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OFFICE OF CLINICAL PHARMACOLOGY

Orally Inhaled Antifungal Drug Development: Clinical Pharmacology Perspective

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Addressing Challenges in Inhaled Antifungal Drug Development
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Disclaimer

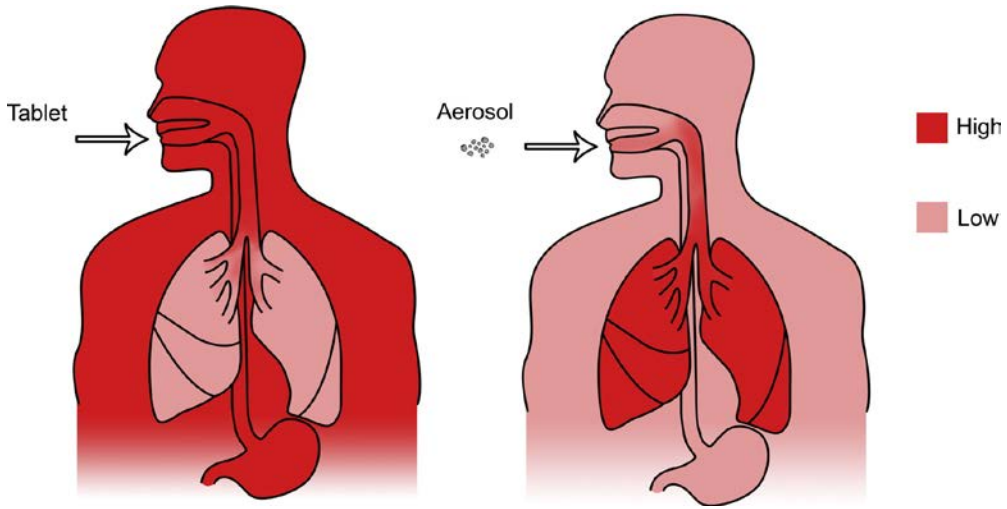
- This presentation reflects the views of the presenter and are not intended to represent official policy of the Food and Drug Administration

Aim & Objectives

- To discuss clinical pharmacology considerations relevant for developing an acceptable orally inhaled antifungal drug product (OIAD)
  - Device Considerations
  - Clinical Pharmacokinetics
  - Dose Finding

Rationale for Inhaled Drugs

- The lung is the target (assumption for this talk)
- Efficacy ➔ local delivery
- Systemic safety ➔ systemic drug exposure
  - Lung absorption
  - GI absorption



