U.S. FOOD & DRUG ADMINISTRATION

Predicting Formulation Performance: Learning from Generic Drugs

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October 23, 2023

AAPS PharmSci 360
Formulation and Delivery Keynote

Simple or Not?

- You might think that generic drugs are copies and what CDER's Office of Generic Drugs does is simple.
- CDER's new drug programs have the gold standard in clinical trials, but they can be so powerful for decision making that we don't need to know why a drug works.
- In the generic program, we use pharmaceutical science and clinical pharmacology to identify what needs to be the same
  - so, we do not have to repeat clinical trials to provide access to competition.

Office of Research and Standards (ORS) Purpose

- We make bioequivalence studies for simple products more efficient.
- We spend significant efforts on establishing the possibility of generic competition for complex products (inhalation, dermal, long-acting injectable or drug-device combination products).
- We coordinate lab research to characterize complex products and build models to describe and predict what they do.

Today!

- Advancing the science of generic drugs has created new knowledge at the interface of formulation science and clinical pharmacology that is valuable for all drug development.

Key Scientific Challenges for Generics

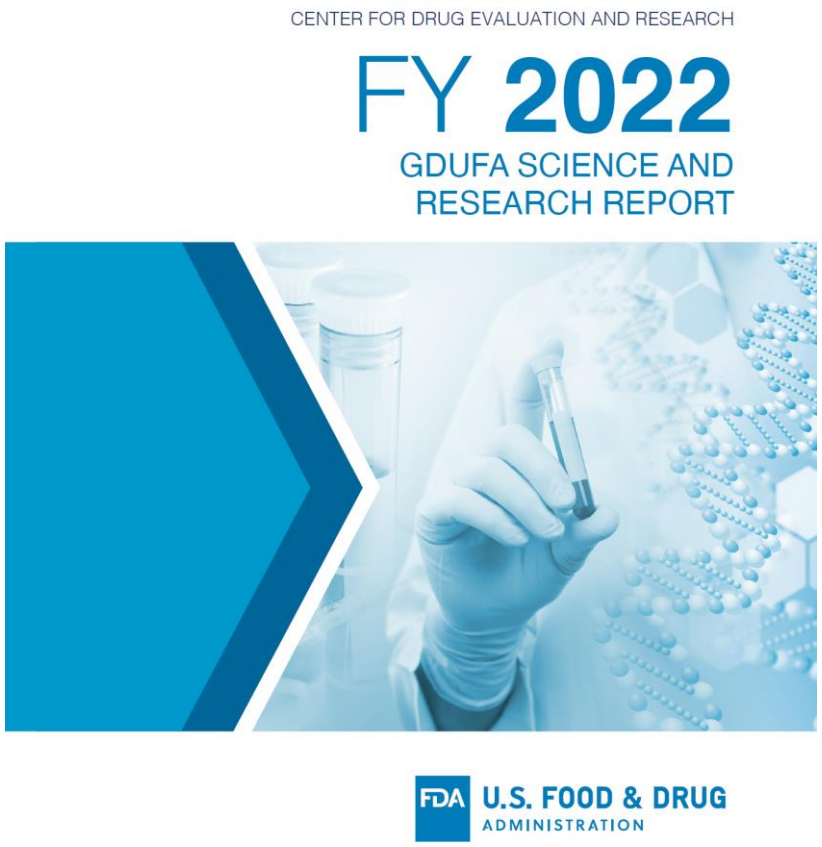
- Bioequivalence (BE) for locally acting products
  - Simple path to generics is a PK BE study for a systemically acting product
- Sameness for complex products
  - Advances in analytical methods and in vitro BE

Unique Features of GDUFA Research

- Tight integration between research and scientific advice to generic applicants
  - Product-Specific Guidance (PSG)
    - Written by staff doing research
  - Pre-ANDA Meetings
    - Led by staff doing research
- Focus on complex generics

GDUFA Science and Research Report

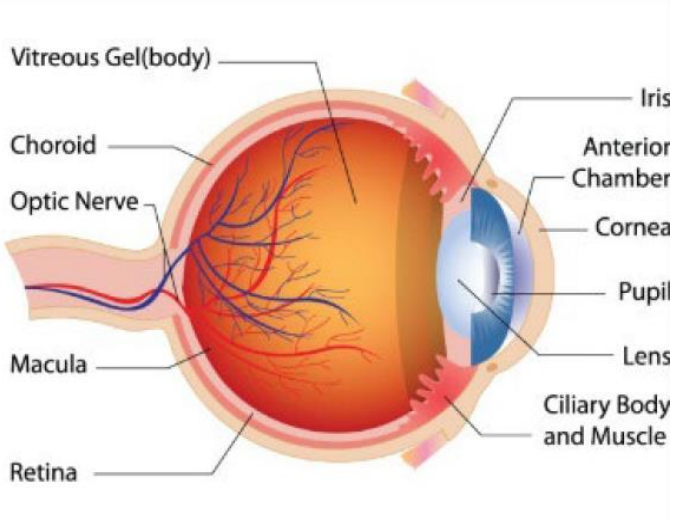
- The FY2022 GDUFA Science and Research Report is available at: https://www.fda.gov/drugs/generic-drugs/fy-2022-gdufa-science-and-research-report
- It highlights the scope and impact of **all** GDUFA-supported research across FDA
- High transparency to the generic industry on what we use GDUFA resources for

