Fiscal Year 2024 Generic Drug Science and Research Initiatives Public Workshop

Integration of Simulation, In Vitro and Clinical Methods to Support Complex Drug Product Development

Will Ganley

20th May 2024

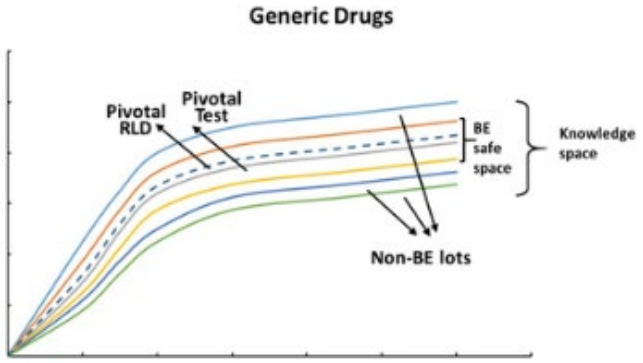
Nanopharm
an Aptar pharma company

Roles of Modelling in Generic Drug Product Development

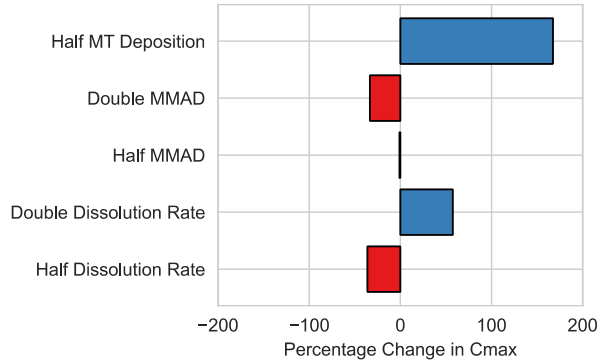
Development Tools

Support product development decision making

Formulation Safe Space



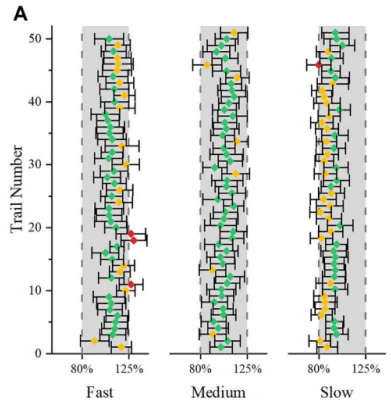
Sensitivity Analysis



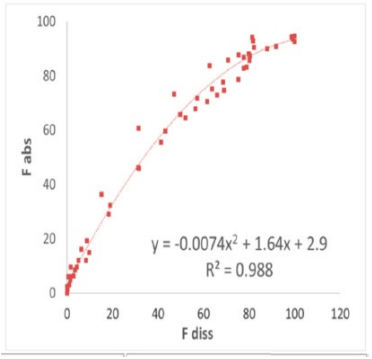
Regulatory Tools

Support regulatory decision making

Virtual Clinical Studies



IVIVC



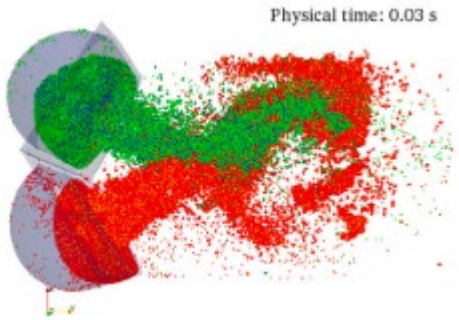
Zhang et al. 10.3389/fphar.2022.808456
Wu et al. 10.1007/s11095-022-03319-6
Bermejo 10.3390/pharmaceutics11030122
Ganley et al. RDD 2023

Nanopharm
an Aptar pharma company

Success in R&D: Augmenting In Vitro and Clinical Studies

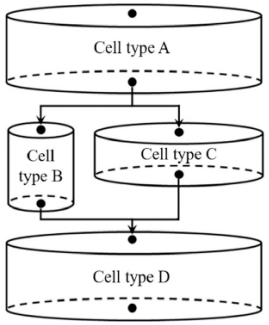
Modelling and simulation methods to elevate in vitro and clinical studies

In Vitro Lab Studies



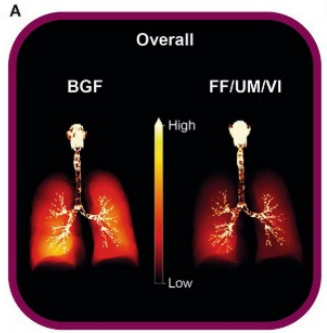
Simulations of Aerosolisation in DPIs Device Designs and Patient Breathing Profiles

