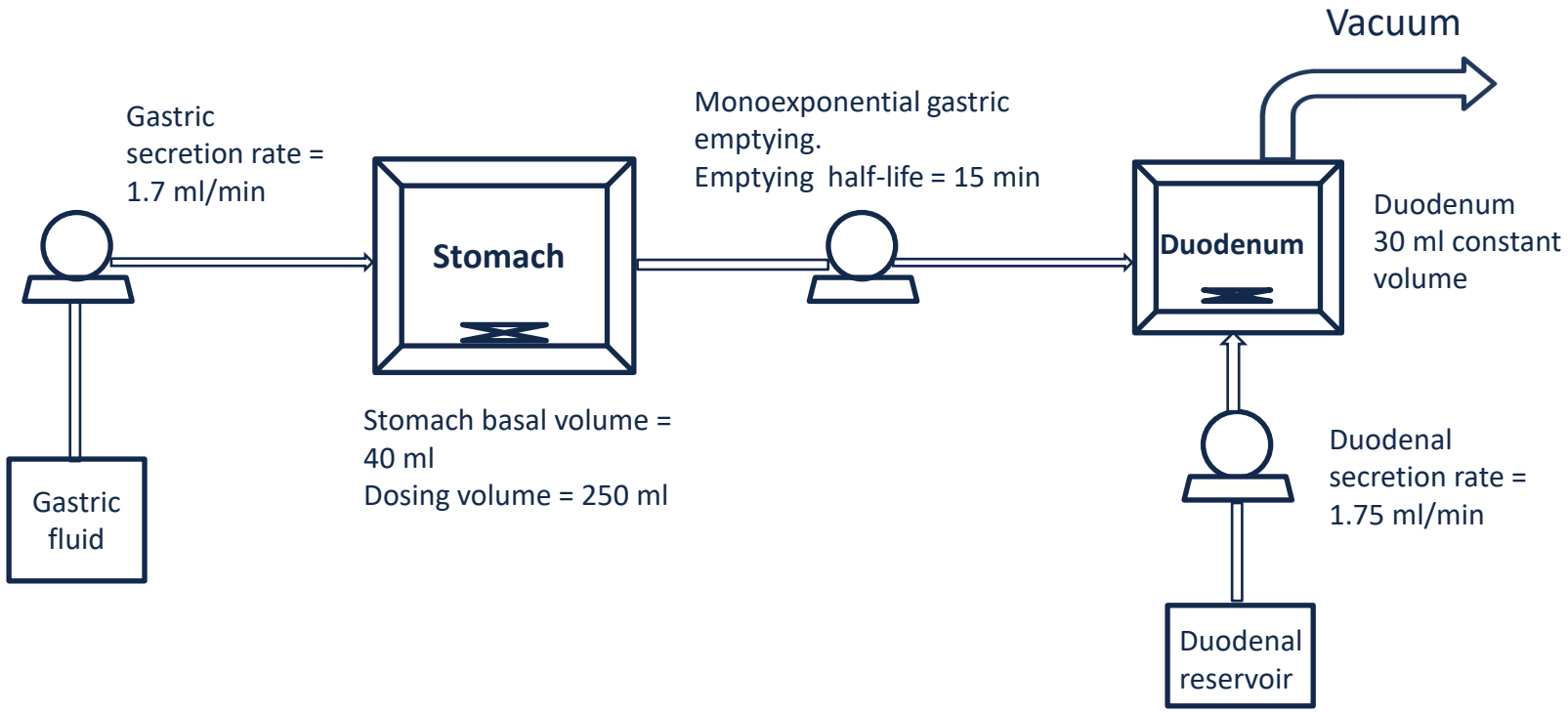
Food and Drug Administration. Historic milestone: 1,000 drugs, biologics have new pediatric use information in labeling. *AAP News*. https://www.fda.gov/media/161414/download

Challenges facing pediatric oral drug product development

- Challenge 1: Absence of standardized *in vitro* dissolution and bioequivalence tests for pediatric oral dosage forms.
  - Biorelevant dissolution tests need to simulate pediatric gastrointestinal luminal volumes, composition, and transfer rates.
- Challenge 2: Adult biopharmaceutics classification system (BCS) cannot be extrapolated to pediatrics.
  - Physiologically relevant fluid volumes and compositions simulative of the different pediatric subpopulations need to be utilized for developing a pediatric BCS (pBCS).

In-house, multi-compartment, dynamic, *in vitro* simulated stomach duodenum (SSD) model for adult populations



SSD model has been shown to provide a reliable, discriminative and predictive tool for investigating the effect of physiological and formulation variables on absorption of poorly soluble drugs with solubility/ dissolution limited absorption. [1,2,3]

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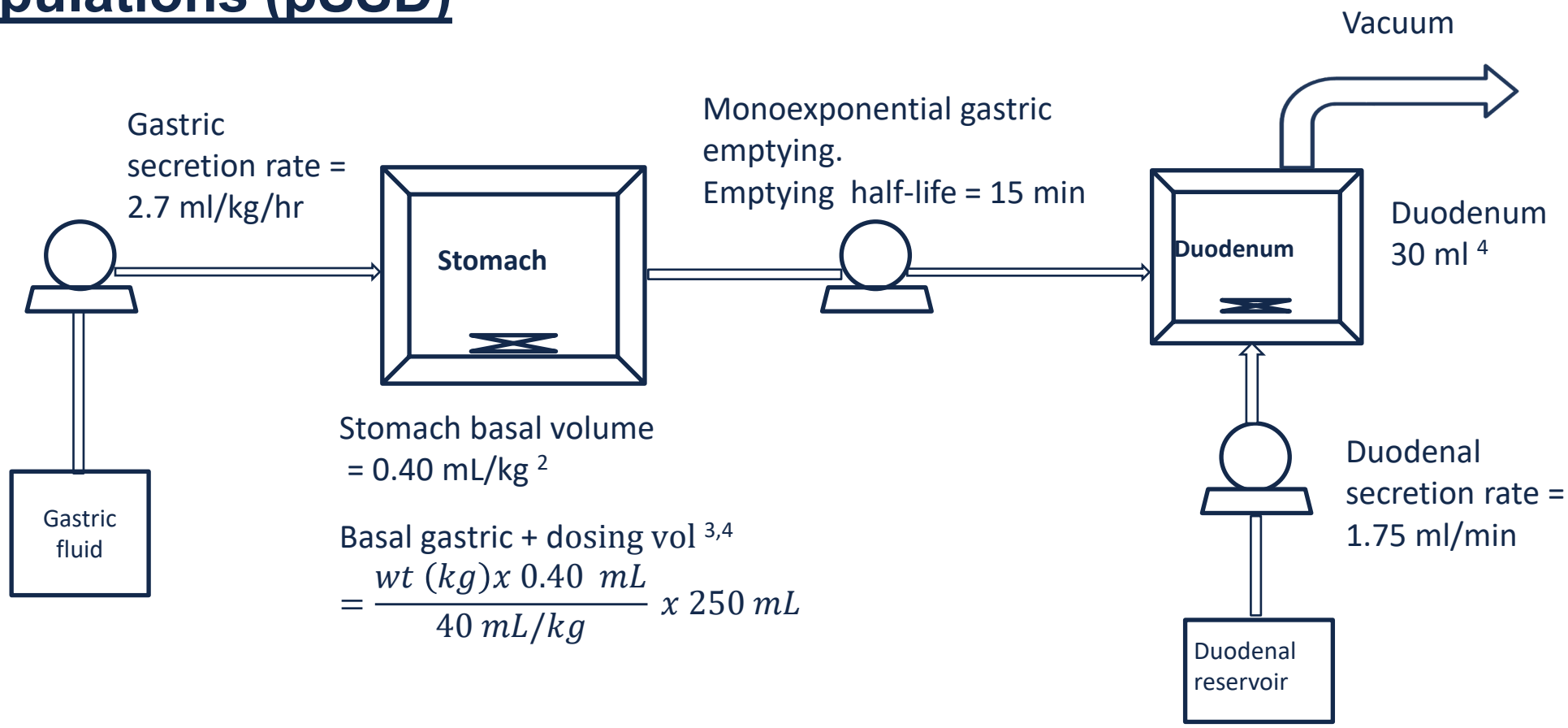
In-house, multi-compartment, dynamic, *in vitro* SSD model for pediatric populations (pSSD)



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Future Directions

- Validation of pediatric simulated stomach duodenum model and correlation to drug bioavailability trends
- Investigation of the impact of heterogeneity of pediatric gastrointestinal physiology on *in vitro* drug release
- Investigation of the impact of different drink/food vehicles and dosing volumes on *in vitro* drug release
- Bridge in vitro studies with PBPK modelling to predict *in vivo* drug absorption

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Public Comments for Session 3

In Person Comments:

- Alexander Shekhtman, PhD, Professor and Chair, Department of Chemistry, University at Albany, State University of New York
- Marco Guerrini, MS Director Istituto di Ricerche Chimiche e Biochimiche
- Jace Jones, PhD Assistant Professor University of Maryland
- Andrew Graves, MS, SCYM Director, Immunogenicity Assessment Teva
- David Borhani Senior Director, Business Development Ginkgo Bioworks
- Ravishankara MN, PhD Senior General Manager (R & D) Sun Pharma
- Marina Juretić, PhD Senior Analytical Scientist, R&D, IVR/IVIVC PLIVA Hrvatska
- Itay Speicher, BSc, MBA Sr. Director of Business Development DigiM Solution
- Jon Lenn, PhD Chief Scientific Officer MedPharm
- Marc Taraban, PhD Associate Research Professor University of Maryland Baltimore
- Grzegorz Garbacz, PhD Co-Founder & CEO Physiolution Polska
- ***Laura Philips, PhD President & CEO, Spheryx, Inc***
- ***Katherine M. Harris, PhD Principal Scientist Carelon Research***
- ***James K. Ferri, PhD Professor Virginia Commonwealth University***

Virtual Comments:

- Conor L. Evans, PhD Associate Professor Harvard Medical School
- Matthias Wacker, PhD Associate Professor National University of Singapore
- Tao Zhang, PhD Assistant Professor, Pharmaceutical Sciences SUNY Binghamton University
- Hannah Batchelor Professor University of Strathclyde
- Jozef Al-Gousous, PhD Adjunct Assistant Professor University of Michigan
- Panos Macheras, PhD Professor Emeritus National and Kapodistrian University of Athens
- Hala Fadda, PhD Professor of Pharmaceutics Butler College
- Kathleen Walsh, MSc, MD Director, Patient Safety Research Center Boston Children's Hospital, Harvard University
- Alexa Simon Meara, MD Associate Professor The Ohio State University Wexner Medical Center
- Jacqueline Griffin Associate Professor Northeastern University
- Molly Moore Jeffery, PhD Robert D. and Patricia E. Kern Honored Investigator in the Science of Health Care Delivery | Scientific Director of Emergency Medicine Research and Platform Knowledge Solutions | Associate Professor Emergency Medicine Mayo Clinic
- Ozlem Ergun, PhD; Daniel Kosmas, PhD Professor Northeastern University
- Fang Yu, PhD Computational Modeling Scientist CONTINUUS Pharmaceuticals, Inc.
- Dongmei Li, PhD Professor, Clinical and Translational Research, Obstetrics and Gynecology and Public Health Sciences University of Rochester School of Medicine and Dentistry
- James Hasty CEO/Founder BHEC
- Peter Gompper Co-Founder, Rubitel

Meeting the Challenge of Establishing Generic Equivalency for Biologics

May 2024

Challenge: Demonstrating Equivalency of Generics

- Safety: Monitoring Protein Aggregation
- Technology needed to detect sub-visible particles:
  - Sensitivity: Reliable detection
  - Differentiation: Distinguishes and ID contaminants
  - Accuracy: Reproducible concentrations of multiple species

Existing technologies do not have the
sensitivity, differentiation, and accuracy
to assure safety, especially at small particle sizes (<5µm)
where the risk of immunogenic response can be most critical

Spheryx

Total Holographic Characterization: Size, Composition and Concentration

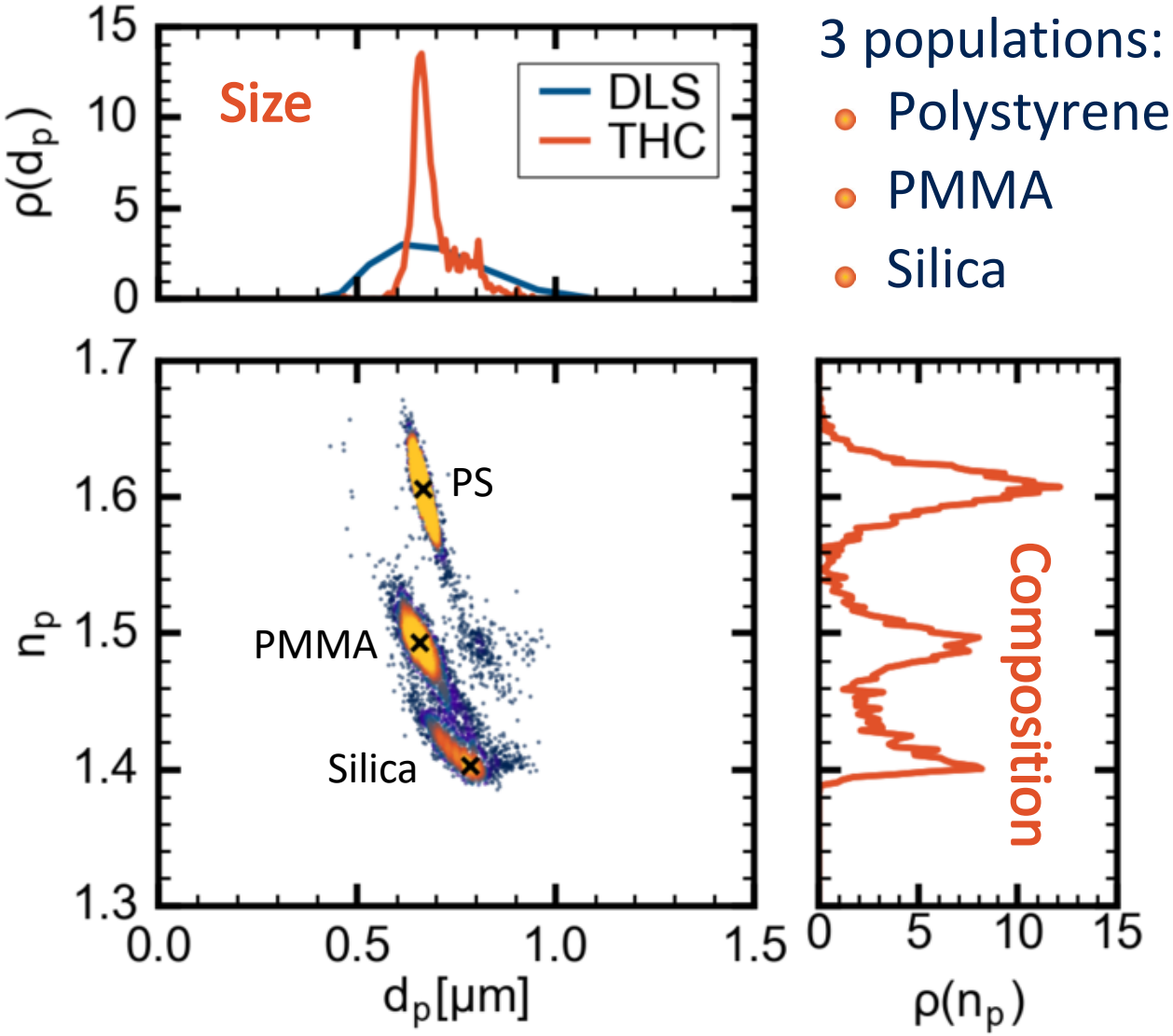
Another dimension of information accessible from particle holograms

For each individual particle

- **Size** (diameter: d_p)
- **Composition** (refractive index: n_p)
- **Morphology**

One particle ⇒ One point
Concentration = # particles/mL

Sets the standard for sensitivity
500 nm – 10μm



3 populations:

- Polystyrene
- PMMA
- Silica

Spheryx

Sensitive Enough to Assure Detection

FROM: J. of Pharm. Sci., 112, 2023, p 985-990. The Strengths of Total Holographic Video Microscopy in Detecting Sub-Visible Protein Particles in Biopharmaceuticals: A Comparison to Flow Imaging and Resonant Mass Measurement, Rahn et al., AbbVie Deutschland GmbH & Co.