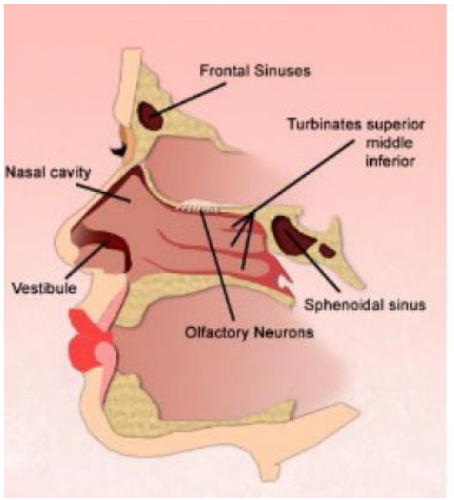


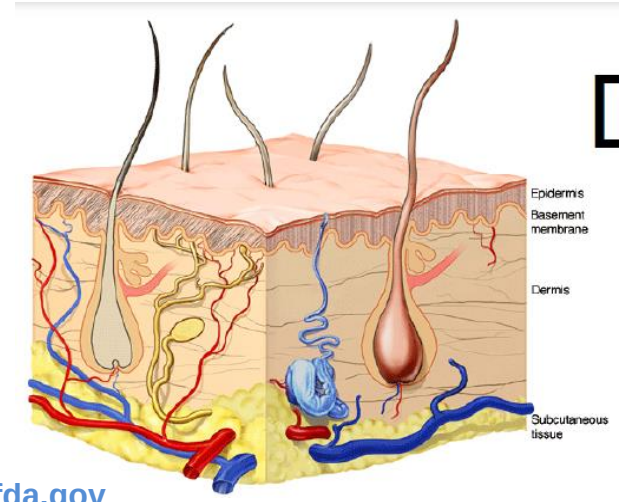
PBPK Modeling

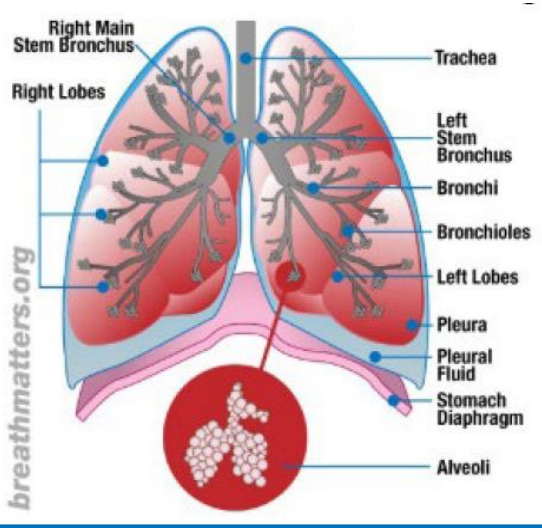
- GDUFA research has supported the development of PBPK models for non-oral routes of delivery over the past 10 years
- These are product where lack of PK makes BE studies challenging
- Outcomes of this research are available in commercially available PBPK software and open-source models
- In 2013, there was nothing available

Eye, Nose, Skin, Lung



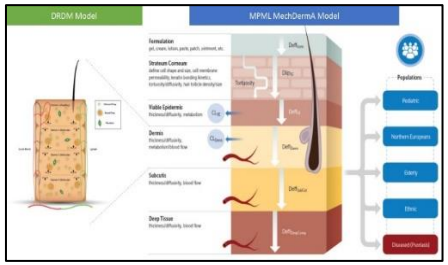






New Data and New Modeling Approaches

CERTARA



Grants:
- 1U01FD005225
- 1U01FD006521
- 1U01FD006522

In collaboration with –
- University of Queensland
- University of South Australia

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

University of South Australia

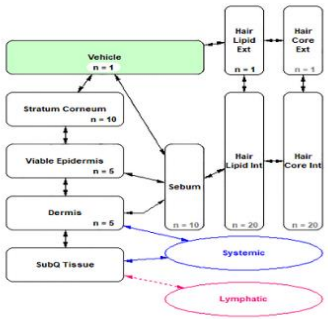
University of South Australia

Grant: 1U01FD005232
In collaboration with
Goethe University Frankfurt

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Dermal PBPK Model

SimulationsPlus
SCIENCE + SOFTWARE = SUCCESS

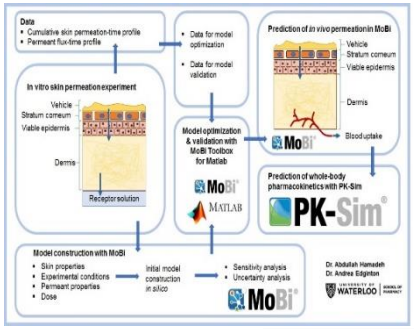


Grant:
1U01FD006526
In collaboration with industry partners

University of South Australia

Grant:
1U01FD006496
In collaboration with
University of Surrey

UNIVERSITY OF SURREY



UNIVERSITY OF WATERLOO

Children's Hospital LOS ANGELES

Grant:
1U01FD006549
In collaboration with –
- University of Waterloo
- Children's Hospital of Los Angeles

FDA Relies on Systemic Exposure for Regulatory Decisions

- New Drug Development
  - Clinical Pharmacology relies on systemic exposure
    - Drug-Drug interactions
    - Exposure-response
    - Population PK analysis
    - Relative BA for bridging studies
- Generic Drug Development
  - PK based bioequivalence supports the approval of the vast majority of generic drugs

All the things FDA and drug developers want to do become more difficult for locally acting products

BA - bioavailability

Approaches for Locally Acting Products

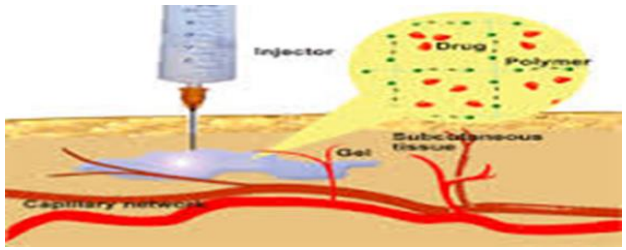
- New Drug Development
  - Rely on safety and efficacy studies
    - Reasonable but not optimal
  - Barrier to product improvement
    - Need to demonstrate BE after formulation change or in product development
- Generic Drug Development
  - Use clinical endpoints for bioequivalence?
    - High cost is a barrier to generic competition
  - Clinical endpoints have high variability/low sensitivity
    - Inefficient detection of formulation differences
  - Unnecessary human testing
    - Often 300-500 patients sometimes larger than original efficacy study

