U.S. FOOD & DRUG ADMINISTRATION

Evaluating Charcoal Block Pharmacokinetics as a Surrogate for Regional Lung Drug Delivery in Orally Inhaled Drug Products

International Society for Aerosols in Medicine (ISAM) Congress 2025
June 25, 2025

Ross L. Walenga,* Kairui (Kevin) Feng, Meng Hu, Andrew H. Babiskin

Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), Silver Spring, MD, USA

*presenting author

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

What is a Charcoal Block Pharmacokinetics (PK) Study?

- For orally inhaled drug products (OIDPs), charcoal block pharmacokinetics (PK) studies are intended to quantify systemic exposure due to lung dose (i.e., total lung deposition [TLD]).
- Charcoal dosing is intended to block gastrointestinal (GI) absorption. Charcoal block efficiency may be tested via co-administration of an oral dosage form and a charcoal block.[1,2]
- Subjects may be instructed to rinse mouth with charcoal solution to prevent buccal absorption.[1]

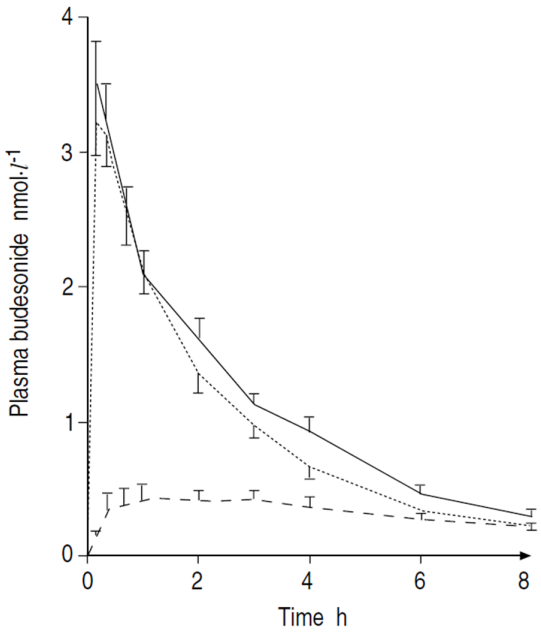


Figure 3a from Thorsson et al.[2], showing mean plasma concentration and variability of budesonide following administration (n = 13) of 1 mg of budesonide inhalation powder with charcoal (solid line) and without charcoal (dotted line) and oral administration with charcoal (dashed line).

Why are Charcoal Block PK Studies Important to FDA (part I)?

- For generic OIDPs, approval in the United States is dependent in part on establishment of bioequivalence (BE) of the test product to its reference listed drug (RLD) or reference standard (RS) product.
  - As stated by 21 CFR 314.3(b), BE is "the absence of a significant different in the rate and extent which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."
- Establishing BE for locally acting OIDPs is especially challenging because there are no studies that can routinely quantify rate and extent of drug delivery to lung tissue.

Why are Charcoal Block PK Studies Important to FDA (part II)?

- Beginning in 2013, BE recommendations in product-specific guidances (PSGs) for locally acting OIDPs have adopted a weight-of-evidence approach that includes demonstration of formulation sameness, device similarity, in vitro BE studies, an in vivo PK study (without a charcoal block), and a comparative clinical endpoint (CCEP) or pharmacodynamics (PD) BE study.

- Recent new and revised PSGs for locally acting OIDPs, beginning in February 2024, have included an option for BE that does not include a CCEP BE or PD BE study. Especially, CCEP BE studies are typically insensitive and may require 1,000 or more subjects to properly power the study.[3]

  - **This new option often includes a recommendation to conduct a charcoal block PK BE study.**

PSGs with Charcoal Block PK Study Recommendations as of May 2025

- Budesonide; Formoterol Fumarate; Glycopyrrolate Inhalation Metered Aerosol (NDA 212122)
- Formoterol Fumarate; Glycopyrrolate Inhalation Metered Aerosol (NDA 208294)
- Mannitol Inhalation Powder (NDA 022368)
- Mannitol Inhalation Powder (NDA 202049)
- Albuterol Sulfate Inhalation Metered Aerosol (NDA 020503, 020983, 021457)
- Fluticasone Propionate; Salmeterol Xinafoate Inhalation Metered Aerosol (NDA 021254)
- Levalbuterol Tartrate Inhalation Metered Aerosol (NDA 021730)
- Treprostinil Inhalation Powder (NDA 214324)
- Budesonide; Formoterol Fumarate; Inhalation Metered Aerosol (NDA 021929)
- Fluticasone Propionate; Salmeterol Xinafoate Inhalation Powder (NDA 021077)
- Formoterol Fumarate Inhalation Powder (NDA 020831)
- Formoterol Fumarate; Mometasone Furoate Inhalation Metered Aerosol (NDA 022518)
- Salmeterol Xinafoate Inhalation Powder (NDA 020692)
- Tiotropium Bromide Inhalation Powder (NDA 021395)

Charcoal Block PK BE Studies – Considerations for Applicants

Applicants are encouraged to use the pre-ANDA meeting process before conducting a study

- Clarify the need for the charcoal block PK data
  - This can depend on the results/interpretability of the unblocked PK study
- Clarify the charcoal block PK study protocol
  - FDA recognizes that this is not a standard study and is open to discuss implementation issues

ANDA: Abbreviated New Drug Application

Can PK Reflect Regional Lung Drug Delivery (part I)?