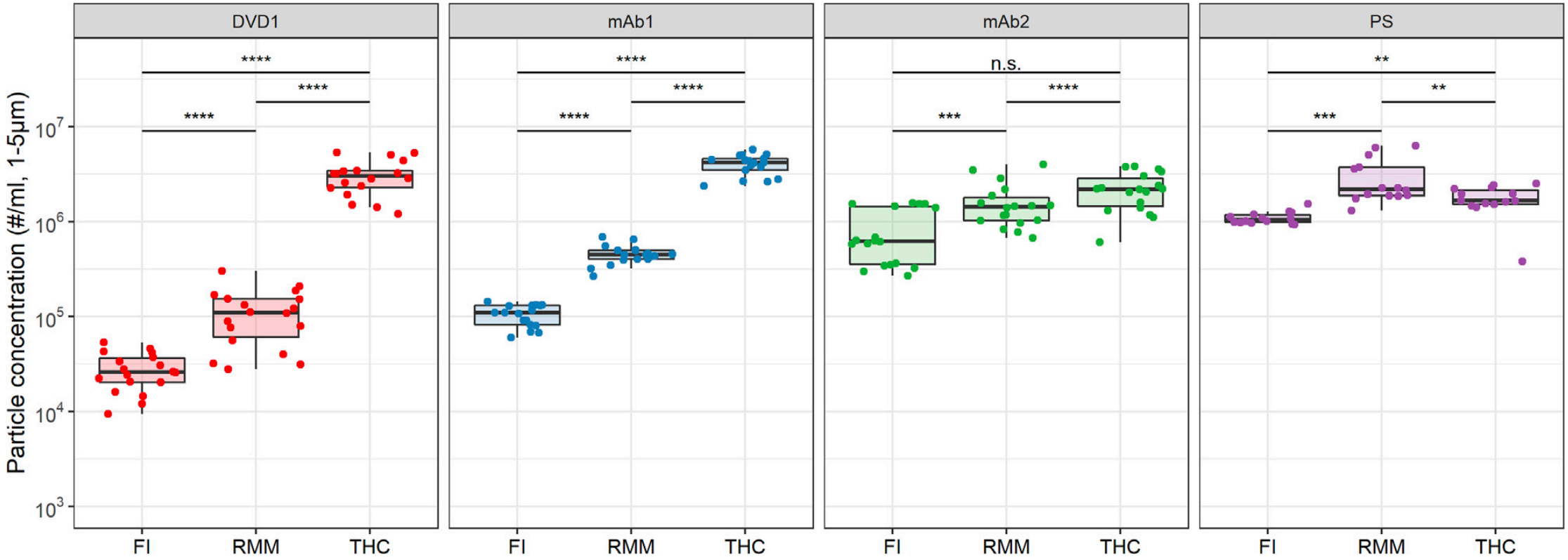
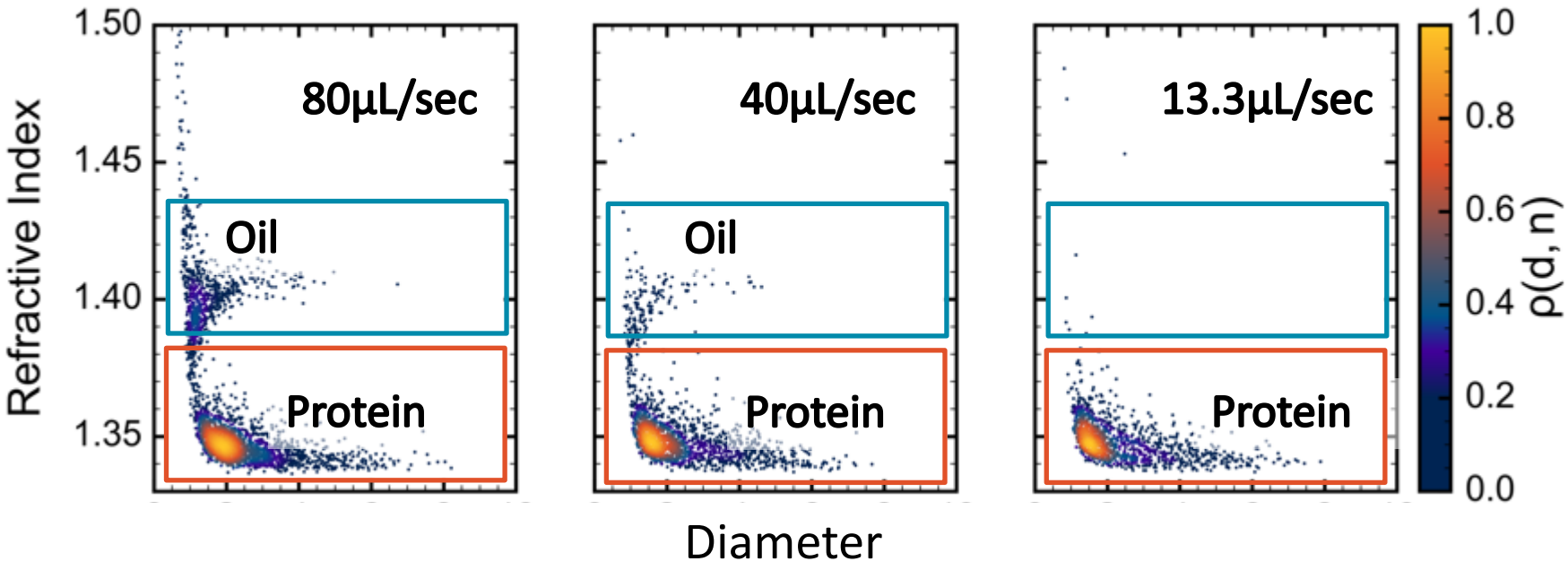


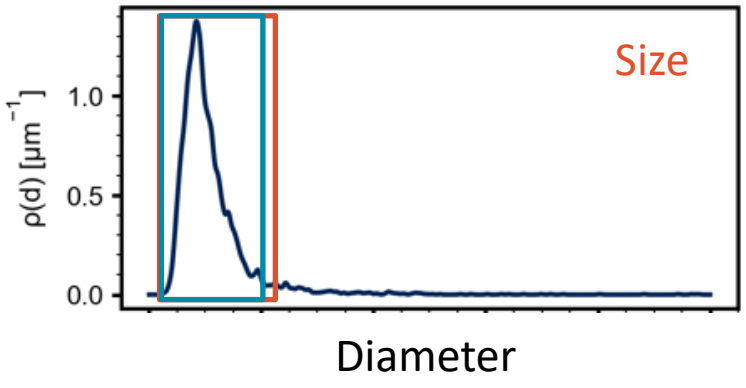
*Figure 3. Comparing different particle types measured with different methods. Comparison of concentration of different particles measured using FI, RMM or THC, where PS and mAb1 concentrations show small difference between methods and mAb2 and DVD1 (dual variable domain) particle concentration seem to be highly dependent on the method of choice. Stated p-values of the pairwise comparisons were done using Wilcoxon rank sum test, where "n.s.", "**", "***", and "****" represents p>0.05, p<0.01, p<0.001, and p<0.0001 respectively. Data shown for particles between 1 and 5 µm.*

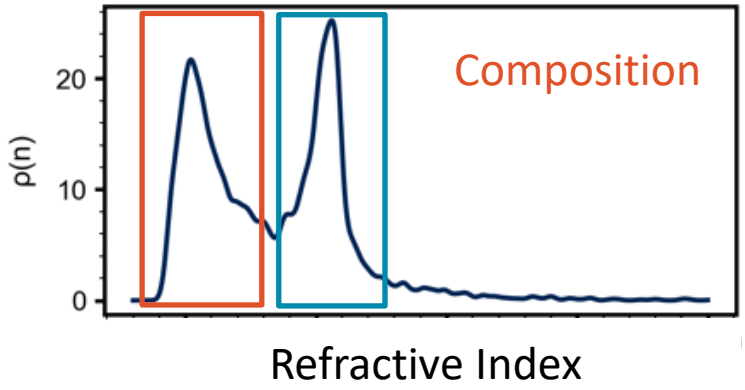
Spheryx

Differentiates Contaminants: Protein Aggregates and Silicone Oil



- IgG solution ejected from a syringe
- Shear forces elute silicone oil
- Aggregates and oil concentrations simultaneously



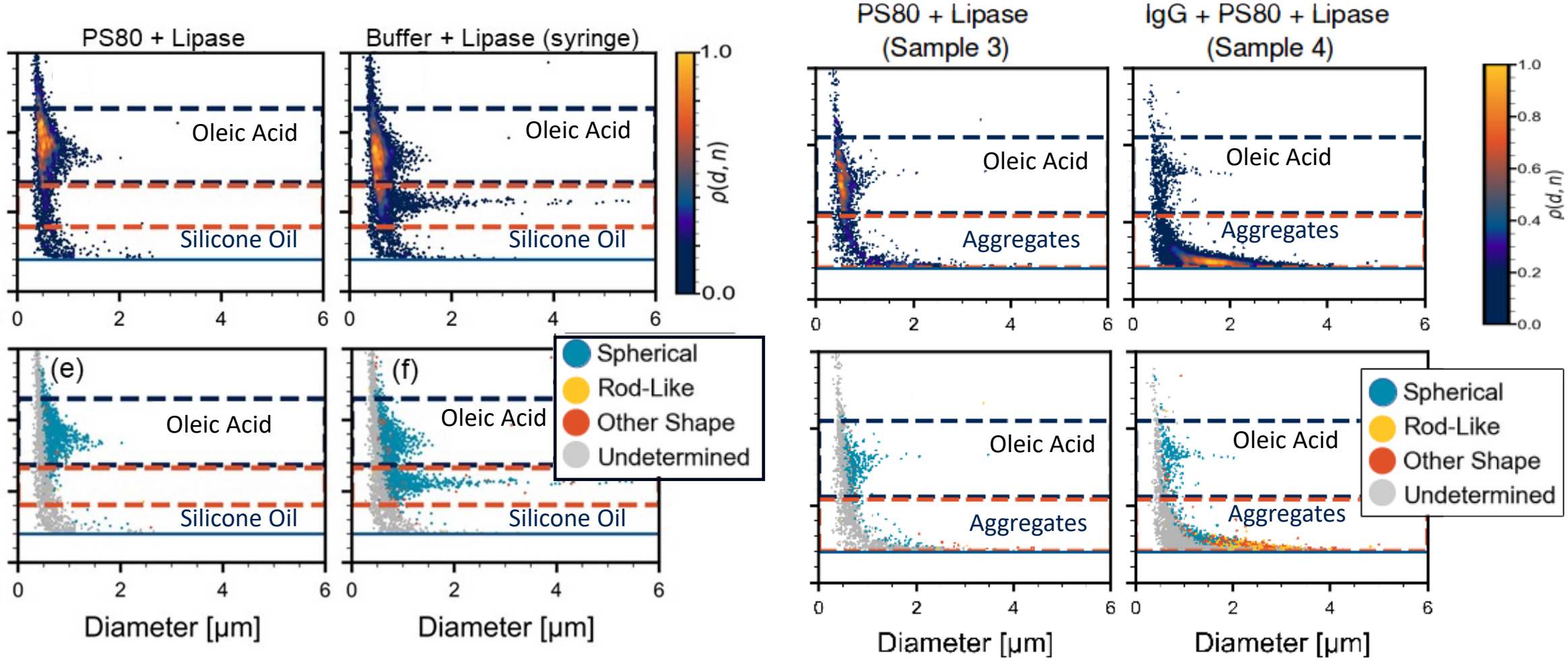


Concentration (Particle/mL x10⁴)

Sample	Protein	Oil	Total
Slow	35	2	38
Medium	40	6	47
Fast	60	63	130

Concentration of multiple species at the same time

Root Cause Analysis: Quantify and Identify Contaminants Even when they are the same size and shape



Example: PS80 degradation and silicone oil contamination

Contact

- Laura Philips, President, CEO and Founder

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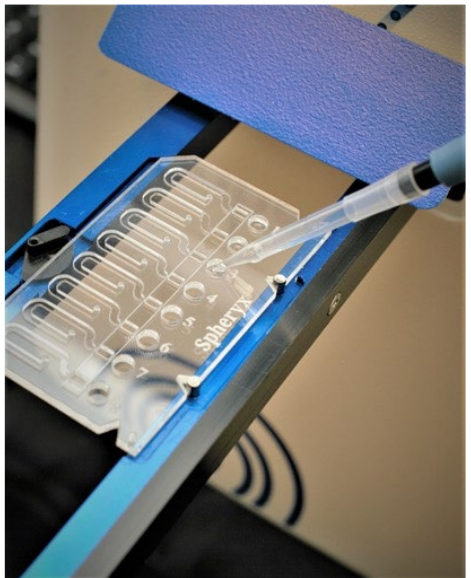
607-738-0100
www.spheryx.solutions



Spheryx

Using national health data to enhance real-world evidence on uptake and effectiveness of generic drugs

Katherine M. Harris, PhD
Principal Scientist
Carelon Research

May 21, 2024

Carelon Research is a healthcare company that works with life sciences companies, government agencies, academia, the Carelon family of companies, Elevance Health, and other healthcare stakeholders on a broad range of services in health economics & outcomes research, safety and epidemiology research, clinical research, and patient-centered research. Carelon Research is a member of FDA's Sentinel Initiative's Operations and Innovation Centers.

Introduction

- Carelon Research investigators recently submitted a response to FDA's FY2024 BAA for Advanced Research and Development of Regulatory Science.
- We proposed to develop and test a conceptual and empirical framework for using national health data to assess and enhance the representativeness of large, integrated healthcare claims databases for generating real-world evidence (RWE) on the incidence of breast, cervical, and colon cancer screening.
- Our proposal is highly relevant to FDA's interest in using RWE on the impact of generic drugs to promote public health.

Representativeness of RWD is fundamental to the credible use of RWE to promote public health[1]

- FDA defines real-world data (RWD) as “data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.”
- The size, scope, and reliability of RWD has grown over the past 20 years with evolution of cloud technology, intraoperatively standards, AI-driven anomaly detection, and capabilities of database management systems, to name a few.
- FDA guidance focuses on promoting the use of RWD from electronic medical health records and medical claims that is transparent, reliable, and relevant, but does not directly address representativeness as a feature of data quality.[2]

References: [1]Liu F, Panagiotakos D. Real-world data: a brief review of the methods, applications, challenges and opportunities. *BMC Med Res Methodol*. 2022;22(1):287. Published 2022 Nov 5. doi:10.1186/s12874-022-01768-6. [2]Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Oncology Center of Excellence. Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products. Draft Guidance for Industry. 2021.

Our BAA submission aims to promote development of methods for assessing representativeness of RWD and enhancing it when lacking

We proposed to achieve these aims using simple, well-established methods implemented in three phases.

Phase 1: Calculate cancer screening rates for analogously defined subgroups based on age and gender using CDC's Behavioral Risk Factor Surveillance System (BRFSS) and Carelon Research's Healthcare Integrated Research Database (HIRD®).

Phase 2: After confirming the statistical reliability subgroup-level, compare their similarity using standardized mean differences, a comparison method used in meta-analyses and to match treatment and comparison groups in the absence of randomization.

Phase 3: Use iterative proportional fitting (or "raking") methods to identify factors contributing to the variance from national benchmarks and re-weight claims data to align with BRFSS benchmarks, as appropriate.

Reference: HIRD technical white paper, 2023, https://lp.carelonresearch.com/rs/621-UKX-708/images/Carelon-Research-HIRD-technical-white-paper-fv.pdf

RWD on generic drugs substitution and effectiveness: The real-world is complicated

Accurate capture of generic drug status	• Generic status or manufacturer of dispensed medications not readily discernable from medical records.
Multi-level effects on generic drug substitution	• Variable state policies in terms of degree of pharmacist discretion, patient notification, patient consent, pharmacist liability.
	• Variable inventories of generic drugs may affect substitutions at the point of sale.
	• Pharmacy benefit design affects relative costs of brand and generic medications and may be affected by deductibles and out-of-pocket maximums.
	• Value-based agreements may limit prescribers use of dispense as written orders.
Missing data on generic drug use	• Out-of-pocket purchases of generic drugs that are not documented in pharmacy billing data.

The FDA context: representative RWD can promote confidence in RWE on generic drug impacts on public health

- The Sentinel Initiative and its health plan and provider partners integrate medical data on safety outcomes and pharmacy data documenting use of generic drugs across the United States.
- Currently, the representativeness of these data is largely uncertain.
- Understanding the representativeness of fit-for-purpose RWD can promote public health by informing and promoting the generalizability of RWE on generic drug safety and effectiveness.

Reference: FDA's Sentinel Initiative, 2023.https://www.fda.gov/safety/fdas-sentinel-initiative

Carelon Research, Inc. appreciates the opportunity to provide public comment on the FDA's science and research priorities related to real-world evidence for post-market surveillance of generic drug substitution and evaluating the impact of generic drugs on public health.


carelon
SM

Enabling Strategic Chemical Supply Chain Resiliency for Pharmaceutical Manufacturing through Seamless Digital Technologies

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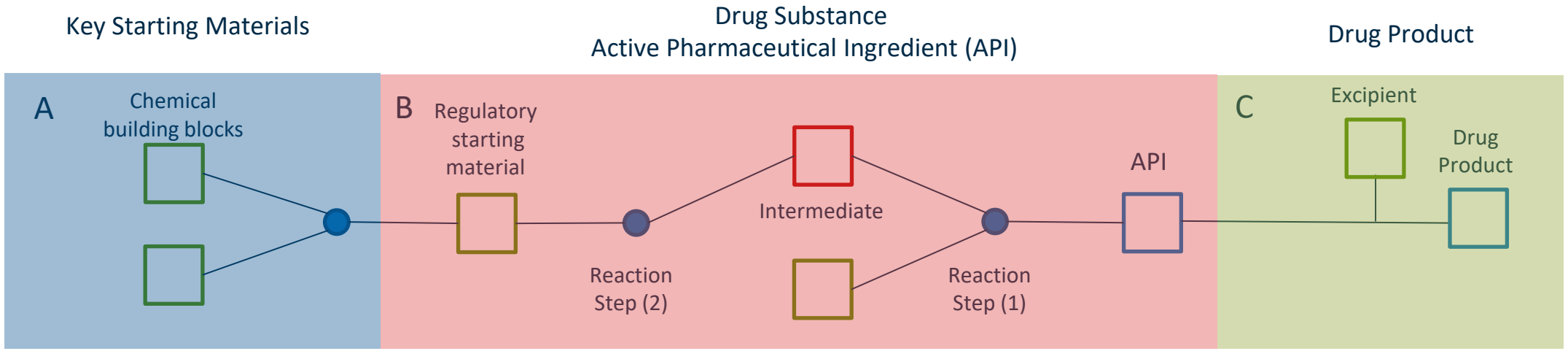
Department of Chemical and Life Science Engineering
College of Engineering
Virginia Commonwealth University

May 21, 2024

Pharmaceutical Manufacturing and the Drug Supply



Key Starting Materials (KSM):

Many synthetic routes to same API with different KSM possible

Chemical process development and engineering required

Drug Substance (API):

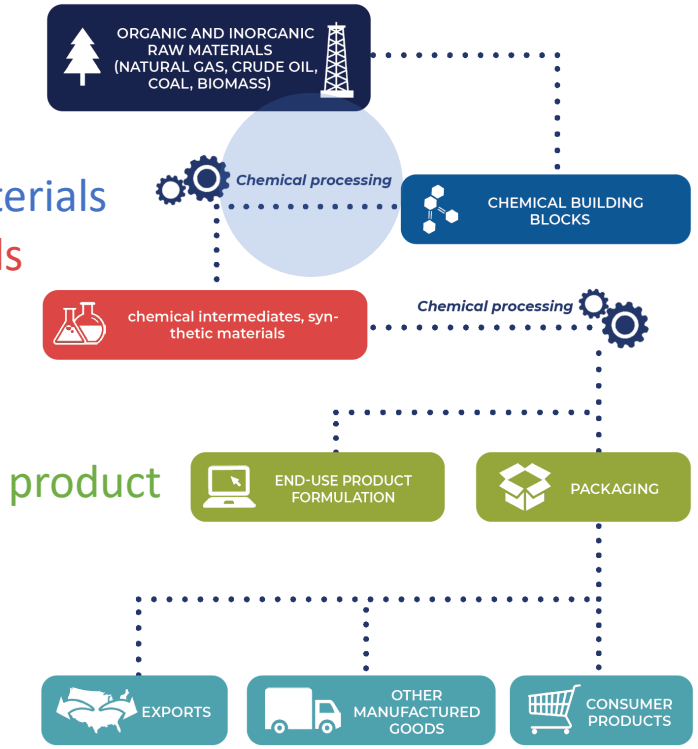
Transformation sequence from raw materials to target is synthetic route

Manufacturing relies on raw materials (resources), reaction (transformation), and the facilities (capital assets)

Process development focuses on transformation sequence; process engineering on facilities and capital assets