Role of PBPK Models

- PBPK models for the local routes of drug delivery aid development of appropriate BE methods
- Capture the current understanding of the complex interplay between product attributes and human physiology for these routes of delivery
- PBPK Models allow Clinical Pharmacology and formulation optimization

Long Acting Injectables

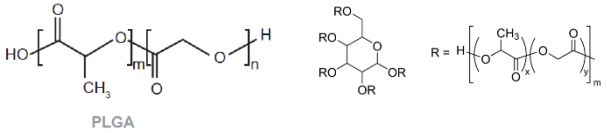
Brand	Drug	Route	Dosing frequency	Dosage Form	Local (L) or Systemic (S) action
RISPERDAL CONSTA	Risperidone	i.m.	2 weeks	Microsphere	S
VIVITROL	Naltrexone	i.m.	1 month	Microsphere	S
LUPRON DEPOT	Leuprolide	i.m.	1, 3, 4, 6 months	Microsphere	S
BYDUREON	Exenatide	s.c.	1 week	Microsphere	S
ZOLADEX	Goserelin	s.c.	1, 3 months	Implant	S
ELIGARD	Leuprolide acetate	s.c.	1, 3, 4, 6 months	In-situ gel	S
EXPAREL	Bupivacaine	s.c.	Single dose	Liposome	L
Mirena	Levonorgestrel	Intrauterine	5 years	Intrauterine device	L
Estring	Estradiol	Intravaginal	90 days	Ring	L
Sinuva	Mometasone furoate	Sinus	90 days	Implant	L



- Challenges for Generics
- Material Science of the Release Controlling Polymers
- PK study designs for month long dosing

Q1 Polymer Sameness

- Poly esters
  - PLG copolymers
  - PLA polymers



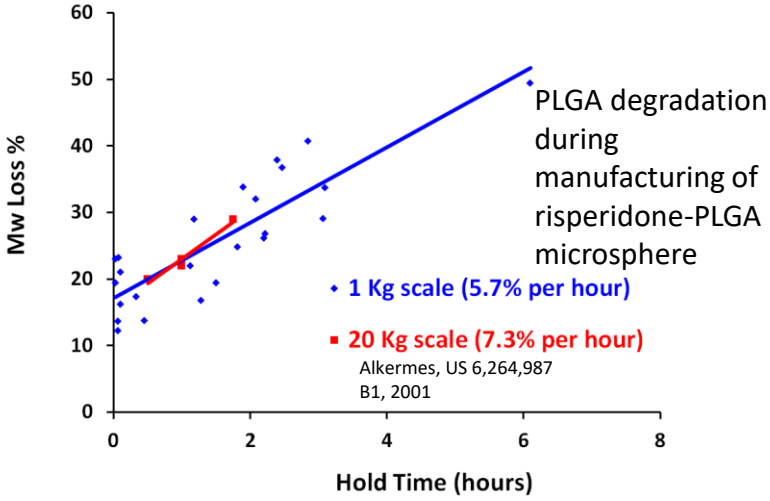
Should provide comparative physicochemical data on PLA/PLGA polymers extracted from the FINISHED Test product and the reference listed drug (RLD)

- Not acceptable to only use the Certificate of Analysis from the excipient vendor
- Not acceptable if characterizing raw polymer vs. polymer extracted from the RLD
- Characterization should include, but is not limited to: Composition (Lactide/Glycolide ratio), molecular weight and molecular weight distribution, polymer structure (i.e., linear or star), inherent viscosity, glass transition temperature, and polymer end-cap

Garnera J et al. A protocol for assay of poly(lactide-co-glycolide) in clinical products. International Journal of Pharmaceutics 495 (2015) 87–92.
This work was supported by FDA grant U01FD05168.

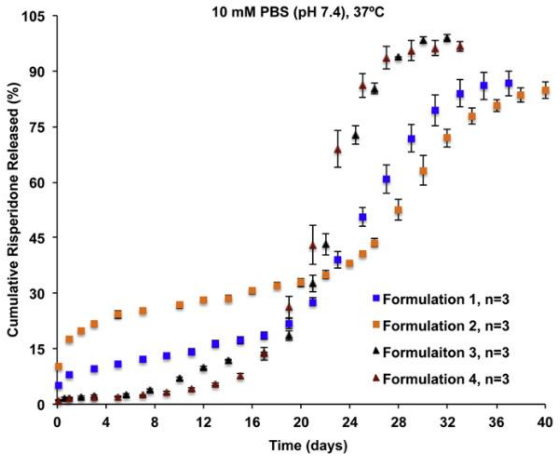
Q1 Polymer Sameness

- Impact of manufacturing conditions on complex inactive ingredients



PLGA degradation during manufacturing of risperidone-PLGA microsphere

- In vitro and in vivo drug release profiles are sensitive to manufacturing differences

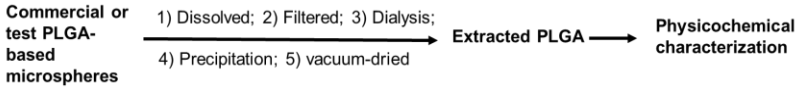


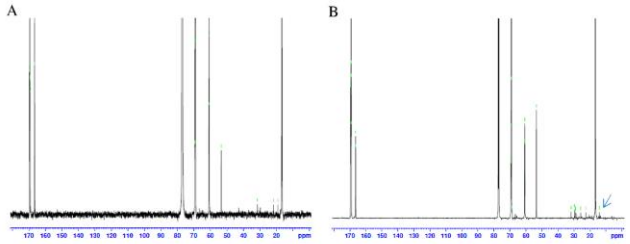
In vitro release profiles of the formulation composition equivalent risperidone microspheres with manufacturing differences obtained using USP apparatus 4 method at 37 °C in 10 mM PBS (pH 7.4)