In Vitro Cell Studies



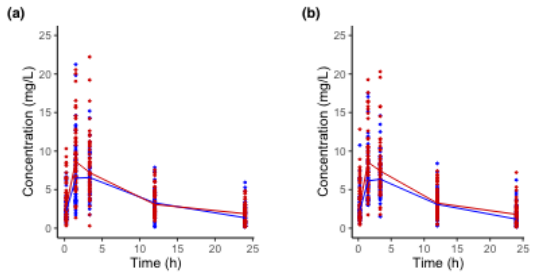
Quasi- 3D Modelling Drug Transport Across the Cornea transcellular and paracellular pathways

Clinical Imaging Studies



Simulated lung deposition for different inhaled products

Pharmacokinetic Studies



Model-based equivalence assessment for sparsely sampled pharmacokinetics

Sulaiman et al. 10.1002/psp4.12960
Pak et al. 10.1016/j.compbiomed.2017.11.009

Usmani et al. 10.1186/s12931-023-02534-y
Tardivon et al. 10.1002/psp4.12960

Nanopharm
an Aptar pharma company

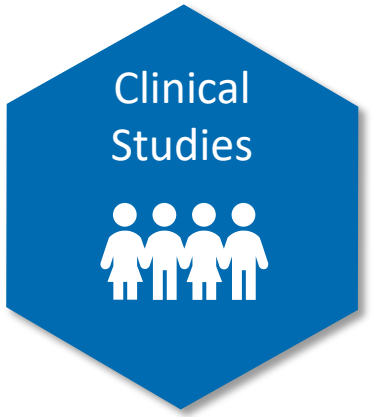
Challenge: How Do We Bring This All Together

- So far, a lot of success we need a roadmap for using modelling and simulation to get more generic drugs to market, particularly for complex dosage forms

- Relevant to local exposure
- BE bounds set using modelling
- Accompanying in silico models

- Extrapolation from in vitro studies
- Incorporation into physiological models

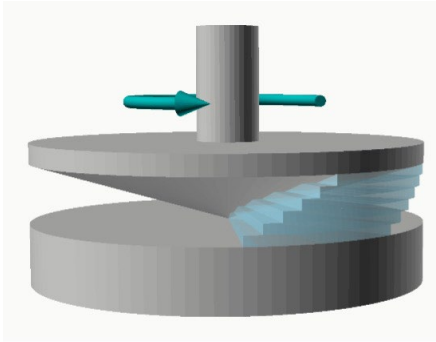
- Sufficient available data for validation
- Common framework
- Routes for adding new models



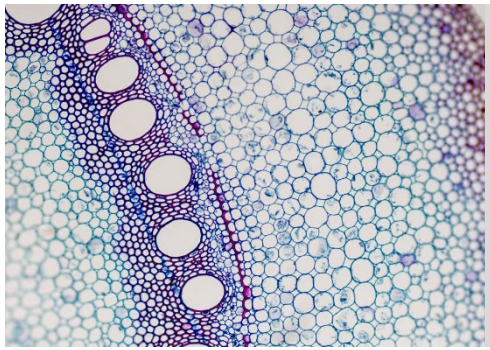
- Robust statistical approaches
- Reduce or replace clinical studies

Nanopharm
an Aptar pharma company

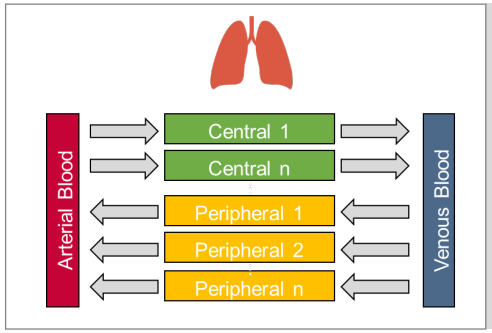
Future Research Areas: Developing Mechanistic Models to Support In Vitro Tools



- **Flow**
  - Biorelevant mucociliary clearance assays
  - Easy extrapolation to local site (i.e. nasal cavity, ocular drainage)
  - Screen for excipient differences (non-Q1/Q2)



- **Permeation and Release**
  - Mechanistic extrapolation from cell lines to physiological models
  - Easy extrapolation to dissolution at the delivery site (e.g. upper/lower airways)
  - Mechanistic models for tandem in vitro dissolution and permeation models



