Studies to further establish PK as central tool for a streamlined approval of generic inhalation drugs

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FDA Generic Drug Research Public Workshop –
May 1, 2019, Silver Spring, Maryland

UF
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Background

- Great need for generic inhaled drugs.
- High pressure to streamline generic development and approval.
- FDA is very active in providing guidance information and participating in discussions with stakeholders. (June 21st 2013, FDA Meeting on Bioequivalence, … GDUFA Meetings, DIA 2018, **today's workshop** …)

Previous Work

FDA HHSF223201610099C, FDA HHSF223201110117A,
FDA HHSF223201610099C, FDA HHSF223201300479A.

Hypothesis for slowly dissolving drugs ($F_{oral} = 0$):
PK can provide information necessary to assess pulmonary bioequivalence.

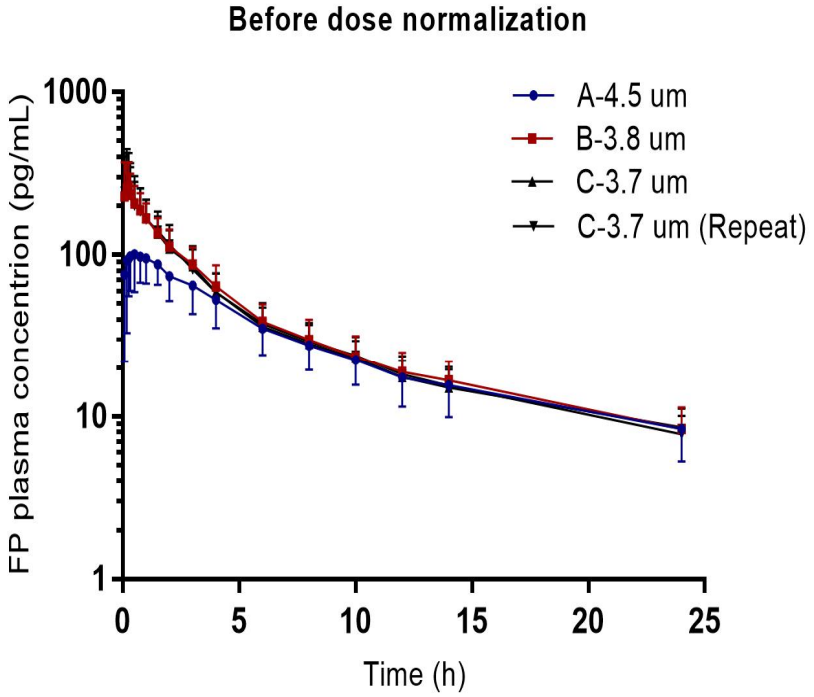
- Pulmonary available dose (AUC)
- Pulmonary residence time (C_{max}, t_{max})
- Regional lung deposition (c/p ratio)

→ A formulation that deposits more centrally is predicted to have:

