

# Pharmacology and Toxicology Considerations for Inhaled Antifungals

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**Addressing Challenges in Inhaled Antifungal Drug Development  
Workshop**

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# Disclaimer

The content of this presentation represents the opinions of the speaker and does not necessarily represent the official position of CDER and FDA.

No conflicts to declare

# Outline

- Pharmacology/Toxicology data recommended by ICH
- Special considerations for inhaled antifungals
- Future

# Inhaled Antifungals

- Tolman, J. et al. Dose tolerability of chronically inhaled voriconazole solution in rodents. *International Journal of Pharmaceutics*. Volume 379, Issue 1, 8 September 2009, (25-31)
- Sole, A., et al. Salvage therapy with topical posaconazole in lung transplant recipients with invasive *Scedosporium* infection. *American Journal of Transplantation*. 2018;18:504–509.
- Hava, D., et al. A phase 1/1b study of PUR1900, an inhaled formulation of itraconazole, in healthy volunteers and asthmatics to study safety, tolerability and pharmacokinetics. *British Journal of Clinical Pharmacology*. 2020;86:723–733
- Colley, T. et al. Antifungal synergy of a topical triazole, PC945, with a systemic triazole against respiratory *Aspergillus fumigatus* infection. *Scientific Reports* (2019) 9:9482

# Regulatory Basis: 21CFR 312.23

- Investigational New Drug application: Content and format.
- **Pharmacology and toxicology information.**
- Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations.
- The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.
- Guidance documents are available from FDA that describe ways in which these requirements may be met.
- <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.23>



# Guidelines

(1) ICH Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2)

<http://www.ich.org>

(2) Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route: Guidance for Industry and Review Staff

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/nonclinical-safety-evaluation-reformulated-drug-products-and-products-intended-administration>

# Nonclinical Package

- Primary Pharmacology
- Secondary Pharmacology
- Safety Pharmacology CV, CNS, Respiratory
- Toxicokinetic and Pharmacokinetic studies
- Acute/Repeat dose Toxicity
- Genetic Toxicology
- Reproductive Toxicity
- Carcinogenicity
- Other toxicity studies (mechanistic, biomarkers)
- Immunotoxicity (if indicated)
- Phototoxicity
- Abuse Liability
- Combination studies
- Juvenile studies





## Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route Guidance for Industry and Review Staff

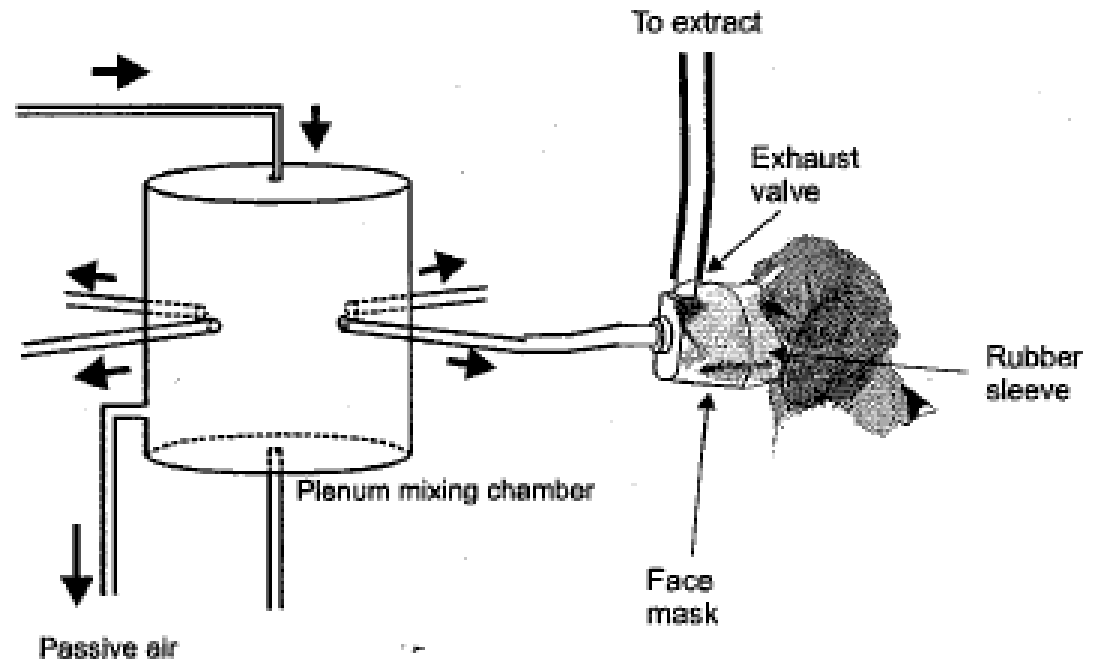
- If a drug substance in the new formulation has not been tested by inhalation, then inhalation toxicity studies should be conducted.
- These studies should consist of short-term studies (2 to 4 weeks) in **two species** (at least one nonrodent) followed by up to a 6-month study in the most appropriate species with the new formulation for a chronically indicated drug.
- Studies for new formulations should include sham (air) control, vehicle control, and complete formulation groups.
- <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/nonclinical-safety-evaluation-reformulated-drug-products-and-products-intended-administration>