J. Shen, S. Choi, W. Qu, Y. Wang, D.J. Burgess. In vitro-in vivo correlation of parenteral risperidone polymeric microspheres. (2015) Journal of Controlled Release. 218, pp. 2-12 http://dx.doi.org/10.1016/j.jconrel.2015.09.051

Q1 Polymer Sameness

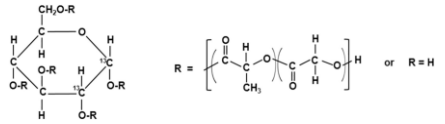
Challenge: Complex reverse engineering as manufacturing process can change PLGA properties
GDUFA research: developed a protocol to extract PLGA from the finished product and developed characterization methods for PLGA.

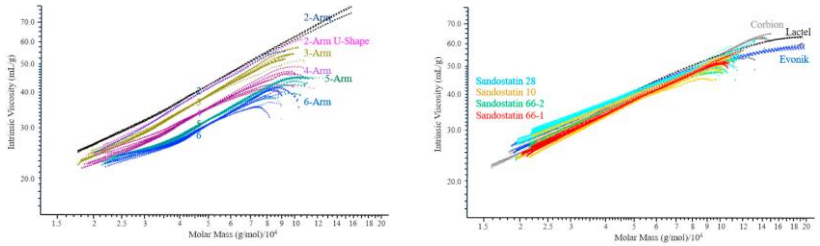




Int. J. Pharm. 495 (2015) 87–92
Grant U01FD05168

Challenge: No readily available method to characterize glucose cored, star-shaped PLGA
GDUFA research: developed characterization method to characterize glucose cored, star-shaped PLGA

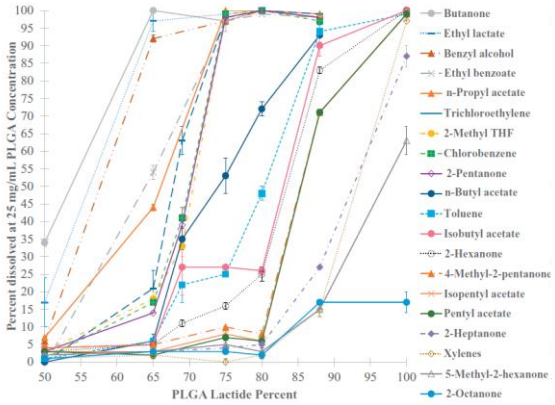




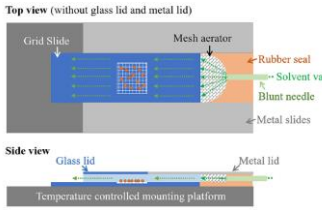
J. Control. Release 204 (2019) 75-89
Contract HHSF223201710123C

Q1 Polymer Sameness

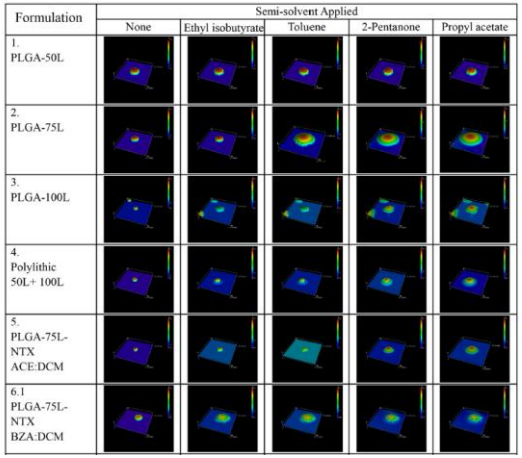
Challenge: Difficult to characterize products containing more than one PLGA
GDUFA research: Semi-solvents were studied to develop method to separate PLGAs based on different lactide to glycolide ratio. SAVI showed potential to reveal composition of PLGA microspheres and to probe structural arrangement differences that arise from different manufacturing process.



J. Control. Release 300 (2019) 174-184
Contract HHSF223201610091C



Surface analysis of sequential semi-solvent vapor impact (SAVI)



J. Control. Release 350 (2022) 600-612
Contract 75F40119C10096

Long-Acting Injectables

- The analytical methods and the correlation of polymer properties with drug delivery is valuable for the development of future long-acting products

Q3 BE for Topicals

- Over the past 10 years, ORS has developed a comprehensive Q3 approach to BE for topical semi-solids
  - Q1 => characterizes the components
  - Q2 => characterizes the specific concentrations of those components
  - Q3 => the arrangement of matter in the drug product characterized by the physicochemical properties of the formulation
- ~50 ANDAs have been approved using Q3 BE instead of clinical endpoint bioequivalence studies

GDUFA Science and Research Creating Competition and Growth

Pre-GDUFA

- Vasoconstrictor assays and older AT rated products support most generics
- Most other generic topical products supported by comparative clinical endpoint BE studies (500+ subjects common)
- 2012 six ANDA approvals supported by CEBE