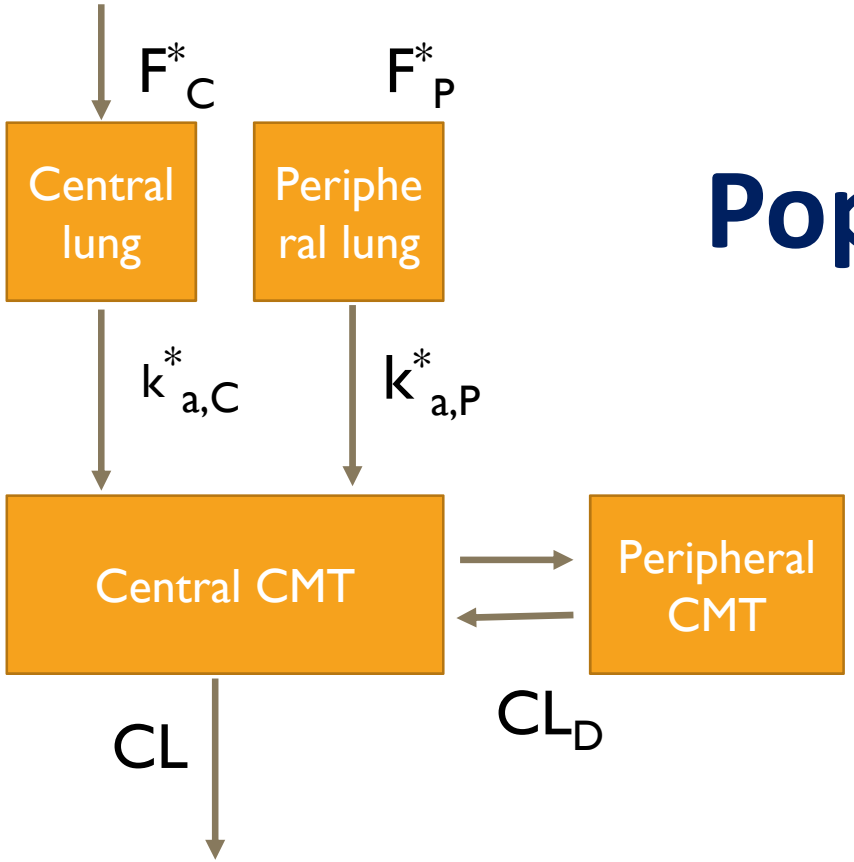
- Lower AUC due to increased mucociliary clearance,
- Lower C_{max}

Study Design and Results (in a nutshell)

- Formulate three Fluticasone DPIs which differ in MMAD (collaboration with Rob Price, Jag Shur)
- In vitro evaluation found differences in
  - Total Lung Dose$_{\text{in vitro}}$ (Mike Hindle)
  - Dissolution rate (UF)
- PK could provide information on:
  - Total lung dose (AUC)
  - Pulmonary residence time (Cmax/D)
  - c/p ratio, based on Cmax/D, but not AUC
  - **Further information on c/p ratio necessary**