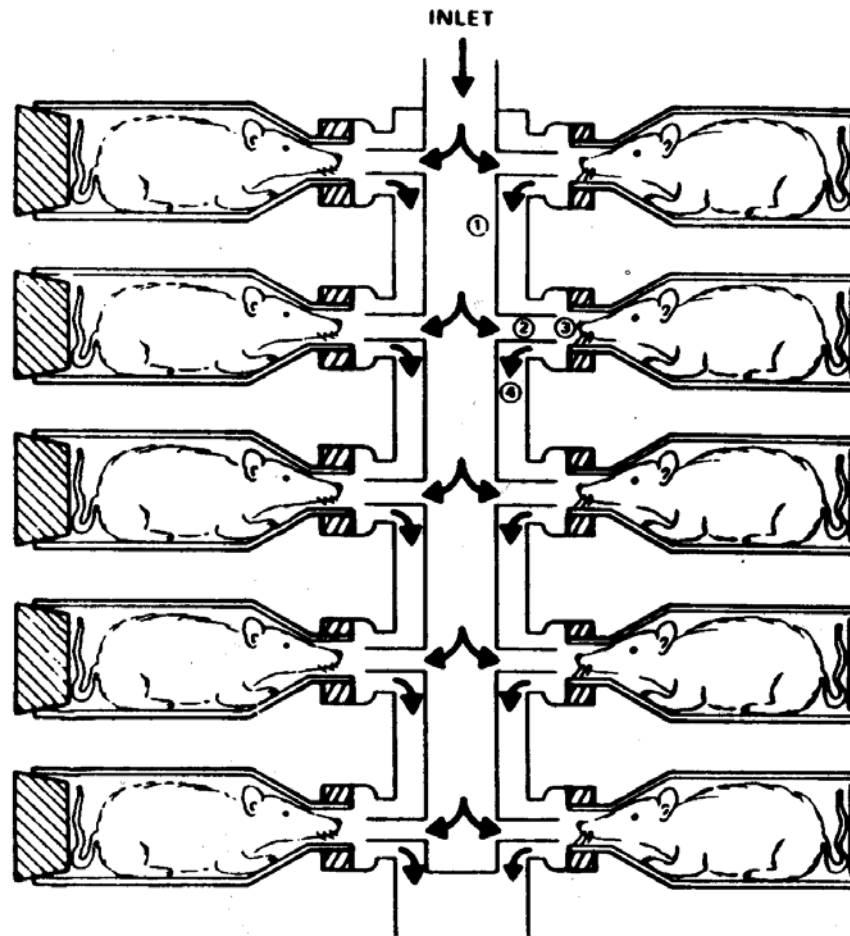
# Modes of Inhalation Exposure

- Nose only
- Oropharyngeal tubes
- Oronasal
- Head only
- Whole body

Dog: Face mask/oronasal inhalation system



# Nose-only exposure



# Estimating Exposures

- Delivered dose (DD) =  $[C \times \text{RMV} \times D \times \text{IF}] / \text{BW}$
- Regional Deposit =  $\text{DD} \times F$
- DD = Delivered dose ( $\mu\text{g}/\text{kg}/\text{day}$ , amount of drug present in the volume of inhaled air)