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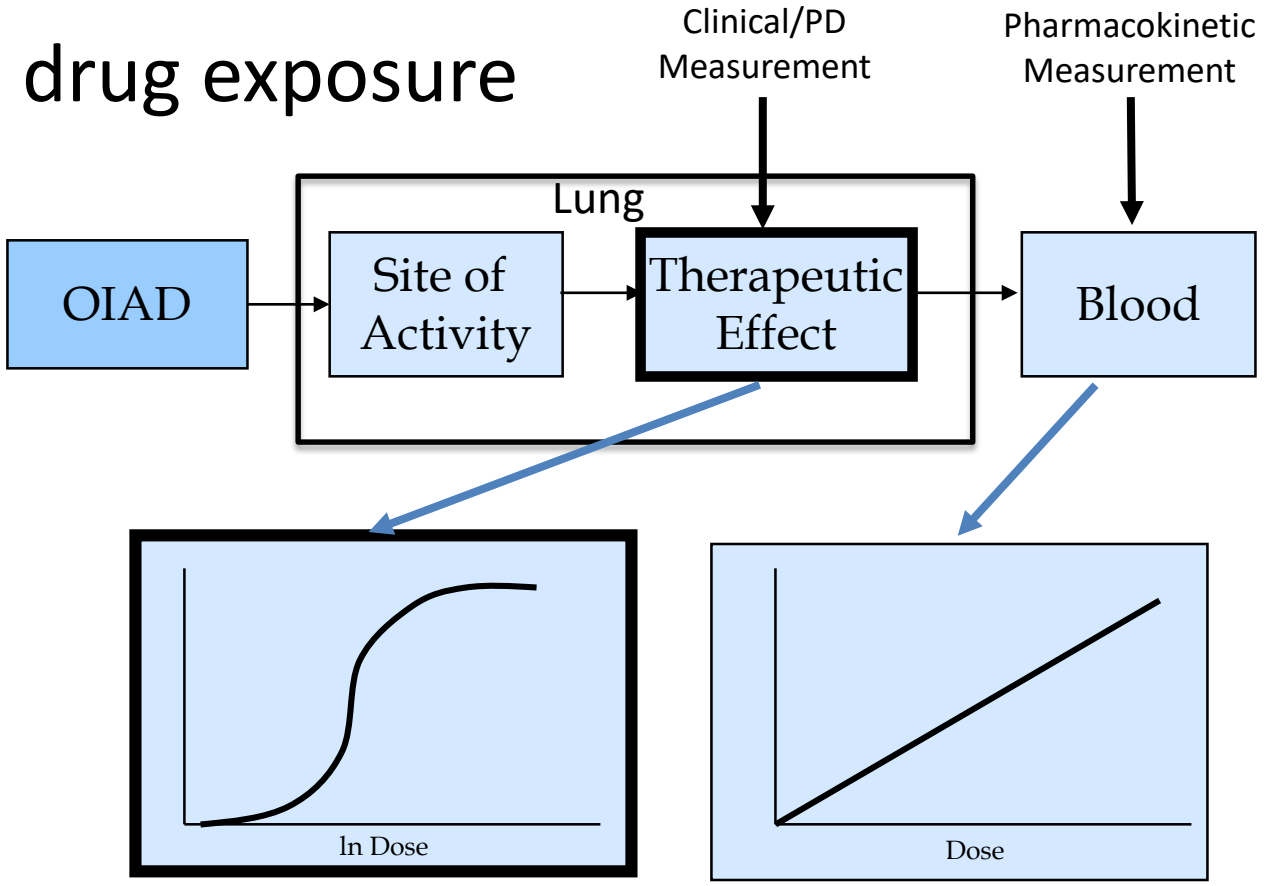

Interface of Drug, Device, and Patient Characteristics

DRUG	DEVICE	PATIENT
• Solubility • Dissolution • Lipophilicity	• Particle size • Velocity • Efficiency	• Disease & disease severity • Mucus / aqueous layer • Mucocilliary clearance • Breathing Technique • Lung function, lung volume

IMPACT

Site of deposition, absorption, and clearance

Non-uniform lung exposure

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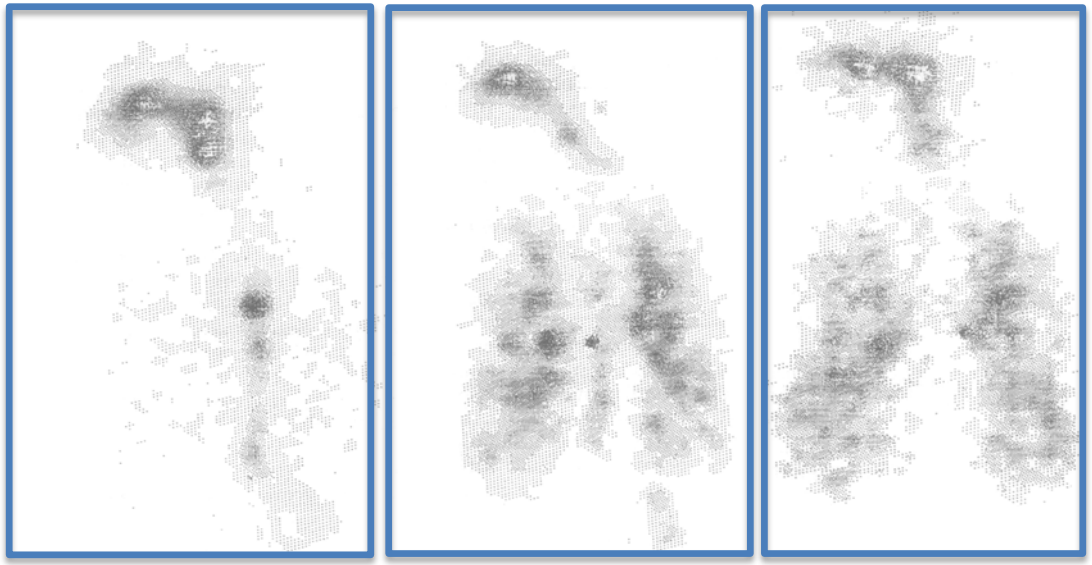
Effect of Patient Factors on Lung Deposition