- **Case study:** FDA funded study (contracts HHSF223201110117A and HHSF223201610099C and grants 1U01FD004950 and 1U01FD005231), Hochhaus et al. (2021),[4] examined impact of aerosol particle size distribution (APSD) differences on PK for fluticasone propionate inhalation powder.
  - Three different formulations were produced by varying lactose fine content.
    - Mass median aerodynamic diameter (MMAD) mean values were 4.5 µm, 3.8 µm, and 3.7 µm for formulations A, B, and C, respectively.
    - Fine particle dose (FPD) < 5 µm mean values were 12.2 µg, 18.7 µg, and 15.9 µg for formulations A, B, and C, respectively.
    - FPD < 3 µm mean values were 5.28 µg, 9.98 µg, and 8.60 µg for formulations A, B, and C, respectively.

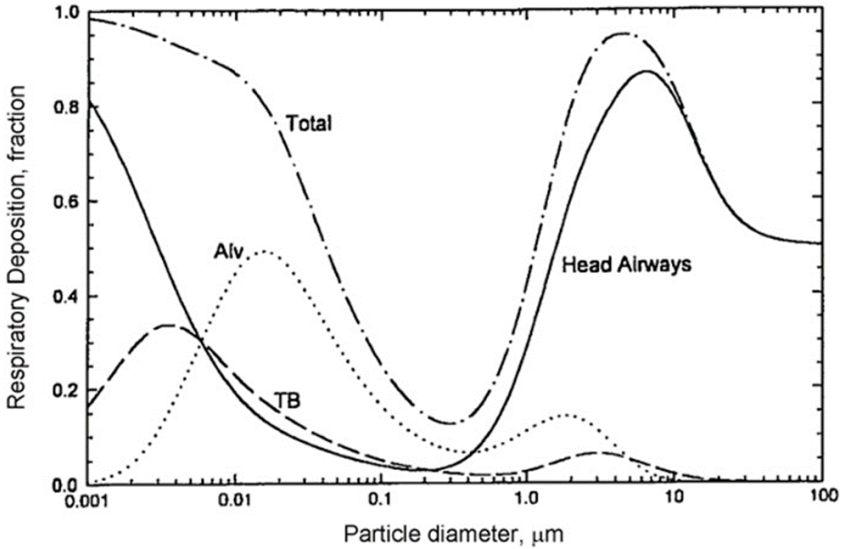


Figure 4 from Carvalho et al.[5] and Hinds[6] showing average deposition in alveolar (Alv), tracheobronchial (TB), head airways, and total using International Commission on Radiation Protection (ICRP) model for nose breathing and light exercise.

Can PK Reflect Regional Lung Drug Delivery (part II)?

