FLUIDDA

DIGITAL TWINS AND IN-SILICO TRIALS TO SUPPORT THE APPROVAL PROCESS OF COMPLEX GENERICS

MOVING TOWARDS QUANTITATIVE MEDICINE

Jan De Backer, Phd, MBA
CEO

MODELING AND SIMULATION IN HEALTHCARE

FLUIDDA

Prior to 2016

MODELING AND SIMULATION IN HEALTHCARE

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Prior to 2016

“patients are not robots”

“Your models are nice, but that is not the reality…”

“impressive technology but it misses…”

QUANTITATIVE MEDICINE

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April 2024

FDA – Center of Excellence for Quantitative Medicine

"QM involves the development and application of exposure-based, biological, and quantitative modeling and simulation approaches derived from nonclinical, clinical, and real-world sources to inform **drug development**, **regulatory decision-making**, and **patient care**."

QUANTITATIVE MEDICINE IN THE DEVELOPMENT OF COMPLEX GENERICS

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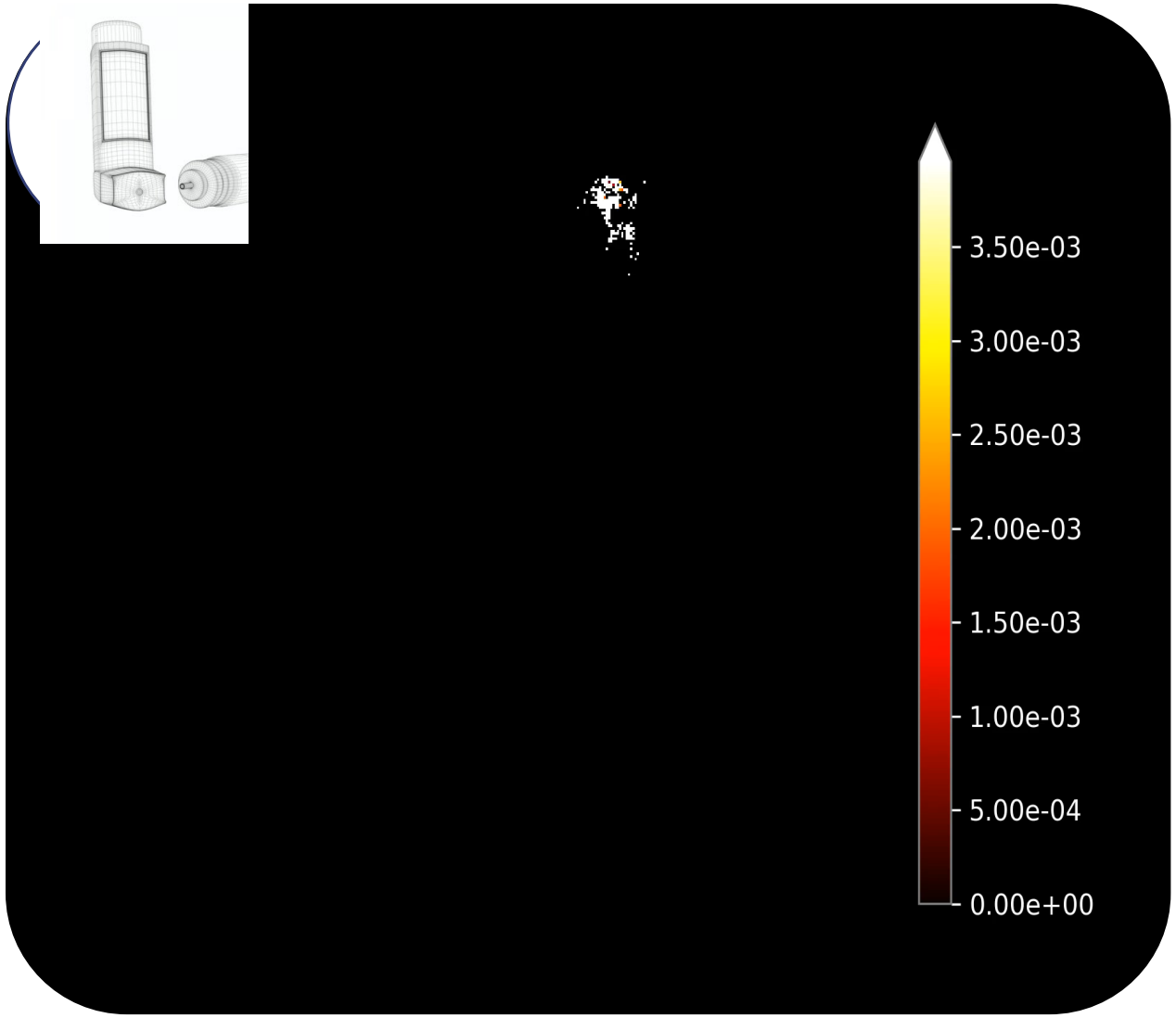
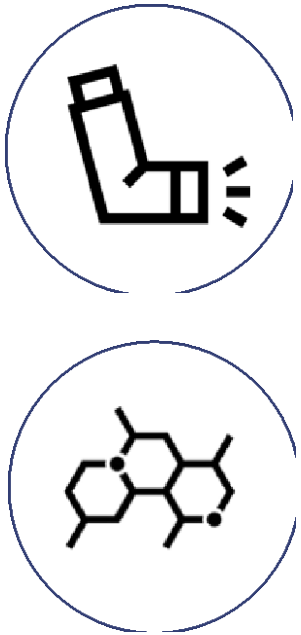
Context of Use

use of in-silico models in combination with in-vitro and PK studies to obtain a **bio-waiver for the clinical endpoints study** for the approval of orally inhaled generics

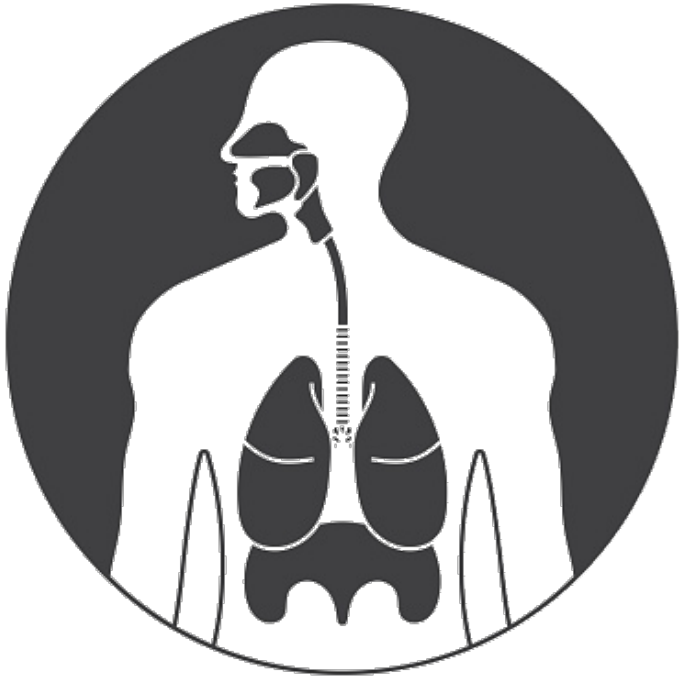


THREE PILLARS FOR BIO-EQUIVALENCE STUDIES

FLUIDDA



DEVICE & FORMULATION



LOCAL EXPOSURE

SYSTEMIC EXPOSURE

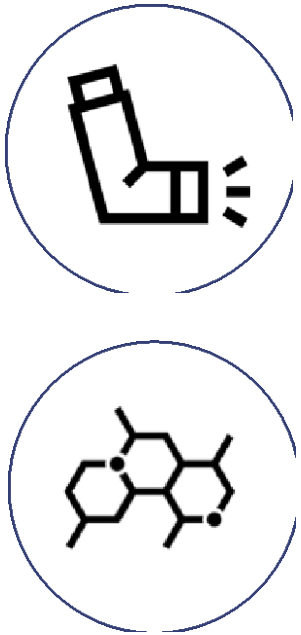
IN-VITRO TEST

CLINICAL ENDPOINT STUDY

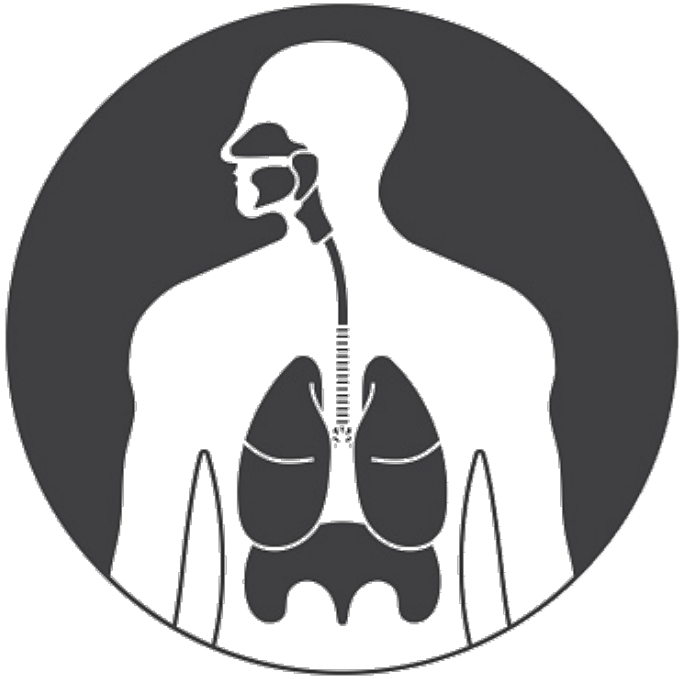
CLINICAL PHARMACOKINETIC STUDY

THREE PILLARS FOR BIO-EQUIVALENCE STUDIES

FLUIDDA



DEVICE & FORMULATION



LOCAL EXPOSURE

SYSTEMIC EXPOSURE

IN-VITRO TEST

CLINICAL ENDPOINT STUDY
High Cost (+$50M)
Long duration (3-5 years)

CLINICAL PHARMACOKINETIC STUDY

THREE PILLARS FOR BIO-EQUIVALENCE STUDIES

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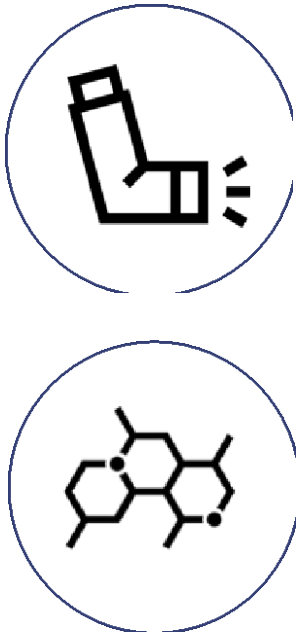
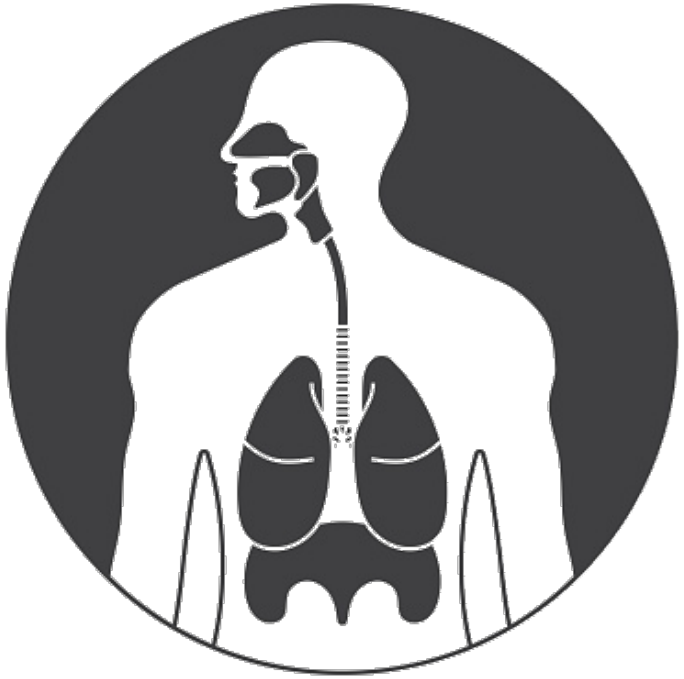