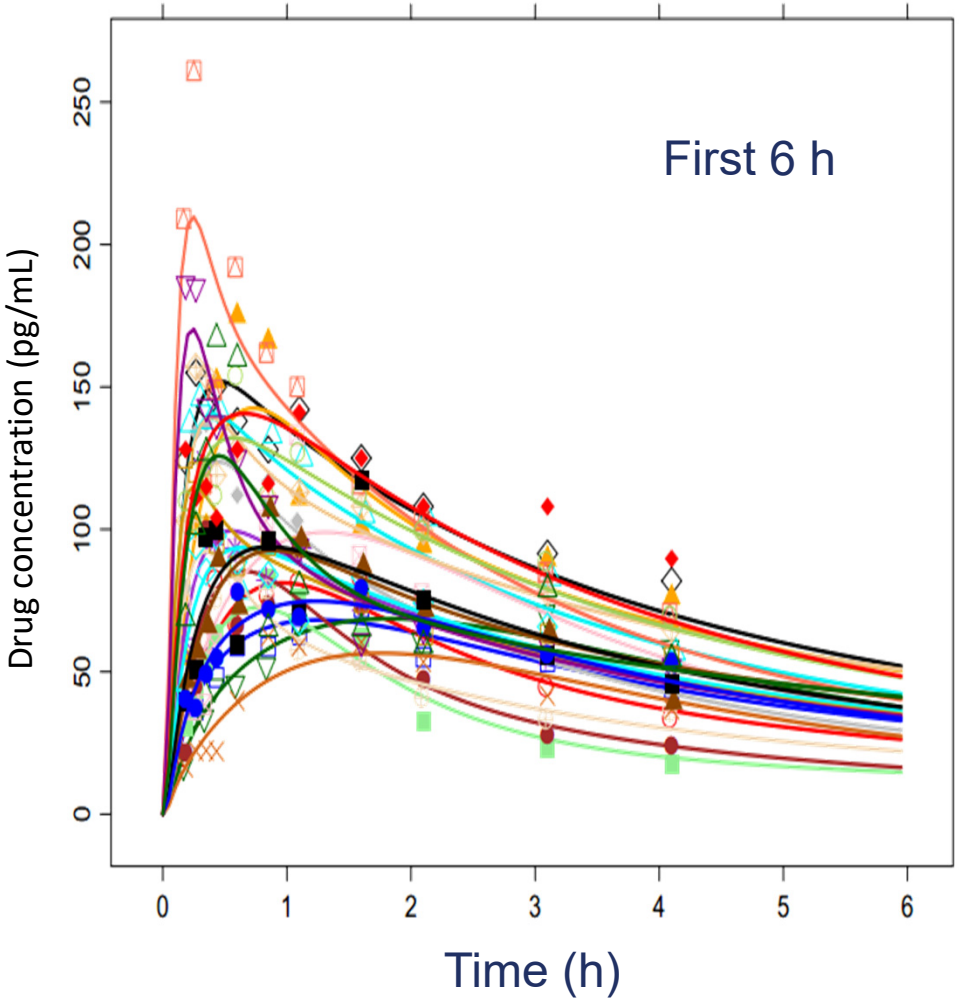


PART 2: Population PK analysis



Fc: absorbed dose fraction from the central region of the lung.

Fp: absorbed dose fraction from the peripheral region of the lung.



Lung related mean PK parameter estimates

Parameters	A- 4.5 µm	B- 3.8 µm	C -3.7 µm
	Mean	Mean	Mean
Absorption $t_{1/2}$ for central lung (h)	**2.7**	**1.6**	**1.7**
Absorption $t_{1/2}$ peripheral lung (h)	**0.27**	**0.13**	**0.13**
Absorbed dose - central lung (%)	**6.1**	**6.1**	**5.3**
Absorbed dose - peripheral lung (%)	**1.7**	**5.7**	**6.0**
c/p ratio	**3.5**	**1.1**	**0.9**

Summary

- Population PK could clearly provide information on the regional lung deposition
- However, population PK is a quite involved technique for standard BE assessment.

→ Future research to evaluate simpler approaches informed by population PK.

Is C_{max} sensitive to the c/p ratio?