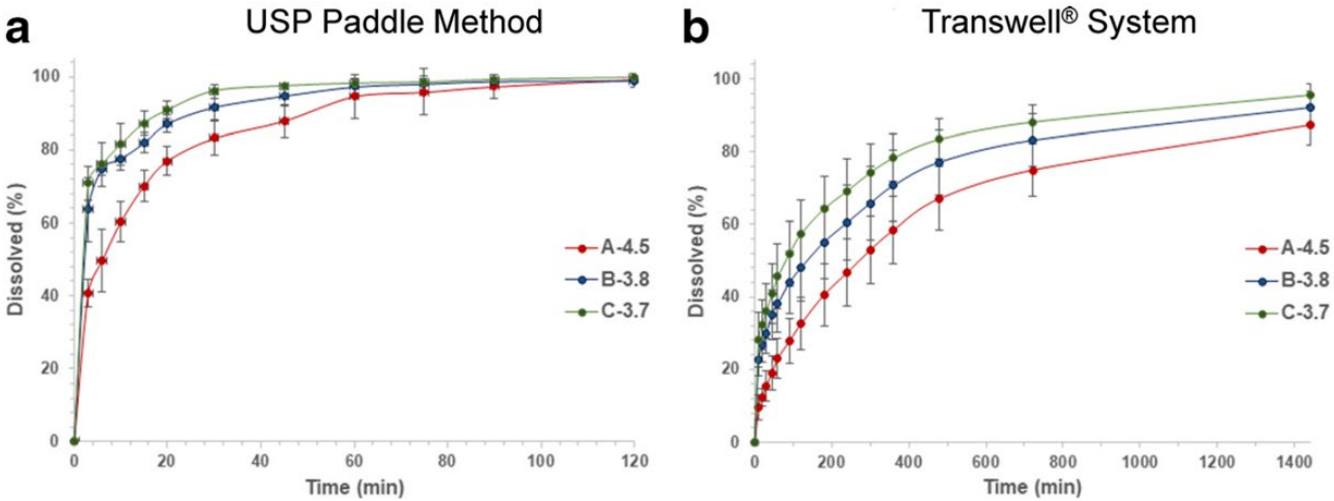


Figure 2 from Hochhaus et al.,[4] showing dissolved amount (as percentage) for formulations A, B, and C, using either a) the United States Pharmacopeia (USP) paddle method or b) the Transwell® system.

Can PK Reflect Regional Lung Drug Delivery (part III)?

Table III from Hochhaus et al.,[4] showing realistic APSD results for fluticasone propionate (FP) formulations A, B, and C in three different mouth-throat (MT) models.

Mouth-throat model	Formulations	FP retained in device (μg)	FP deposited in MT (μg)	$TLD_{in\ vitro}$ (μg)	$TLD_{in\ vitro}$ ratio[a]
VCU medium (n=10)	A-4.5	28.2 (3.5)	48.8 (5.1)	9.24 (1.34)	1.00
	B-3.8	15.4 (2.3)	62.0 (1.5)	16.7 (1.9)	1.81
	C-3.7	14.9 (2.1)	66.2 (2.6)	13.0 (1.6)	1.41
AIT (n=5)	A-4.5	32.6 (1.9)	44.9 (2.4)	11.4 (1.0)	1.00
	B-3.8	14.4 (1.3)	51.4 (6.5)	13.2 (2.0)	1.16
	C-3.7	15.9 (5.8)	64.3 (6.6)	14.8 (2.4)	1.30
OPC medium (n=5)	A-4.5	26.5 (4.2)	36.1 (2.4)	17.7 (1.0)	1.00
	B-3.8	14.3 (2.7)	54.3 (0.2)	20.2 (1.7)	1.14
	C-3.7	16.4 (6.9)	56.2 (7.7)	17.9 (1.7)	1.01
Average of three MT models[b]	A-4.5			12.8	1.00
	B-3.8			16.7	1.32
	C-3.7			15.2	1.21

VCU medium, Virginia Commonwealth University medium MT model; AIT, Alberta Idealized MT model; OPC medium, oropharyngeal consortium medium MT model. [a] Referred to as "dose normalization factor (DNF)" in the text. [b] *Calculated as the ratio of the average of the $TLD_{in\ vitro}$ from VCU, AIT, and OPC with FP DPI formulation A-4.5um being the reference*
Values shown as mean (standard deviation) of n samples indicated below

Can PK Reflect Regional Lung Drug Delivery (part IV)?

- Even after dose normalization, large difference in maximum plasma concentration (C_{max}) for formulation A compared to B and C.
- Although dissolution was thought to contribute significantly to C_{max} difference, a PK model suggested that dissolution only accounted for about a third of the difference.[3]
- Authors concluded that differences in regional deposition may account for the rest of the difference in C_{max}, and that population PK and PBPK modeling are warranted to further explore the question.

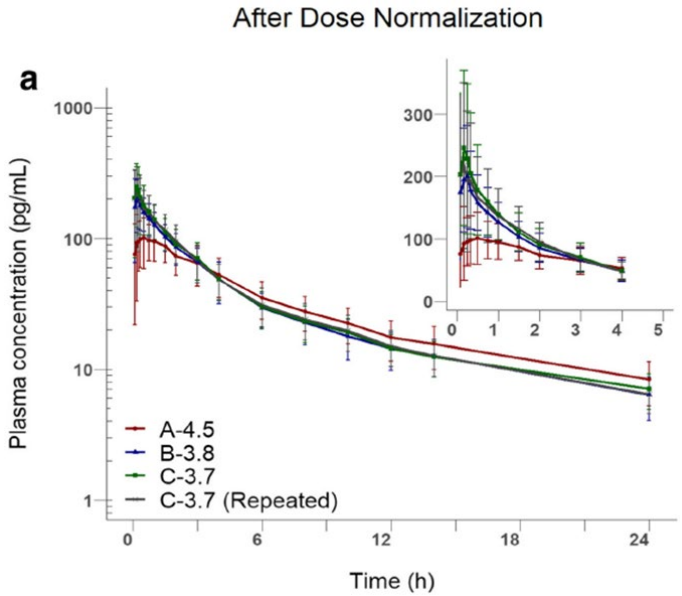


Figure 3a from Hochhaus et al.,[4] showing dose normalized (by in vitro total lung deposition) mean plasma concentration and variability of fluticasone propionate following administration (n = 23) of formulations A, B, and C (two replicate study arms).