DEVICE & FORMULATION



LOCAL EXPOSURE

SYSTEMIC EXPOSURE

IN-VITRO TEST

IN-SILICO DEPOSITION STUDY

NEW

CLINICAL PHARMACOKINETIC STUDY

RECENT PRODUCT SPECIFIC GUIDANCES

FLUIDDA

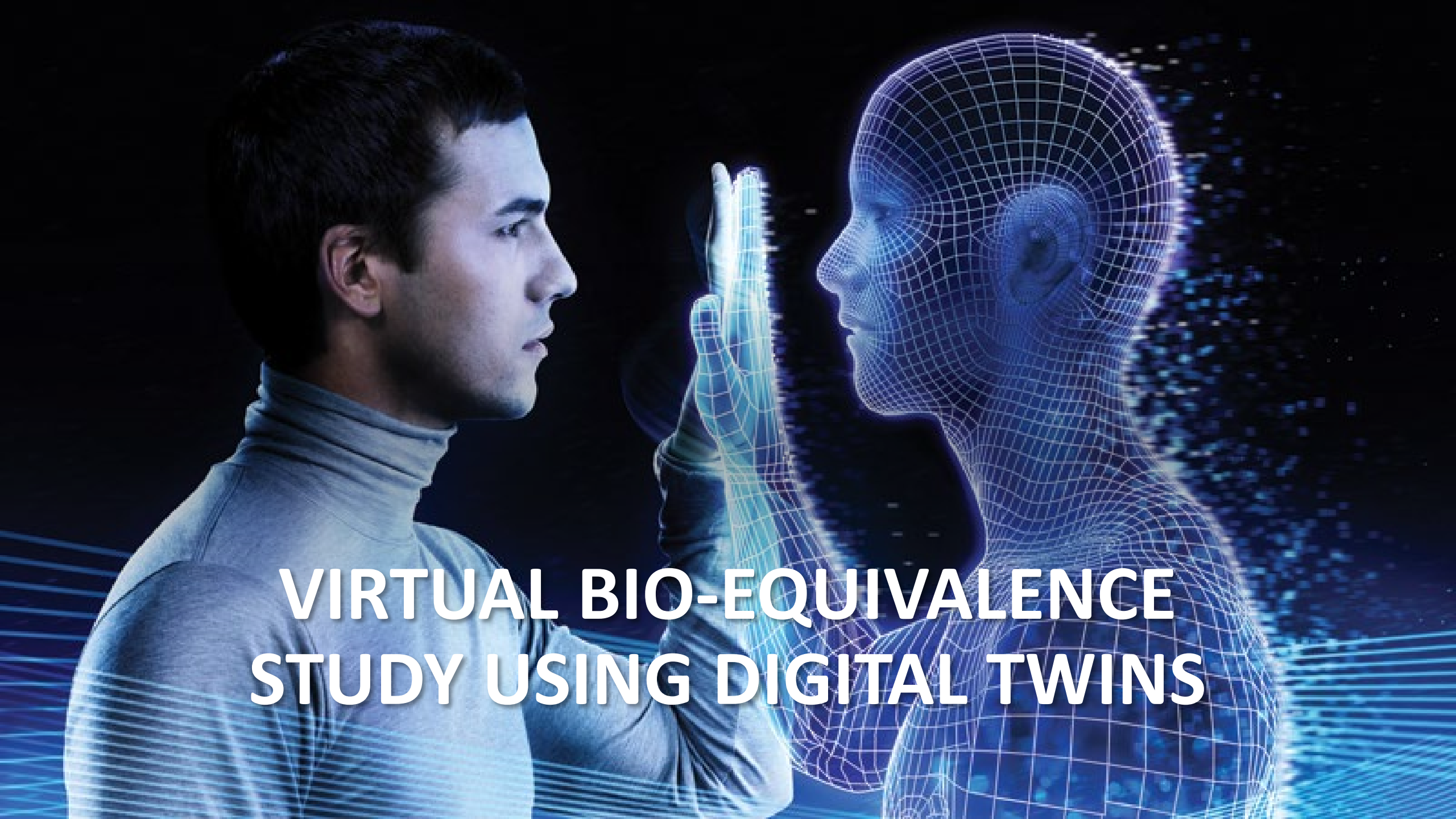
Draft Guidance on Formoterol Fumarate; Glycopyrrolate

February 2024

"[ ] the model may be used to assess the bioequivalence in terms of regional lung deposition by conducting virtual bioequivalence simulations."

"[ ] differentiate the impact of different products (i.e., device and formulation) on regional drug delivery, such that the results may be used to establish biorelevant limits for bioequivalence [ ]"

"To support the stated model purpose(s), the modeling approach may include a regional deposition model that may use either a computational fluid dynamics (CFD) or semi-empirical method to predict central and peripheral region deposition for each active ingredient."


VIRTUAL BIO-EQUIVALENCE
STUDY USING DIGITAL TWINS

KEY PARAMETERS FOR DEPOSITION OF INHALED DRUGS

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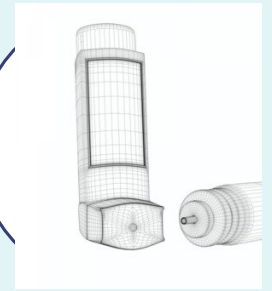
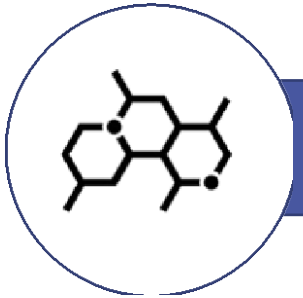
DIGITAL EQUIVALENT

DEVICE

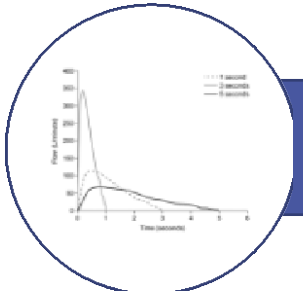
COMPUTER GEOMETRY DEVICE





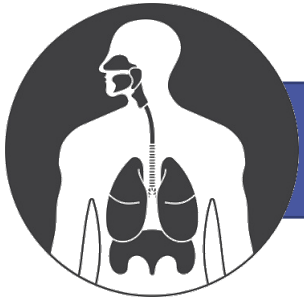
DRUG FORMULATION

IN-VITRO CHARACTERIZATION



INHALATION PROFILE

IN-VIVO MEASUREMENT



LUNG STRUCTURE & FUNCTION

FUNCTIONAL RESPIRATORY IMAGING

FUNCTIONAL RESPIRATORY IMAGING

FLUIDDA

1. CT SCAN

CONVENTIONAL
CT ANALYSES

2. VISUAL READ

FUNCTIONAL RESPIRATORY IMAGING

FLUIDDA

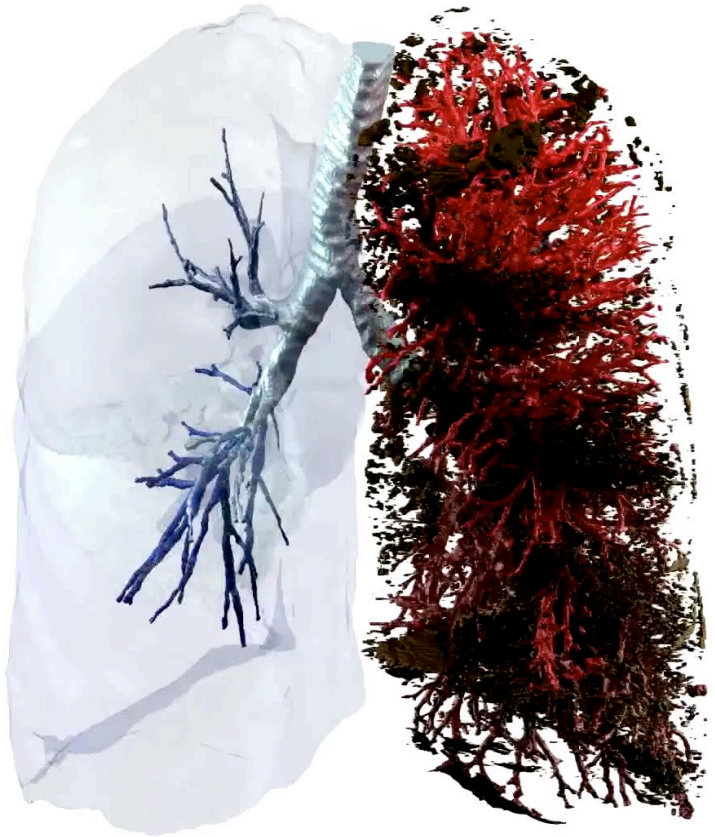
1. CT SCAN

2. CLOUD UPLOAD

20min

FUNCTIONAL RESPIRATORY IMAGING (FRI)

3. REPORTS



FUNCTIONAL RESPIRATORY IMAGING

FLUIDDA

1. CT SCAN

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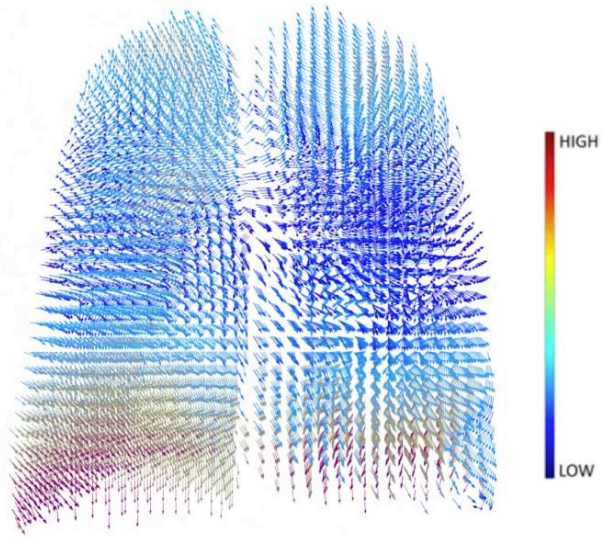
20min

FUNCTIONAL RESPIRATORY IMAGING (FRI)