- C = Aerosol drug concentration ( $\mu\text{g}/\text{L}$  air)
- RMV = Respiratory minute volume (L/min)
- D = Duration of daily exposure (min/day)
- IF = Inhalable fraction (1 – 5  $\mu\text{m}$  particles)
- RD = Regional deposits/exposure ( $\mu\text{g}/\text{kg}/\text{day}$ , e.g., nasal or pulmonary)
- F = Deposition factor for the region of interest

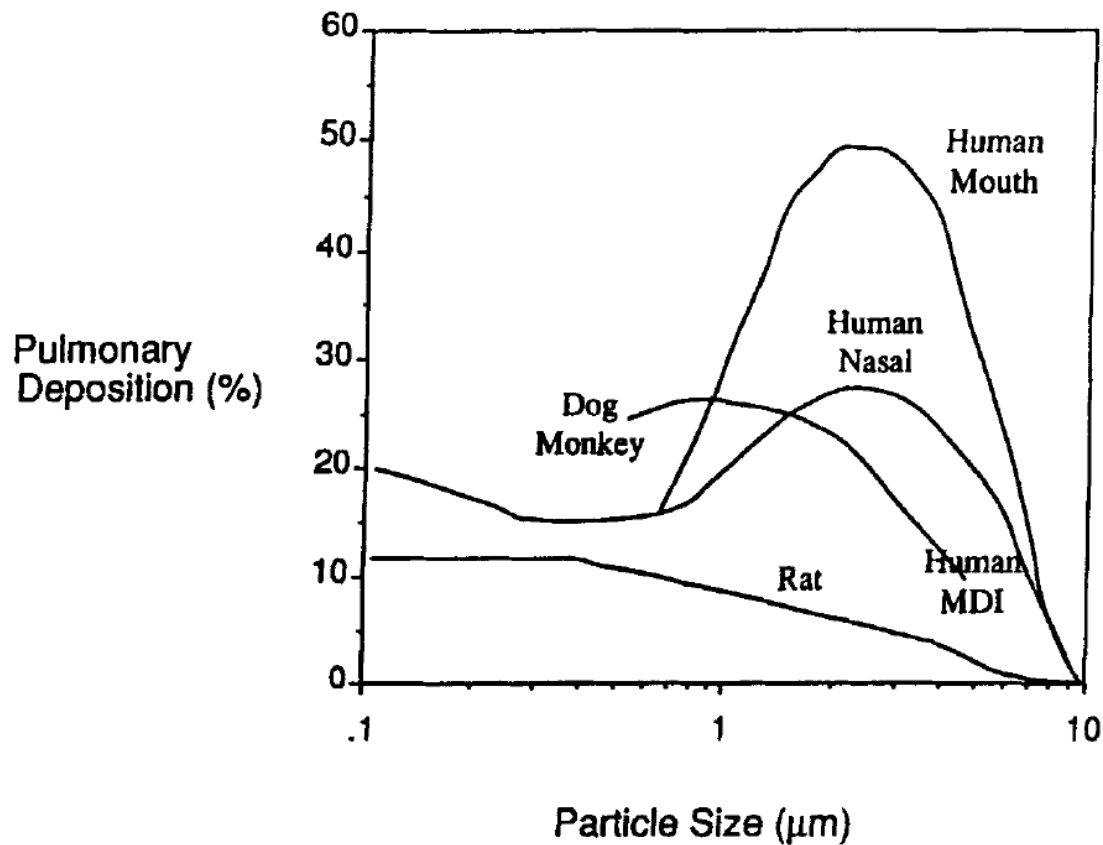


# Pulmonary Deposited Dose (PDD)

Delivered dose x Deposition Factor (DF)