PK Modeling to Predict Regional Lung Drug Delivery

- Contract 1U01FD007936 (University of Florida)
  - Principal Investigator: Jürgen Bulitta
  - End date: 9/29/2025
- Methodology
  - Utilize Population PK and PBPK modeling to predict impact of formulation differences on regional lung drug delivery
  - Leverage systemic PK data to infer regional lung drug delivery based on expected differences in dissolution and permeation across different lung regions
- **Impact:** Such a modeling approach may potentially be used to understand how systemic PK profiles reflect regional lung drug delivery, considering various drug properties (i.e., particle size, dissolution rate) and mucociliary clearance.

Mechanistic Modeling Approach to Examine Relationships Between Charcoal Block PK Metrics and Regional Deposition

- Can charcoal block PK studies be used to quantify ***regional*** deposition?
- PBPK modeling was used internally to predict systemic PK following administration of a suspension-based metered dose inhaler (MDI) for budesonide; formoterol fumarate dihydrate inhalation metered aerosol, and results were presented as a poster at Respiratory Drug Delivery (RDD) 2024.[7]
- Model-based sensitivity analyses explored potential relationships between systemic PK and regional deposition.

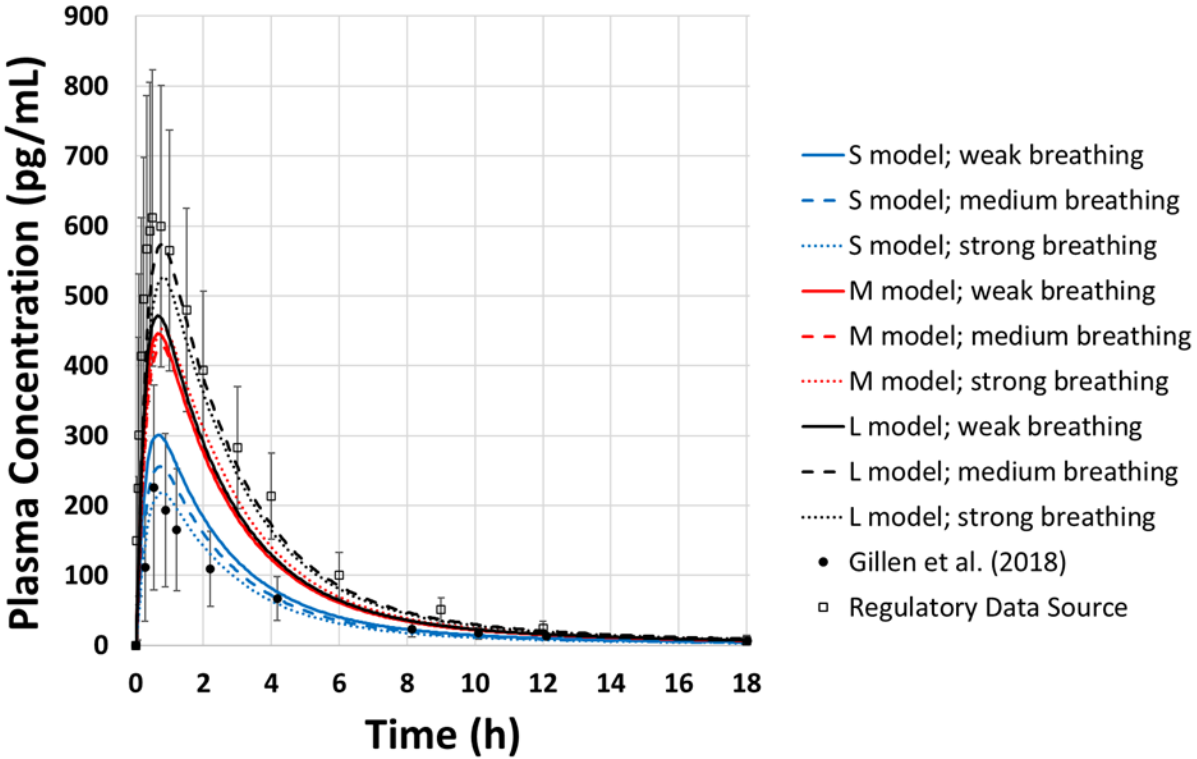
Methods

- GastroPlus® 9.8.3 (Simulations Plus, Inc., Research Triangle Park, NC, USA)
  - Pulmonary Compartmental Absorption & Transit (PCAT™)
- Model parameters determined based on literature search.
  - Intravenous (IV) PK data not available for formoterol fumarate dihydrate.
- Two-compartment PK models were used to describe systemic PK. GI absorption was described by setting a fixed first-pass effect for budesonide, but not for formoterol fumarate. Amount of drug that deposited in the MT that was rinsed and therefore not swallowed was assumed to be 85%.
- For inhalation PK simulations, input parameters for dissolution, particle size distribution (PSD), and extrathoracic deposition were based on pooled APSD data.
  - Collected for Contract 75F40119C10154 by the University of Florida and Emmace Consulting AB, using three realistic MT models produced by the Oropharyngeal Consortium (OPC) and Virginia Commonwealth University (VCU) and three breathing profiles.
- A central-to-peripheral deposition ratio (C/P) of 1 and exhaled fraction of 0.6% were assumed for the purposes of model development (Usmani et al. [2021]).[8]