GDUFA I

- Science and research on in vitro BE approaches begins

GDUFA II

- PSG and pre-ANDA meetings on product-specific in vitro approaches

Current State

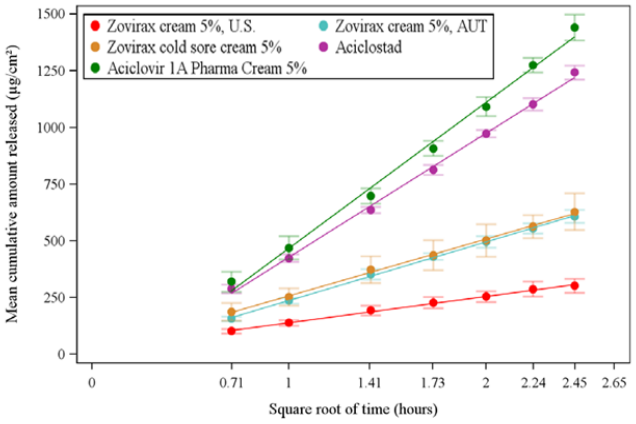
- Oct 2022: Three general guidances on in vitro approaches and 80 PSG updates posted
- Past ~~three~~ 3 years of ANDA submissions
  - 16 Comparative clinical endpoint BE studies
  - 75 Q3 BE submissions
- Science and research investment created new business opportunities and expanded generic competition

GDUFA III

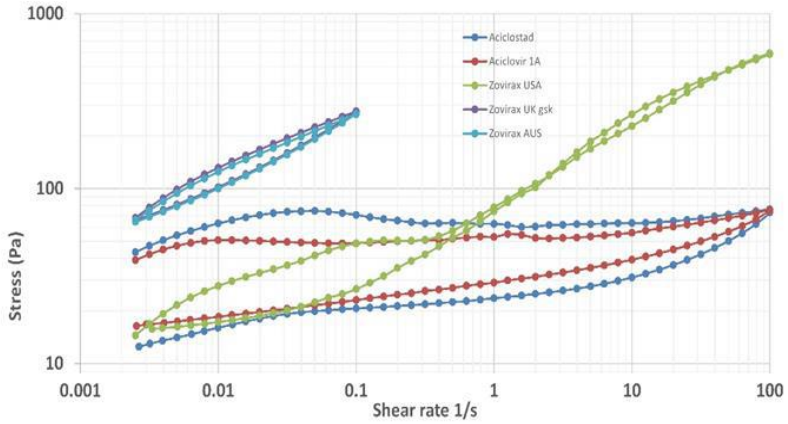
- New mechanisms to accelerate assessments of complex generic submissions

Q3 Foundation

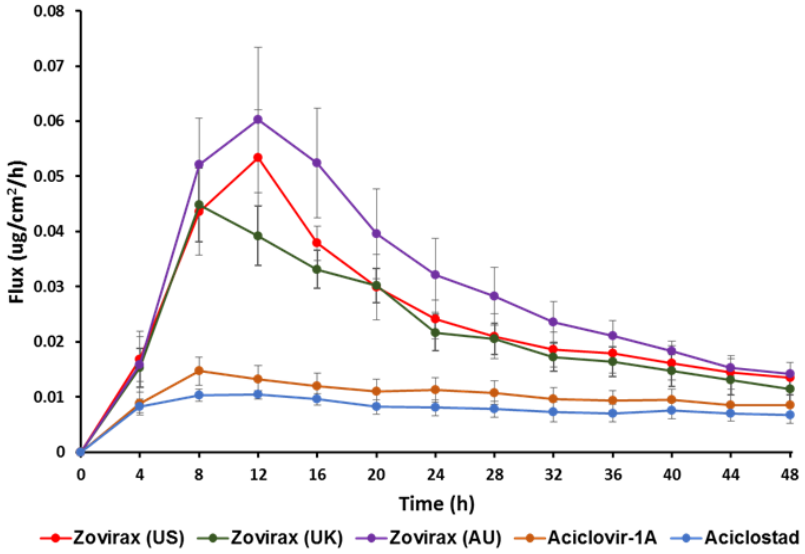
- Research on the following tools
- **Physical & Structural Characterization** as relevant to the nature of the product
- **IVRT**(In Vitro Release Test) for moderately complex products
- **IVPT**(In Vitro Permeation Test) or another bio-relevant assay for more complex drug products



In Vitro Release Test (IVRT)



Thixotropic Rheology



In Vitro Permeation Test (IVPT)

Topical Semi-solids

- Strong scientific foundation for formulation development of topical products
- Integration with PBPK models

Complex Peptides and Oligonucleotides

- Large Peptides
  - Dec 2020: ANDA 208086
    - Glucagon injectable
    - first synthetic peptide referencing recombinant
- Oligonucleotide-based therapeutics

- Characterization
  - Methods to identify peptide impurities
  - Characterization of oligonucleotide products

- Immunogenicity
  - Develop methods to evaluate innate immune response

Oligonucleotide-based Products

Proprietary name	Active ingredient	Category	Length of Oligonucleotide
VITRAVENE	Fomivirsen sodium	Phosphorothioate ASO	21
MACUGEN	Pegaptanib sodium	Phosphate oligonucleotide aptamer	28
KYNAMRO	Mipomersen sodium	Phosphorothioate ASO	20
EXONDYS 51	Eteplirsen	Phosphorodiamidate morpholino ASO	30
SPINRAZA	Nusinersen sodium	Phosphorothioate ASO	18
ONPATTRO	Patisiran sodium	Double-stranded siRNA	19+2 (antisense)
TEGSEDI	Inotersen sodium	Phosphorothioate ASO	20
GIVLAARI	Givosiran sodium	Double-stranded siRNA	21+2 (antisense)
VYONDYS 53	Golodirsen	Phosphorodiamidate morpholino ASO	25
VILTEPSO	Viltolarsen	Phosphorodiamidate morpholino ASO	21
OXLUMO	Lumasiran	Double-stranded siRNA	21+2 (antisense)
AMONDYS 45	Casimersen	Phosphorodiamidate morpholino ASO	22
LEQVIO	Inclisiran	Double-stranded siRNA	21+2 (antisense)
AMVUTTRA	Vutrisiran	Double-stranded siRNA	21+2 (antisense)