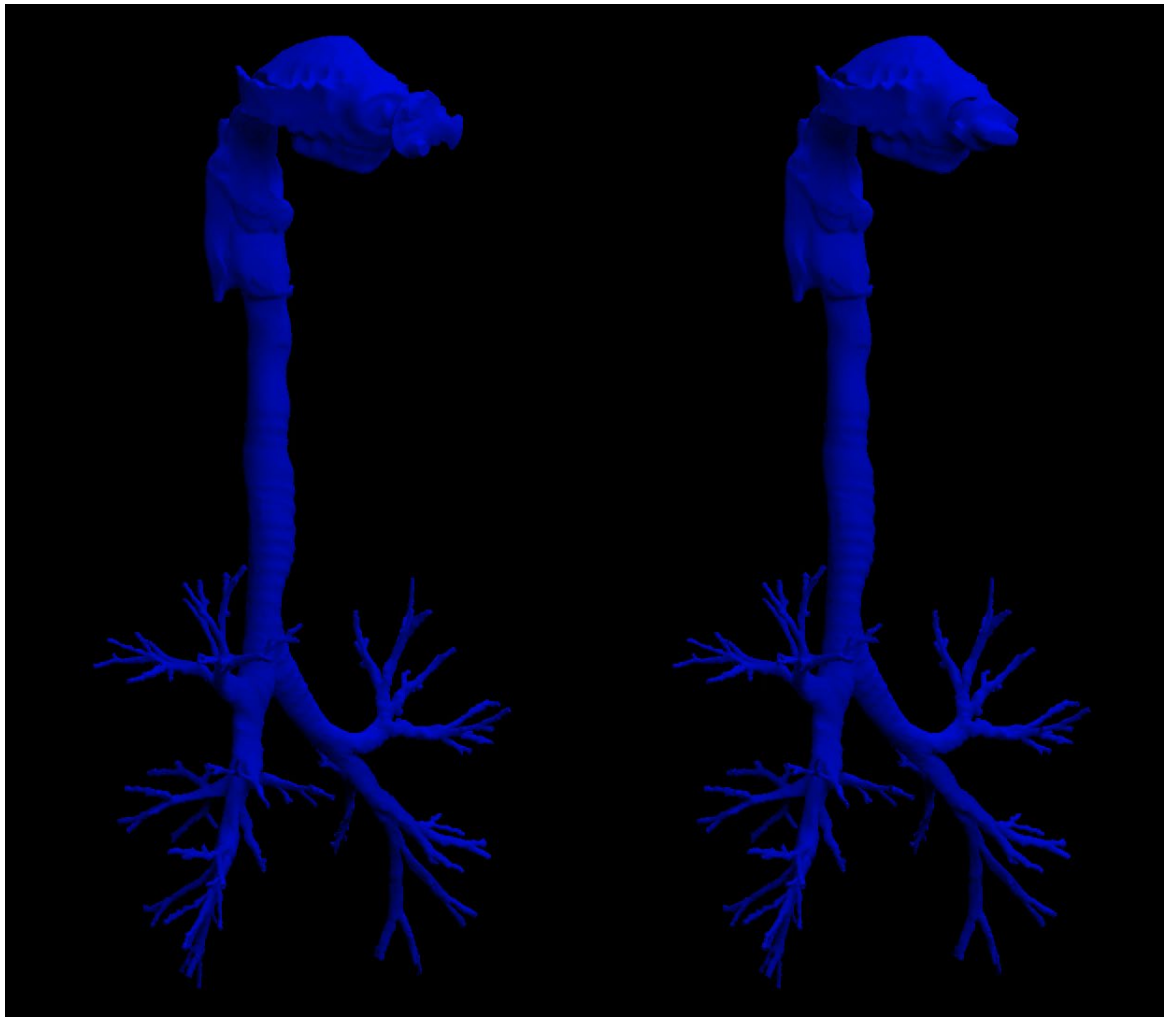
3. REPORTS

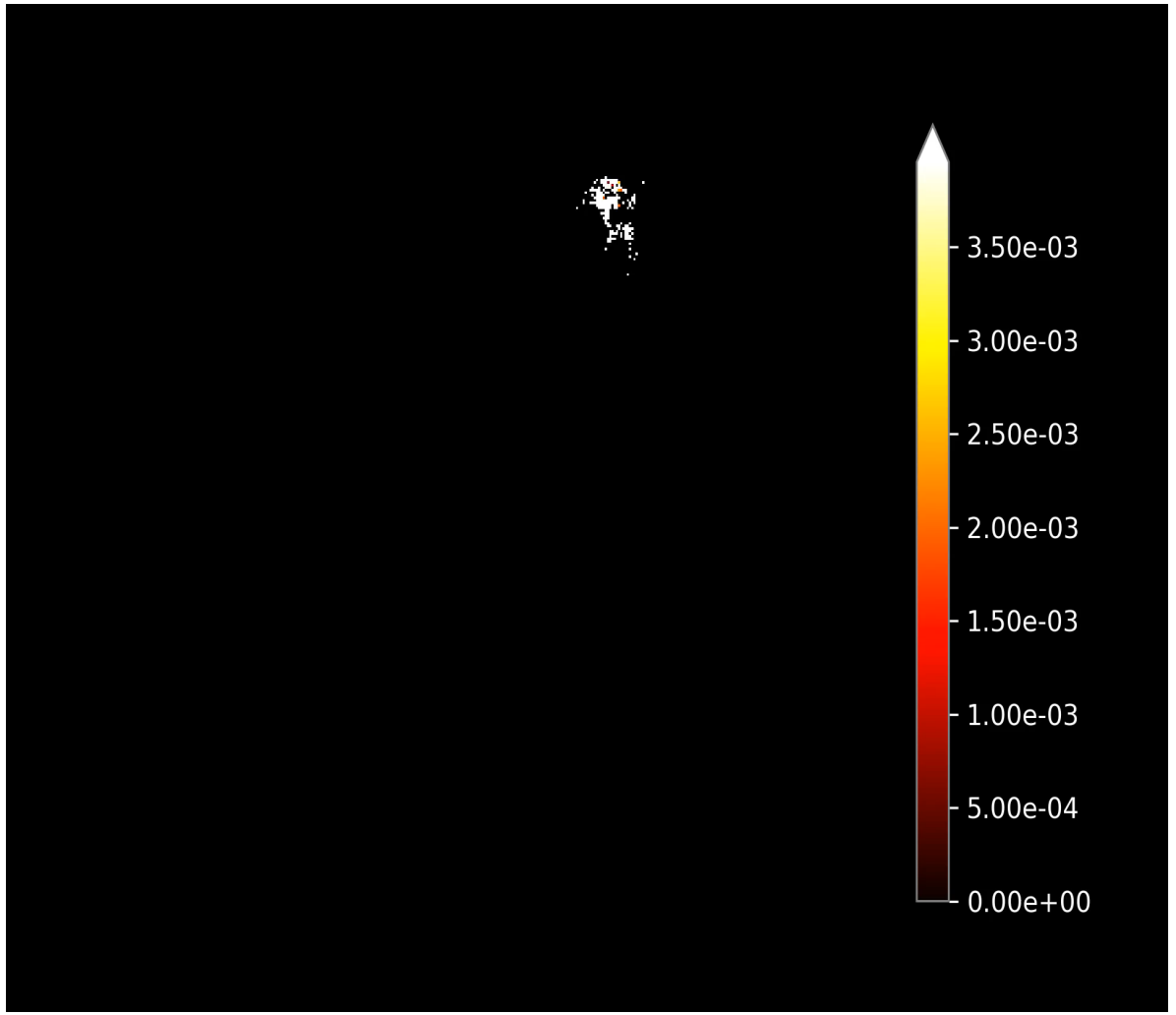


AEROSOL DEPOSITION

FRI yields drug deposition without the need for radiolabeling

FLUIDDA





COMPARISON FRI VS SCINTIGRAPHY

TOTAL LUNG DOSE

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Product	FRI [%Lung Dose]	Scintigraphy [%Lung Dose]
Foster® in COPD	28 [1]	31-34 [2,3]
Flutiform® in Asthma	42 [4]	41 [5]
Symbicort® in Asthma	23 [4]	22 [6]
Qvar® in Asthma	54 *	53 [7]
I-neb® nebulization	45 [8]	42 [9]
eFlow® nebulization	18 [8]	17 [10]
LC Sprint® nebulization	9 [11]	10-15 [12]
AKITA® nebulization	34 [11]	31 [12,13]

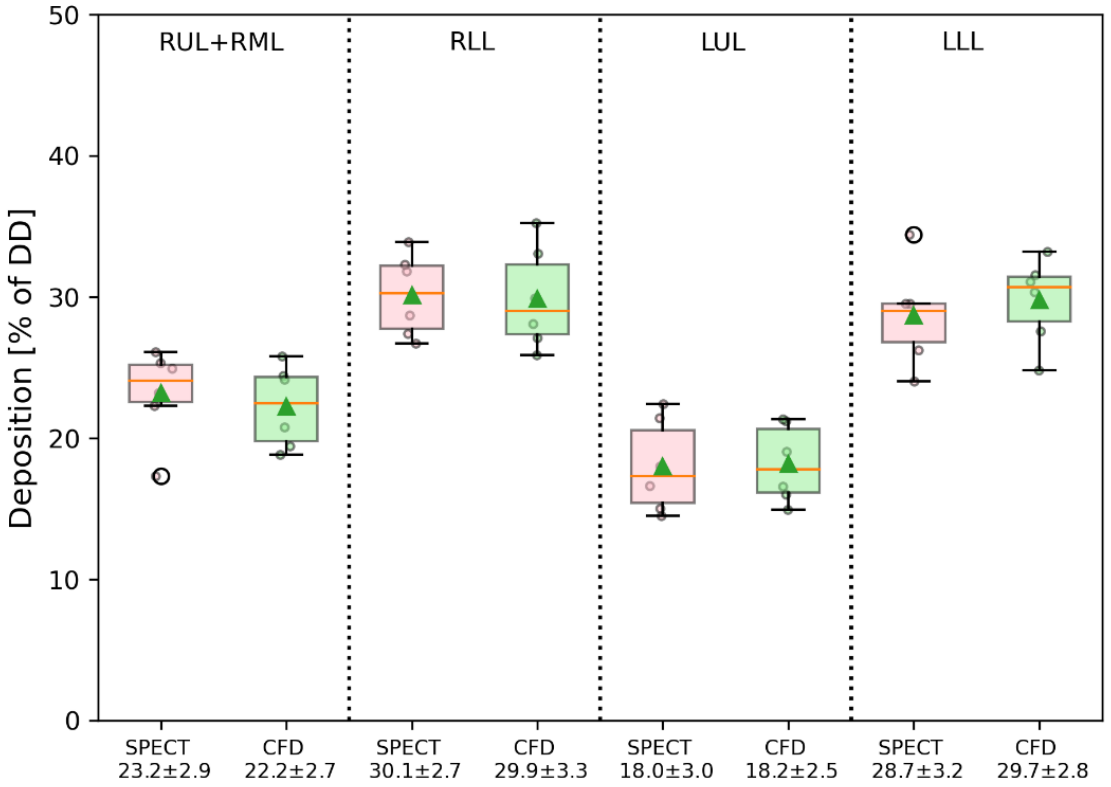
1. Usmani O et al. Proc 28th Int Congr Eur Respir Soc. 2018 Sep.
2. De Maria R et al. Comb Prod Ther. 2014 Feb 1;4.
3. De Backer W et al. J Aerosol Med Pulm Drug Deliv. 2010 Jun;23(3):137–48.
4. Iwanaga T et al. Pulm Ther. 2017;3(1):219–231.
5. Kappeler D et al. Eur Respiratory Soc; 2017.
6. Hirst PH et al. Respir Med. 2001;95(9):720–727.
7. Leach CL et al. J Aerosol Med Pulm Drug Deliv. 2016;29(2):127–133.
8. Hull D et al. J Cyst Fibros. 2018 Jun 1;17:S26.
9. Nikander K et al. J Aerosol Med Pulm Drug Deliv. 2010;23(S1):S–37.
10. Lenney W et al. J Cyst Fibros. 2011;10(1):9–14.
11. Munro S et al. Drug Deliv Lungs. 2017;
12. Fischer A et al. Eur J Med Res. 2009;14(4):71.
13. Müllinger B et al. J Cyst Fibros. 2005 Jan 1;4:S53.