Input Deposition Fraction (DF) Parameters – Budesonide

MT Model(s)	Breathing Profile	Extra-thoracic DF (%)	Tracheo-bronchial DF (%)	Bronchiolar DF (%)	Alveolar-Interstitial DF (%)
VCU and OPC pooled small	Weak	71.0	14.200	7.100	7.100
	Medium	75.1	12.150	6.075	6.075
	Strong	78.4	10.500	5.250	5.250
VCU and OPC pooled medium	Weak	55.7	21.850	10.925	10.925
	Medium	55.5	21.950	10.975	10.975
	Strong	51.1	24.150	12.075	12.075
VCU and OPC pooled large	Weak	53.2	23.100	11.550	11.550
	Medium	39.0	30.200	15.100	15.100
	Strong	42.8	28.300	14.150	14.150

Validation – Budesonide



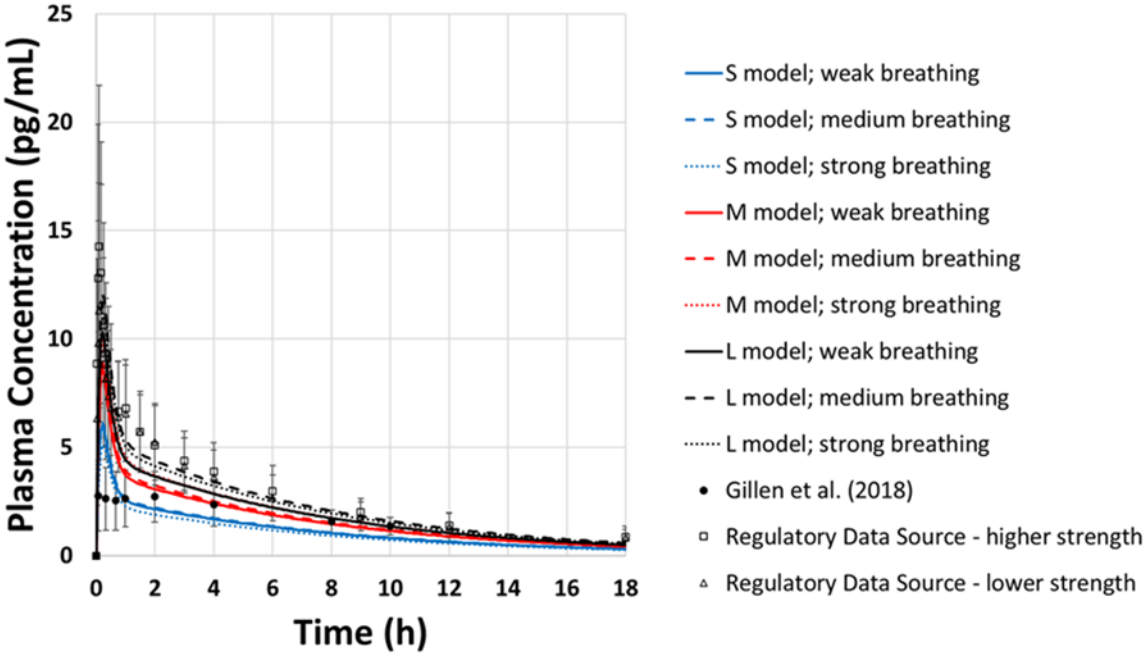
- Plasma concentration predictions in a single subject intended to represent the population mean
- Two inhalations of the 0.16 mg/inh; 0.0045 mg/inh strength of the reference listed drug (RLD) product without a charcoal block
- Compared with in vivo PK data from Gillen et al.[9] (n = 49) and a regulatory data source (n = 96)
- Model inputs based on realistic APSD data collected with small (S), medium (M), and large (L) MT models under various breathing conditions, taken from Contract 75F40119C10154.