Comparison of Impurities

Peptide-related impurities

- Often exist in a single, optically pure active pharmaceutical ingredient (API)
- Oxidation, acylation and deamidation happen on certain amino acids
- 20+ unique amino acids
- UPLC-MS/MS method can provide highly sensitive method for impurity identification/characterization

ASO-related impurities

- Exist in an API which is often a mixture of huge number of diastereomers (2^{n-1})
- Can happen in any nucleotide unit and/or backbone linkage
- Very limited number of bases (A, C, G, T, U), resulting in many repeating nucleotide unit in an ASO
- Currently, very to identify/characterize a single product-related impurity among all the impurities

Risk-based Immunogenicity for Peptides

- Depending on the risk-analysis a PSG for ANDA development may recommend
  - Comparative impurity profile
  - Comparative aggregation
  - Innate immune response
  - Adaptive immune response (MHC binding)

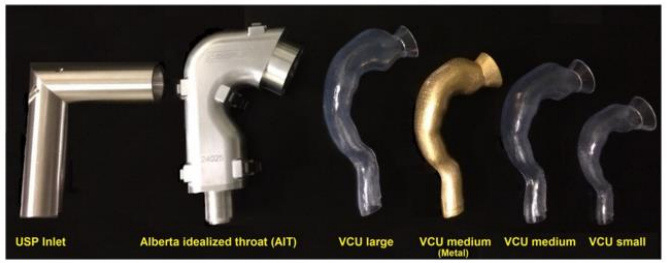
Broader Value

- Move away from clinical studies for immunogenicity
  - Allow synthetic generics to reference recombinant RLD
- This has impacted the evaluation of B2 applications
- Critical to access to generic version of synthetic peptides for emerging weight-loss indications

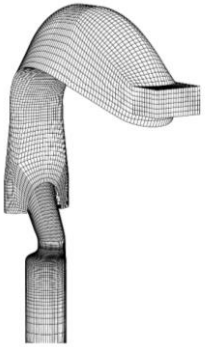
Nasal and Inhalation Products

- ORS has supported the development of methods to evaluate the local delivery of nasal and inhalation products
  - Improved realistic in vitro methods
  - Advances in CFD models to understand drug deposition
  - Material Characterization

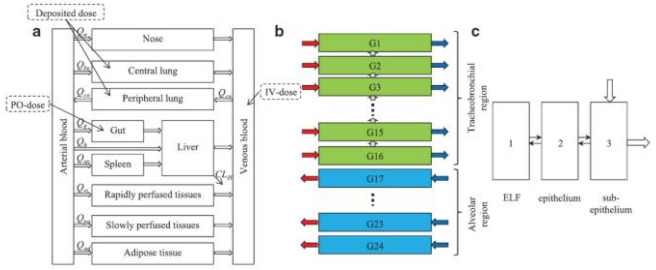
Alternative BE Approaches



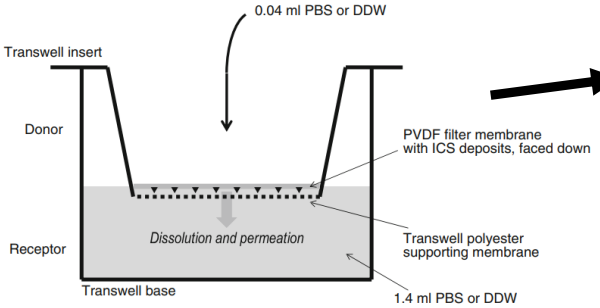
Realistic mouth-throat APSD[8]



Computational fluid dynamics (CFD)[13]

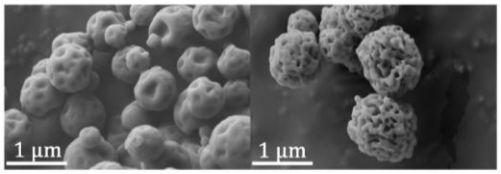


Physiologically based pharmacokinetic modeling[12]

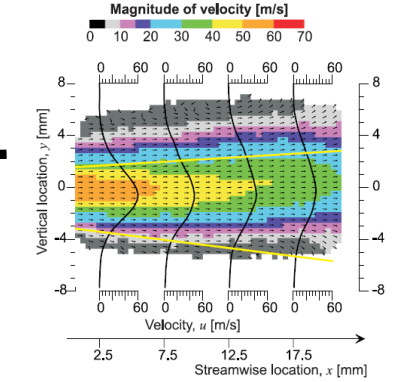


Dissolution[9]

BE at the site of action

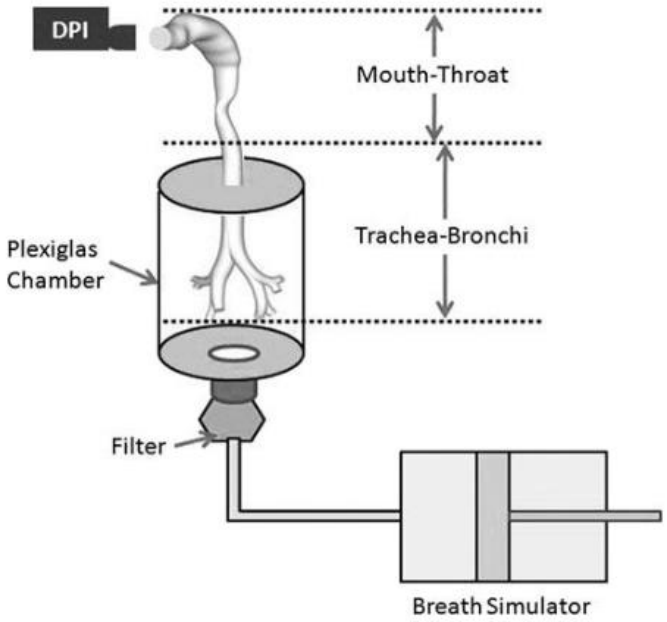


Morphology[10]