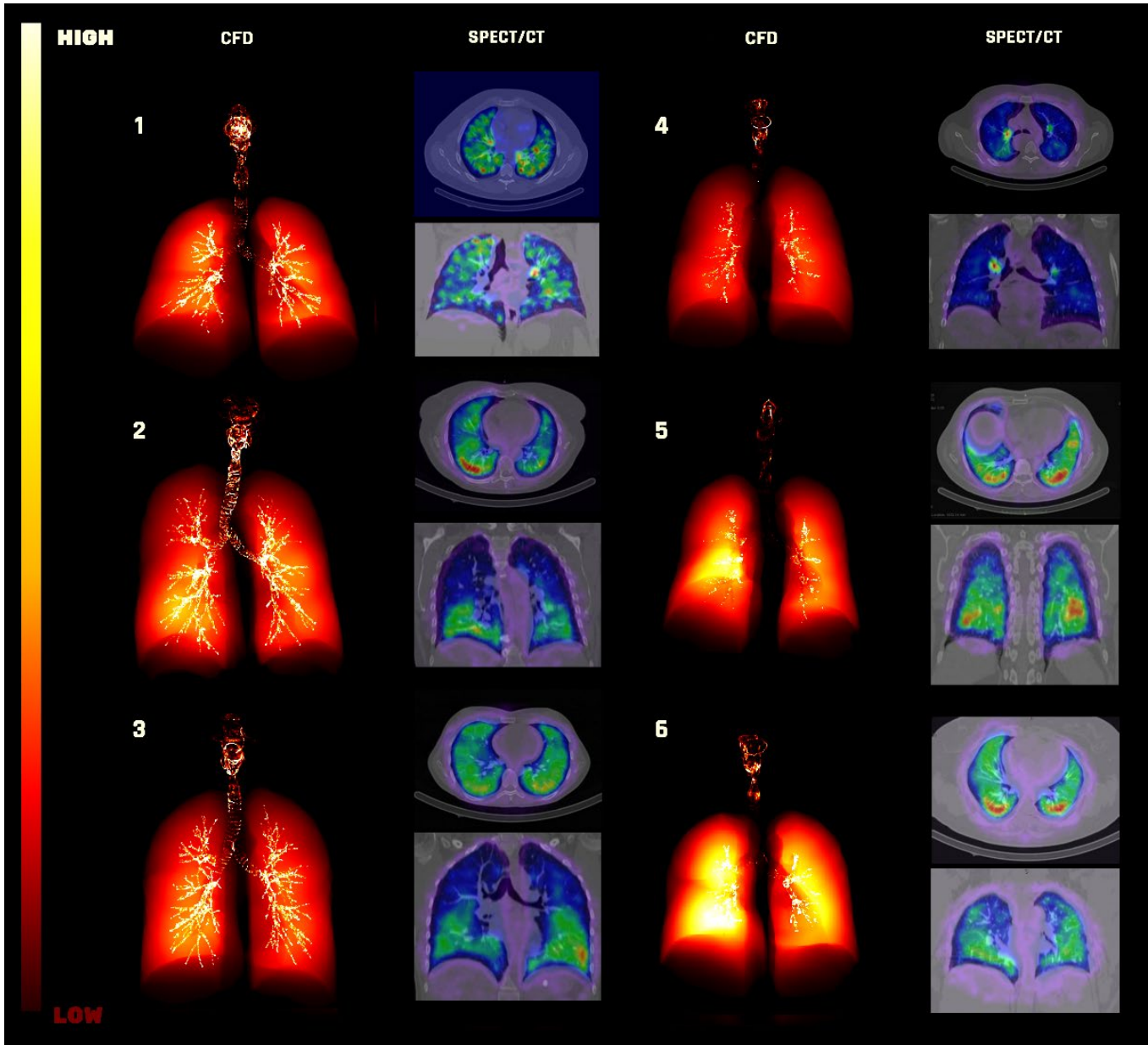
*. Data on file

COMPARISON FRI VS SPECT

LOBAR DOSE

- 6 patients (3F/3M) with mild asthma
- Average age = 46 years ± 17





De Backer et al. Radiology 2010
Sadafi et al. Scientific Reports, 2024

FDA GRANT U01FD007987

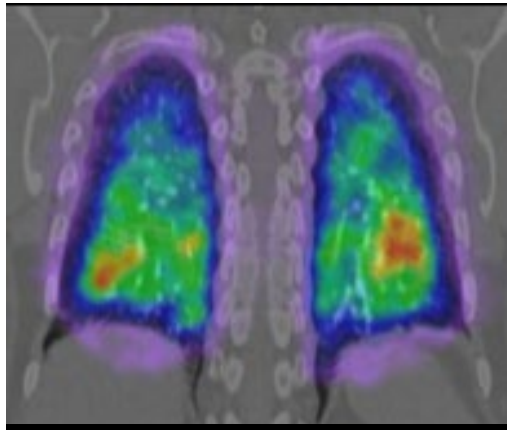
BRANCH LEVEL DOSE

FLUIDDA

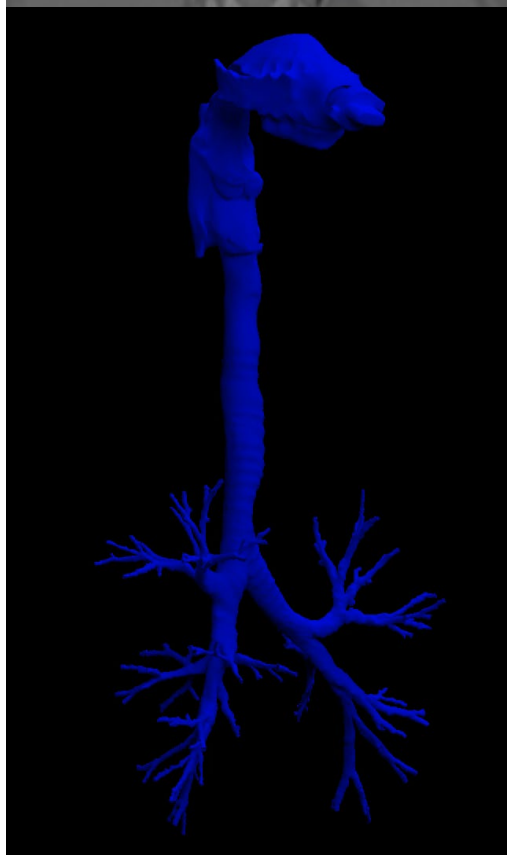
A Prospective Study to Support Validation of Lung Deposition Models with Nuclear Medicine Imaging Methods (U01FD007987)

A grant awarded to Fluidda Inc. focuses on conducting an in vivo nuclear imaging deposition study in human lungs that will produce high resolution branch-level deposition observations that may be used to validate future in silico regional lung deposition predictions

