What are the knowledge gaps that need to be filled before one can approve generic inhalation drugs on *in vitro* and PK studies alone?

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Disclaimer

- The opinions expressed in this presentation are those of the speaker and not necessarily those of the University of Florida and Funding Agency.
- Consultant for pharmaceutical industry in inhalation space

Questions relevant for pulmonary equivalence?

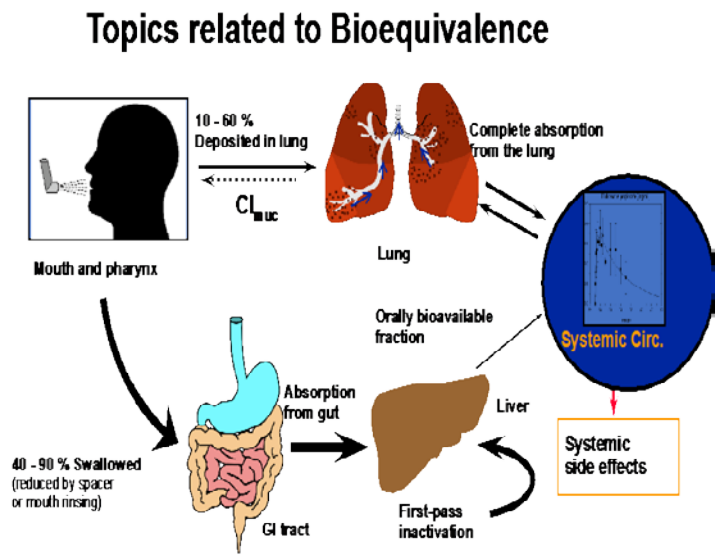
- What is the deposited dose?
- What is the regional deposition?
- What is the pulmonary residence time?

What is FDA recommending?

- In vitro (cascade impactor, delivered dose)
- Pharmacokinetics (systemic safety)
- Clinical study

Hypothesis?

- In vitro tests and PK should be sufficient



Performed Work (HHSF223401610099C; Preliminary Results)

- Designed three DPI formulations:
  - Differences in c/p ratio

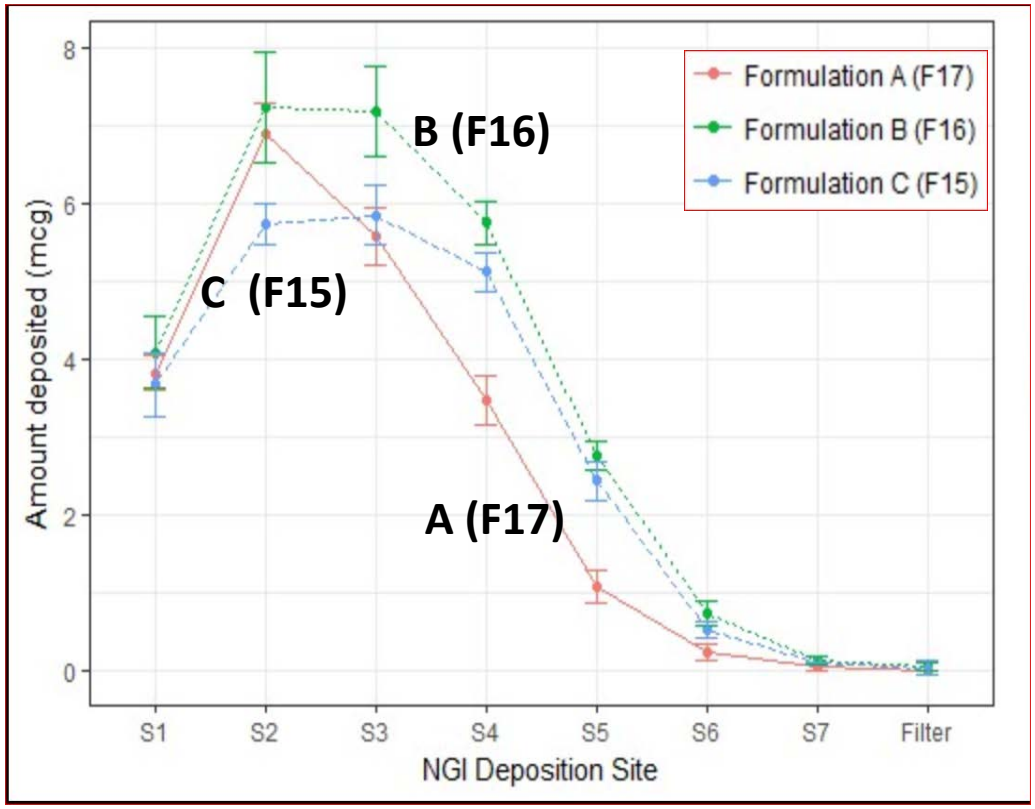
- Assessed in vitro performance
  - Cascade impactor, anatomical throats, inhalation profiles mirroring in vivo
  - Dissolution tests