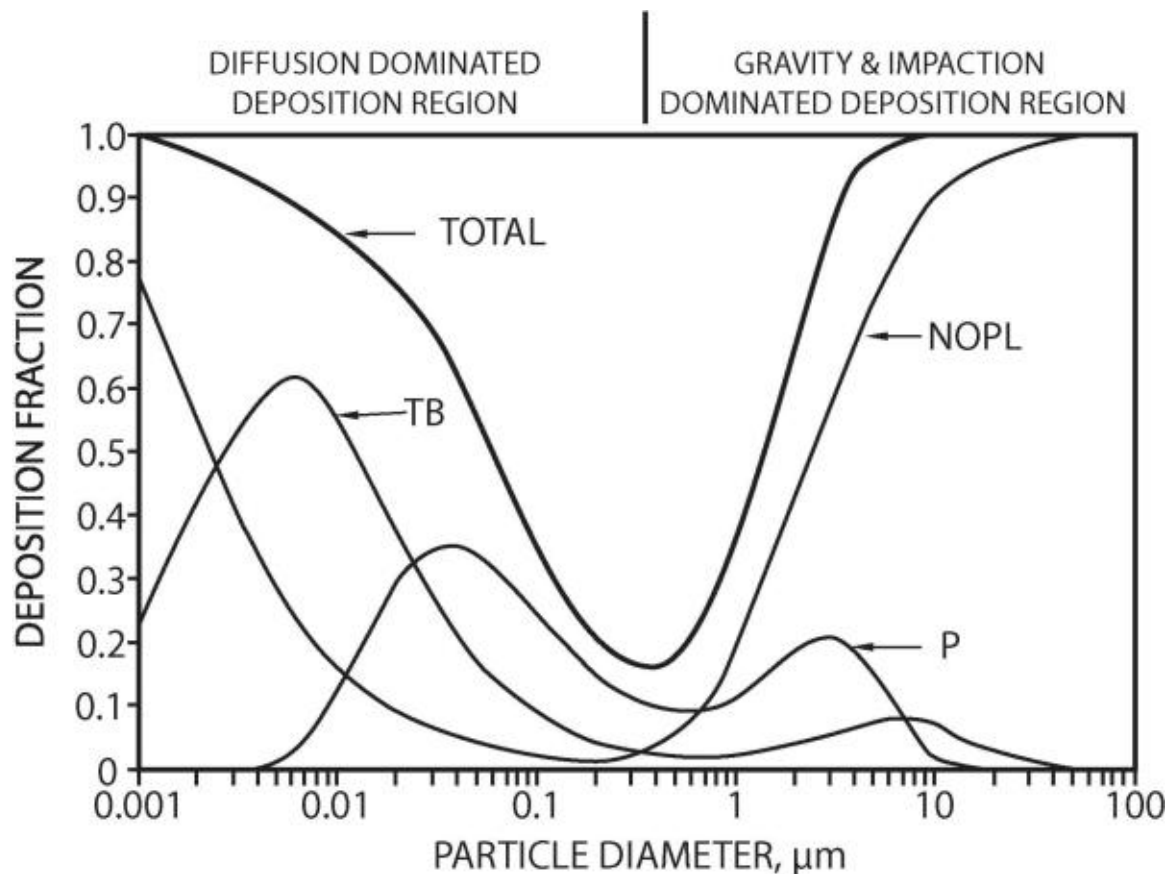
Deposition factors of 0.1, 0.1, 0.25, 0.25 and 1.00 in mice, rats, dogs, monkeys and humans, respectively, used to derive the pulmonary exposure levels of inhaled drugs (MMAD\* of 1 – 5  $\mu\text{m}$ ).