SPECT/PET

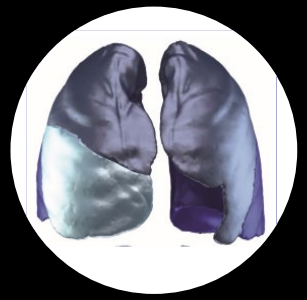


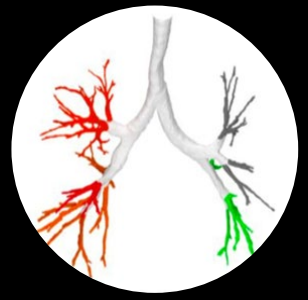
COMPUTATIONAL FLUID DYNAMICS



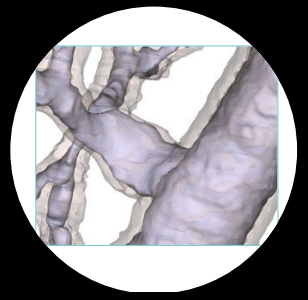
FRI PROVIDES COMPREHENSIVE SET OF QUANTITATIVE OUTCOME PARAMETERS

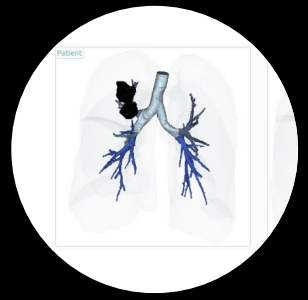
FLUIDDA


Lung Volumes

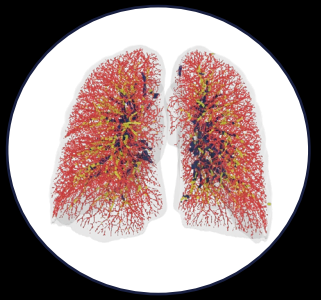

Airway Volumes

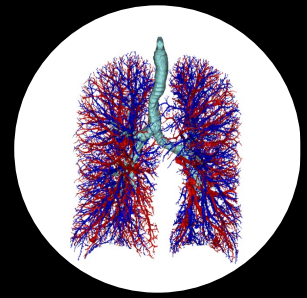

Mucus plugs

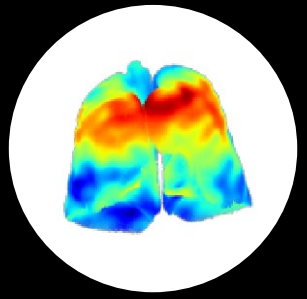

Airway Wall Volumes


Nodules

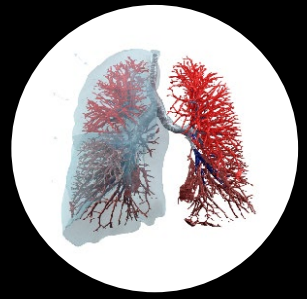

Emphysema

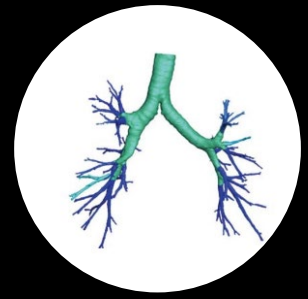

BVX


Arteries Veins

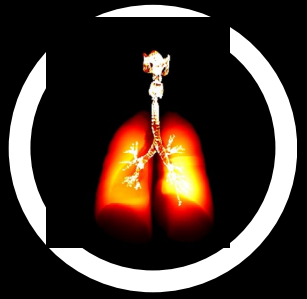

Ventilation


Air Trapping

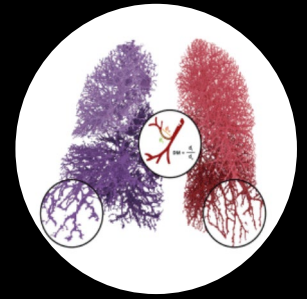

Ventilation/ Perfusion


Airway Resistance


Fibrosis


Aerosol Deposition


Blood Vessel Wall Thickness


Vessel Tortuosity

DRY POWDER INHALERS

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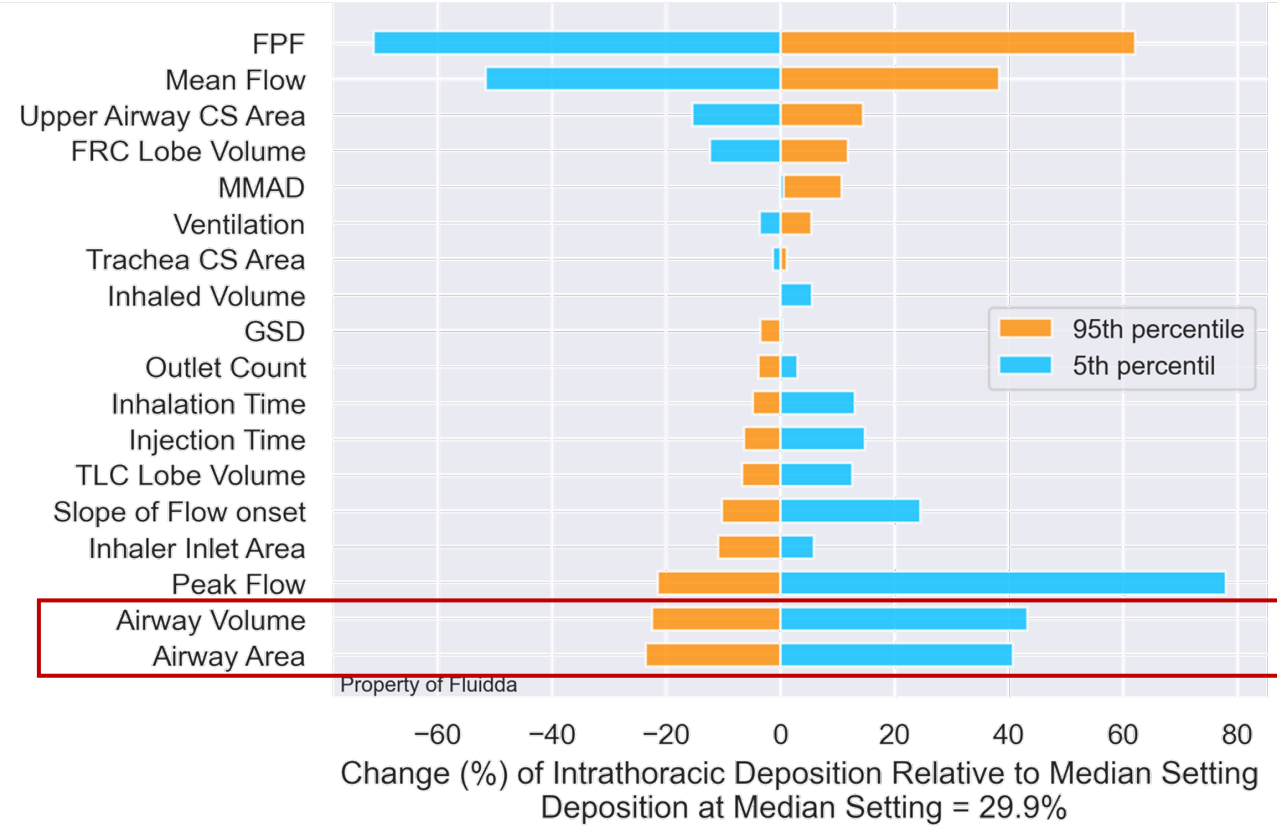
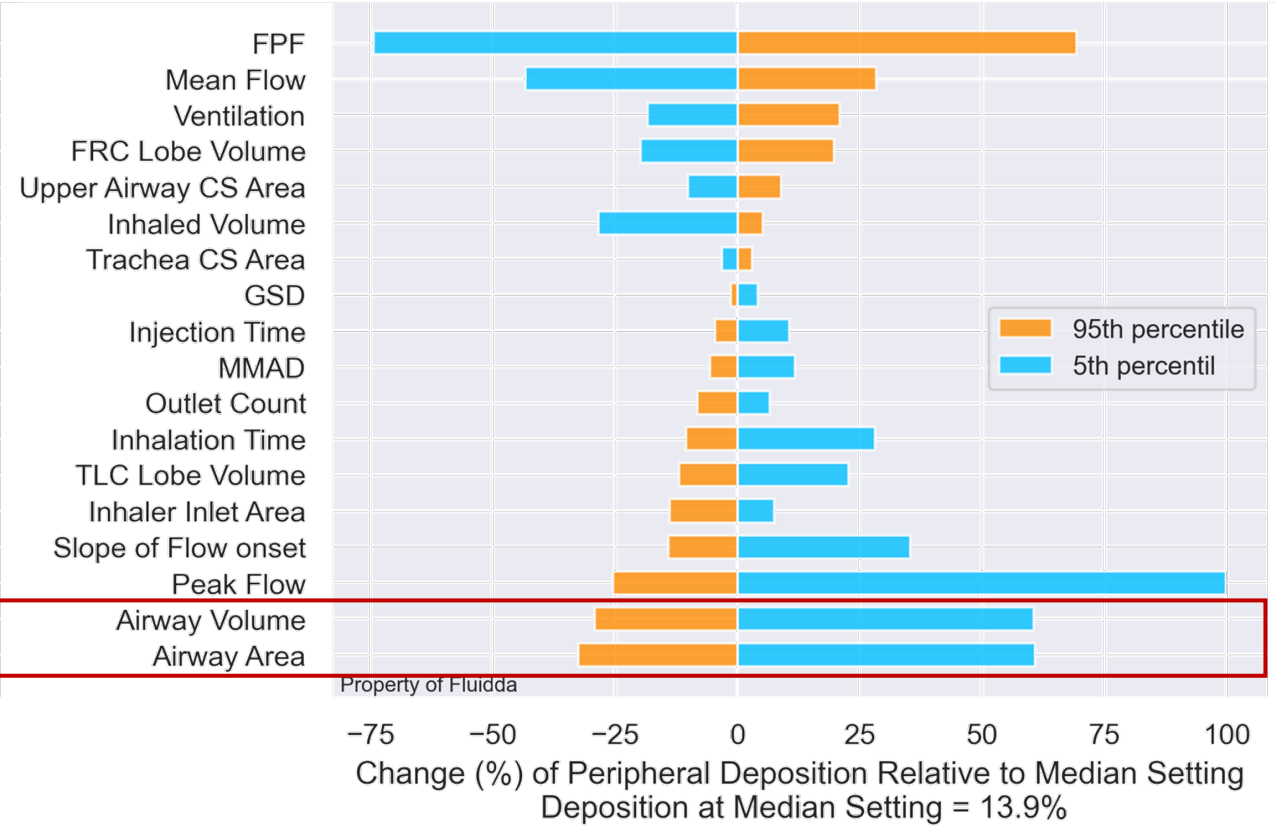
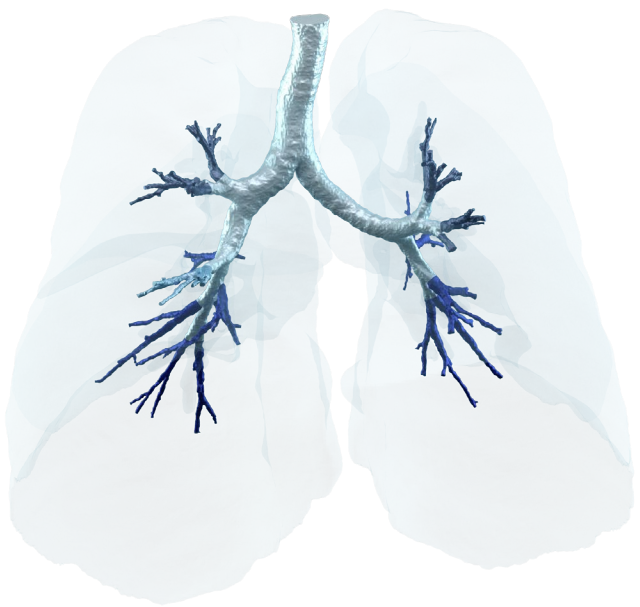
INTRATHORACIC DEPOSITION



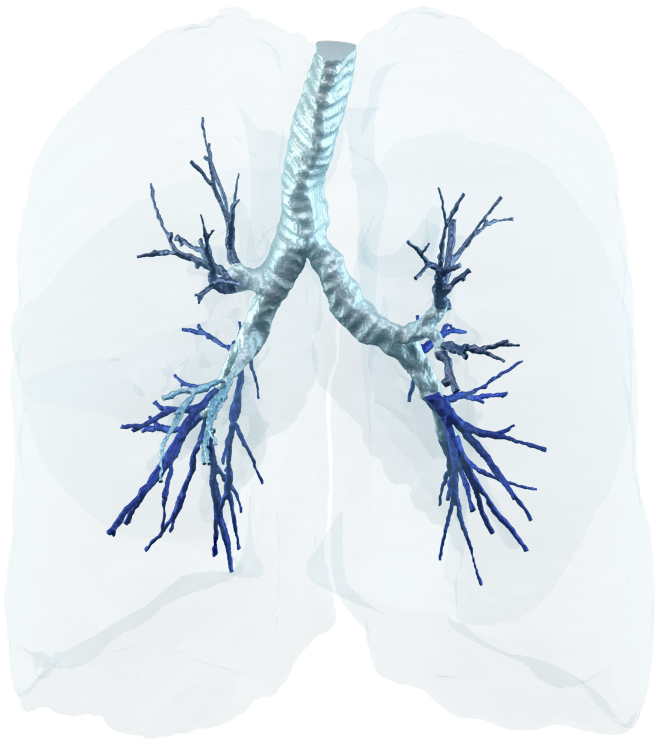
PERIPHERAL DEPOSITION



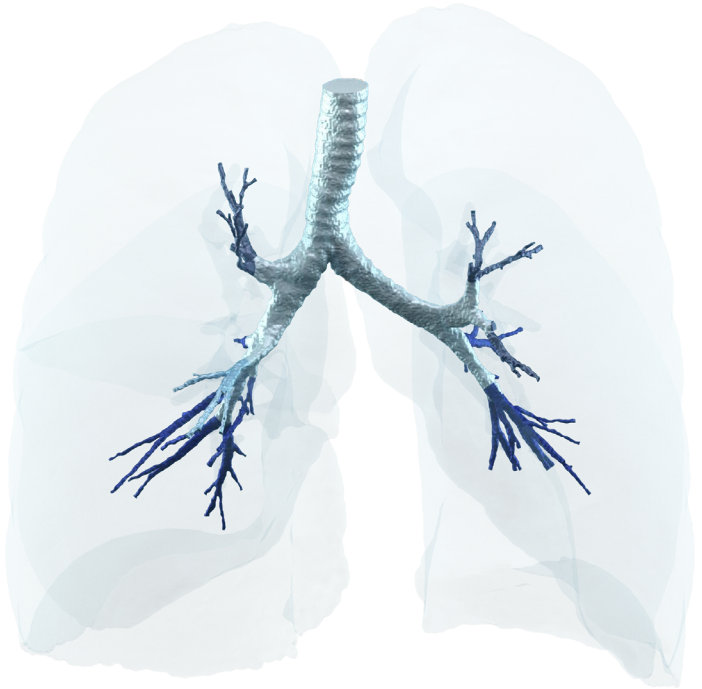
IMPORTANCE OF CAPTURING DISEASED AIRWAYS



Healthy
FEV1 = 108%p



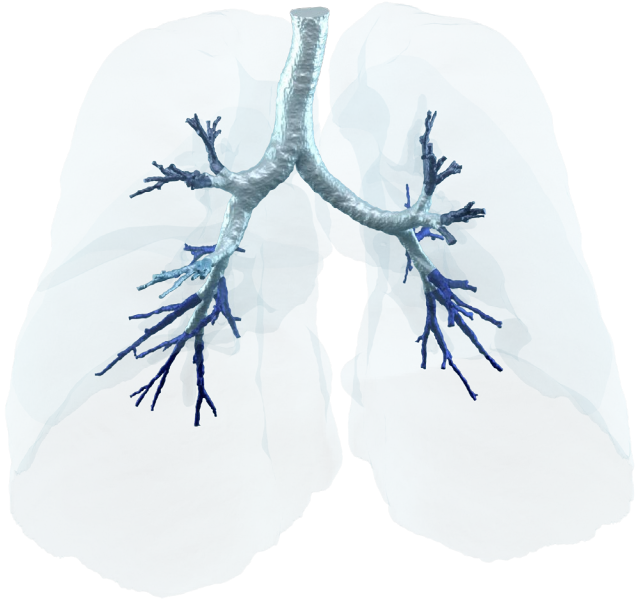
COPD
FEV1 = 52%p



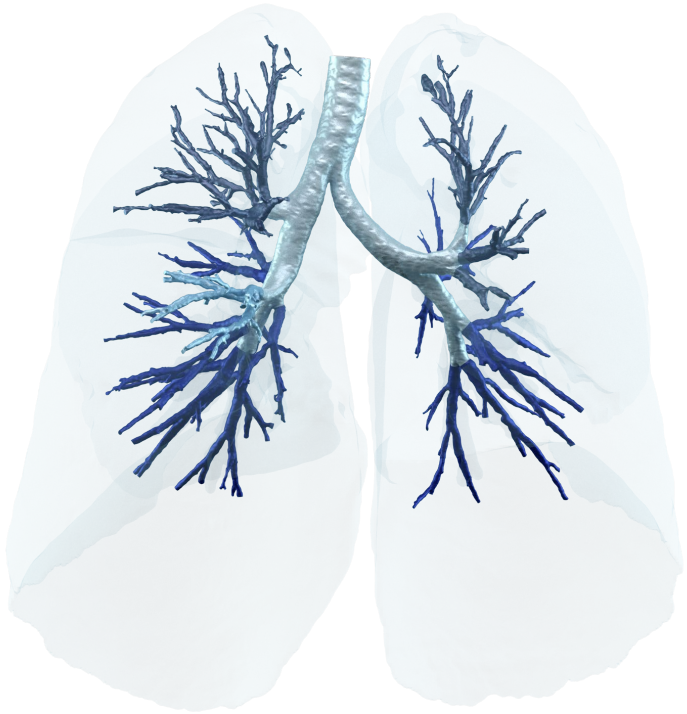
asthma
FEV1 = 72%p

De Backer et al. Introduction to Functional Respiratory Imaging ISBN9789082620207