- PK Bioequivalence study
  - Non-compartmental Analysis (NCA)
  - Compartmental Analysis (NONMEM®)

Product Name	Formulation (% w/w)
F16, Formulation C	FP: 0.80
	Respitose SV003: 96.72
	Lactohale LH300: 2.48
F17, Formulation A	FP: 0.80
	Respitose SV003: 79.36
	Lactohale LH201: 19.84
F15, Formulation B	FP: 0.80
	Respitose SV003: 89.28
	Lactohale LH230: 9.92

- Are in vitro + PK studies able to identify differences in: dose, pulmonary residence time, c/p ratio (mucociliary clearance of central lung)

Cascade Impactor Studies

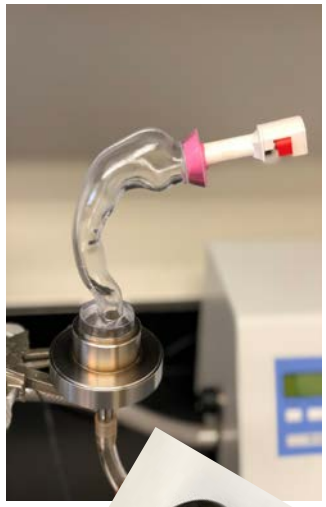


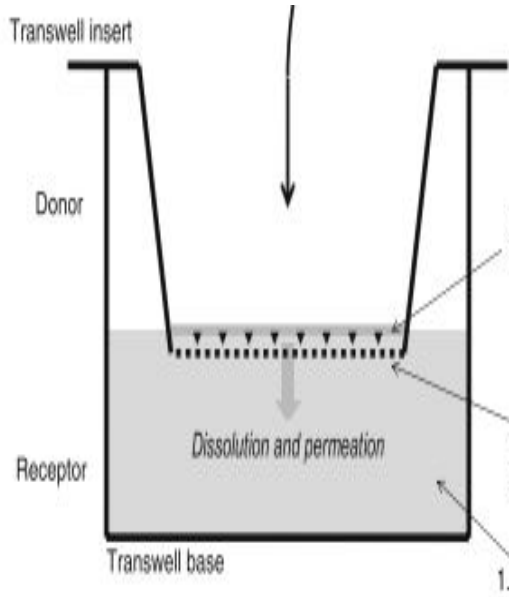
Formulation	Stage 1-3	Stage 4-7	MMAD
	µg	µg	µm
A (F17)	16	**4.6**	4.6
B (F16)	19	9.3	3.9
C (F15)	16	8.3	3.7