Chemical Manufacturing and the United States

Chemical manufacturing:
From raw materials to consumer products



Key Starting Materials
Regulatory Starting Materials
Drug Substance
Excipients

Drug product

Consumer products

The US is:

a net exporter chemical building blocks

depends on **China** for intermediates / drug substance

Figure 4.1 - Basic Chemicals Shipments, 2021

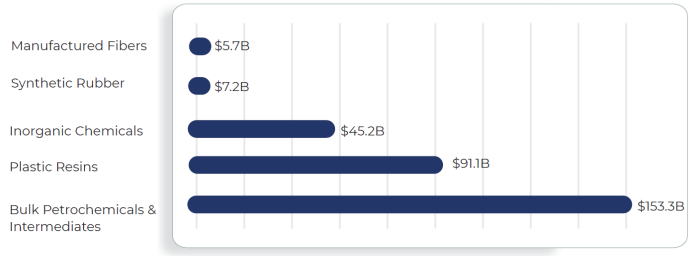


Table 5.2 - Top Chemicals Import Countries of Origin, 2017-2021

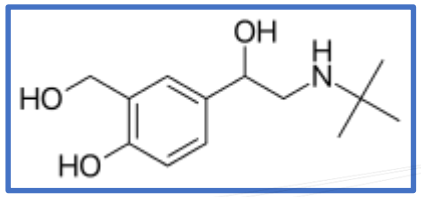
	2017	2018	2019	2020	2021
			in $millions		
Canada	17,992	19,465	18,074	16,520	23,245
China	12,910	15,801	11,488	11,535	14,626
Germany	7,698	8,253	8,086	7,730	9,333
Japan	6,002	6,728	7,093	6,320	7,242
Ireland	3,902	4,839	5,530	6,692	6,884
Mexico	4,917	5,389	5,340	5,421	6,527
France	4,492	4,683	4,601	4,377	5,548
South Korea	3,312	3,828	3,699	3,679	5,514
Switzerland	3,820	4,357	4,077	4,008	4,790
India	3,026	3,392	3,732	3,525	4,761

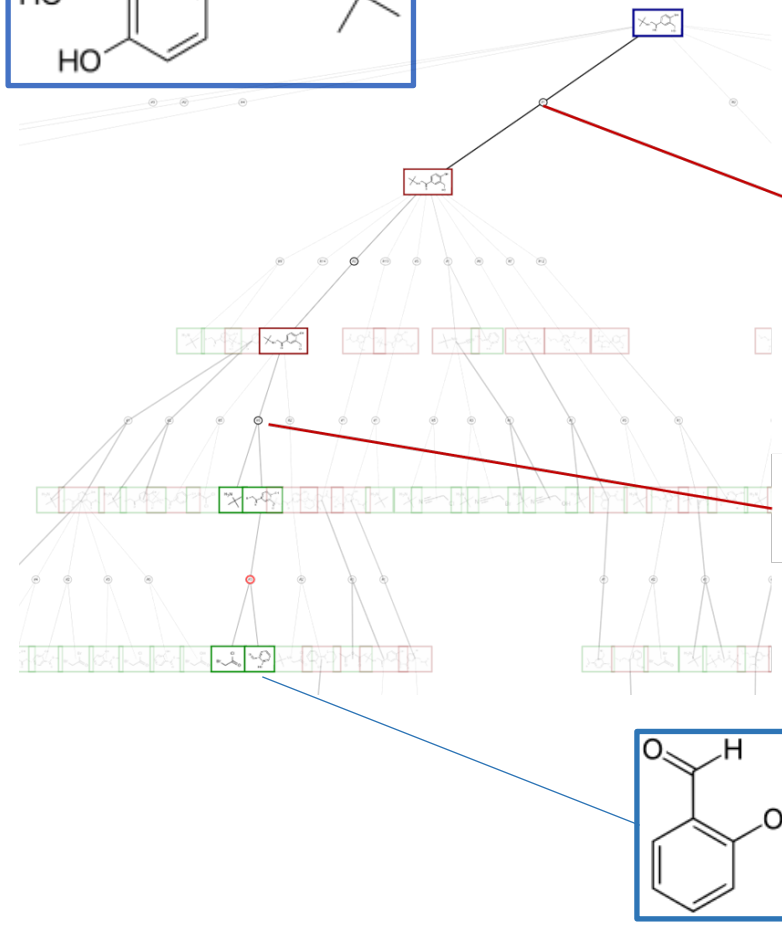
Note. In descending order based on 2021 imports.

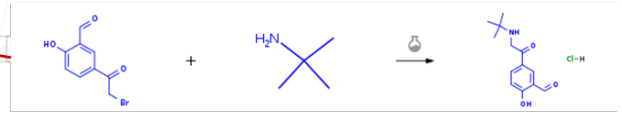
2022 Guide to the Business of Chemistry

Retrosynthetic Analysis: API to Regulatory Starting Material Source

Example: Albuterol
(FDA Current Shortage, November 2022)







Regulatory starting material

Regulatory starting materials in API manufacturing: Sourced in China

Port of Loading
SHANGHAI

Origin Country
China

US Imports

Date	HTS Code	Description	Port of Loading	Port of Discharge
Oct 06 2022		SALICYLALDEHYDE	SHANGHAI	NEW YORK/NEWARK AREA, NEWARK, NJ
Jun 07 2022	270600	9000 KILOGRAMS OF SALICYLALDEHYDE (DISTILLED)		TACOMA, WA
Apr 14 2022	900130	SALICYLALDEHYDE FAX 86-21-3251-5502 WI 53085-2814 USA TEL 314-236-3175 CONTACT PERS	SHANGHAI	LOS ANGELES, CA
Jan 19 2022		SALICYLALDEHYDE	SHANGHAI	NEW YORK/NEWARK AREA, NEWARK, NJ
May 28 2021		SALICYLALDEHYDE		NEW YORK/NEWARK AREA, NEWARK, NJ
Apr 27 2021		SALICYLALDEHYDE	SHANGHAI	NEW YORK/NEWARK AREA, NEWARK, NJ
Dec 09 2020	291249	SALICYLALDEHYDE CHEMICALS N.O.I. HTS#: 2912.49.2600 24 HOUR EMERGENCY CONTACT: THE ERI PROVIDER IS CHEM-TREC CCN: 213 DOMESTIC: 1-800-424-9300 INTERNA...	SHANGHAI	NEW YORK/NEWARK AREA, NEWARK, NJ
Dec 07 2020		SALICYLALDEHYDE	SHANGHAI	NEW YORK/NEWARK AREA, NEWARK, NJ
Oct 17 2020	290930	SALICYLALDEHYDE P CRESYL METHYL ETHER	SHANGHAI	NEW YORK/NEWARK AREA, NEWARK, NJ

India Imports

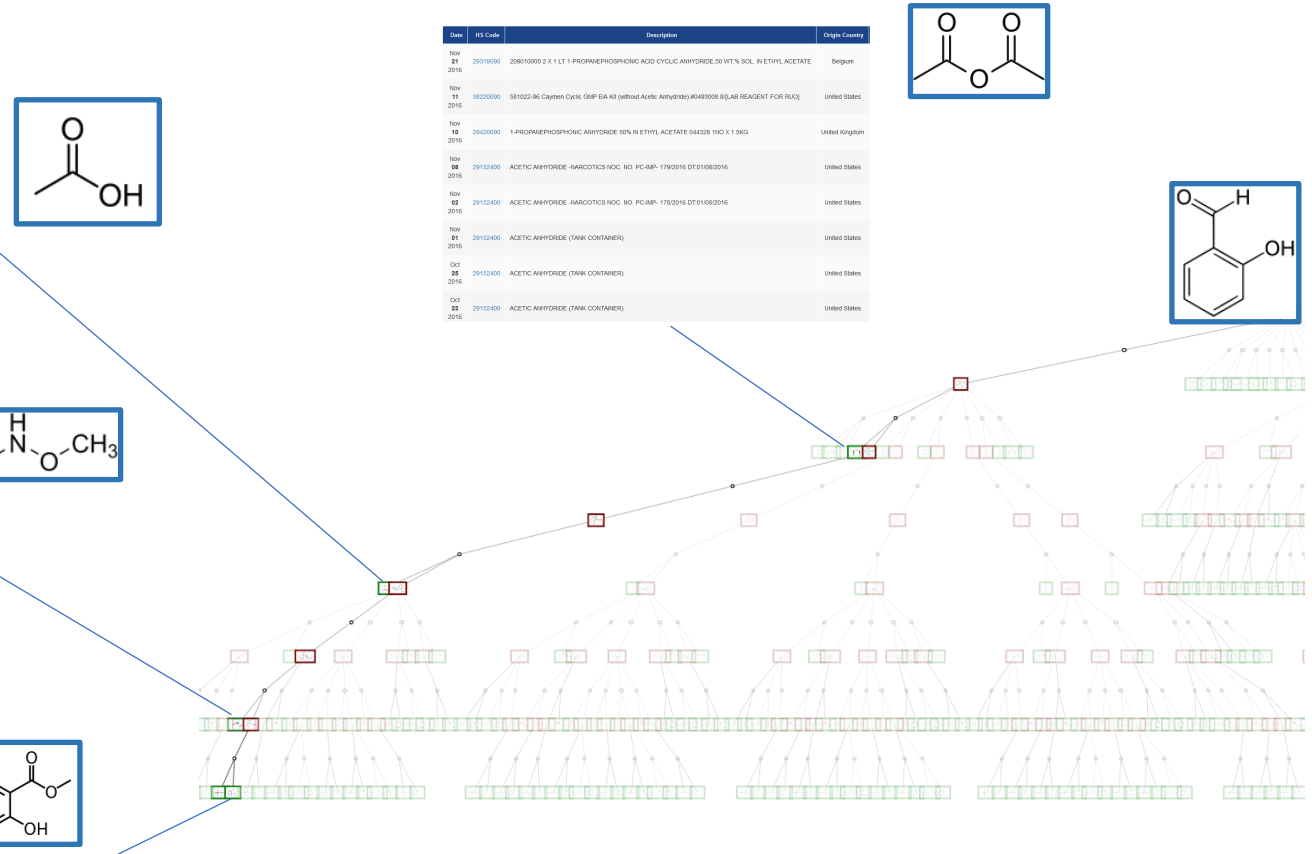
Date	HS Code	Description	Origin Country	Port of Discharge
Nov 11 2016	29121990	S356-100G SALICYLALDEHYDE 98% [ORGANIC CHEMICAL]	China	Banglore Air Cargo
Nov 08 2016	29124999	SALICYLALDEHYDE	China	Nhava Sheva Sea
Oct 29 2016	29124999	SALICYLALDEHYDE	China	Nhava Sheva Sea

Retrosynthetic Analysis: Chemical Building Blocks Source

Date	HS Code	Description	Origin Country
Nov 22 2016	29339900	S1318-5MG STO-609 ACETIC ACID [ORGANIC CHEMICAL]	United States

Date	HS Code	Description	Origin Country
Oct 25 2016	29319090	N,O-DIMETHYLHYDROXYLAMINE HYDROCHLORIDE(NOT RESTRICTED/ PROHIBITED)(LAB RESEARCH CHEMICAL)	United States
Oct 18 2016	29333990	N,O-Dimethylhydroxylamine, HCl [6638-79-5] 98%, 100g (1 Num) (Lab Chemical)	United States
Aug 12 2016	29280090	A17469.06 1 X 5g N,O-Dimethylhydroxylamine hydrochloride, 98%	United Kingdom
Jul 22 2016	29280090	A17469.06 1 X 5g N,O-Dimethylhydroxylamine hydrochloride, 98%	United Kingdom

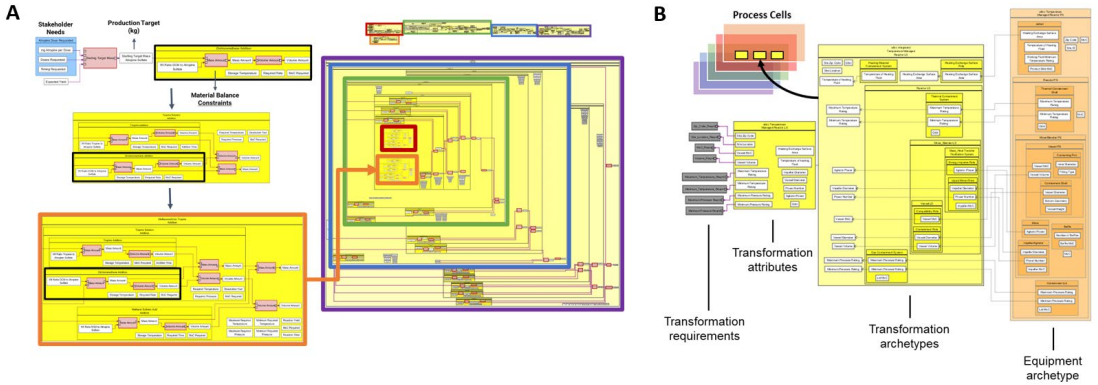
Date	HS Code	Description	Origin Country
Nov 08 2016	38220090	USP-1437450_METHYL SALICYLATE - 2 ML) - (PHARMACEUTICAL REFERENCE STANDARDS)	United States
Nov 08 2016	38220090	USP-1437461_METHYL SALICYLATE RELATED COMPOUND A - 50 MG) - (PHARMACEUTICAL REFERENCE STANDARDS)	United States
Nov 08 2016	29182990	M6752-250ML METHYL SALICYLATE TM 99% [ORGANIC CHEMICAL]	United States

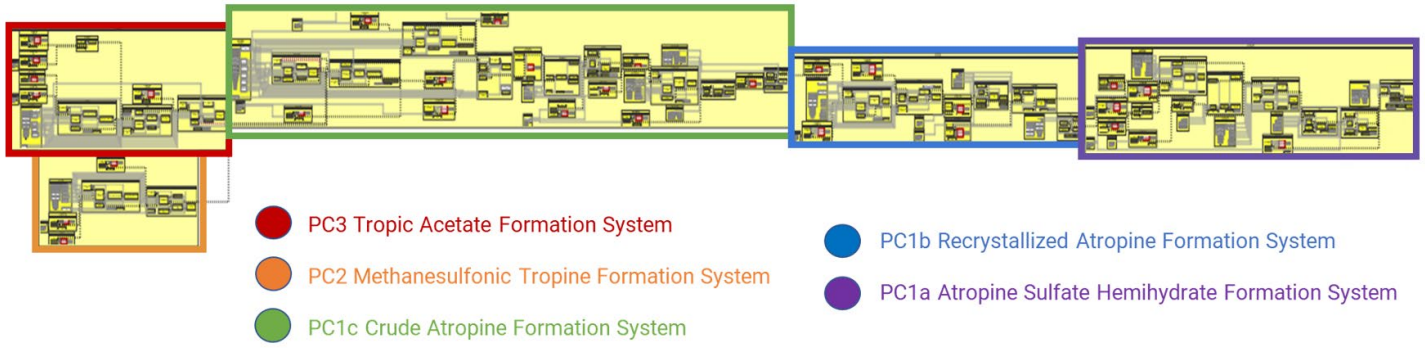


Seamless Digital Thread Technologies for Managing Manufacturing Requirements

Model Based Systems Engineering enables:

- Process development
- Recipe management





Manufacturing Systems Models can:

- Supply chain design
- Digital technology transfer

Process Development Alternatives via Digital Thread

Considerations

- Starting material (provenance)
- Manufacturability
- Environmental impact
- Cost (Starting material, manufacturing)
- Total Score
- Process alternatives




Target	SM	Mfg	ESG	Cost	Score
AAA	8.6	3.1	8.2	3.8	6.2
BBB	4.0	1.9	3.7	8.5	2.9
CCC	2.3	5.2	6.2	4.3	2.3
DDD	6.1	7.8	2.8	5.9	6.7

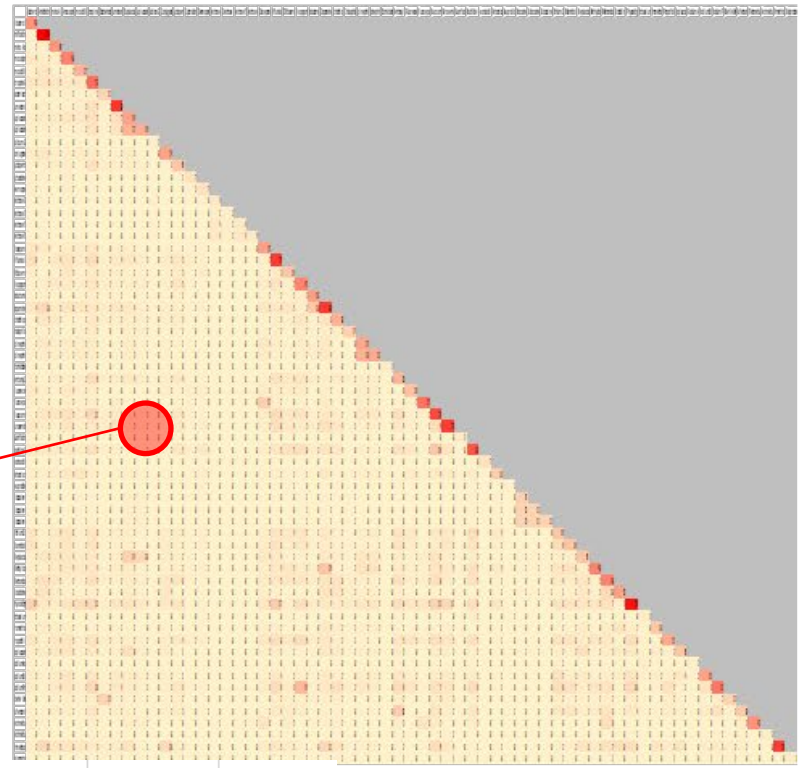
Pharmaceutical Supply and Portfolio Level Decisioning