Input DF Parameters – Formoterol Fumarate Dihydrate

MT Model(s)	Breathing Profile	Extra-thoracic DF (%)	Tracheo-bronchial DF (%)	Bronchiolar DF (%)	Alveolar-Interstitial DF (%)
VCU and OPC pooled small	Weak	66.0	16.700	8.350	8.350
	Medium	65.0	17.200	8.600	8.600
	Strong	77.4	11.025	5.513	5.513
VCU and OPC pooled medium	Weak	51.0	24.200	12.100	12.100
	Medium	48.8	25.300	12.650	12.650
	Strong	41.0	29.200	14.600	14.600
VCU and OPC pooled large	Weak	41.7	28.850	14.425	14.425
	Medium	30.2	34.600	17.300	17.300
	Strong	34.1	32.650	16.325	16.325

Validation – Formoterol Fumarate Dihydrate

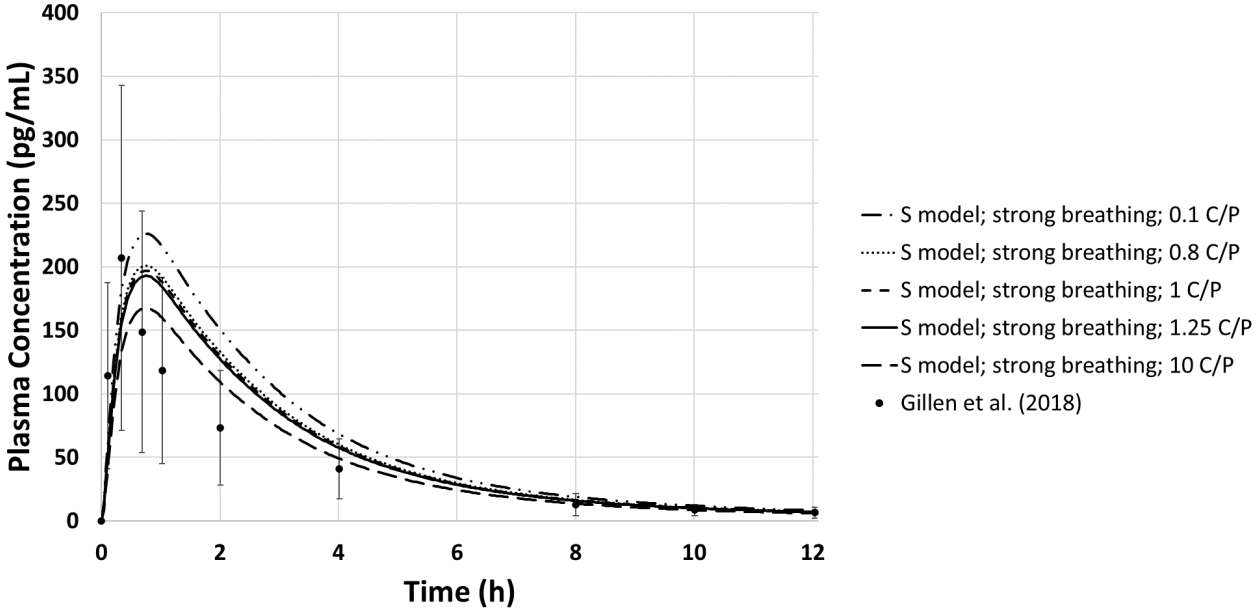
www.fda.gov



- Two inhalations of the 0.16 mg/inh; 0.0045 mg/inh RLD product without a charcoal block for all cases except "Regulatory Data Source – lower strength," where the dosing was two inhalations of the 0.08 mg/inh; 0.0045 mg/inh RLD product
  - All cases represent dosing of 0.009 mg of formoterol fumarate