Spray velocity and evaporation[11]

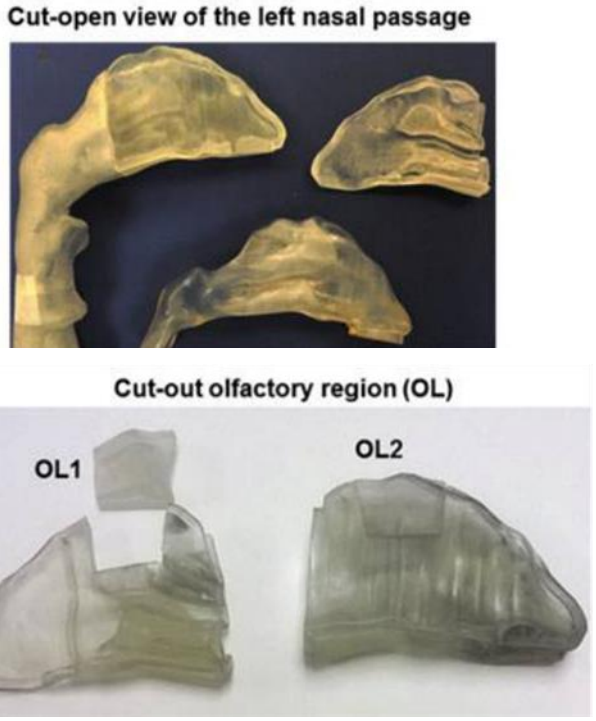
Regional Deposition – In Vitro



Mouth-throat and lung model in vitro setup
(Figure from Delvadia et al.[14])

- Realistic mouth-throat models
  - Rapid prototyping
  - High performance liquid chromatography
  - May include tracheobronchial region but limited to large airways

Nasal In Vitro Models

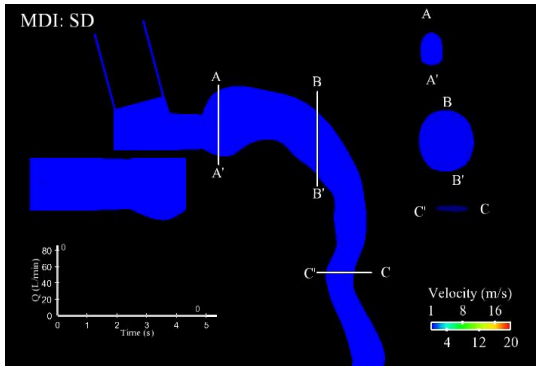


Nasal in vitro model that allows for measurement of olfactory region deposition. (Adapted from Fig. 1c of Xi et al.[15])

- Drug product is actuated into nasal model
- Deposited drug is measured from removable sections using high performance liquid chromatography (HPLC)
- Deposition may show significant intersubject variability according to anatomical differences
- Olfactory deposition may be measured with separate section

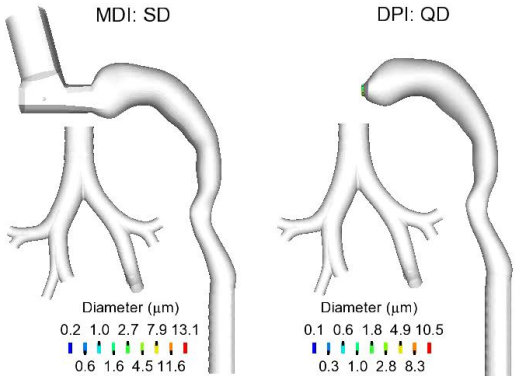
Computational Fluid Dynamics (CFD) Modeling

- Prediction of fluid and particle transport
- Allows for consideration of realistic geometries
- Validated with in vitro or in vivo data



Metered Dose Inhaler (MDI)

Simulations from Longest et al.[16]



Dry Powder Inhaler (DPI)

Central and Peripheral Regions

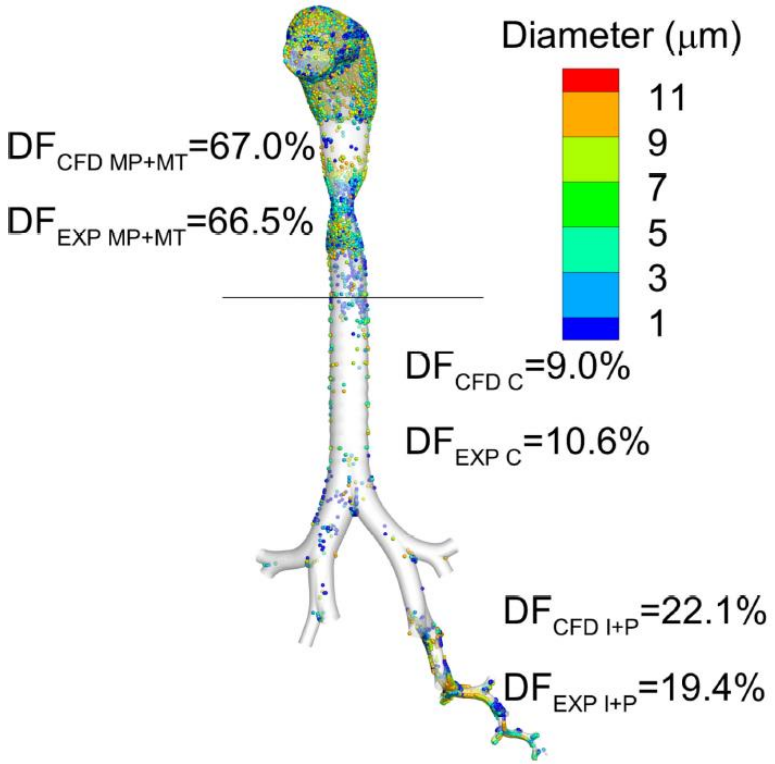


Figure 6 from Tian et al.[17]