Pick r = 2
(n = 63, nCr = 1,953) $\frac{n!}{r!(n-r)!}$

Current and Resolved Drug Shortages and Discontinuations Reported to FDA

U.S. FOOD & DRUG ADMINISTRATION

Drug	Status	Canonical SMILES
Albuterol Sulfate Inhalational Solution	Currently in Shortage	CC(C)(C)NCC(O)c1ccc(O)c(CO)c1.CC(C)(C)NCC(O)c1ccc(O)c(CO)c1.O=S(=O)(O)O
Alprostadil (Muse) Suppository	Currently in Shortage	CCCCC[C@H](O)/C=C/[C@H]1[C@H](O)CC(=O)[C@@H]1CCCCCCC(=O)O
Amifostine Injection	Currently in Shortage	NCCCNCCSP(=O)(O)O
Amino Acids / LEUCINE	Currently in Shortage	CC(C)C[C@H](N)C(=O)O
Amoxapine Tablets	Currently in Shortage	Clc1ccc2c(c1)C(N1CCNCC1)=Nc1ccccc1O2
Amoxicillin Oral Powder for Suspension	Currently in Shortage	CC1(C)S[C@@H]2[C@H](NC(=O)[C@H](N)c3ccc(O)cc3)C(=O)N2[C@H]1C(=O)O.O.O.O
Amphetamine Aspartate; Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate Tablet5	Currently in Shortage	CC(N)Cc1ccccc1
Atropine Sulfate Injection	Currently in Shortage	CN1C2CCC1CC(OC(=O)C(CO)c1ccccc1)C2
Azacitidine for Injection	Currently in Shortage	Nc1ncn([C@@H]2O[C@H](CO)[C@@H](O)[C@H]2O)c(=O)n1
Azithromycin (Azasite) Ophthalmic Solution 1%	Currently in Shortage	CC[C@H]1OC(=O)[C@H](C)[C@@H](O[C@H]2C[C@@](C)(OC)[C@@H](O)[C@H](C)O2)[C@](C)(O)C[C@@H](C)[C@H]1N(C)C
Bacteriostatic 0.9% Sodium Chloride Injection	Currently in Shortage	[Na+].[Cl-]
Bacteriostatic Water for Injection	Currently in Shortage	O
Belatacept (Nulojix) Lyophilized Powder for Injection	Currently in Shortage	No Structure Fouind
Belladonna and Opium Suppositories	Currently in Shortage	No Structure Fouind
Bumetanide Injection	Currently in Shortage	CCCCNc1cc(C(=O)O)cc(S(N)(=O)=O)c1Oc1ccccc1
Bupivacaine Hydrochloride and Epinephrine Injection	Currently in Shortage	CCCCN1CCCCC1C(=O)Nc1c(C)cccc1C.[Cl-].[H+]
Bupivacaine Hydrochloride Injection	Currently in Shortage	CCCCN1CCCCC1C(=O)Nc1c(C)cccc1C.[Cl-].[H+]
Calcium Disodium Versenate Injection	Currently in Shortage	[CaH2].[Na].[Na]
Calcium Gluconate Injection	Currently in Shortage	O=C([O-])[C@H](O)[C@@H](O)[C@H](O)[C@H](O)CO.O=C([O-])[C@H](O)[C@@H](O)[C@H](O)[C@H](O)CO.[Ca+2]
Cefazolin Injection	Currently in Shortage	Cc1nnc(SCC2=C(C(=O)O-])N3C(=O)[C@@H](NC(=O)Cn4cnnn4)[C@H]3SC2)s1.[Na+]
Cefixime Oral Capsules	Currently in Shortage	C=CC1=C(C(=O)O)N2C(=O)[C@@H](NC(=O)/C(=N\OCC(=O)O)c3csc(N)n3)[C@H]2SC1
Cefotaxime Sodium Injection	Currently in Shortage	CO/N=C(\C(=O)N[C@@H]1C(=O)N2C(C(=O)[O-])=C(COC(C)=O)CS[C@H]12)c1csc(N)n1.[Na+]
Cefotetan Disodium Injection	Currently in Shortage	CO[C@@]1(NC(=O)C2SC(=C(C(N)=O)C(=O)[O-])S2)C(=O)N2C(C(=O)[O-])=C(CSc3nnnn3C)CS[C@@H]21.[Na+].[Na+]
Chloroprocaine Hydrochloride Injection	Currently in Shortage	CC[NH+](CC)CCOC(=O)c1ccc(N)cc1Cl.[Cl-]
Conivaptan Hydrochloride (Vaprisol) in 5% Dextrose Plastic Container	Currently in Shortage	Cc1nc2c([nH]1)CCN(C(=O)c1ccc(NC(=O)c3ccccc3-c3ccccc3)cc1)c1ccccc1-2.[Cl-].[H+]
Conjugated Estrogens/Bazedoxifene (DUAVEE) Tablet, Film Coated / Bazedoxifene	Currently in Shortage	Cc1c(-c2ccc(O)cc2)n(Cc2ccc(OCCN3CCCCCC3)cc2)c2ccc(O)cc12
Cyclopentolate Ophthalmic Solution	Currently in Shortage	CN(C)CCOC(=O)C(c1ccccc1)C1(O)CCCC1
Cytarabine Injection	Currently in Shortage	Nc1ccn([C@@H]2O[C@H](CO)[C@@H](O)[C@@H]2O)c(=O)n1
Dacarbazine Injection	Currently in Shortage	CN(C)N/N=C1/N=CN=C1C(N)=O
Desmopressin Acetate Nasal Spray	Currently in Shortage	CC(=O)O.NC(=O)CCC1NC(=O)C(Cc2ccccc2)NC(=O)C(Cc2ccc(O)cc2)NC(=O)CC5SCC(C(=O)N2CCCC2C(=O)NC(CCCN=C(N)N)C(=O)N
Dexamethasone Sodium Phosphate Injection	Currently in Shortage	C[C@@H]1C[C@H]2[C@@H]3CCC4=CC(=O)C=C[C@]4(C)[C@@]3(F)[C@@H](O)C[C@]2(C)[C@@]1(O)C(=O)CO
Dexmedetomidine Injection	Currently in Shortage	Cc1ccccc[C@H](C)c2cnc[nH]2)c1C
Dextrose 10% Injection	Currently in Shortage	O=C[C@H](O)[C@@H](O)[C@H](O)[C@H](O)CO
Dextrose 25% Injection	Currently in Shortage	O=C[C@H](O)[C@@H](O)[C@H](O)[C@H](O)CO
Dextrose 5% Injection	Currently in Shortage	O=C[C@H](O)[C@@H](O)[C@H](O)[C@H](O)CO
Dextrose 50% Injection	Currently in Shortage	O=C[C@H](O)[C@@H](O)[C@H](O)[C@H](O)CO
Diazepam Rectal Gel	Currently in Shortage	CN1C(=O)CN=C(c2ccccc2)c2cc(Cl)ccc21



Drug	Status	Canonical SMILES
Albuterol Sulfate Inhalational Solution	Currently in Shortage	CC(C)(C)NCC(O)c1ccc(O)c(CO)c1.CC(C)(C)NCC(O)c1ccc(O)c(CO)c1.O=S(=O)(O)O
Mannitol Injection	Currently in Shortage	OC[C@@H](O)[C@@H](O)[C@H](O)[C@H](O)CO

We have done r = 2, ..., 6
nCr [o] 10^7

Discussion is welcome

James K. Ferri

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james@occamsystems.com

Public Comments for Session 3

In Person Comments:

- Alexander Shekhtman, PhD, Professor and Chair, Department of Chemistry, University at Albany, State University of New York
- Marco Guerrini, MS Director Istituto di Ricerche Chimiche e Biochimiche
- Jace Jones, PhD Assistant Professor University of Maryland
- Andrew Graves, MS, SCYM Director, Immunogenicity Assessment Teva
- David Borhani Senior Director, Business Development Ginkgo Bioworks
- Ravishankara MN, PhD Senior General Manager (R & D) Sun Pharma
- Marina Juretić, PhD Senior Analytical Scientist, R&D, IVR/IVIVC PLIVA Hrvatska
- Itay Speicher, BSc, MBA Sr. Director of Business Development DigiM Solution
- Jon Lenn, PhD Chief Scientific Officer MedPharm
- Marc Taraban, PhD Associate Research Professor University of Maryland Baltimore
- Grzegorz Garbacz, PhD Co-Founder & CEO Physiolution Polska
- Laura Philips, PhD President & CEO Spheryx, Inc
- Katherine M. Harris, PhD Principal Scientist Carelon Research
- James K. Ferri, PhD Professor Virginia Commonwealth University

Virtual Comments:

- Conor L. Evans, PhD Associate Professor Harvard Medical School
- Matthias Wacker, PhD Associate Professor National University of Singapore
- Tao Zhang, PhD Assistant Professor, Pharmaceutical Sciences SUNY Binghamton University
- Hannah Batchelor Professor University of Strathclyde
- Jozef Al-Gousous, PhD Adjunct Assistant Professor University of Michigan
- Panos Macheras, PhD Professor Emeritus National and Kapodistrian University of Athens
- Hala Fadda, PhD Professor of Pharmaceutics Butler College
- ***Kathleen Walsh, MSc, MD Director, Patient Safety Research Center Boston Children's Hospital, Harvard University***
- ***Alexa Simon Meara, MD Associate Professor The Ohio State University Wexner Medical Center***
- ***Jacqueline Griffin Associate Professor Northeastern University***
- ***Molly Moore Jeffery, PhD Robert D. and Patricia E. Kern Honored Investigator in the Science of Health Care Delivery | Scientific Director of Emergency Medicine Research and Platform Knowledge Solutions | Associate Professor Emergency Medicine Mayo Clinic - No slides available, only video***
- ***Ozlem Ergun, PhD; Daniel Kosmas, PhD Professor Northeastern University***
- ***Fang Yu, PhD Computational Modeling Scientist CONTINUUS Pharmaceuticals, Inc. – No Slides Available, only video***
- ***Dongmei Li, PhD Professor, Clinical and Translational Research, Obstetrics and Gynecology and Public Health Sciences University of Rochester School of Medicine and Dentistry***
- ***James Hasty CEO/Founder BHEC***
- ***Peter Gompper Co-Founder, Rubitel***

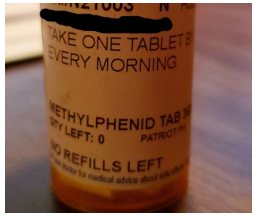
Measuring the Safe Use of Generic Pediatric Medications at Home

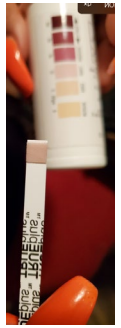
Kathleen E. Walsh, M.D., M.S.

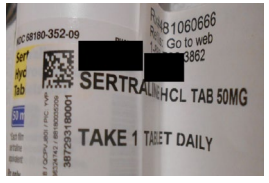
Director, Patient Safety Research Program
Director, Harvard-wide Pediatric Health Services Research Fellowship
Division of General Pediatrics
Boston Children's Hospital

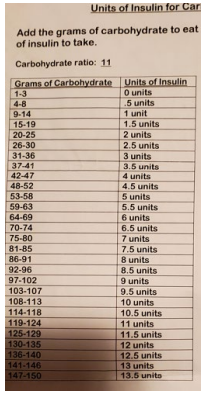
Clinical case

- An 8 year old with type 1 diabetes, depression, and ADHD takes insulin , methyphenidate, sertraline, glucagon, acetaminophen and needs to check glucose, correct for carbohydrates, log data
- After school, if her mother is working, her 12 year old sibling helps her check her carbohydrates and administer her insulin
- During our home visit, her mother dialed the correct insulin dose on the pen, however, pulled the pen out immediately after administration of dose causing insulin to squirt out









Capturing the complexity of pediatric medication use at home

Obtain diagnoses and medication list from medical record

↓

Home Visit:
Direct Observation
Medication review
Parent Interview

Chart review

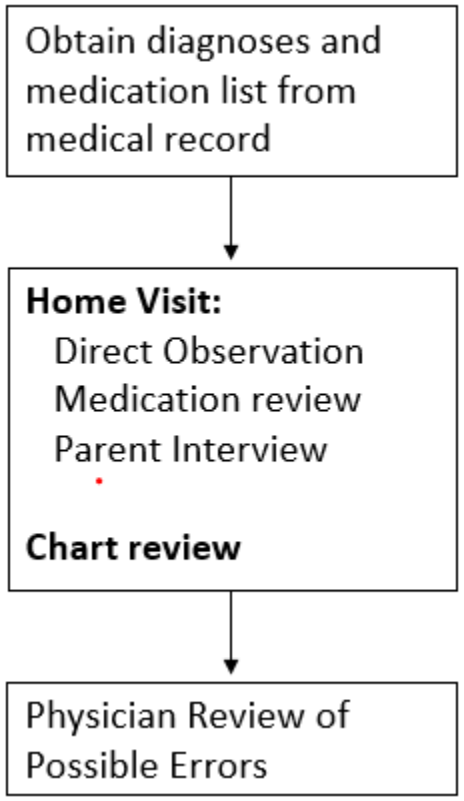
↓

Physician Review of Possible Errors

Interobserver reliability k = 0.72 (95% CI: 0.4-1)
Interrater reliability for error K = 0.94 (95%CI 0.87-1.0)
for severity K= 0.71 (95%CI:0.54-0.88).

Walsh et al. Voll. 4. Technology and Medication Safety: Agency for Healthcare Research and Quality, August 2008

Capturing the complexity of pediatric medication use at home



Interobserver reliability k = 0.72 (95% CI: 0.4-1)
Interrater reliability for error K = 0.94 (95%CI 0.87-1.0)
for severity K= 0.71 (95%CI:0.54-0.88).

Results of 545 home visits

- Errors are common and dangerous
  - E.g. 10% children with cancer injured by outpatient medication errors over 6 months
- Home administration errors were most frequent cause of injury in every study
- Drug-device combinations can be especially challenging

Wong Cl. *Cancer.* 2023;129(7):1064-1074.
Kirkendall ES. *Pediatric quality &safety.* 2023;8(3):e649.
Walsh et al. Voll. 4. Technology and Medication Safety: Agency for Healthcare Research and Quality, August 2008.
Walsh KE. *Pediatrics.* 2013;131(5):e1405-14.
Walsh KE. *Arch Dis Child.* 2011;96(6):581-6.
Walsh KE. *J Oncol Pract.* 2014;10(6):373-6.

What is needed to improve safety of medication use at home?

- Errors at home can be prevented by interventions in the clinic or pharmacy but widespread use limited by lack of measure

Schumacher PM, *Epilepsy and Behavior* 2018;84:37-43.
McMahon SR. *Pediatrics*. 1997;100(3):330-333.
Yin HS. *Acad Pediatr*. 2014;14(3):262-70.
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Hixson R. *Paediatric anaesthesia*. 2010;20(7):612-619.
Yin HS. *Arch Pediatr Adolesc Med*. 2008;162(9):814-822
Yin HS et al. *Academic Pediatrics*. 2011;11(1):50-57.

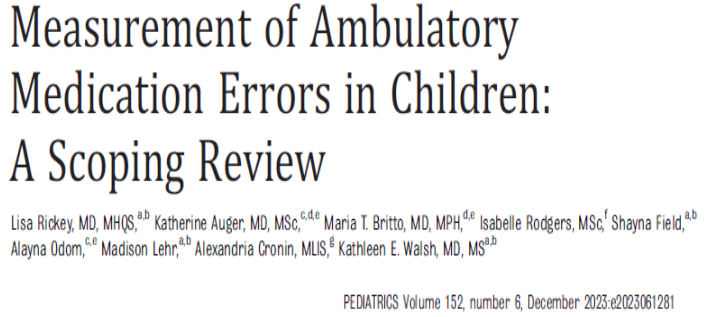
Institute for Healthcare Improvement NPSF
TOGETHER FOR SAFER CARE

No Place Like Home: Advancing the Safety of Care in the Home

Report of an Expert Panel Convened by the Institute for Healthcare Improvement

What is needed to improve safety of medication use at home?

- Errors at home can be prevented by interventions in the clinic or pharmacy but widespread use limited by lack of measure
- FDA funded scoping review: No scalable measures of medication administration errors exist


Measurement of Ambulatory Medication Errors in Children: A Scoping Review

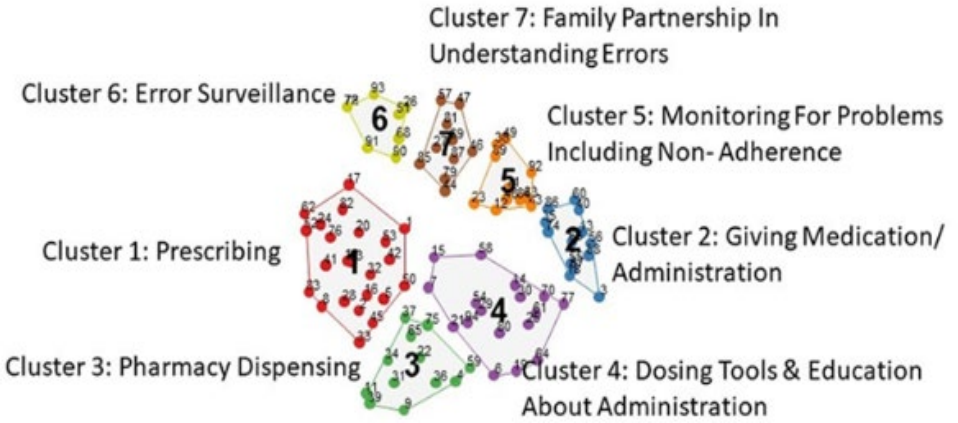
Lisa Rickey, MD, MHQS,[a,b] Katherine Auger, MD, MSc,[c,d,e] Maria T. Britto, MD, MPH,[d,e] Isabelle Rodgers, MSc,[f] Shayna Field,[a,b] Alayna Odom,[c,e] Madison Lehr,[a,b] Alexandria Cronin, MLIS,[g] Kathleen E. Walsh, MD, MS[a,b]

PEDIATRICS Volume 152, number 6, December 2023:e2023061281

FDA Contract 74F40120C00126

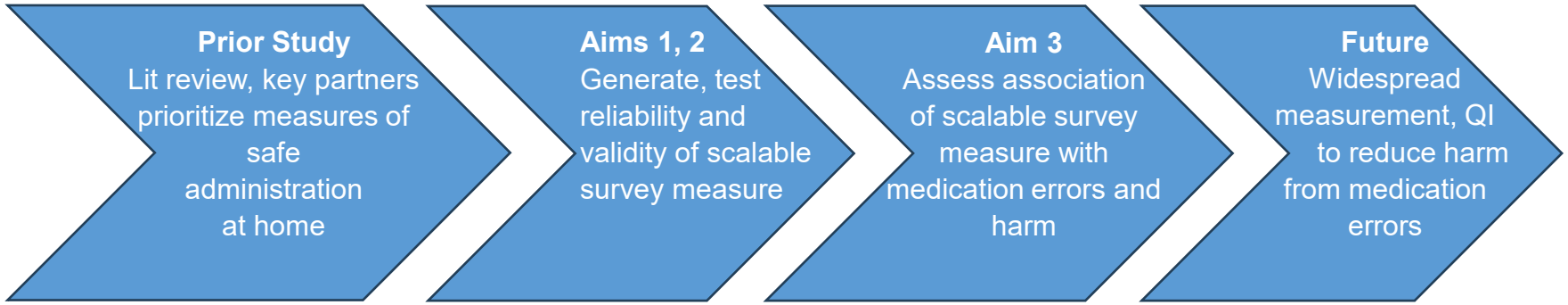
What is needed to improve safety of medication use at home?