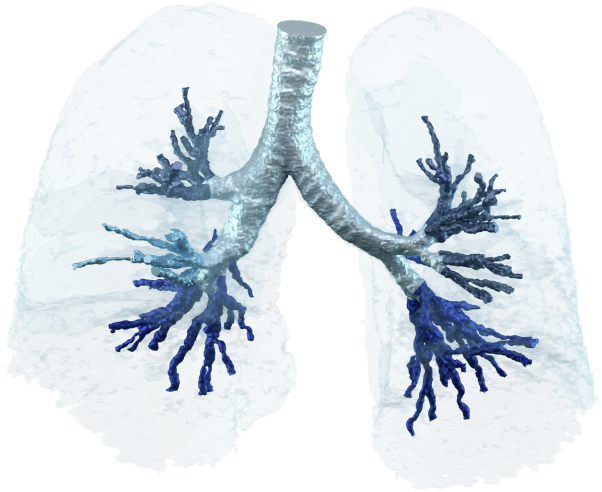
IMPORTANCE OF CAPTURING DISEASED AIRWAYS



Healthy
FEV1 = 108%p



Cystic Fibrosis (CF)
FEV1 = 57%p



Idiopathic Pulmonary Fibrosis (IPF)
FVC = 42%p

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METERED DOSE INHALERS

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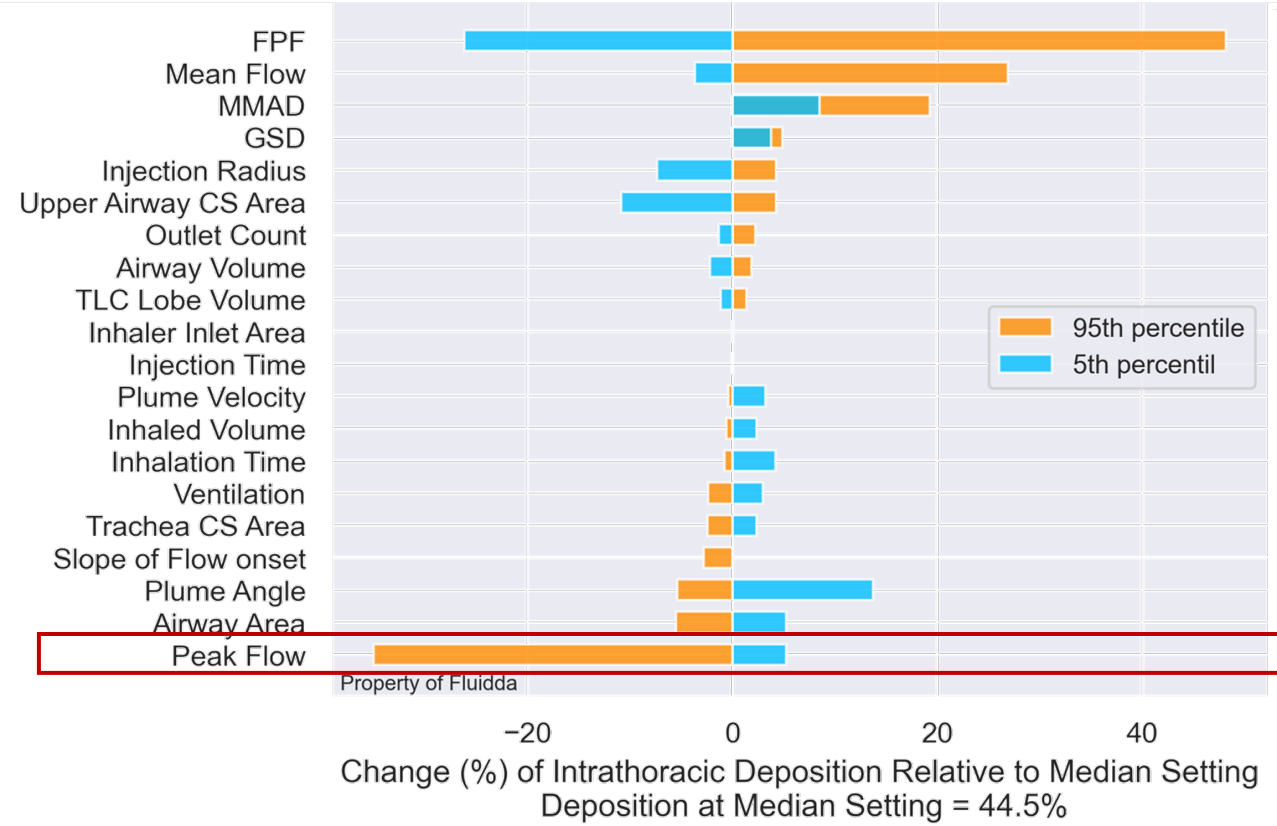
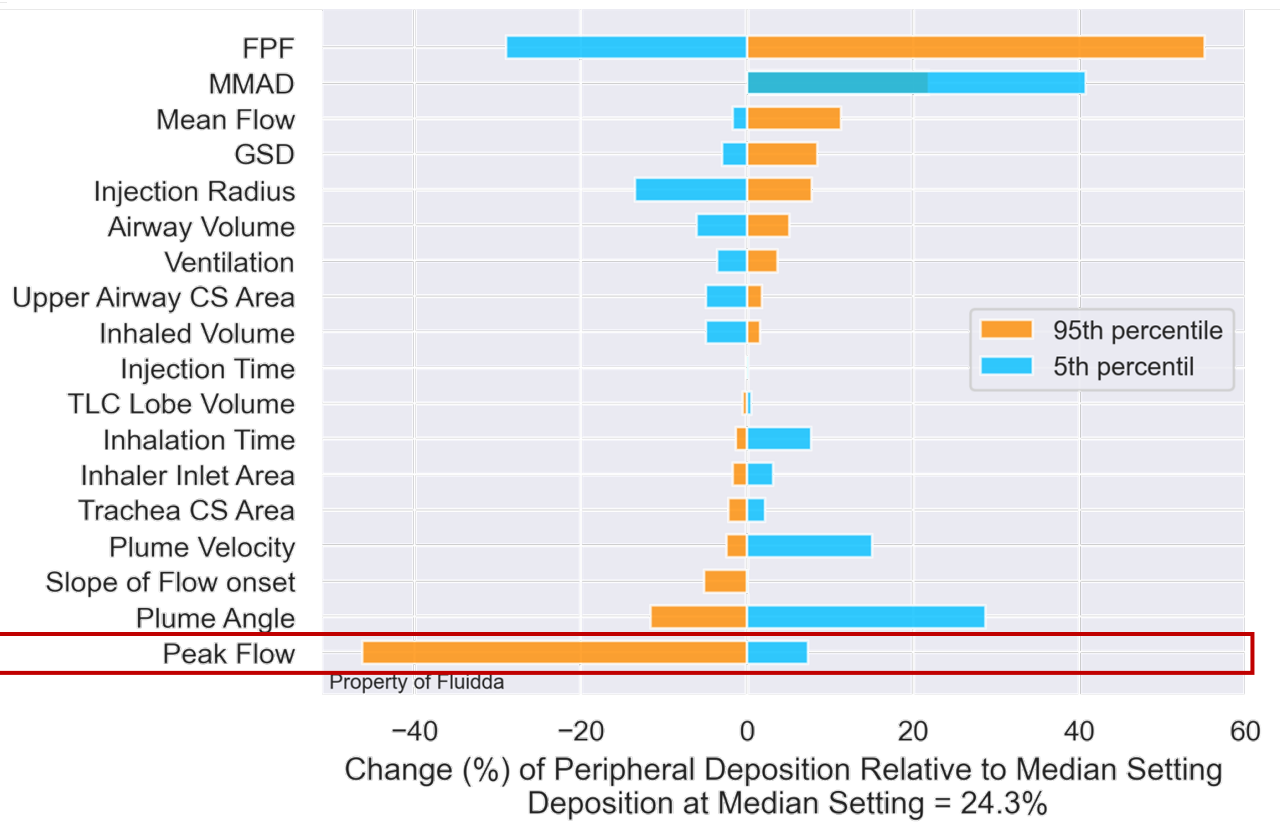
INTRATHORACIC DEPOSITION