- Generic Drug User Fee Amendments (GDUFA)-funded research
  - Virginia Commonwealth University (PI: P. Worth Longest)
  - Grant #1U01FD004570
- Predict regional deposition fraction (DF) (mouthpiece (MP), mouth-throat (MT), central (C), intermediate (I), and peripheral(P)) for DPI (pictured on left) and soft mist inhaler
- Stochastic individual path (SIP)
- Compare with in vivo gamma scintigraphy data[18]

Alveolar Region

- Grant #1U01FD004570
- Used moving-wall CFD model to investigate variety of alveolar model orientations and the effect of additional alveolar duct generations on deposition
- Produced correlations based on aerodynamic particle diameter and particle residence time in the alveolar region

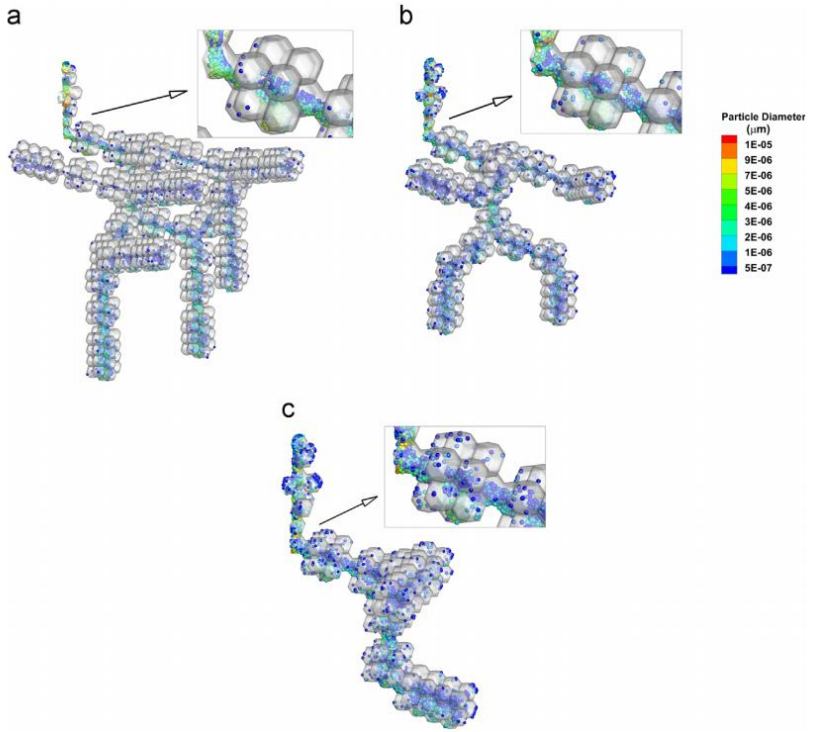
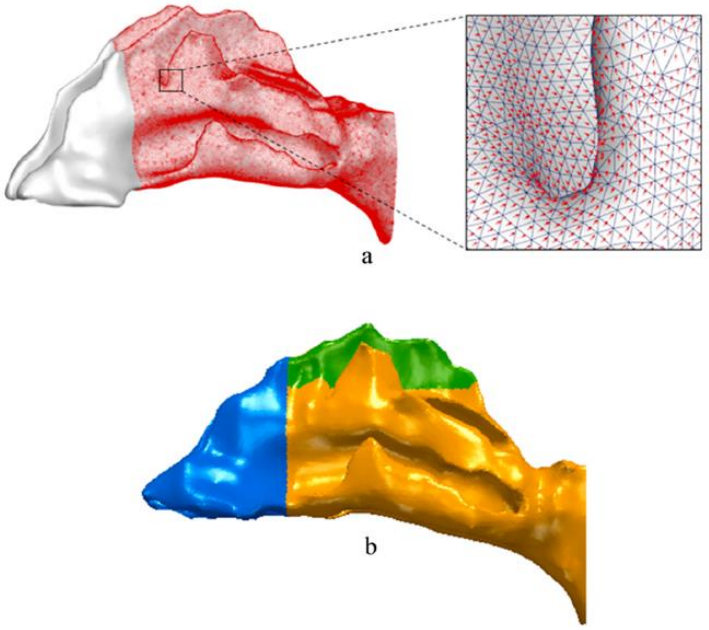


Figure 7 from Khajeh-Hosseini-Dalasm and Longest[19]

3D Nasal Model



Nasal MCC model features, including a) 6 mm/min mucus velocity vectors in mucus layer and b) regional definitions including olfactory (red), nasal vestibule (blue), and nasal cavity (orange) regions. (Fig. 1 of Chari et al.[14])

- North Carolina State University
  - PI: Clement Kleinstreuer
  - Grant #1U01FD006537: 2018-2021
- 3D CFD model is used to predict regional deposition of NDPs
- Particle deposition locations are directly translated to fully 3D mucus layer model
- Nasal MCC model predicts transit, dissolution, and absorption simultaneously
- Can be used for predicting olfactory region deposition and absorption

Nasal and Inhalation Products

- ORS has integrated CFD modeling into the pharmaceutical science of nasal and inhalation products
- Valuable for all inhalation and nasal development programs

Summary

- Advances in science and research related to core challenges facing generic drug development are general valuable for pharmaceutical product development
- Much of the value the ORS has created has come from working at the intersection of clinical pharmacology and pharmaceutical science
- For generic drug applications, the key question is the clinical significance of formulation changes
- For products with local action, the generic drug scientific foundation is broadly useful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