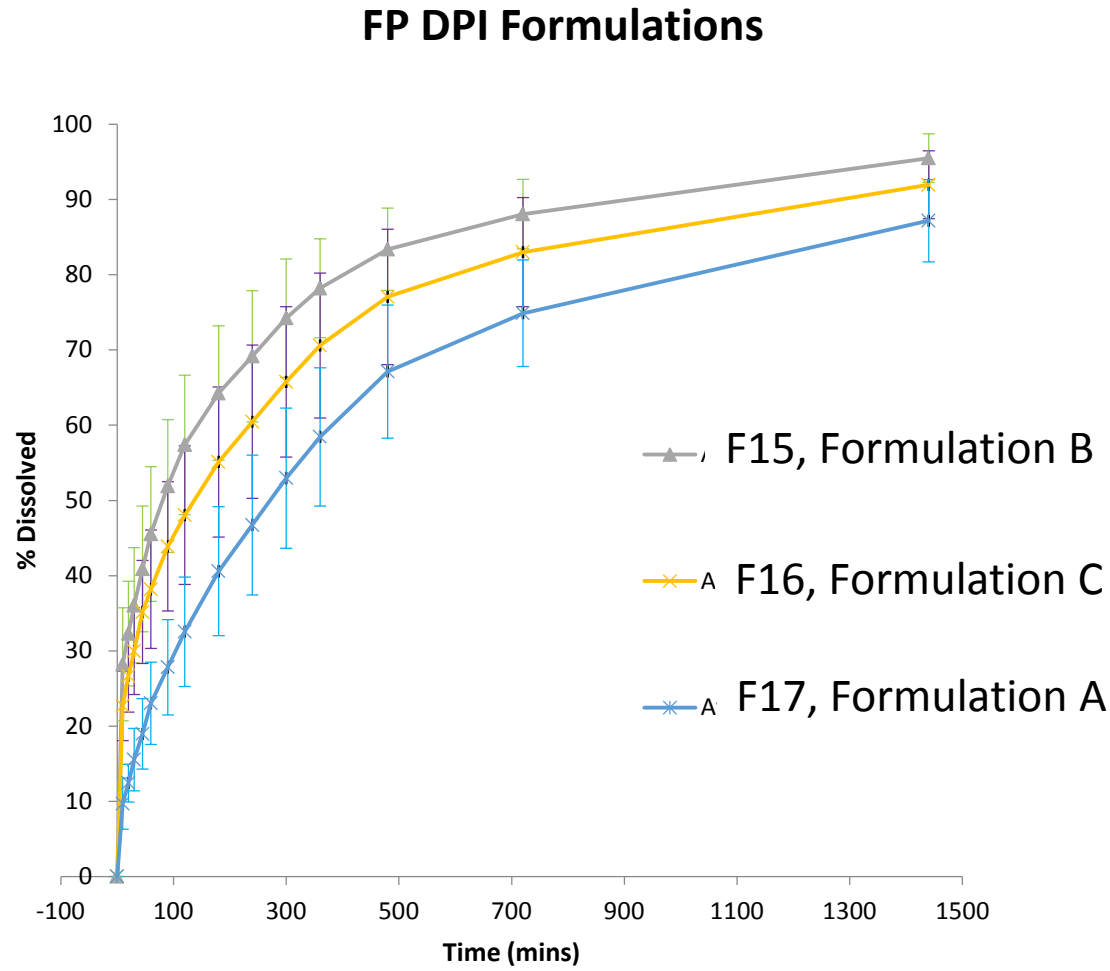
Future work:

- What anatomical throats or combination of throats should be used to predict "deposited dose"
- Need for implementing **statistical tests** for profile comparison (User friendly App…..)
- Further work needs to **relate differences in profiles to differences in geography** of lung deposition (in vitro/in silico/PK)

In vitro methods: Dissolution rate and in vivo absorption rates







Arora, D., (2010)