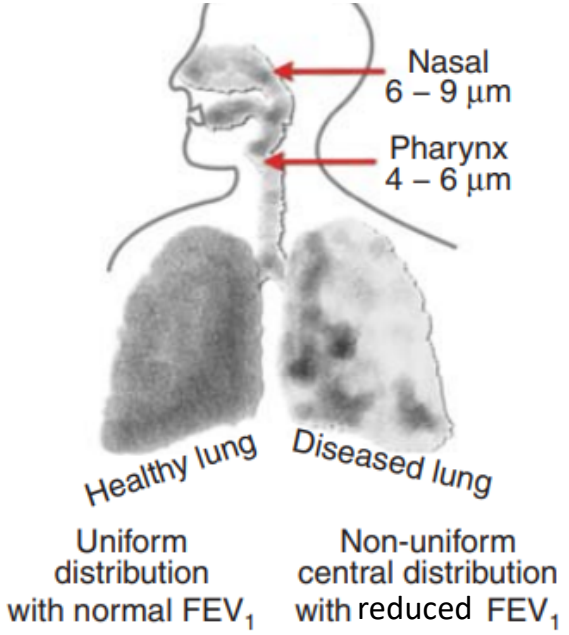
Technique Challenges



Untrained **Trained** **Untrained**

Press-and-Breath MDI **Breath-actuated MDI**

Physiological Challenges



- Lung distribution of OIAD dependent on coordination between device actuation and patient breathing
- Lung distribution of OIAD dependent on pathology and severity of disease

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Effect of Inhalation Device on Efficacy

	Device 1					Device 2
Dose (mcg)	**1.25**	**2.5**	**5**	**10**	**20**	**18**
FEV1 (L)	0.10	0.05	0.15	0.13	0.15	0.23

*Device 1 represents the test; Device 2 the comparator of the same drug.

- Efficacy was deemed to be acceptable with 3-fold lower dose with Device 1
- Efficacy and safety depend on both drug formulation and device
- The to-be-marketed inhaled formulation & device are needed in clinical trials

PMID 18268929.

OIAD Clinical PK Considerations

- Single and multiple dose PK in healthy subjects and/or targeted patient population
- Systemic PK, along with in vitro metabolism data, can be used to evaluate potential clinical drug-drug interactions
- Dose adjustment in renal or hepatic impairment are not possible because of local drug effect in lungs
- For antifungals with approved systemic formulations, systemic OIAD PK can be used to bridge systemic safety for the OIAD
- Efficacy for OIAD cannot be bridged using systemic PK to the approved systemically administered antifungals

Initial Dose Regimen Selection

- Nonclinical / animal models of fungal lung disease
  - Estimation of clinical starting dose / dose regimen
  - Lung PK-PD targets for initial dose regimen selection
    - Evaluation of ELF and alveolar macrophage drug concentrations provide information on drug penetration into the lungs & potential for clinical efficacy
    - Gap regarding nonclinical lung PK-PD targets to clinical efficacy
- In patients with invasive fungal lung infections
    - Interpretation of sputum, ELF, and/or alveolar macrophage antifungal drug concentrations are challenging due to:
      - High degree of variability, especially sputum
      - Not always reflective of lung target-site of action

Clinical Dose Regimen Selection

- **Dose-Response and/or Dose-Finding should be an integral part of the Phase 2 drug development program**
  - Phase 3 dose regimen should be informed by Phase 2 trials
  - Multiple ascending dose Phase 2 trial(s) need to include the anticipated Phase 3 inhaled clinical dose regimen and evaluate a range of dose regimens (low and high) & associated efficacy / safety
  - Important to enroll patients that will be reflective of Phase 3 target patient population

Conclusion

- Many influential factors - drug formulation, device, fungal lung disease severity, patient use - affect pulmonary PK of OIAD
- Nonclinical / animal models of fungal lung disease may be informative
- Phase 2 trial(s) needed to support the Phase 3 dose regimen
- To-be-marketed inhaled drug formulation & device need to be used in the Phase 2 / 3 development program

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