- Errors at home can be prevented by interventions in the clinic or pharmacy but widespread use limited by lack of measure
- FDA funded scoping review: No scalable measures of medication administration errors exist
- FDA funded interviews and concept mapping: measures of safe use at home the top priority

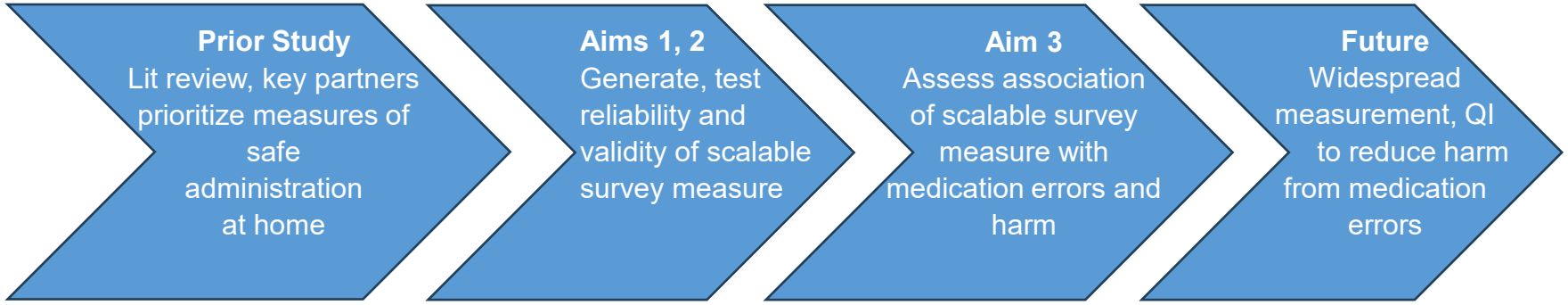


FDA Contract 74F40120C00126

Develop scalable measures of safe pediatric use at home



Develop scalable measures of safe pediatric use at home



- Immediately available to health systems, pharmacists, others seeking to improve safe outpatient use in children
- Study team pharmacist and physician leaders well positioned to implement this measure regionally, locally, and nationally to maximize the impact
- Advances FDA goal to “evaluate and increase the safety of post approval drug use” as part of FDAs post marketing surveillance program
- Aligns with FDA’s vision to eliminate medication errors in the U.S. healthcare system

Thank you

- Pediatric medication use at home is complex, error prone. Use of drug-device combination products increase that complexity
- Parents, clinicians, and organizational leaders need scalable measures of safe medication use at home
- Building on 25 years of experience measuring safe use at home, we are well positioned to develop and implement such measures

Kathleen.walsh2@childrens.harvard.edu

FDA: TOPIC #8
REAL WORLD EVIDENCE

ALEXA SIMON MEARA, MD

ASSOCIATE PROFESSOR

THE OHIO STATE UNIVERSITY

Problems with RWE

- Facts on real world evidence:
  - It is dependent on ICD9/10 codes
  - ICD9/10 codes are how drugs are coded for billing and insurance for drug access
  - Availability of drugs has drastically declined due to barriers raised by PBMs and insurance companies
  - Heath care team “work-around” to care for patients- change ICD9/10 codes to match needs of insurance companies to allow the drugs to be accessible
  - Therefore ICD9/10 coding system is inaccurate to use for RWE
- RWE data is dependent on chart review:
    - Who will pay for chart review on large scale?

RWE and AI Algorithms

- Facts on AI
  - The best AI algorithm is dependent on the validation cohorts
  - The larger the validation cohort the more reliable to the algorithm
  - Validation cohorts on large scale requires a chart reviews
  - Chart review require time and money
- Who is to pay for this infrastructure?
  - How do we know the power required for the validation?
  - How do we ensure there is a diverse enough population?

RWE and Large Populations

- RWE requires individual data to be combined
- Academic centers have such significant bureaucratic legal issues preventing data sharing due to potential for data breach as perceived risk?

- How do we develop cohorts of large data to answer important clinical RWE questions?
  - Who should provide guidelines?
  - Where should this data be held?

GDUFA PUBLIC WORKSHOP PROPOSED RESEARCH FOCUS

BY JACQUELINE GRIFFIN, PHD
NORTHEASTERN UNIVERSITY

GDUFA PRIORITY INITIATIVES

8A. 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**

GDUFA PRIORITY INITIATIVES

A CRITICAL ROLE OF GENERIC DRUGS IS TO INCREASE PATIENT ACCESS TO MEDICATION WHILE ALSO REDUCING PATIENT COSTS

A CRITICAL ROLE OF GENERIC DRUGS IS TO INCREASE PATIENT ACCESS TO MEDICATION WHILE ALSO REDUCING PATIENT COSTS

IN ADDRESSING THIS ROLE, A KEY COMPONENT TO ASSESSING THE IMPACT ON PUBLIC HEALTH IS TO ALSO FOCUS SURVEILLANCE ON DRUG SHORTAGE TRENDS AMONG GENERICS.

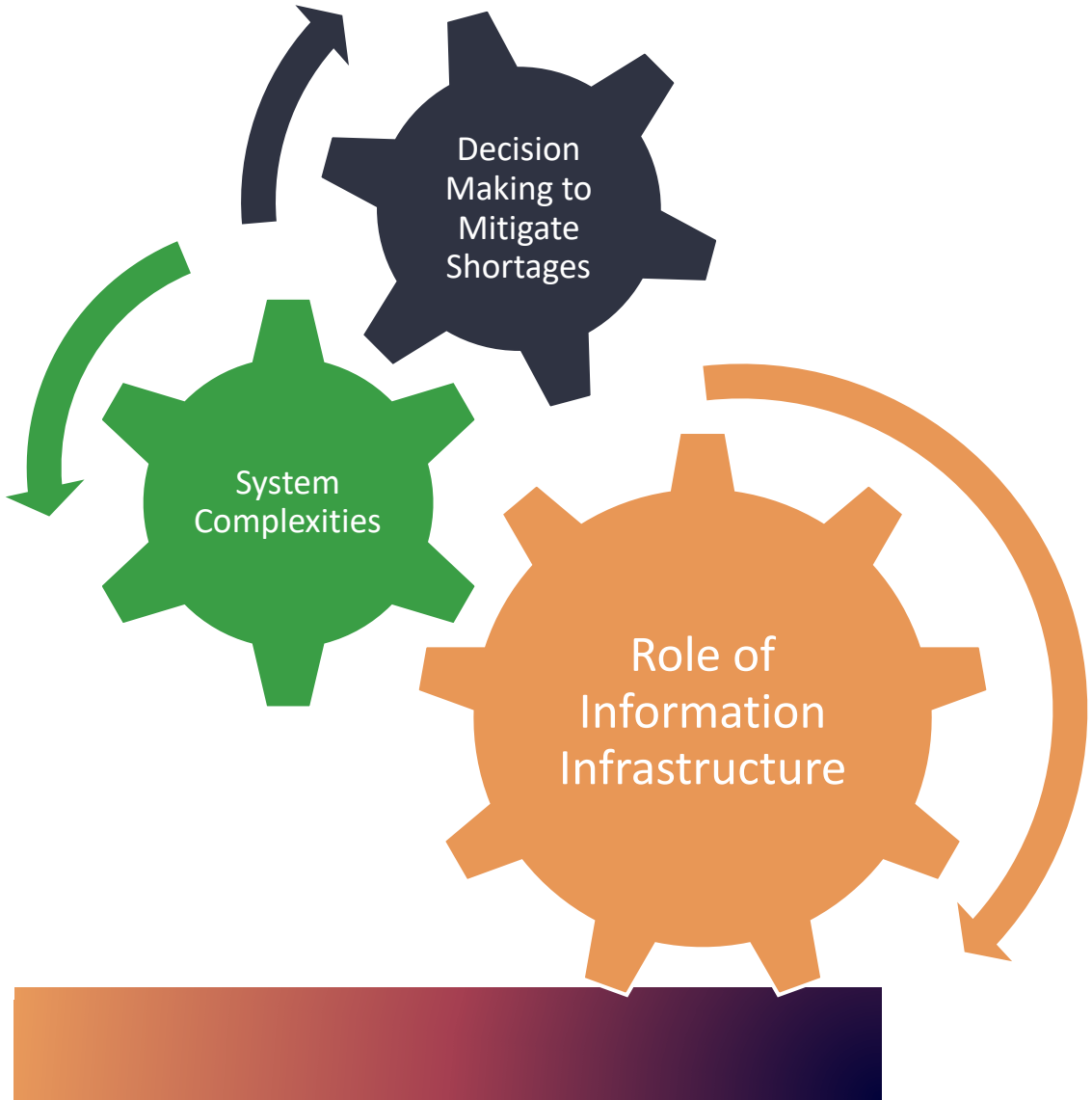
SURVEILLANCE OF GENERICS WITH A FOCUS ON DRUG SHORTAGES

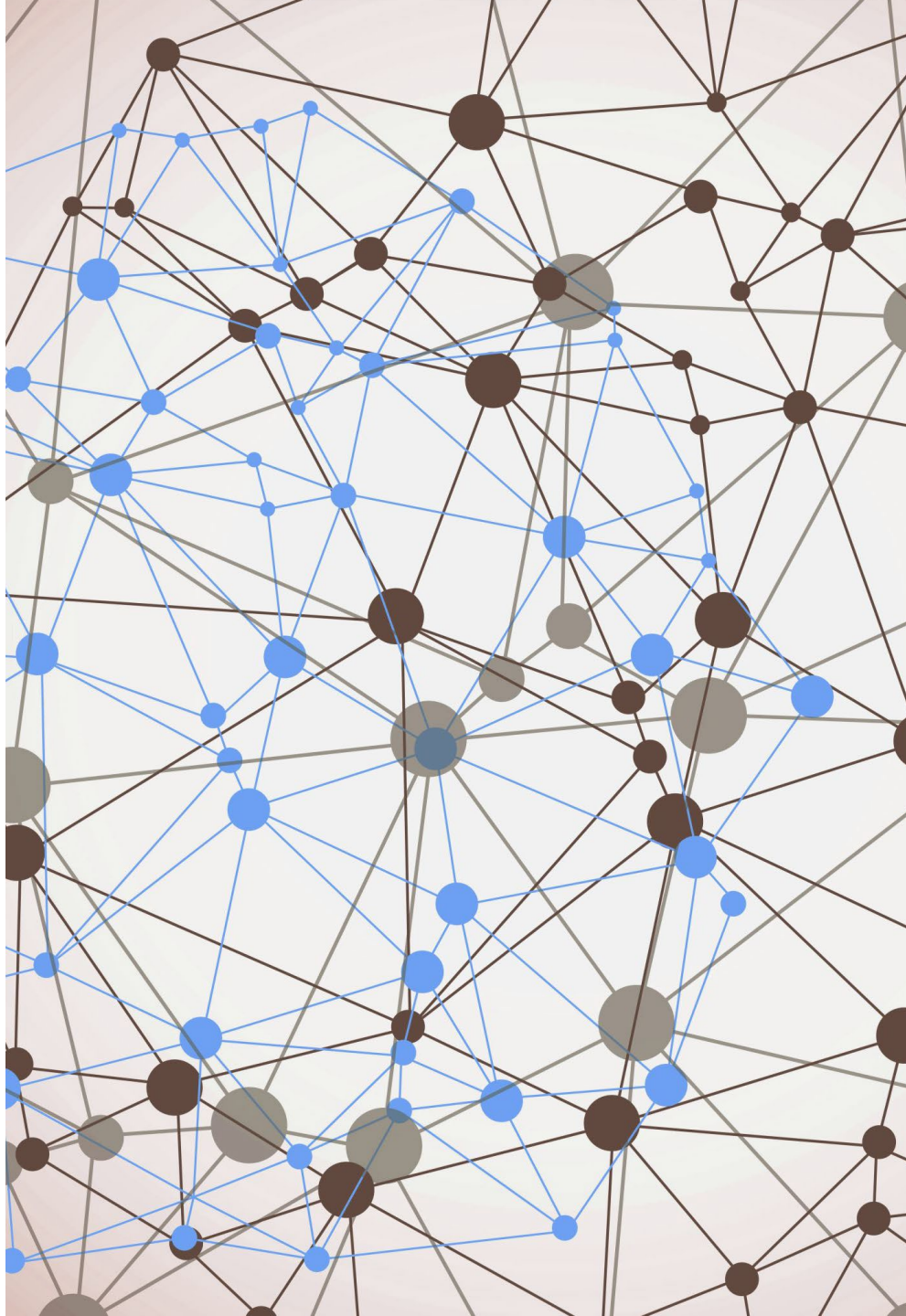
THIS COULD INCLUDE

- DETECTING WHICH GENERIC PRODUCTS WOULD HAVE THE GREATEST PUBLIC HEALTH IMPACT IF POOR QUALITY LEAD TO PRODUCTION SUSPENSION OR RECALL

- HIGHLIGHTING THE ROLE GENERIC DRUGS CURRENTLY AND POTENTIALLY CAN HAVE ON MITIGATING SHORTAGES

NORTHEASTERN UNIVERSITY DRUG SHORTAGE RESEARCH TEAM





PROPOSED RESEARCH FOCUS: EMPLOYING ANALYTICS AND MODELING OF GENERICS IN DRUG SHORTAGES

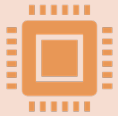
Employing Data Analytics, Machine Learning, and Artificial Intelligence Methods develop new models and methods for

Identifying generic products that are “too big to fail” and for which quality or production issues would drive significant market shortages

Prioritizing surveillance based on public disruption or quality issues or impact of a production disruption

Identifying trends in the dynamics of detection of quality concerns among generic products, with a vision towards remediation in the future

Prioritizing surveillance strategies based on historical spatio-temporal patterns observed in information flows.

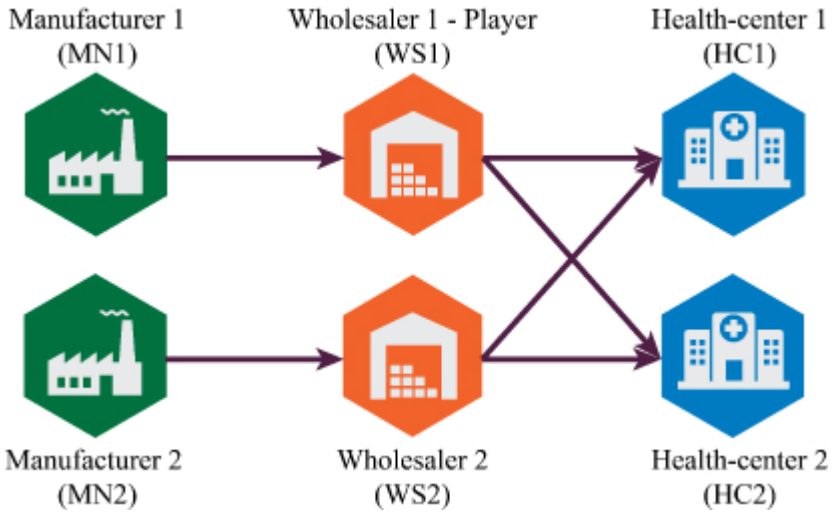


Identifying the critical types of information needed for answering these questions

Designing the future infrastructure for information detection and detection methods.

THANK YOU

Jackie Griffin, PhD
Northeastern University
ja.griffin@northeastern.edu


Manufacturer 1
(MN1)
Wholesaler 1 - Player
(WS1)
Health-center 1
(HC1)
Manufacturer 2
(MN2)
Wholesaler 2
(WS2)
Health-center 2
(HC2)

PROPOSED RESEARCH FOCUS: EMPLOYING ANALYTICS AND MODELING OF GENERICS IN DRUG SHORTAGES

Employing Data Analytics, Machine Learning, and Artificial Intelligence Methods develop new models and methods for

- Identifying generic products that are “too big to fail” and for which quality or production issues would drive significant market shortages
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  - **Prioritizing surveillance strategies based on historical spatio-temporal patterns observed in information flows.**
- Identifying the critical types of information needed for answering these questions
  - **Designing the future infrastructure for information detection and detection methods.**

Mitigating Drug Shortages through Better Inspection Planning

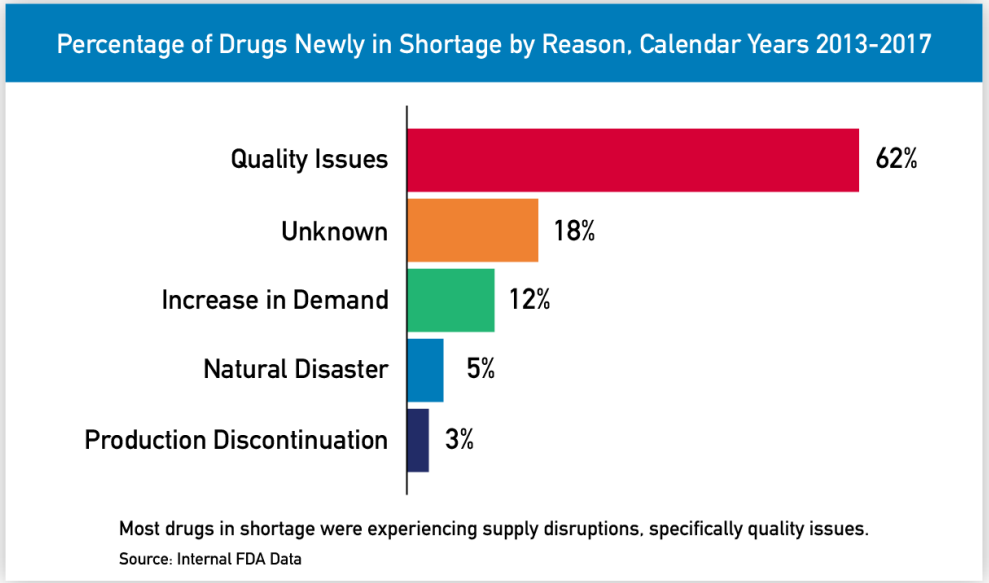
Daniel Kosmas, PhD, Northeastern University (d.kosmas@northeastern.edu)

Özlem Ergun, PhD, Northeastern University (o.ergun@northeastern.edu)

FY 2024 GDUFA Public Workshop

Background on Drug Shortages

a) Health impacts of drug shortages[1]



b) Root causes of drug shortages[1]

1. HTTPS://WWW.FDA.GOV/DRUGS/DRUG-SHORTAGES/REPORT-DRUG-SHORTAGES-ROOT-CAUSES-AND-POTENTIAL-SOLUTIONS

Impact of FDA Inspections

More frequent inspections can result in less unexpected disruptions, but:

- It requires more FDA resources
- Pharmaceutical manufacturing companies may be required to perform more maintenance than is optimal, which can cause supply shortages
  - Excess maintenance costs can cause low-profit products to be discontinued, which can lead to supply shortages

Problem: How can the FDA ensure compliance with regulations while not forcing pharmaceutical manufacturing companies out of the market?

Proposed Research Ideas

- How can AI/ML help the FDA determine:
  - When to inspection?
  - Which facilities to inspect?
- Can data sharing between the manufacturers and FDA improve compliance with regulations and reduce costs?
  - Can we determine which data to share and how frequently the data should be shared?
- Can AI/ML/remote sensing methods and data sharing for analyzing the supply chains of substitutable products allow for the FDA to improve inspection decisions to better mitigate drug shortages?