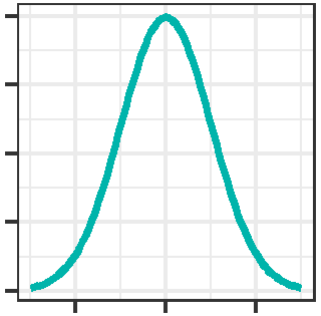
- **Model Structures**
  - Coarse graining – lung nose regions, ocular/epithelial tissue layers

https://fluidan.com/different-types-of-rheometers/

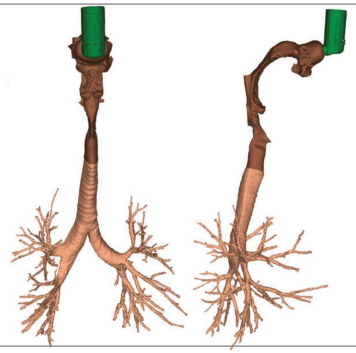
Nanopharm Simhalation™ Graphic

Nanopharm
an Aptar pharma company

Future Research: Simulation of Local Site or Disease State



- **Selection of Disease State Characteristics**
  - Sensitivity analysis – which characteristics are important
  - Variance in population including correlation with other metrics

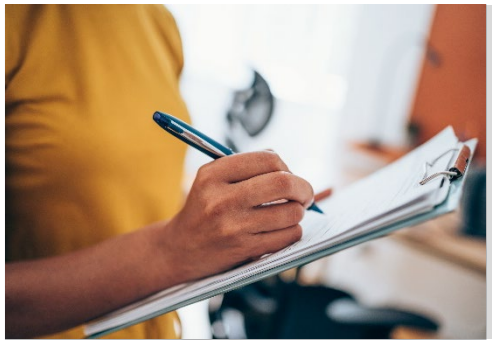


- **Representation of Disease-state Characteristics**
  - Replicated in silico (CFD meshes of airways, mechanistic representations in PBPK)?
  - Replicated in vitro (dissolution media, casts or organ-on-chip)

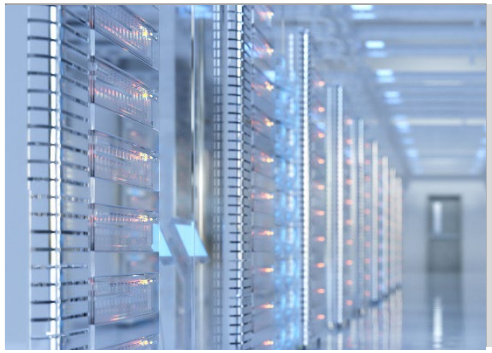
Usmani el al. 10.1089/jamp.2020.1601

Nanopharm
an Aptar pharma company

Future Research: Management of Model Risk



- **Understanding of Risk for Different Use Cases**
  - Alternative bioequivalence
  - Justifying in vitro BE bounds
  - Investigating in vitro BE failure
  - Replacing in vitro studies



- **Governance of Publicly Available Data for Model Validation**
  - Academic data stored
  - Private data can be entered
  - Access controlled

Future Research: In Silico Clinical Studies

- **Patient Selection**
  - Selection criteria – extend beyond age, disease state etc.
  - Generation of virtual patients (which parameters to vary, correlation between parameters)
  - Propagation of variance from inputs to endpoints

$$\frac{(\mu_{\mathrm{T}}-\mu_{\mathrm{R}})^2+\sigma_{\mathrm{TT}}^2-\sigma_{\mathrm{TR}}^2}{\max(\sigma_0^2,\sigma_{\mathrm{TR}}^2)}$$

- **Statistics**
  - BE statistics
  - Control of error

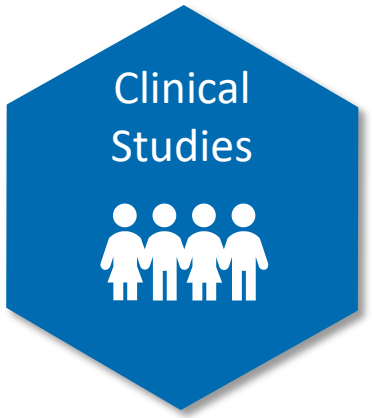
Integrated Generic Drug Product Development Platform

- Outcomes of potential research programmes
  - Mechanistic models of in vitro models
  - New in vitro methods to investigate local exposure
  - Methods for disease state representation in silico (including virtual patient selection)
  - Worked examples of credibility requirements for wider range of scenarios
  - More robust guidance on model-informed evidence

- Relevant to local exposure
- BE bounds set using modelling
- Accompanying in silico models

- Extrapolation from in vitro studies
- Incorporation into physiological models

- Sufficient available data for validation
- Common framework
- Routes for adding new models



- Robust statistical approaches
- Reduce or replace clinical studies

Nanopharm
an Aptar pharma company

Thank you!

Nanopharm
an Aptar pharma company