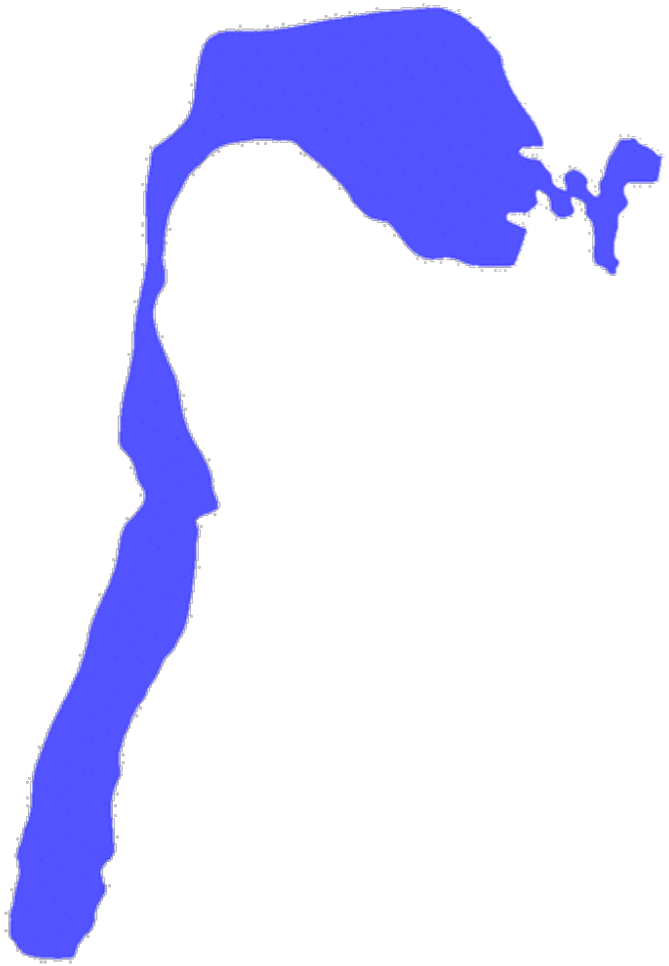


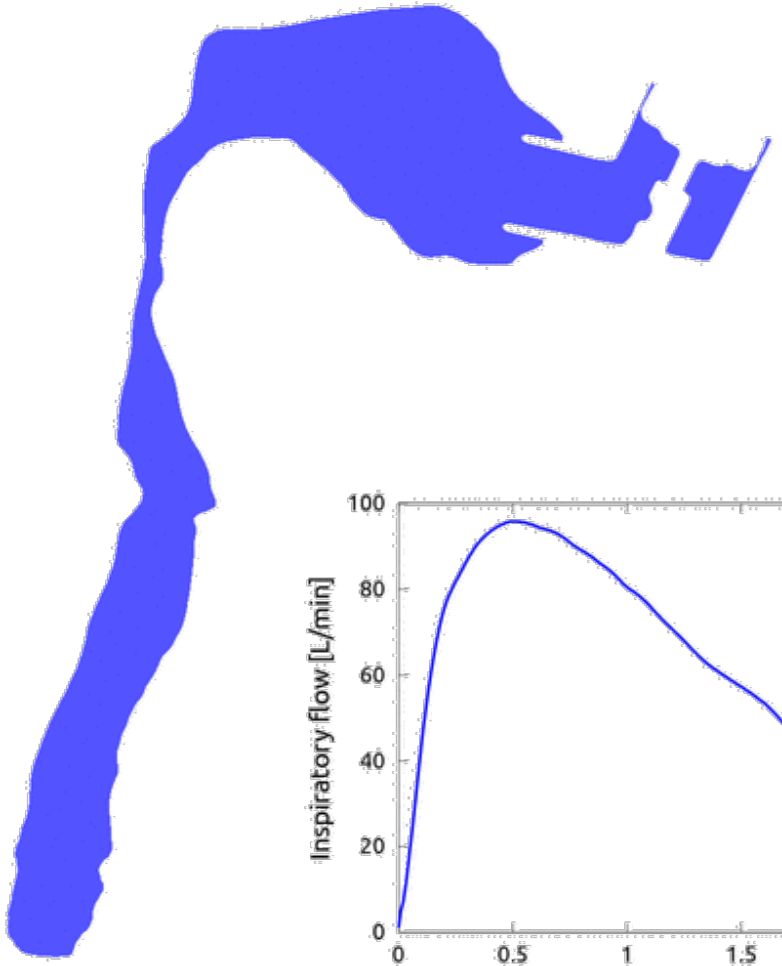
PERIPHERAL DEPOSITION

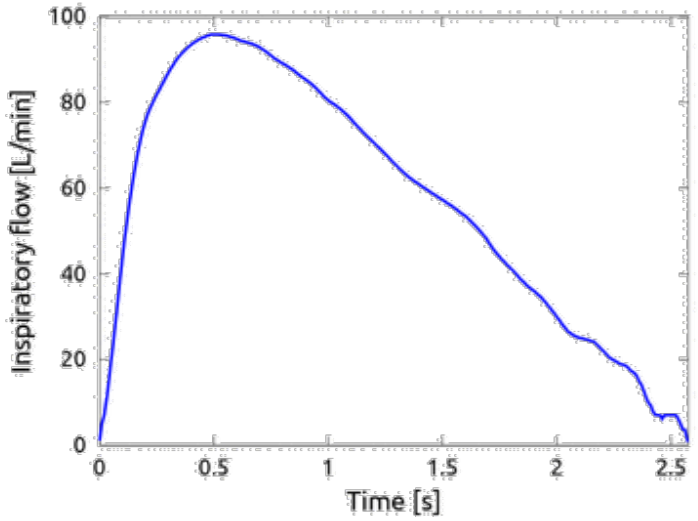


IMPORTANCE OF INCLUDING THE DEVICE

FLUIDDA



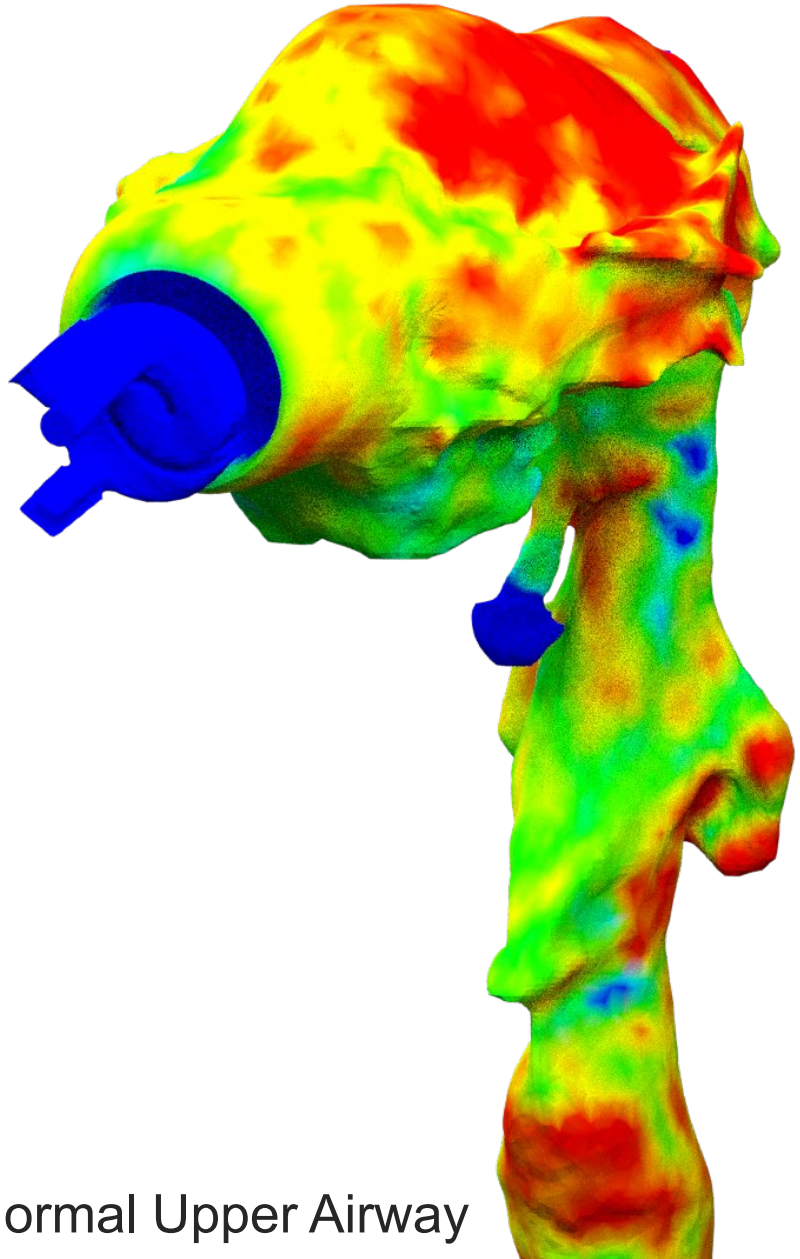




IMPORTANCE OF UPPER AIRWAYS

FLUIDDA

Narrow Upper Airway



Normal Upper Airway

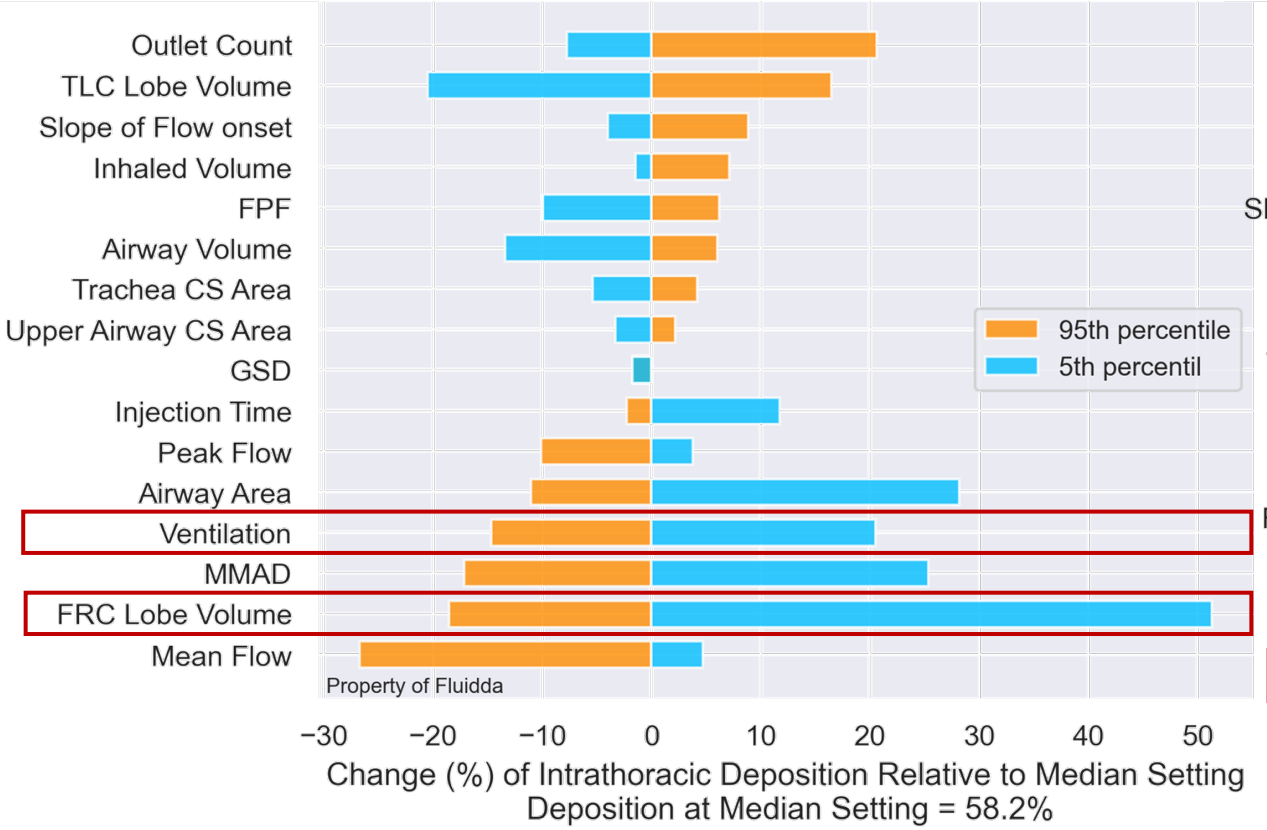
High

Low

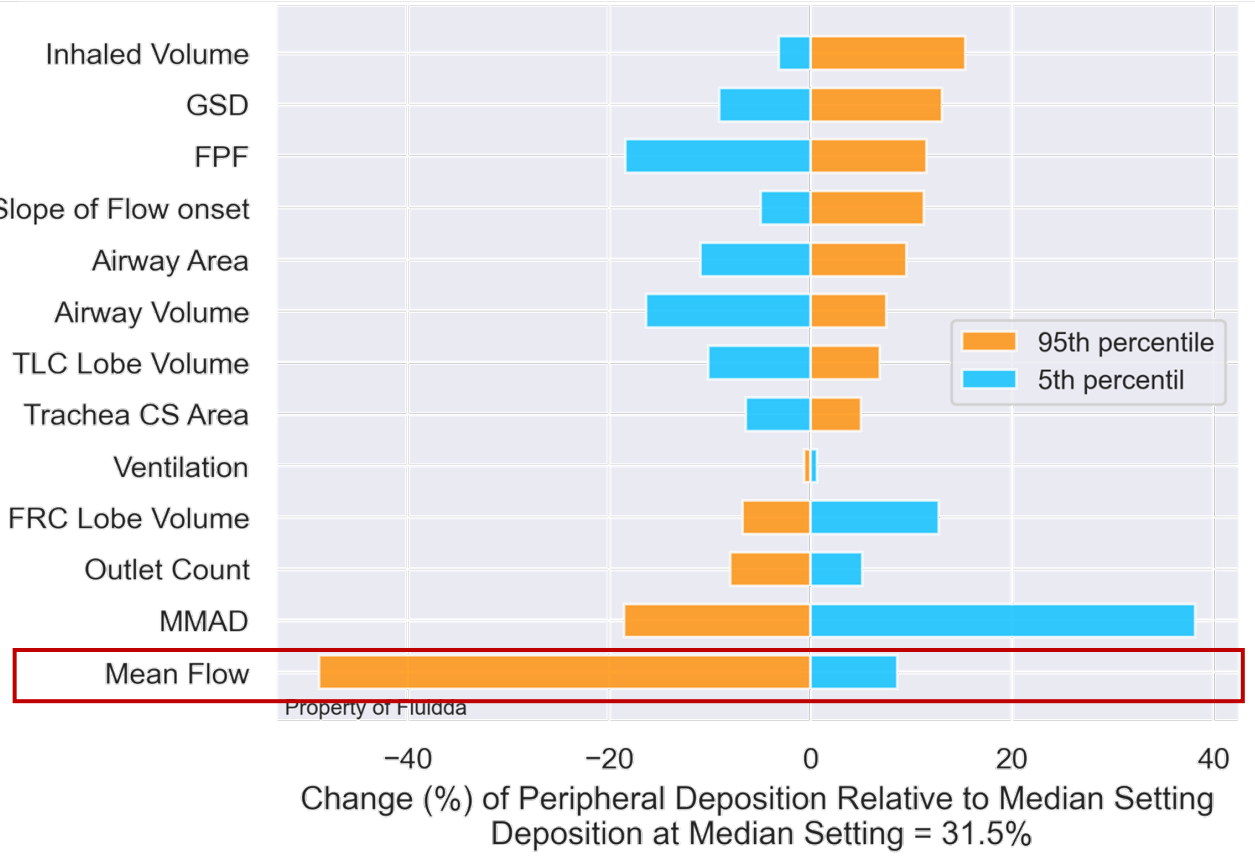
NEBULIZERS

FLUIDDA

INTRATHORACIC DEPOSITION



PERIPHERAL DEPOSITION

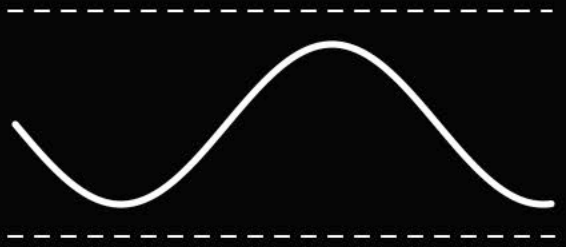


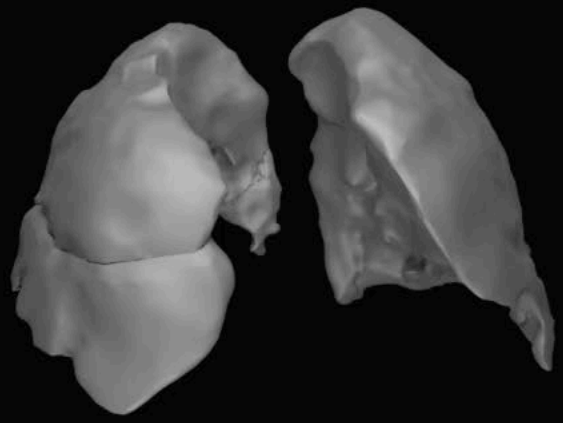
Confidential

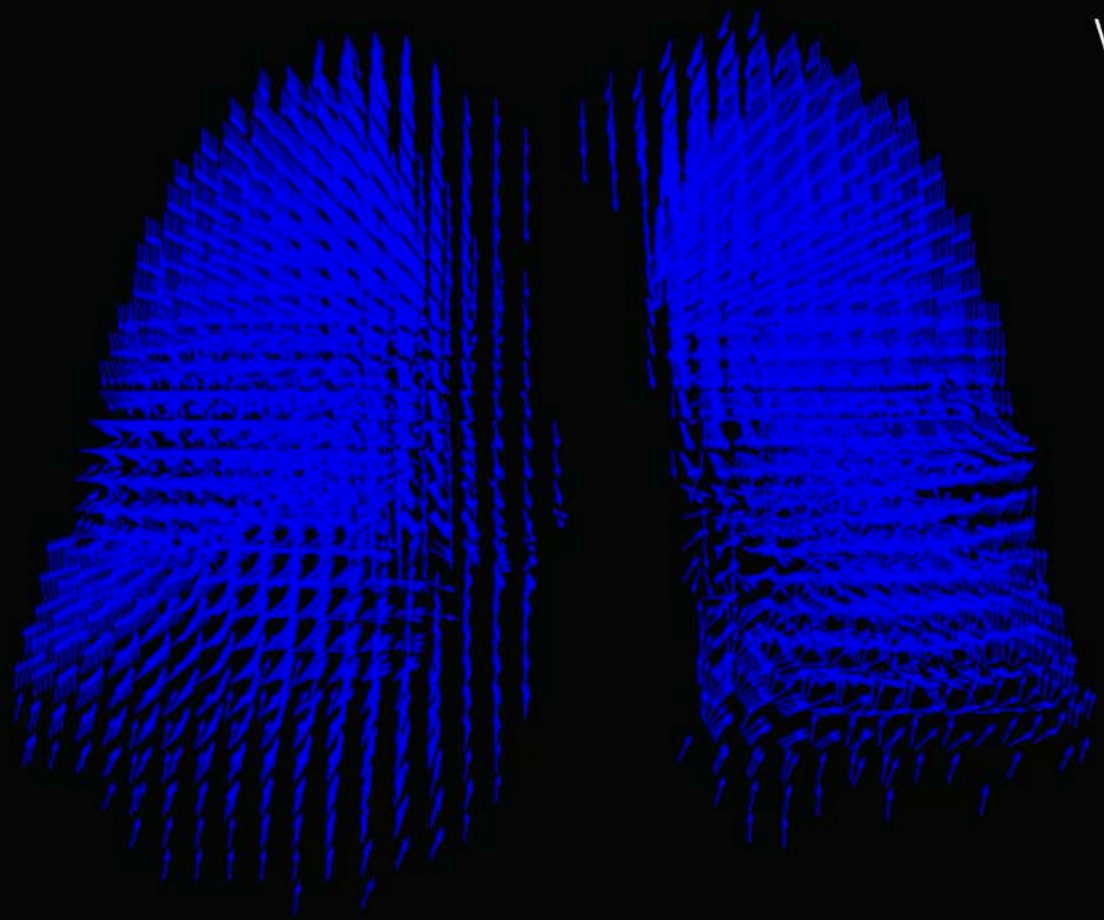
REGIONAL VENTILATION IN IPF PATIENT >

FLUIDDA

BREATHING PROFILE







VALIDATION APPROACH

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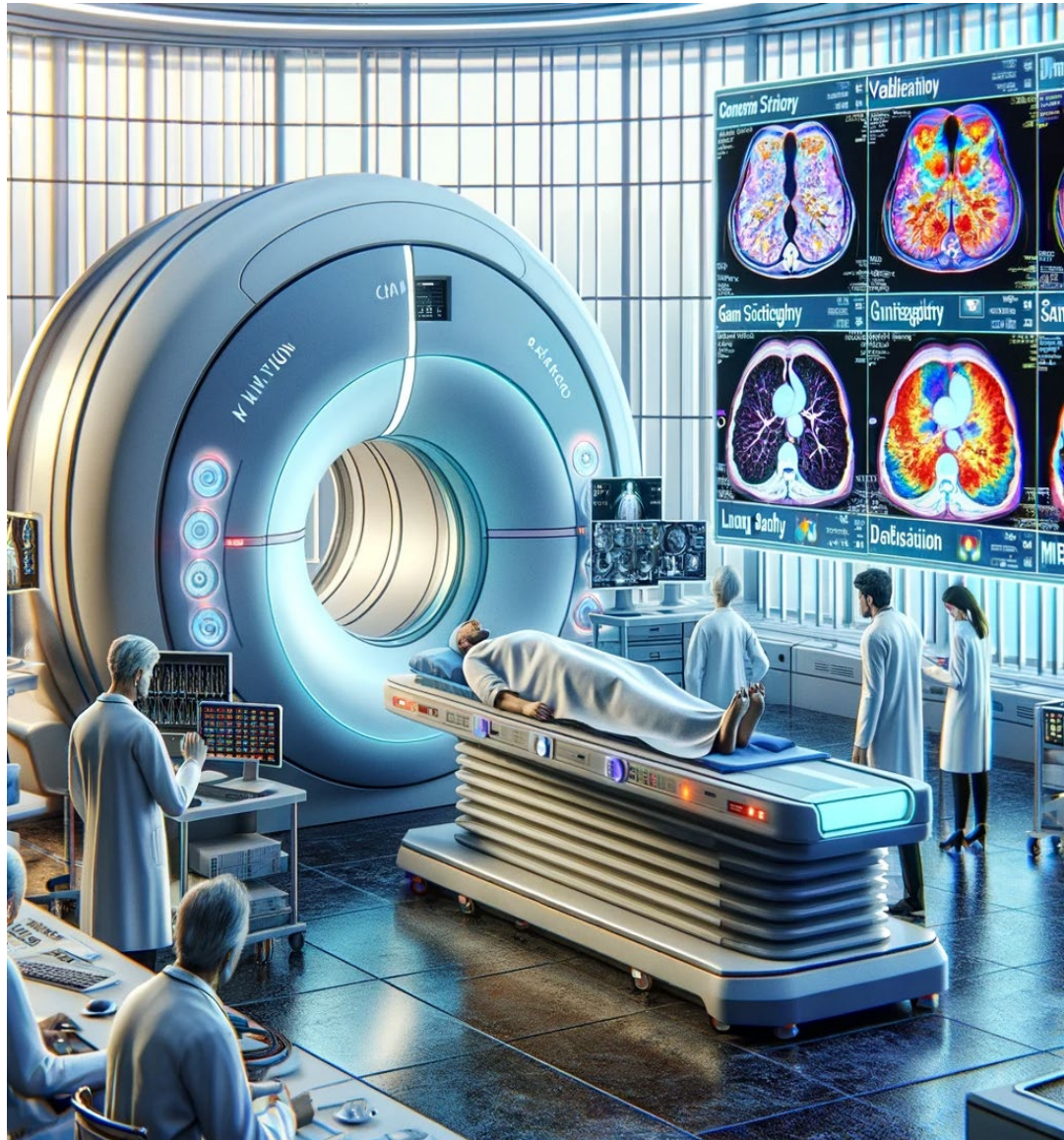
- Existing validation:
  - Strong evidence for total lung dose
  - Good evidence for lobar dose

- Prospective cross over study using SmartTrack:
  - 2 formulations with substantially different APSD
  - Healthy volunteers
  - Diseased patients
  - Gamma scintigraphy
  - FRI deposition based on subject's HRCT



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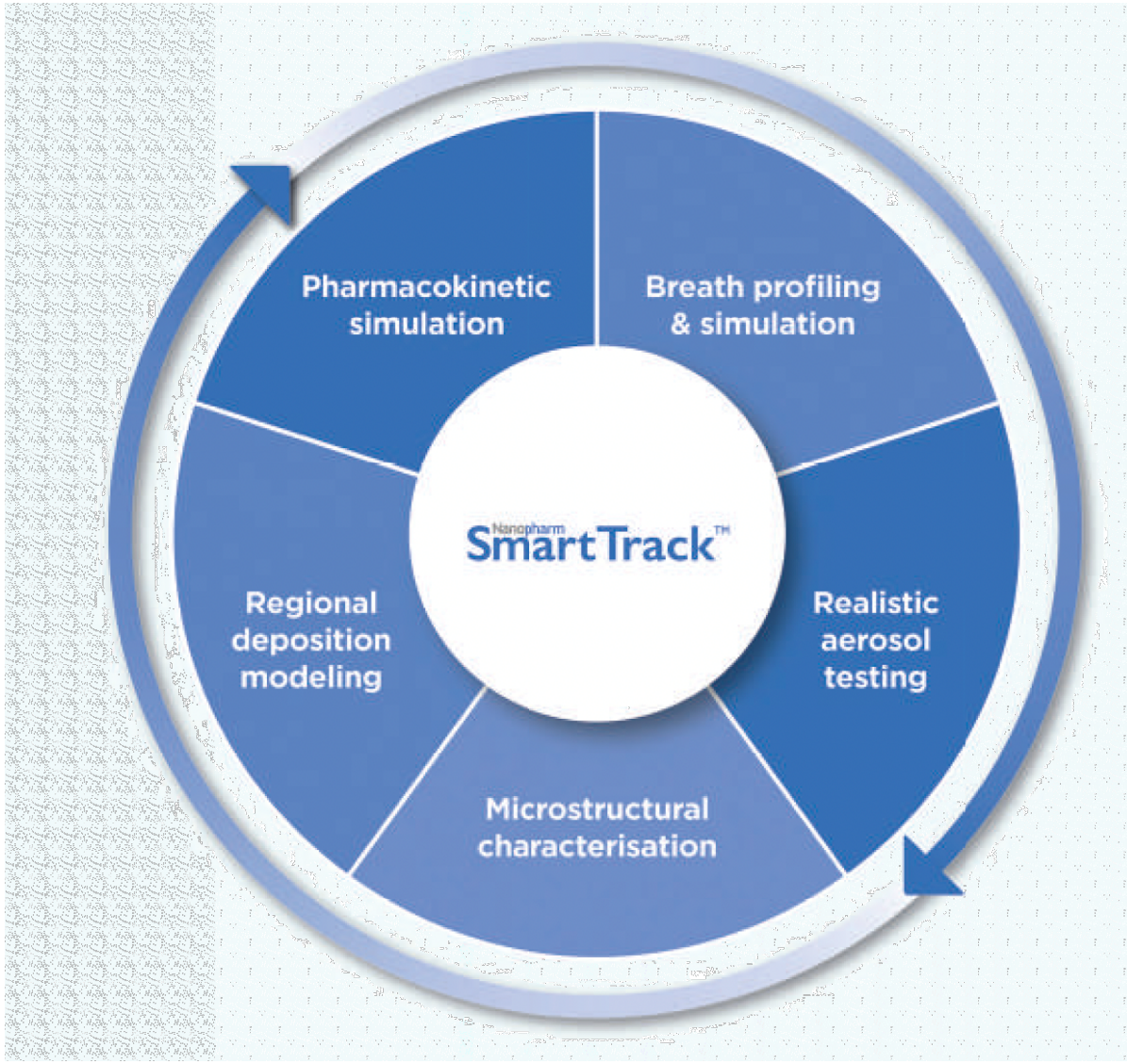

FUTURE RESEARCH DIRECTIONS

FLUIDDA

- Avoid bias in digital twin approaches by **ensuring diversity** in:
  - HRCT scans
  - Inhalation profiling
- **Replacing in-vivo PK studies** in healthy volunteers with Quantitative Medicine tools in the relevant patients
- Creation of **Model Master Files** to streamline the approval process involving quantitative medicine tools

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THANK YOU!