Sensitivity to Differences in C/P – Budesonide

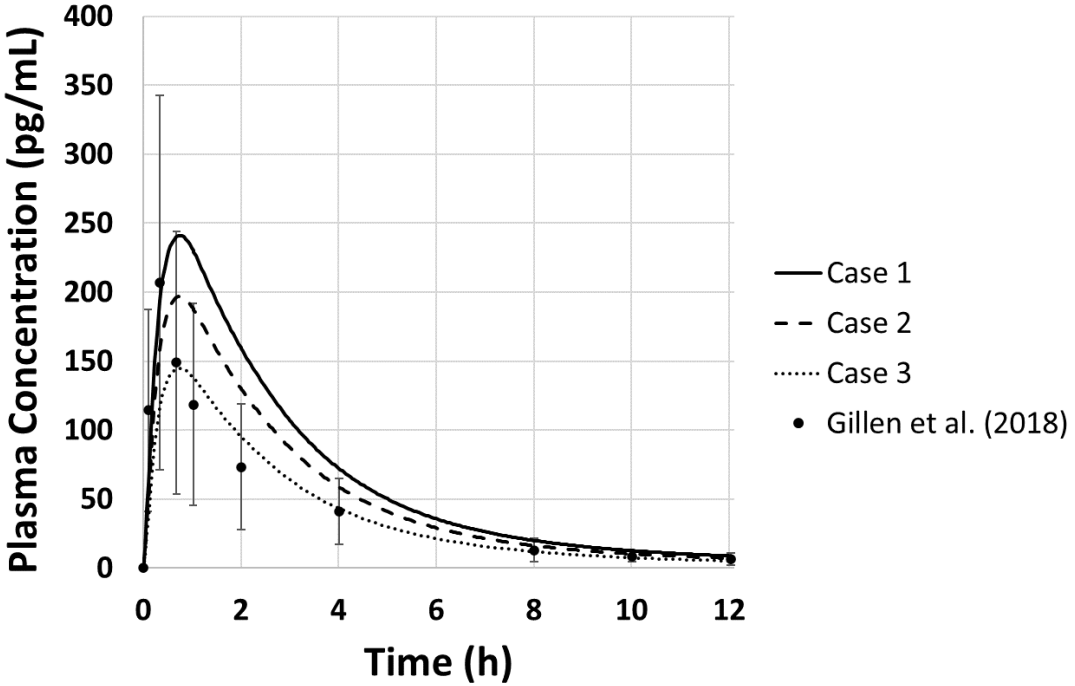
www.fda.gov



- Only C/P was altered; total lung deposition (TLD) was kept constant
- Differences in PK are due to regional differences in permeation and dissolution
- Similar results were observed for formoterol fumarate dihydrate

Sensitivity to Differences in C/P and TLD – Budesonide

www.fda.gov



- Hypothesis was that C/P and TLD may be inversely correlated
- One-to-one inverse correlation of was assumed.
- Case 1
  - C/P = 0.8, 120 % of $TLD_{in\ vitro}$
- Case 2
  - C/P = 1, 100 % of $TLD_{in\ vitro}$
- Case 3
  - C/P = 1.25, 75 % of $TLD_{in\ vitro}$

Sensitivity Analyses

Predicted values of maximum plasma concentration (C_{max}), area under the plasma concentration time curve from time 0 to time t (AUC_{0-t}), and area under the plasma concentration time curve from time 0 to infinity ($AUC_{0-\infty}$) in a single subject intended to represent the population mean when a one-to-one inverse correlation between C/P and TLD is assumed.

Active Ingredient	C/P	% of $TLD_{in\ vitro}$	C_{max} (pg/mL)	AUC_{0-t} (pg-h/mL)	$AUC_{0-\infty}$ (pg-h/mL)
Budesonide	0.8	120	241.1	811.5	864.8
	1	100	197.0	662.1	705.5
	1.25	75	144.8	485.9	517.8
Formoterol Fumarate Dihydrate	0.8	120	6.3	16.3	24.7
	1	100	5.1	13.2	19.9
	1.25	75	3.7	9.5	14.5

Machine Learning Techniques to Support Population PK Modeling of OIDPs

- Population PK may be used to estimate contributions of regional deposition to systemic PK, based on available PK data.
- A new machine learning toolbox called pyDarwin was created that enables machine learning-based model selection for use with population PK model built using the commercial software package NONMEM (Icon PLC, Dublin, Ireland).[10]
- A sample case was provided for quetiapine, an antipsychotic medication delivered orally, that concluded to a two-compartment model with absorption lag time and no zero-order input as the best performing model.[10]

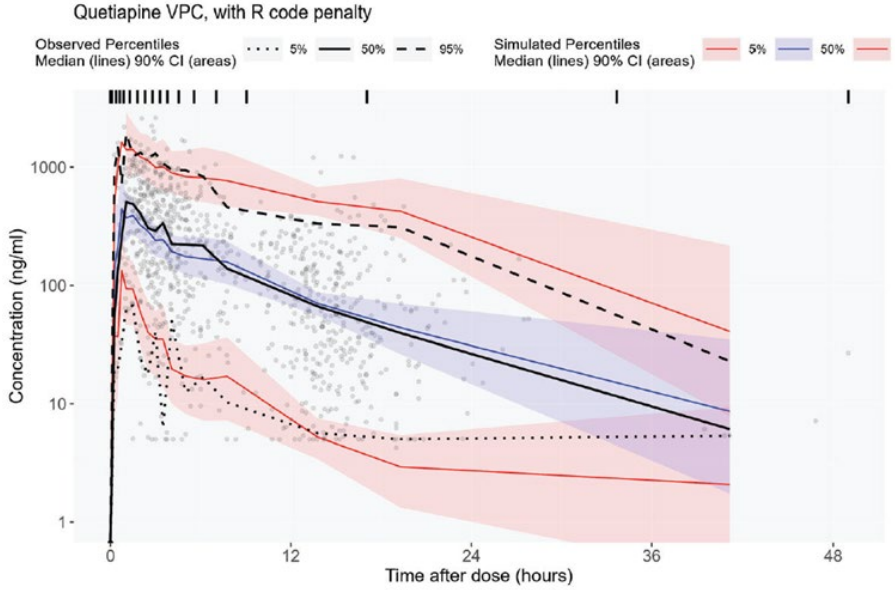


Figure 6 from Li et al.,[10] showing plasma concentration predictions as compared with observed data for quetiapine in the 5th, 50th, and 95th percentiles with 90% confidence intervals (CIs), produced after applying a penalty C_{max}.