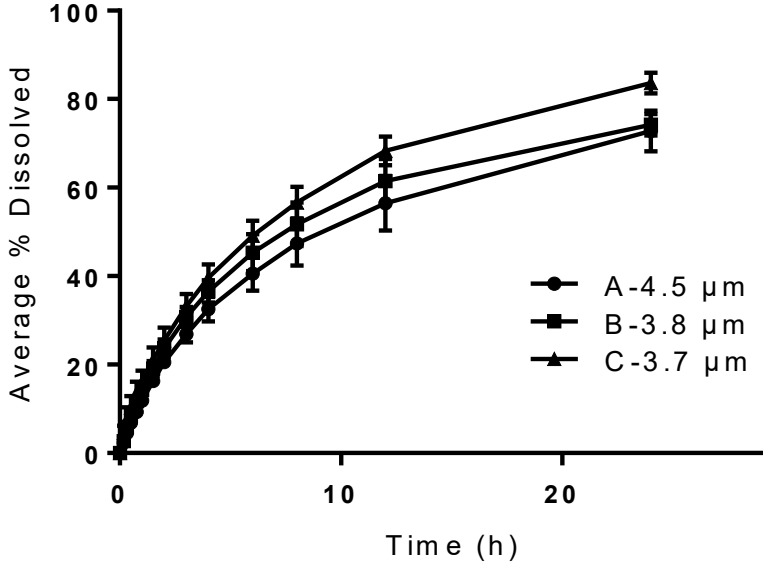
Differences in Dissolution Rate

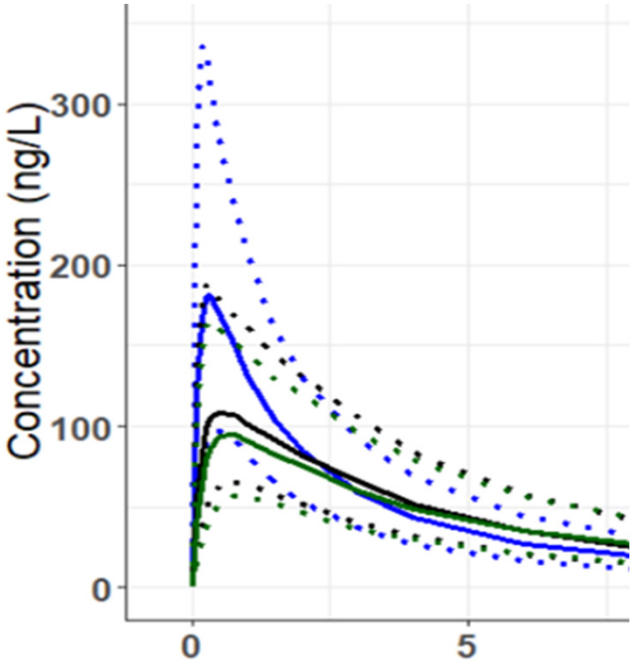
	MDT (h)	Relative surface area
A-4.5 µm	19.2	0.5
C-3.7 µm	13.4	1