UNIVERSITY of ROCHESTER

PREDICTIVE TOOLS FOR GENERIC PRODUCT DEVELOPMENT & ASSESSMENT

MAY 20, 2024

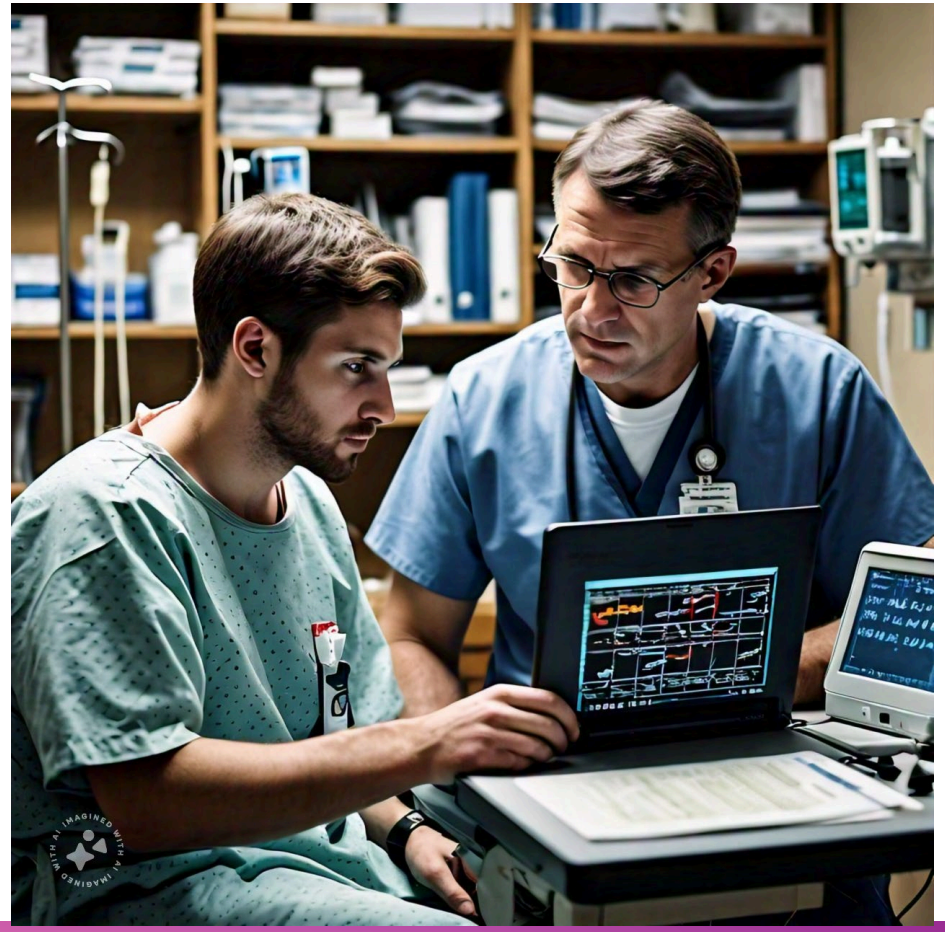
DONGMEI LI, PHD

PROFESSOR

UNIVERSITY OF ROCHESTER

EXPAND THE USE OF ARTIFICIAL INTELLIGENCE (AI) AND MACHINE LEARNING (ML) TOOLS

- 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.

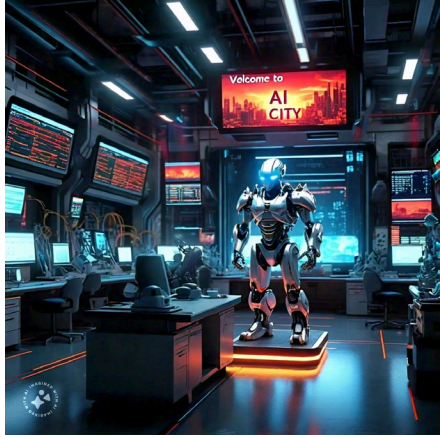


The image is generated using Meta AI

CURRENT CHALLENGES IN GENERIC DRUG EVALUATION

- Safety and Quality of the Generic Drug Supply Chain is a growing concern for the United States and the global drug supply (Brown, 2020).
- Current drug safety and quality control through the “Site Selection Model”, “FDA Adverse Event Reporting System (FAERS)”, and “MedWatch program” is limited considering the increasing number of manufacturing facilities.
- Real-world data in the post-marketing surveillance period has the potential to overcome this limitation.
- A case study using the FDA’s Sentinel Initiative distributed data network identified clear differences between manufacturers’ products.
- Another case study comparing the brand and two generic versions of a specific drug leads to the recall of the generic versions during the initial generic marketing period.

HOW AI AND MACHINE LEARNING TOOLS COULD HELP WITH THE CHALLENGES



- AI tools such as natural language processing tools can be used to analyze EHR data, social media data, and online forums to identify potential adverse events and concerns about generic drug substitutions.
- Machine learning algorithms can be used for early detection of potential issues of generic drug substitutions through analyzing large real-world data such as claims data.
- Predictive models for potential outcomes of the generic drug substitutions could be built using AI algorithms using historical and real-time surveillance data.
- Real-time alerts and notifications could be provided to the FDA, patients, and healthcare professionals regarding potential issues of generic drug substitutions using AI systems.

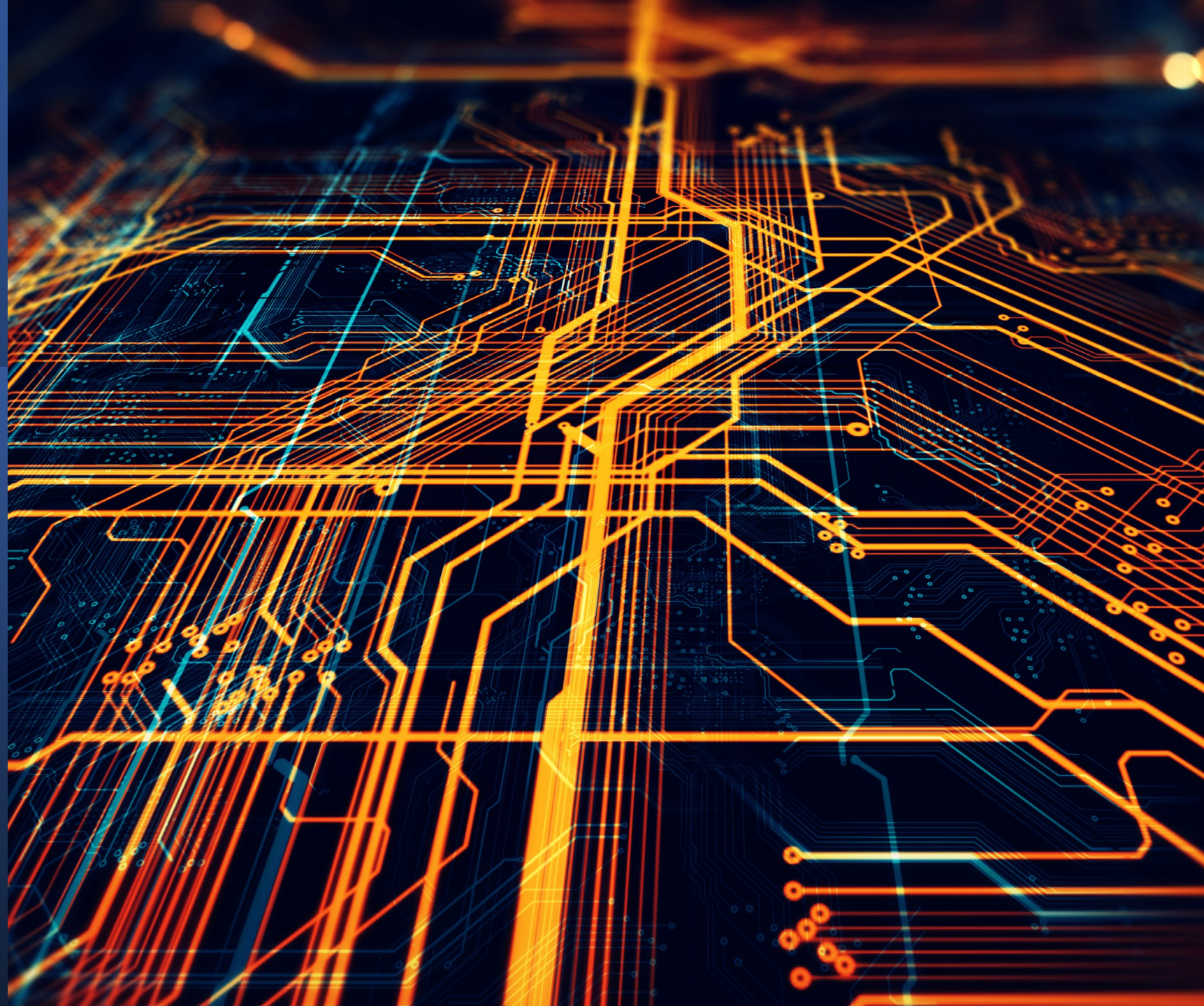
HOW AI AND MACHINE LEARNING TOOLS COULD HELP WITH THE CHALLENGES

- With the help of AI algorithms, personalized medicine could be realized with tailored treatment for each patient based on their characteristics to improve the effectiveness and safety of generic drug substitutions.
- The impact of generic drugs on public health could also be evaluated using AI tools to identify patterns and trends for regulatory purposes.
- Compliance with regulations and guidelines related to generic drug substitutions could be monitored using AI tools.
- AI tools could also be used to assess the drug efficacy by analyzing clinical trials and real-world evidence of the generic drugs and their brand counterparts.
- AI-powered natural language processing algorithms could be used to summarize and analyze a large volume of literature on safety, efficacy, and utilization of generic drug substitutions to inform FDA for decision-making.

REFERENCES

- Brown JD. A Call to Action to Track Generic Drug Quality Using Real-World Data and the FDA's Sentinel Initiative. J Manag Care Spec Pharm. 2020 Aug;26(8):1050. doi: 10.18553/jmcp.2020.26.8.1050. PMID: 32715968; PMCID: PMC10390989.

Enhancing ANDA with AI/ML: A Prescription for Efficiency



By James Hasty

CEO B&H Engineering Concepts Inc.

Introduction

Background: The Abbreviated New Drug Application (ANDA) process is critical for generic drug approvals.

Challenge: Increasing workload, manual reviews, risk evaluation and mitigation strategy requirement (REMS requirement), and resource constraints.

Solution: An Artificial Intelligence/ Machine Learning (AI/ML) tool to revolutionize ANDA process and reduce the challenges/pain points of the ANDA process.

Benefits of an AI/ML Tool

1. Speed and Efficiency:

•AI algorithms can analyze vast datasets faster and with better accuracy than humans.
•Accelerate ANDA reviews, reducing approval timelines, while maintaining the integrity and objectiveness of the reviews

2. Automating routine Tasks:

•Provide Risk Assessments based on drug formulations and manufacturing processes
•Automate Regulatory reports and documentation
•Monitor Adverse Event(s) reported after drug's approval to identify potential safety concerns with the product(s)

3. Quality Assurance:

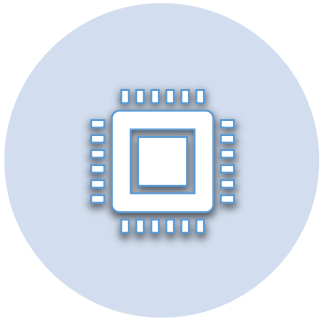
•ML models can detect anomalies, ensuring data accuracy.
•Improve consistency and reliability in regulatory decision-making.

Impact of AI/ML tool through Predictive Modeling

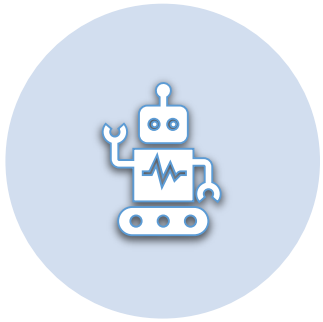
- **Predicting Bioequivalence**:
  - AI can predict bioequivalence outcomes based on formulation data.
  - Virtual Bioequivalence (VBE) utilizing modeling and simulation in lieu of clinical studies
- Identify potential issues early, based on historical data, product recalls, and regulatory enforcement actions which can assist with the review process.
- Develop AI/ML models to assess the risks associated with specific drug formulations, manufacturing processes, or regulatory strategies.
- Employ techniques like ensemble learning or deep learning to integrate information from multiple data sources and improve risk assessment accuracy.
- Employ techniques like logistic regression, random forest, or deep learning for adverse event prediction.

Future of AI/ML Tool Usage within the FDA

Personalized Medicine: AI/ML models will play a crucial role in advancing personalized medicine approaches within the ANDA process. By analyzing patient data, genetic information, and clinical outcomes, AI can help identify patient subpopulations that may benefit from specific drug formulations or treatment strategies



Integration with Emerging Technologies: AI/ML tools will be integrated with emerging technologies such as blockchain, Internet of Things (IoT), and augmented reality (AR) to create innovative solutions for drug development and regulatory compliance. For example, blockchain technology may be used to ensure the integrity and traceability of clinical trial data, while IoT devices may enable real-time monitoring of drug manufacturing processes.



Regulatory Compliance Automation: AI/ML tools will be used to automate regulatory compliance tasks within the ANDA process, including document preparation, submission tracking, and compliance monitoring. Natural language processing (NLP) algorithms may be employed to analyze regulatory guidelines and streamline the submission process.

Real-Time Monitoring and Surveillance: AI/ML algorithms will be used for real-time monitoring and surveillance of drug safety and efficacy within the post-market phase. Automated adverse event detection systems, pharmacovigilance algorithms, and social media monitoring tools may be employed to identify emerging safety signals and monitor drug performance in real-time.

Conclusion

In conclusion, the implementation of an AI/ML tool within the Food and Drug Administration's Abbreviated New Drug Application (ANDA) program is imperative for several reasons;

- Firstly, AI/ML can significantly enhance the efficiency and accuracy of the regulatory review process by automating routine tasks such as document parsing, data extraction, and regulatory compliance monitoring.
- Secondly, AI/ML models can provide predictive insights into drug formulation optimization, regulatory compliance prediction, risk assessment, and adverse event monitoring, thereby improving decision-making and accelerating the approval process for generic drugs.
- Thirdly, the integration of AI/ML technologies can facilitate real-time monitoring and surveillance of drug safety and efficacy during the post-market phase, ensuring timely identification of emerging safety signals and enhancing patient care.
- Ultimately, by leveraging AI/ML tools within the ANDA program, the FDA can streamline operations, improve regulatory oversight, and advance public health outcomes in a rapidly evolving pharmaceutical landscape

Thank you for your time.

- James Hasty CSQE, CMDA
- CEO/Founder B&H Engineering Concepts Inc.
- Where we “Augment Expertise with Technology”
- Email:J_Hasty@audittech.net

Digital Unit-Level Drug Monitoring in Real-World Settings

Research Proposal, GDUFA Public Workshop on May 20-21, 2024

Peter Gompper

Co-founder at Rubitel, Inc.

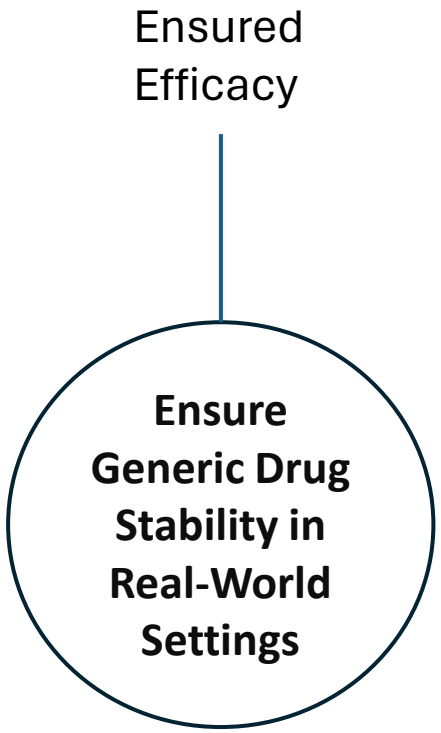
Email: contact@rubitel.com

Digital Unit-Level Drug Monitoring in Real-World Settings

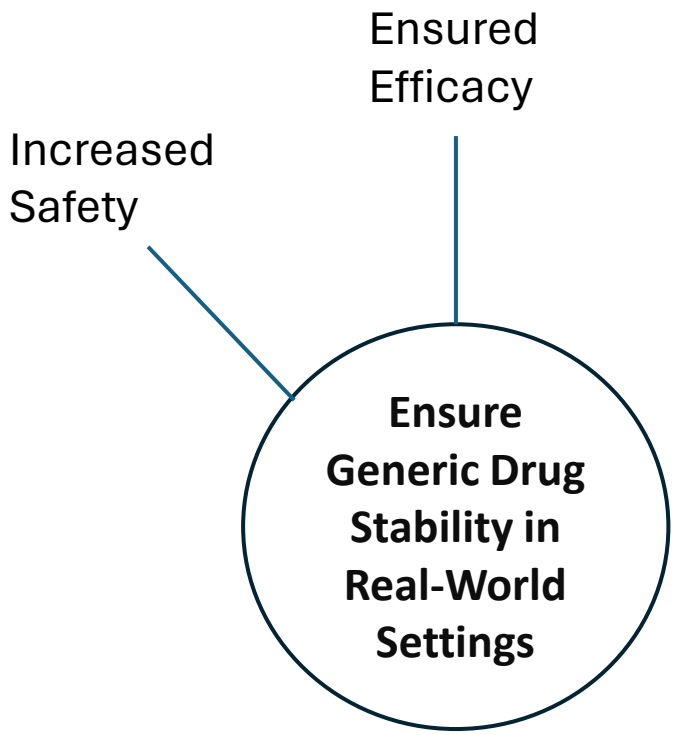
RUBITEL

Ensure Generic Drug Stability in Real-World Settings

Digital Unit-Level Drug Monitoring in Real-World Settings



Digital Unit-Level Drug Monitoring in Real-World Settings



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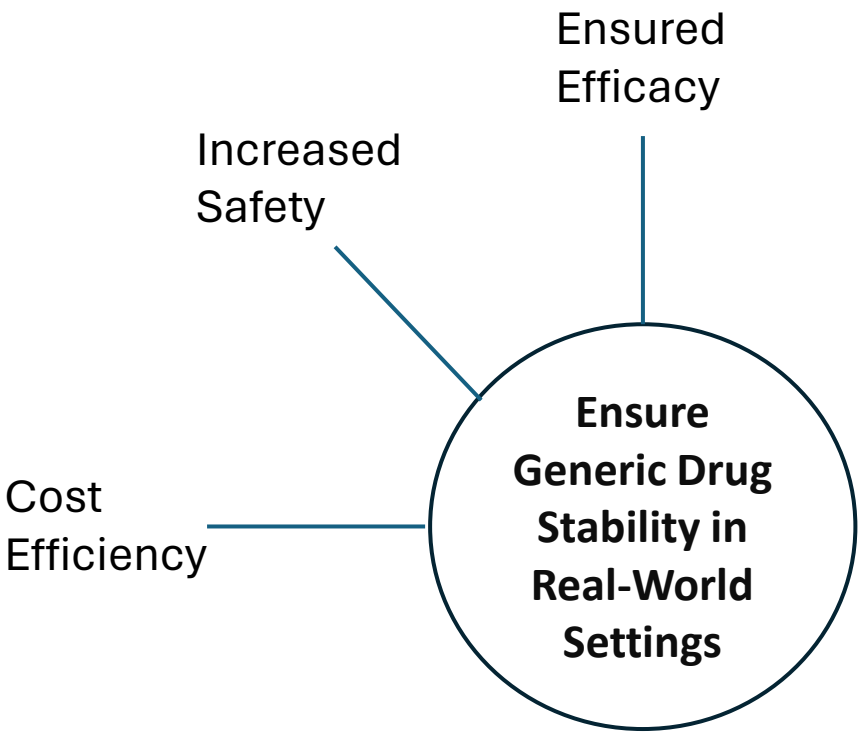