Ongoing Research Topics

1. When is a charcoal block PK BE study needed for the BE option that does not include CCEP BE or PD BE study?
2. How can computational modeling either inform FDA recommendations or provide industry with tools that can accelerate product development and approval?
3. Under what circumstances may a PK BE study without a charcoal block be needed for lower drug product strengths?

Conclusions

1. Use the pre-ANDA meeting process to discuss the incorporation of Charcoal block PK BE studies into ongoing OIDP development programs.
2. Ongoing computational modeling research aims to better understand the potential that metrics from charcoal block PK BE studies may reflect regional lung drug delivery.
3. Modeling results suggest that differences in C/P may produce significant differences in PK when correlated with TLD.
4. Machine learning may be used to enhance and accelerate population PK modeling to evaluate relationships between regional lung drug delivery and systemic PK.
5. FDA is currently considering when charcoal block PK BE studies may be appropriate and how computational modeling may aid decision-making and product development. Partial AUC metrics may provide a means for interpreting PK data collected without a charcoal block such that a charcoal block PK study may not needed, for some products.

Acknowledgements

- FDA/CDER/OGD/ORS
  - Steven Chopski
  - Khondoker Alam
  - Bora Sul
  - Morgan Thomas
  - Abdullah Al Shoyaib
  - Deniz Ozdin
  - Peijue Zhang
  - Yuqing Gong
  - Mingliang Tan
  - Elizabeth Bielski
  - Susan Boc
  - Liangfeng Han
  - Anubhav Kaviratna
  - Bryan Newman
- FDA/CDER/OGD/ORS (cont'd)
  - Lanyan (Lucy) Fang
  - Markham Luke
  - Yan Wang
  - Sameersingh (Sam) Raney
  - Jasdeep (Jessie) Floura
  - Lei Zhang
  - Robert Lionberger
- University of California San Francisco
  - Liang Zhao
- University of Florida
  - Jürgen Bulitta
  - Günther Hochhaus
  - Yongzhen Zhang
  - Xindi Shan

We Are OGD

Ask me why...

"I make sure that the **generic** drug and the **brand** drug work **the same**."

"The first time I was able to buy my son's inhaler as a generic and realized that my out of pocket dropped, I cried and was able to breathe a sigh of relief."

www.fda.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

References

1. Cheng Y, Zhou X, Wang Z, He G, Yang L, Hou S. Calculating the charcoal blockade efficiency for bioequivalence study of inhaled ipratropium bromide using a model method. Journal of Pharmaceutical Sciences. 2022;111(7):2107-15.
2. Thorsson L, Edsbacker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. European Respiratory Journal. 1994;7(10):1839-44.
3. Lee J, Feng K, Conti DS, Walenga R, Wientjes M, Wang H, Newman B, Han L, Dhapare S, Bielski E, Babiskin A. Considerations for the Forced Expiratory Volume in 1 Second-Based Comparative Clinical Endpoint Bioequivalence Studies for Orally Inhaled Drug Products. Clinical Pharmacology & Therapeutics. 2022;112(5):982-9.
4. Hochhaus G, Chen MJ, Kurumaddali A, Schilling U, Jiao Y, Drescher SK, Amini E, Kandala B, Tabulov C, Shao J, Seay B. Can pharmacokinetic studies assess the pulmonary fate of dry powder inhaler formulations of fluticasone propionate?. The AAPS journal. 2021;23:1-4.
5. Carvalho TC, Peters JI, Williams III RO. Influence of particle size on regional lung deposition–what evidence is there?. International journal of pharmaceutics. 2011;406(1-2):1-0.
6. Hinds WC. 11: Respiratory Deposition. Aerosol Technology: Properties, Behavior, and Measurement of Airborne Particles. 1999:233-59.
7. Walenga R, Tsakalozou E, Chopski S, Fang L, and Zhao L. Sensitivity of Charcoal Block PK Metrics to Differences in Regional Deposition for Budesonide and Formoterol Fumarate Dihydrate. Respiratory Drug Delivery 2024. 2024;1:448-451.
8. Usmani O, Roche N, Wahab E, Israel S, Jenkins M, Trivedi R, Dorinsky P, Aurivillius M. A scintigraphy study of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler in patients with moderate-to-very severe chronic obstructive pulmonary disease. Respir Res 2021;22:261.
9. Gillen M, Forte P, Svensson JO, Lamarca R, Burke J, Rask K, Nilsson UL, Eckerwall G. Effect of a spacer on total systemic and lung bioavailability in healthy volunteers and in vitro performance of the Symbicort®(budesonide/formoterol) pressurized metered dose inhaler. Pulm Pharmacol Ther 2018;52:7-17.
10. Li X, Sale M, Nieforth K, Bigos KL, Craig J, Wang F, Feng K, Hu M, Bies R, Zhao L. pyDarwin: a machine learning enhanced automated nonlinear mixed-effect model selection toolbox. Clinical Pharmacology & Therapeutics. 2024;115(4):758-73.