Integrate in PBPK Model Nernst-Brunner Fick's Law

C_{max} ratio, if only dissolution differs

C_{max} ratio	Predicted	Measured
C/A	1.15	1.8



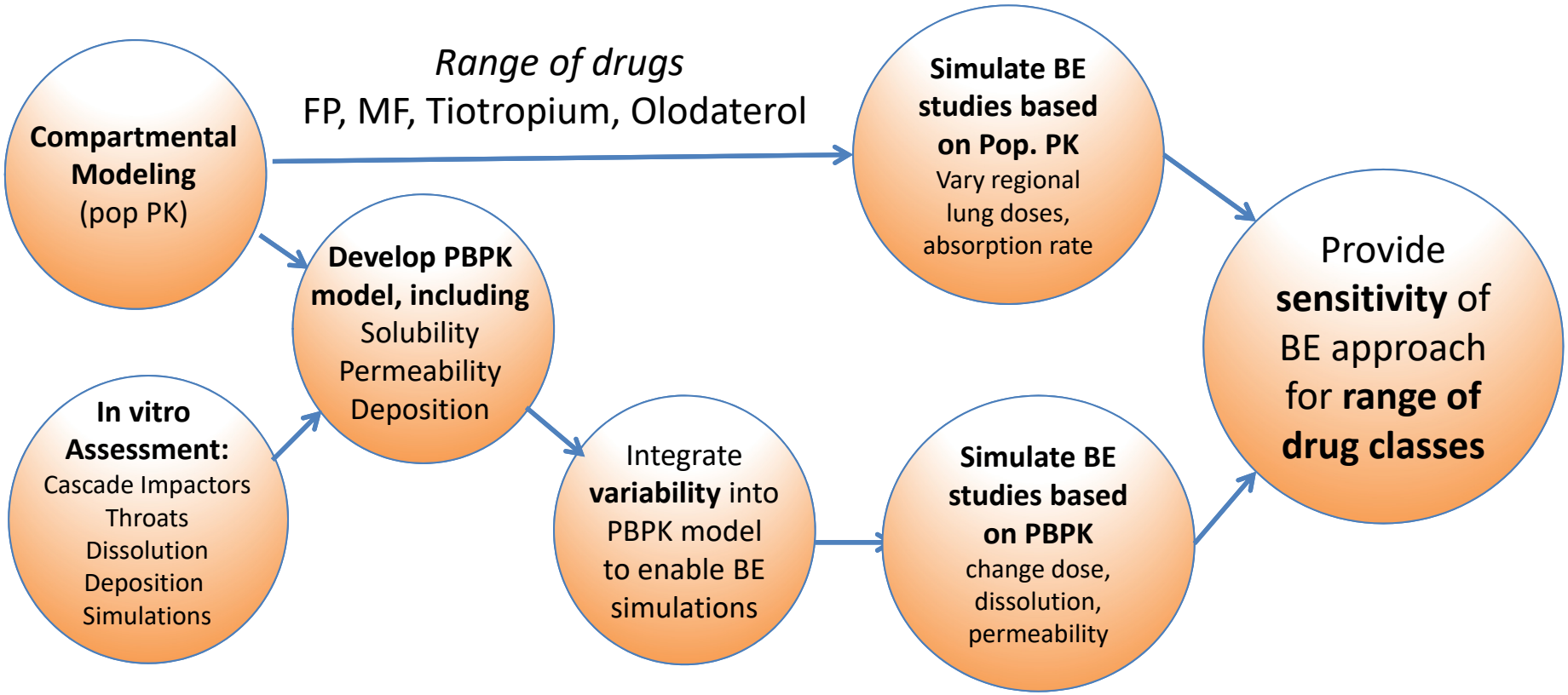


Summary

- NCA-PK can provide information on
  - Dose
  - Pulmonary residence time
  - Regional deposition
    - Cmax seems to be sensitive to the c/p ratio

- Open Questions – Future Research:
  - Is NCA analysis (Cmax) a robust parameter?
    - A PBPK/popPK based simulation approach should be able to answer this question.
  - How can we generalize this approach to other corticosteroids, long-acting beta-agonists (LABAs), and anti-muscarinic agents

Future Research I: Novel BE approaches to study regional distribution of inhalation drugs supported by PBPK and PopPK



Future Research II: Systematic evaluation of the ex-throat plume properties of MDI formulations

Droplet Size Distribution (DSD)

Plume geometry via laser diffraction

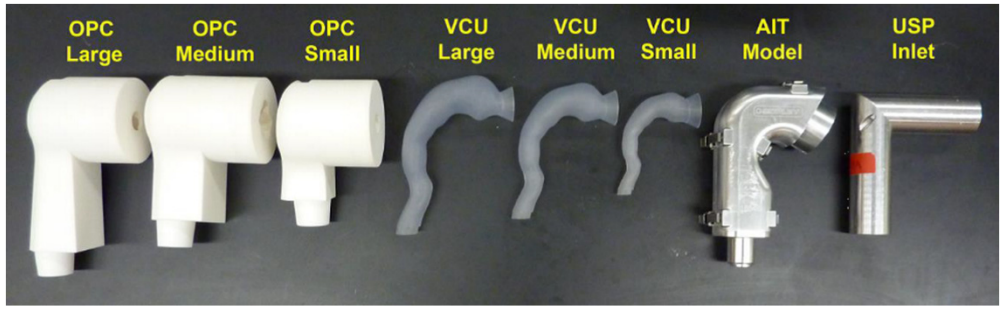
Dissolution profiles

Aerodynamic Particles Size Distribution (NGI)

Computational fluid dynamics

MDIs: Advair, Symbicort and QVAR

Eight available throat models



→ Improved understanding of realistic testing conditions.

Acknowledgements

- Mongjen Chen, Yuanyuan Jiao, Stephanie Drescher, Elham Amini, Uta Schilling, Abhinav Kurumaddali, Sagar Bachhav, Sandy Baumstein, UF-CTSI clinical team
- Mike Hindle, Xiangyin Wei (VCU)
- Jag Shur, Rob Price (University of Bath)
- Worldwide Clinical Trials, Austin, TX (LC-MS/MS bioanalysis)

- **FDA scientists:** Denise Conti, Murewa Oguntimein, Minori Kinjo, Renish Delvadia, Susan Boc, Mohammad Absar, Larry Lee, Bavna Saluja, Kimberly Witzmann, Robert Lionberger, …
  - U01FD004950 (Dissolution)
  - 5U01FD004943-05 (MDI)
  - FDA-SOL-1120918 (Nasal Spray)
  - HHSF223401610099C (DPI)