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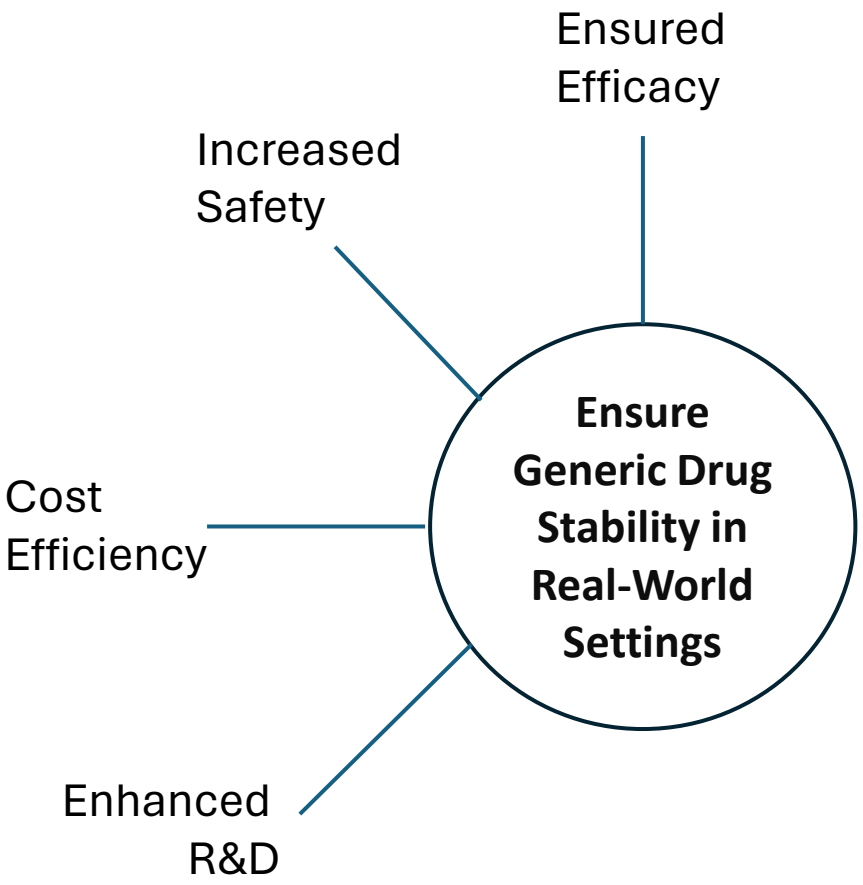

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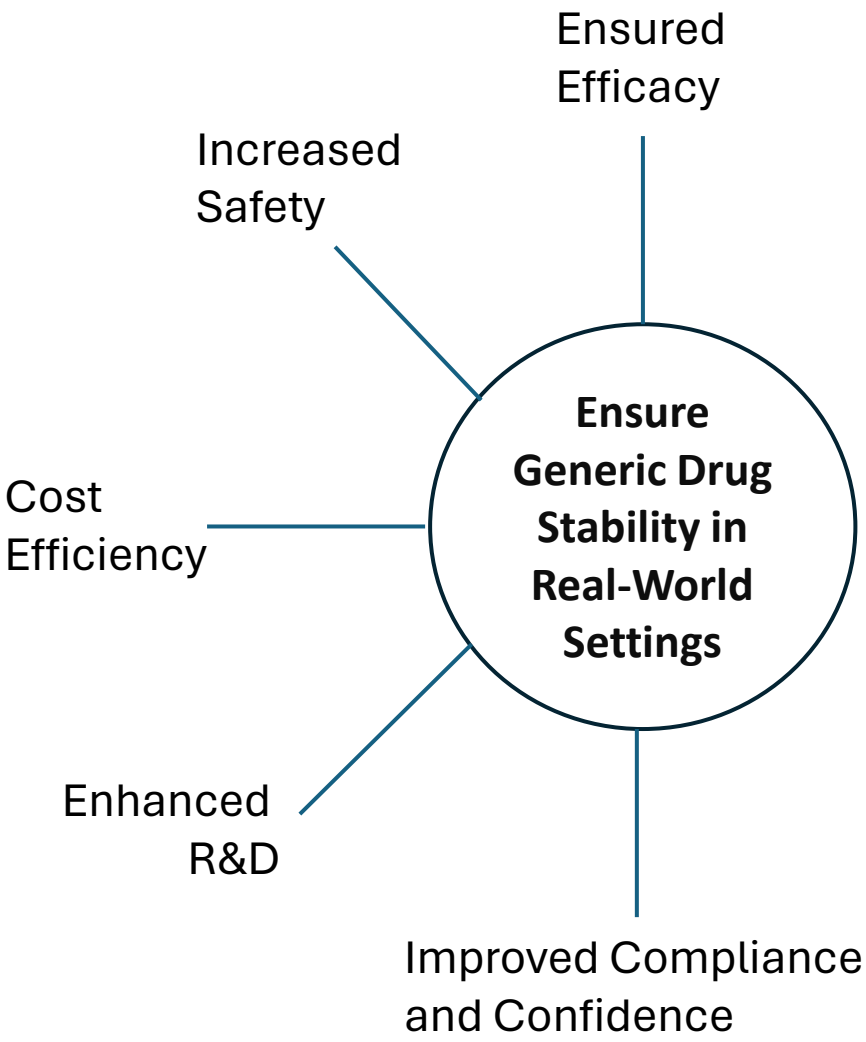

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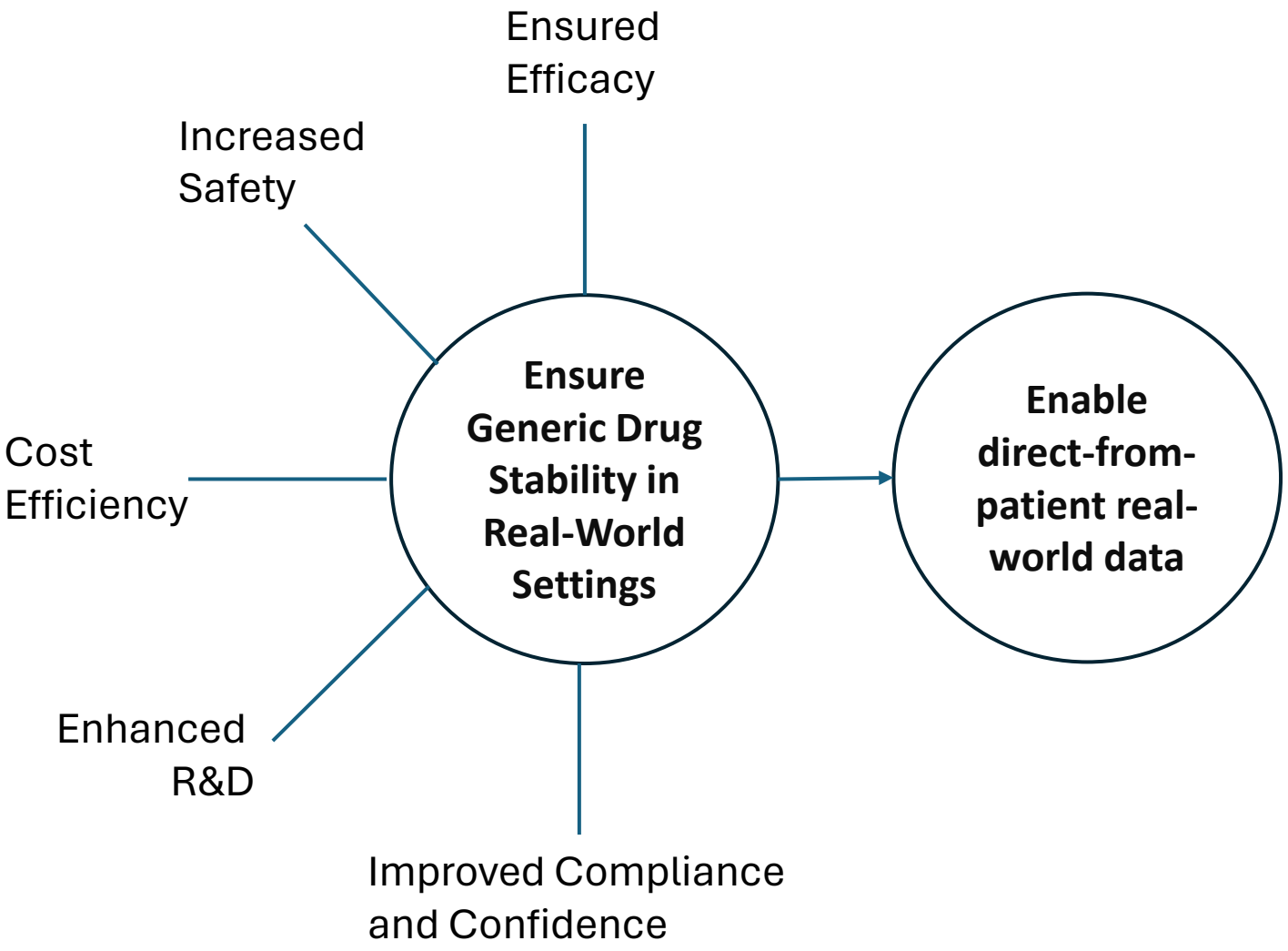

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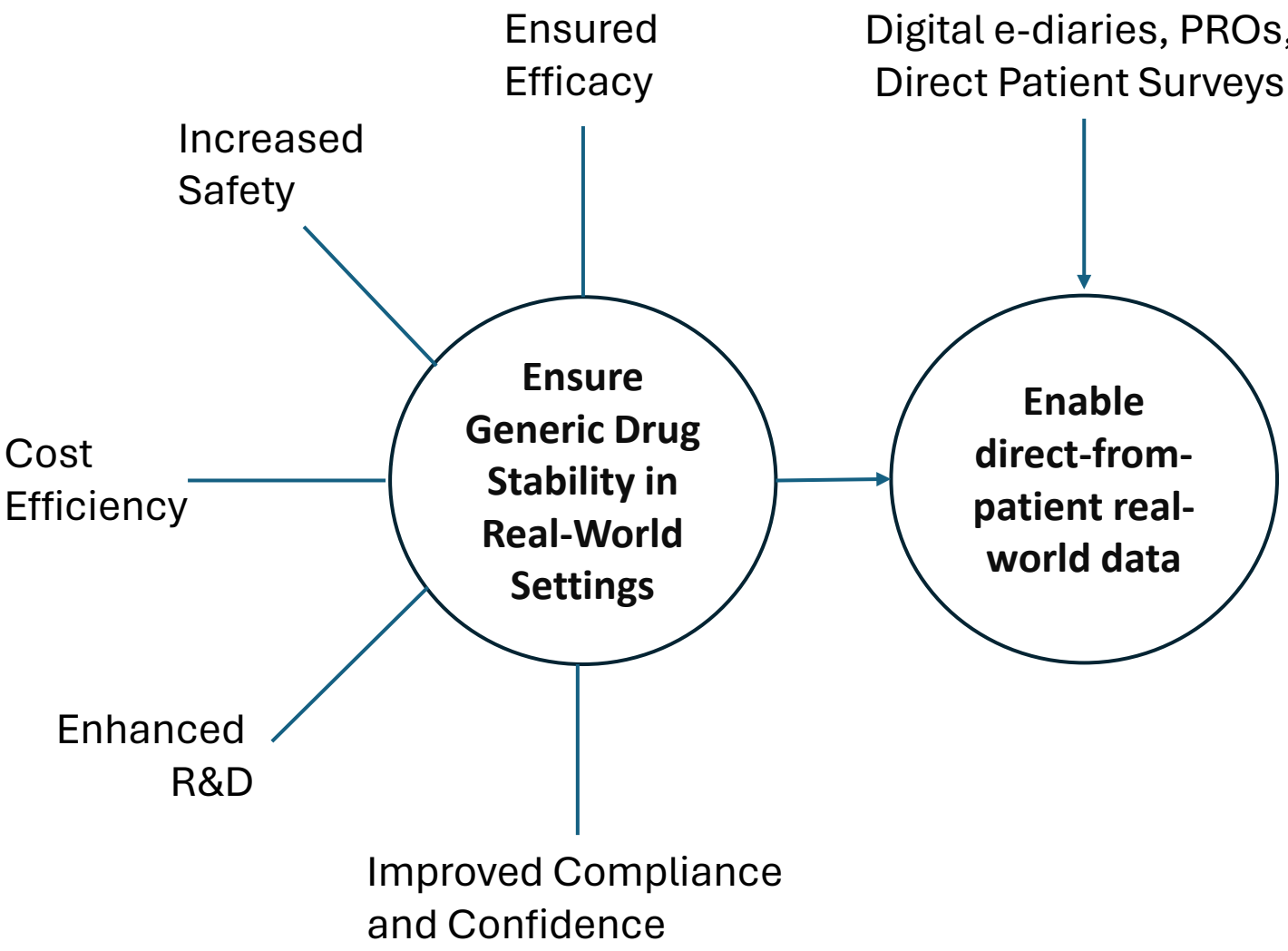

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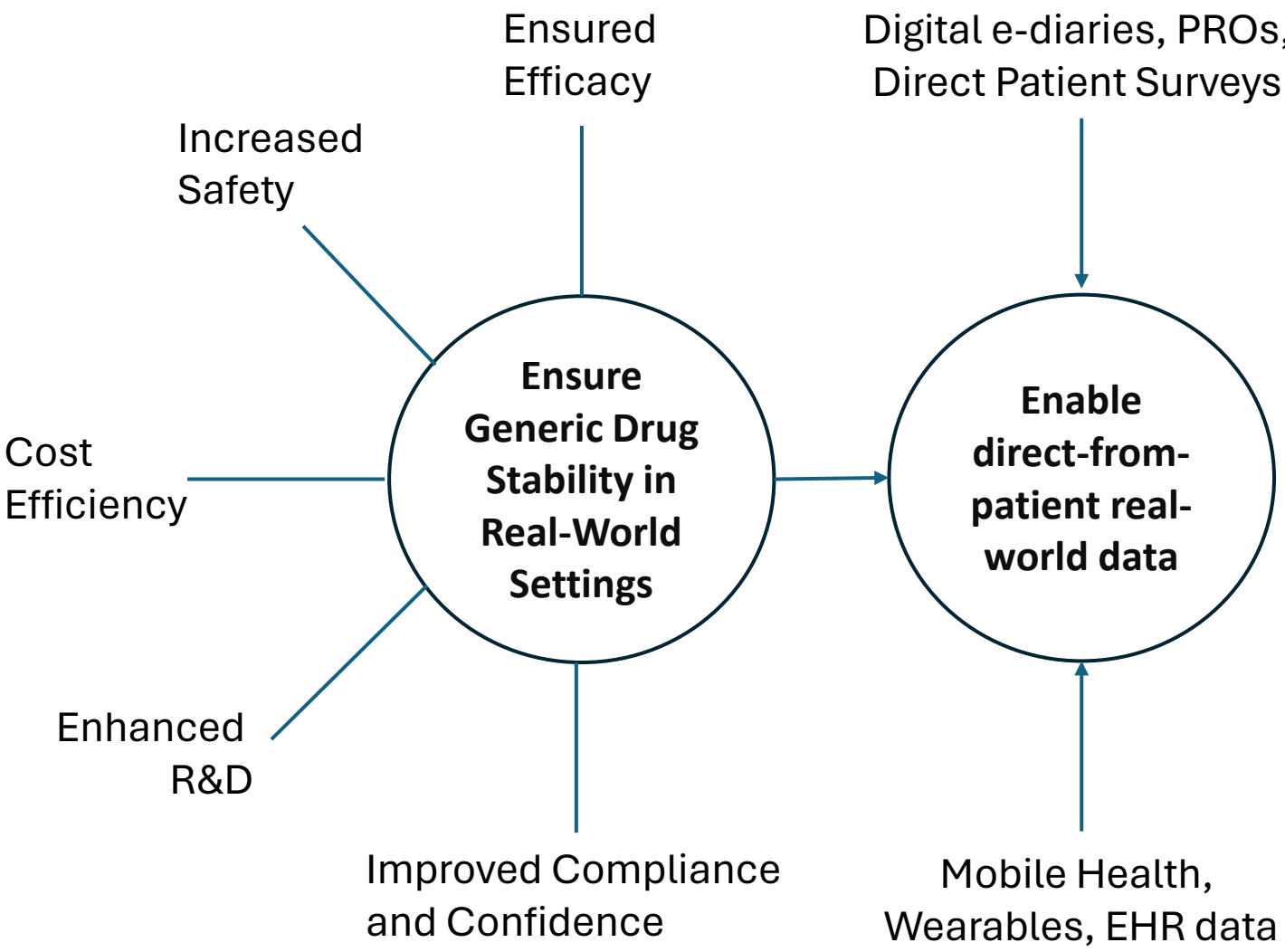
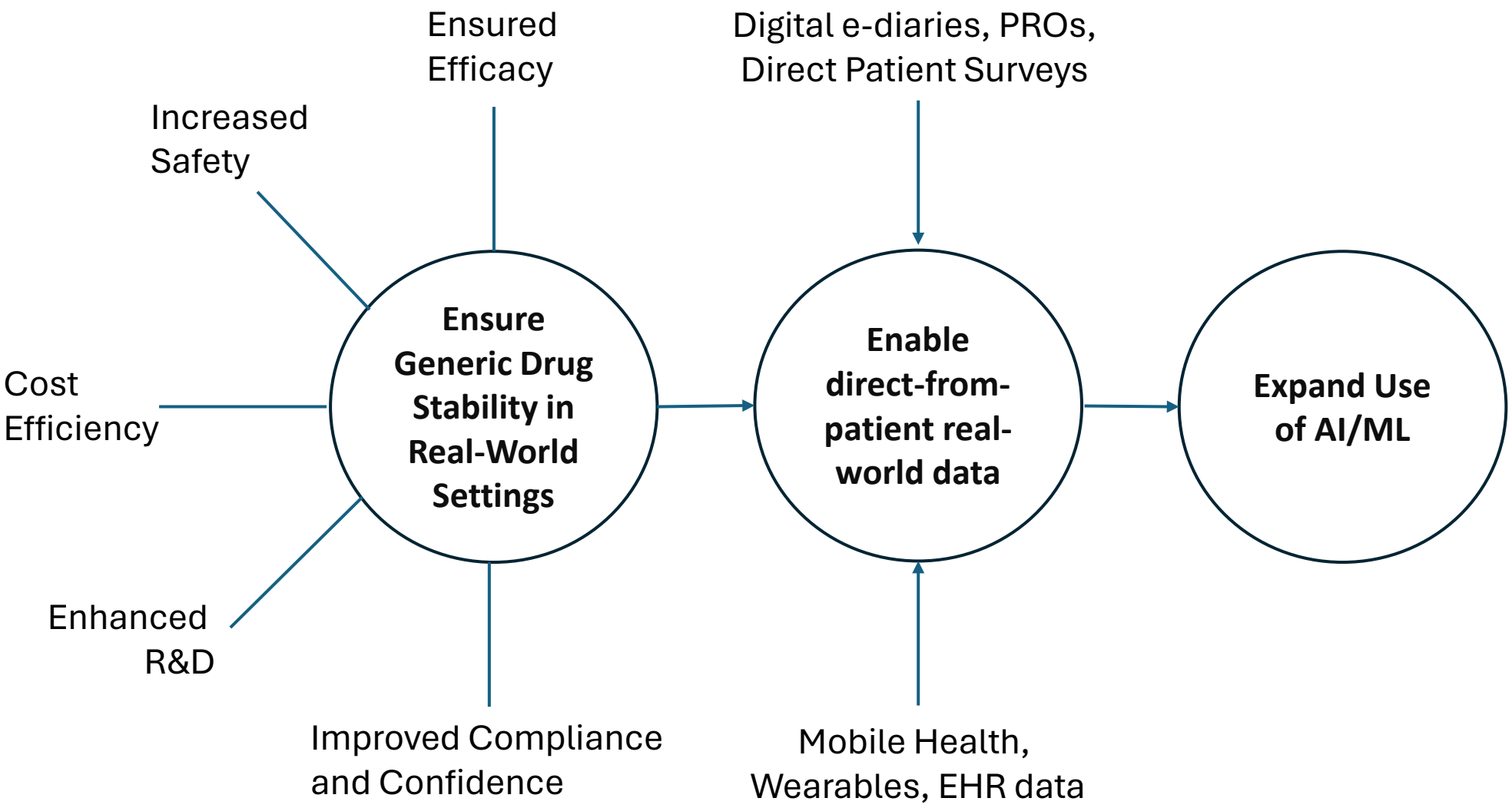