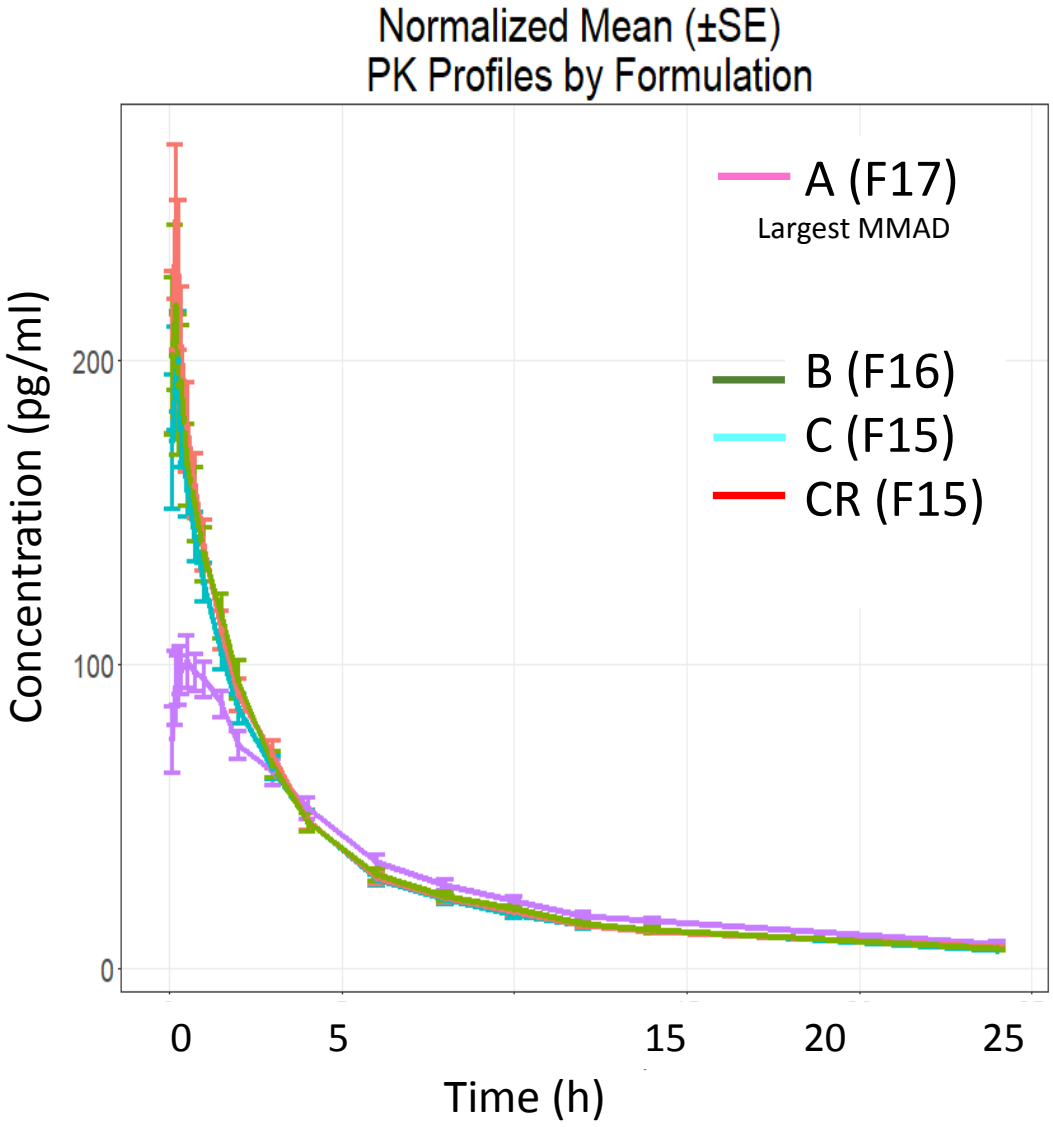
Potential Applications of Dissolution tests

- Dissolution profiles should be included in the array of in vitro tests

Further work:

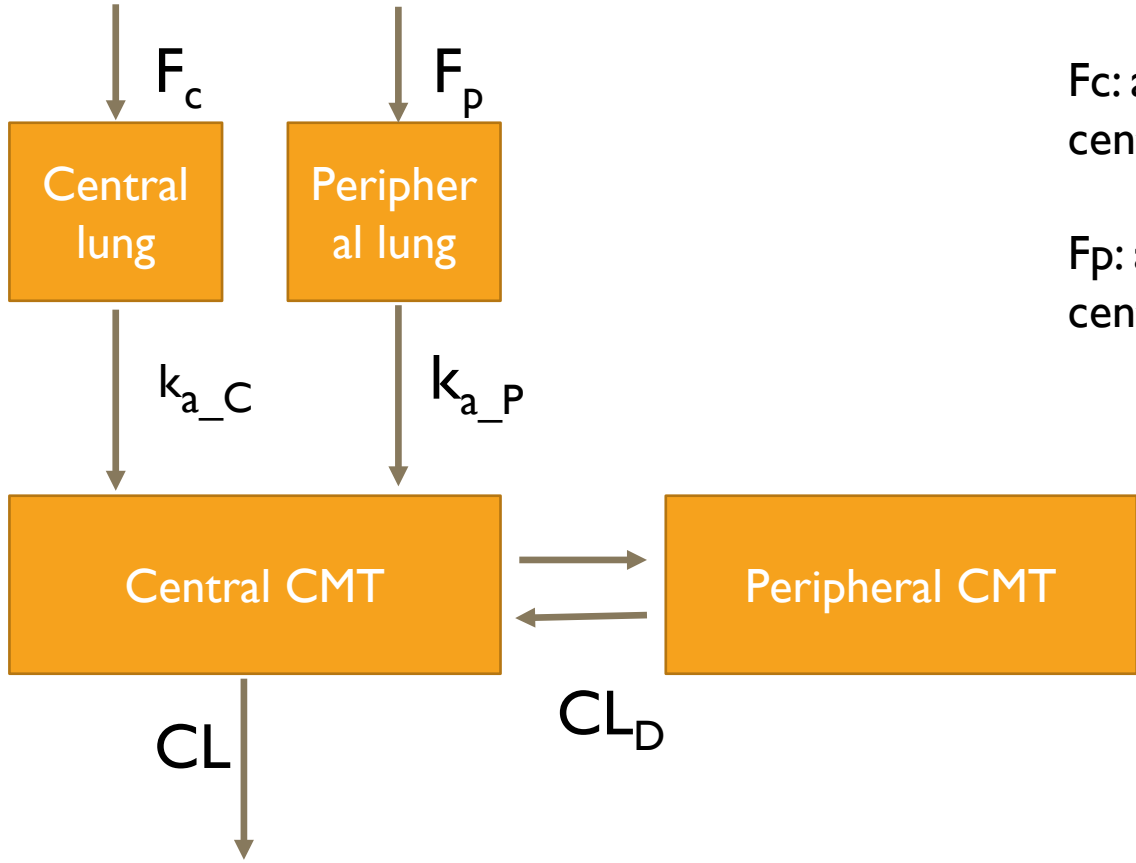
- Which method (USP, Transwell®)?
- Research on which compounds should be performed (BCS)?
- Assess sensitivity of dissolution tests to predict differences in absorption profiles (ivic correlations)
- Which statistical test (f1/f2 test suitable?)
- Acceptance criteria (Calibrate acceptance criteria with PK: relate dissolution rate differences to differences in Cmax)

PK RESULTS



- PK is able to detect difference in pulmonary available dose (AUC)
- PK detected differences in C_{max} (differences in absorption rate, differences in c/p ratio?)

Population PK analysis.



Fc: absorbed dose fraction from the central region of the lungs

Fp: absorbed dose fraction from the central region of the lungs

Parameter Estimates

Deposited Dose

Dose central (%)		K_a central (h^{-1})	
A (F17)	5.4	A (F17)	0.08
B (F16)	5.4	B (F16)	0.10
C (F15)	5.0	C (F15)	0.09

Absorption Rate

Dose peripheral (%)		K_a peripheral (h^{-1})	
A (F17)	**5.2**	A (F17)	**0.58**
B (F16)	8.7	B (F16)	1.1
C (F15)	8.0	C (F15)	1.2

Population PK seems to be able to identify differences in c/p deposition within this study.

Summary

- In vitro + PK might holds promise to assess BE (for slowly dissolving inhalation drugs)
- Potential for more work:
  - **Evaluation of ex throat/cascade impactor profiles**
    - Develop easy to use validated statistical tool with suitable user interface for mCSRS test
    - Develop less complex statistical test with similar statistical behavior than mCSRS
    - Which throat/combination of throats should be used to provide a good estimate of lung dose for wide range of inhalation products. Research is proposed to design/identify such solutions
  - **Dissolution tests**
    - Identify best experimental approach (Transwell vs USP, sample preparation)
    - Evaluate whether f1/f2 statistical test is able to make discriminatory decisions. PBE approaches using alternative metrics (e.g. mean dissolution time, dissolution rate..)
    - Identify "confidence intervals", e.g. through comparison with PK absorption behavior (Cmax, tmax), Identify for which class of compounds test is relevant (BCS system)
  - **Evaluate PK Approaches** to identify differences in pulmonary fate (c/p)
    - Use of compartmental methods to identify differences in c/p deposition seems very promising. More work is needed (PopPK, statistics)
  - **Further Integration** of *in vitro/ in silico* assessments into PopPK or PBPK models

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