- MMAD\*: mass median aerodynamic diameter



**Pulmonary deposition in nose-breathing rats, dogs and in nose-breathing and mouth-breathing humans**

R K. Wolff & M. A. Dorato (1993) Toxicologic Testing of Inhaled Pharmaceutical Aerosols, Critical Reviews in Toxicology, 23:4, 343-369



**Particle deposition curves for an adult male at rest according to the NCRP 1997 model. Not corrected for inhalability. NOPL = naso-oro-pharyngo-laryngeal; TB= tracheobronchial; and P = pulmonary**

Phalen, R. et al. Dosimetry considerations for animal aerosol inhalation studies. Biomarkers 2009 July; 14 Suppl 1 (63-66)



# Safety Pharmacology

Investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions ..\*

Cardiovascular

BP, HR, EKG, hERG

CNS

Motor activity, behavioral changes, coordination, sensory/motor reflex responses and body temperature

Respiratory

Respiratory rate, tidal volume, hemoglobin, oxygen saturation

Should be conducted prior to human exposure. May be incorporated into general toxicity studies

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s7a-safety-pharmacology-studies-human-pharmaceuticals>

# Pharmacokinetics

- Prior to human clinical trials
- *In vitro* metabolic and plasma protein binding data for humans and animals.
- *In vivo* pulmonary and systemic exposure data in test species.
  
- Prior to Phase III
- Absorption, distribution, metabolism, excretion in test species.
- *In vitro* drug interaction data.
  
- Unique human metabolites (not detected in the test species) may require additional testing



# Repeat-Dose Toxicology Studies

- One rodent and one nonrodent species
- Duration equaling or exceeding proposed duration of clinical trial
- Adequate high dose
  - Maximum tolerated dose
  - large exposure multiples (50x)
  - saturation of exposure
  - maximum feasible dose
- Include extensive detailed histopathological evaluations.
- Reversibility arms to evaluate if toxicities resolve or get worse after the end of dosing.
- New excipients and impurities can be qualified in repeat-dose studies.



# Repeat Dose Study Design

Group	Dose Level (mg/kg/day)		Number of animals used			
	Target	Achieved	Main		Recovery	
			Male	Female	Male	Female
Air control	0	0	4	4	2	2
Lactose control	0	0	4	4	2	2
Low dose	0.25	0.34	4	4	0	0
Mid dose	0.5	1.11	4	4	2	2
High dose	1.5	1.77	4	4	2	2



# Genotoxicity Testing- Standard Battery

- Test for gene mutation in bacteria such as Bacterial reverse mutation test (Ames)
- An *in vitro* test with cytogenetic evaluation of chromosomal damage with mammalian cells or an *in vitro* mouse lymphoma tk assay.
- An *in vivo* test for chromosomal damage using rodent hematopoietic cells.
- *In vitro* results required prior to human testing.
- *In vivo* results required prior to Phase 2 trial.

# Reproductive Toxicology

- Fertility and early embryonic development (Prior to Phase 3)
- Pre- and postnatal development, including maternal function (NDA)
- Embryo-fetal development (Prior to Phase 3)
- Typically rats and rabbits
  
- Route may be different from clinical route
- Various designs are permissible

# Carcinogenicity Studies

- One long-term (2 year) rodent carcinogenicity study

## Plus

- -Short or medium-term in vivo rodent test systems such as transgenic mice or
- -Second long-term rodent carcinogenicity study
- May be conducted by inhalation route
- Needed if expected clinical use is at least six months



# Special Studies

- Combination studies
  - - Co-packaged drugs.
  - - If there is limited clinical information regarding the combination
- Juvenile
- Immunotoxicity
- Abuse potential
- Toxicity of impurities/ metabolites/Leachables (device combination)

# Gaps

- Device design
- Anatomical differences
- Pharmacokinetic parameters are not directly measured but estimated.
- Healthy animals vs infected animals/patients.



# Summary

- The Nonclinical Pharmacology, Toxicology and Pharmacokinetics studies recommended to characterize the toxicity of inhaled antifungals are described in ICH(M3) and FDA's Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route: Guidance for Industry and Review Staff.
- These data help to define safe clinical doses, develop inclusion/exclusion criteria and inform safety monitoring.
- Understanding the limitations of these animal models, relating to test article administration, pharmacokinetics evaluations and test species allows a more realistic characterization of the risk to experimental subjects and patients.
- Novel toxicology studies, such as toxicology studies in animals with fungal infections, could further enhance the predictive ability of toxicity testing in these agents.