Digital Unit-Level Drug Monitoring in Real-World Settings

RUBITEL



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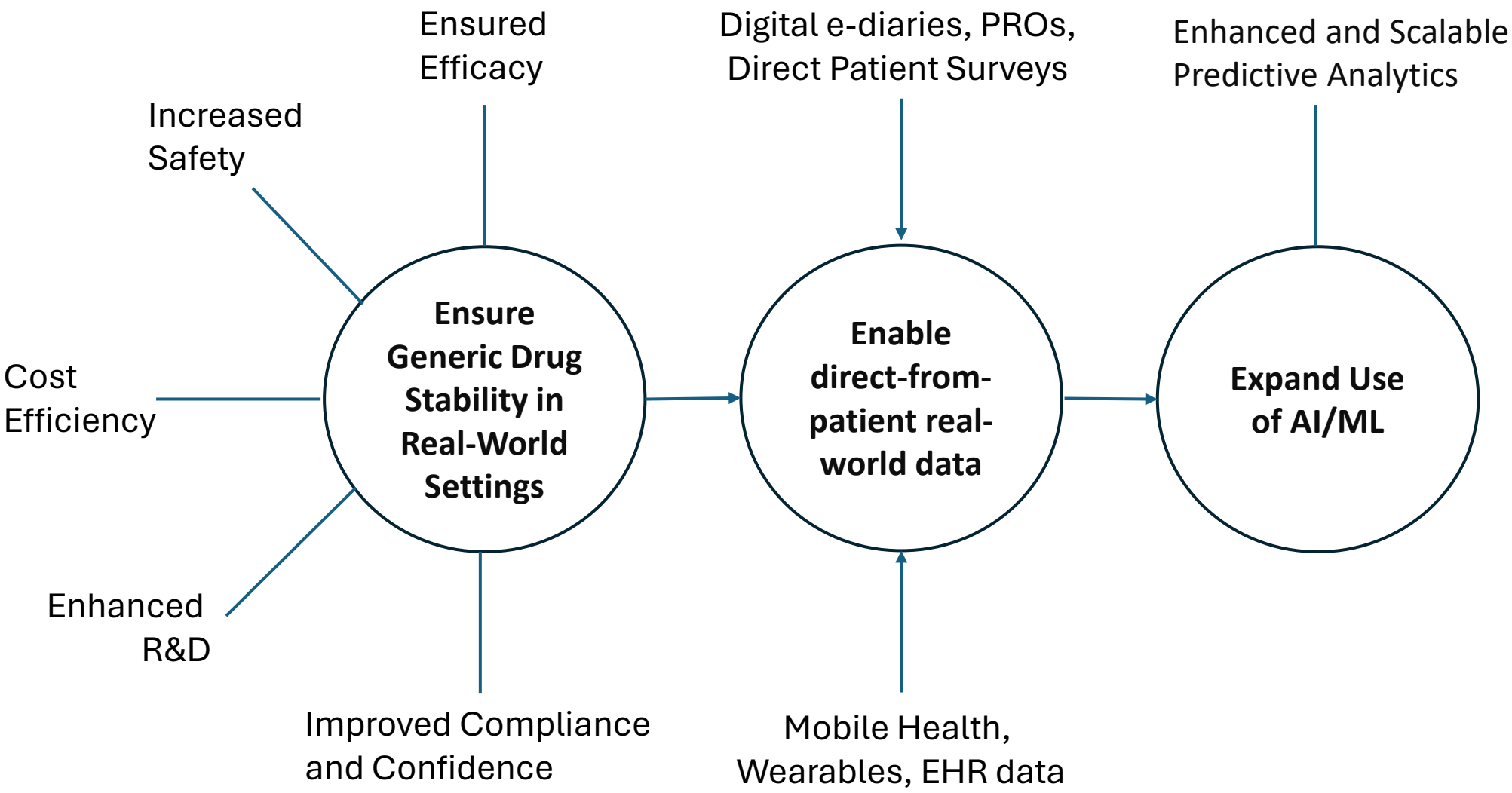

Digital Unit-Level Drug Monitoring in Real-World Settings

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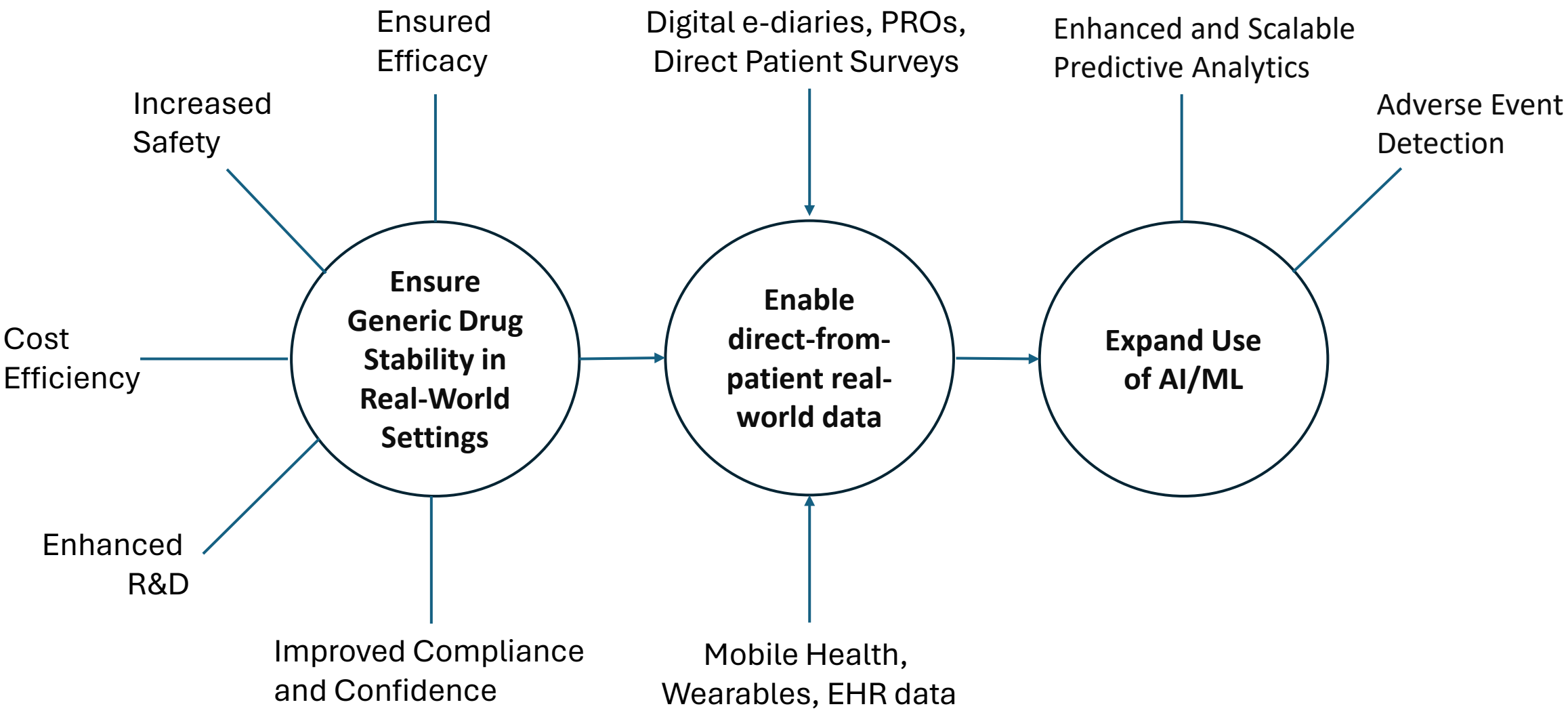

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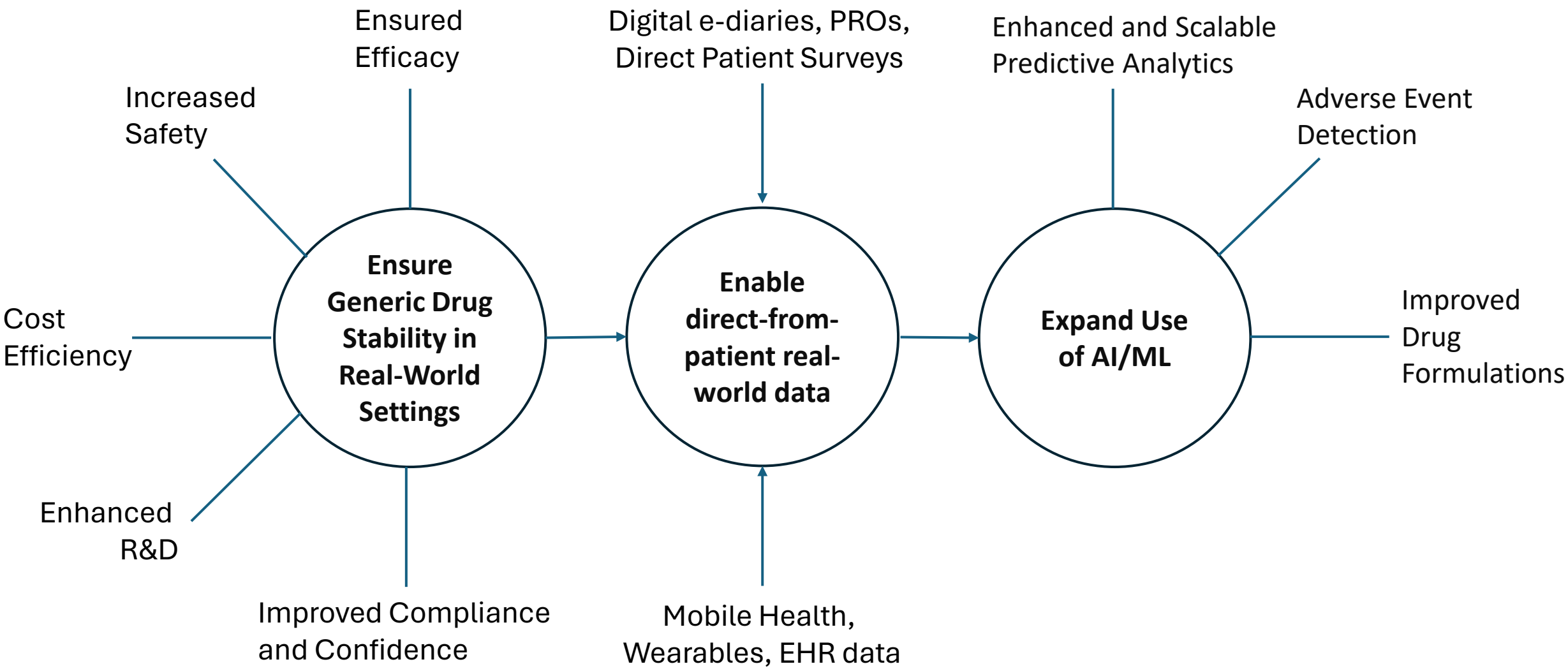
RUBITEL



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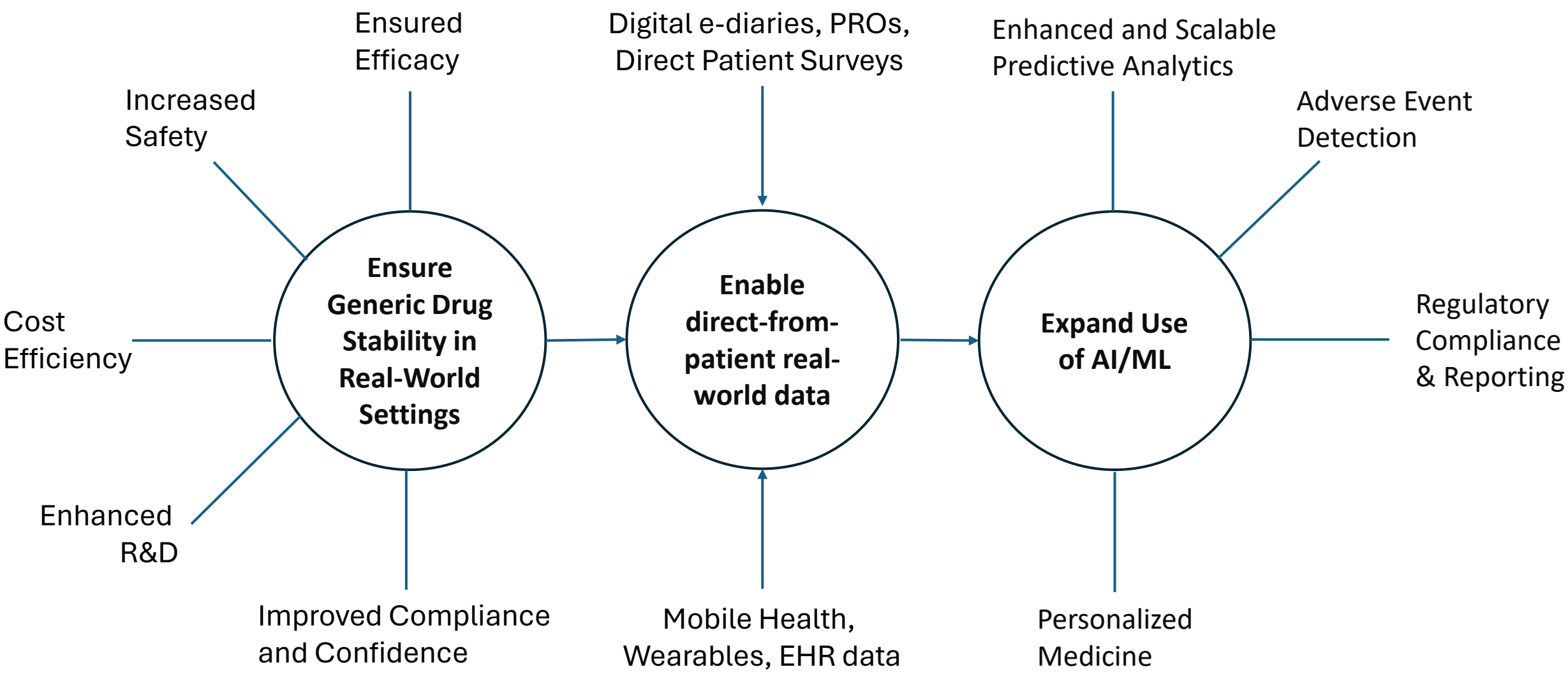

RUBITEL

Questions

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Co-founder at Rubitel, Inc.

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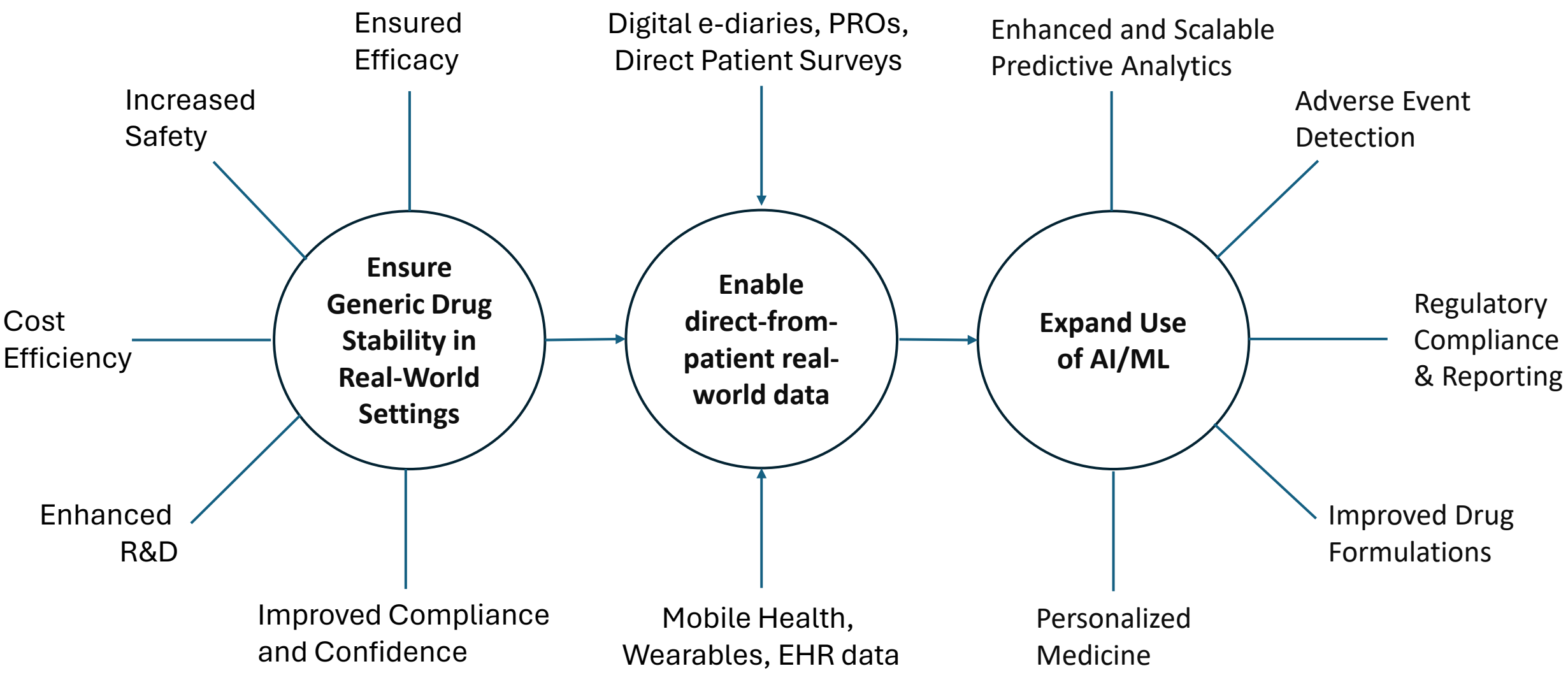
Digital Unit-Level Drug Monitoring in Real-World Settings



Fiscal Year 2024
Generic Drug Science & Research Initiatives
Public Workshop

For more information, please visit:

Coffee Break

We will begin promptly at 11:30 A.M Eastern Time (GMT -4)