

In Silico Modeling to Guide Charcoal Block PK BE Study Recommendations for Orally Inhaled Drug Products

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Overview



- Understand the rationale for conducting charcoal block pharmacokinetics (PK) bioequivalence (BE) studies
- Describe how physiologically based pharmacokinetic (PBPK) modeling was used by the U.S. Food and Drug Administration (FDA) to inform product-specific (PSG) recommendations related to charcoal-block PK BE studies
- Explain how a partial area under the plasma concentration-time curve (AUC) approach may be used in lieu of a charcoal block PK BE study

Charcoal Block PK BE Studies

Recent PSG recommendations from the FDA for orally inhaled drug products (OIDPs) provide options for demonstrating BE that do not include a comparative clinical endpoint study.

For many of these OIDPs, the corresponding PSG includes a recommendation to conduct a PK BE study with a charcoal block.

Co-administration of charcoal with the drug product prevents gastrointestinal (GI) absorption, such that the resulting PK data may be expected to largely reflect drug absorbed through the lung.

When is a Charcoal Block PK BE Study Unnecessary (According to EMA)?



According to European Medicines Agency (EMA), when “the contribution from the gastrointestinal (GI) tract to total systemic bioavailability following inhalation is negligible (<5%)” a charcoal block PK BE study is unnecessary for evaluating lung exposure.¹

EMA recommends that for ODPs that have median time to maximum plasma concentration ($C_{\max}$) ($t_{\max}$) values ≤ 5 min and when “contribution from the GI tract to the total systemic exposure following inhalation is $\geq 5\%$,” that in addition to standard PK metrics applicants evaluate BE according to $AUC_{0-30\text{min}}$.¹

When is a Charcoal Block PK BE Study Unnecessary (According to FDA)?



FDA agrees with EMA that when the contribution of absorption via the GI tract to total systemic bioavailability is minimal, then a charcoal block PK BE study is unnecessary. This assessment is made on a case-by-case basis.

FDA is evaluating the potential for using the partial AUC approach adopted by EMA on a case-by-case basis, for instances when the contribution of absorption via the GI tract to total systemic bioavailability is substantial.

Beclomethasone Dipropionate Inhalation Metered Aerosol

In Silico Modeling to Evaluate Need for Charcoal Block PK BE Study

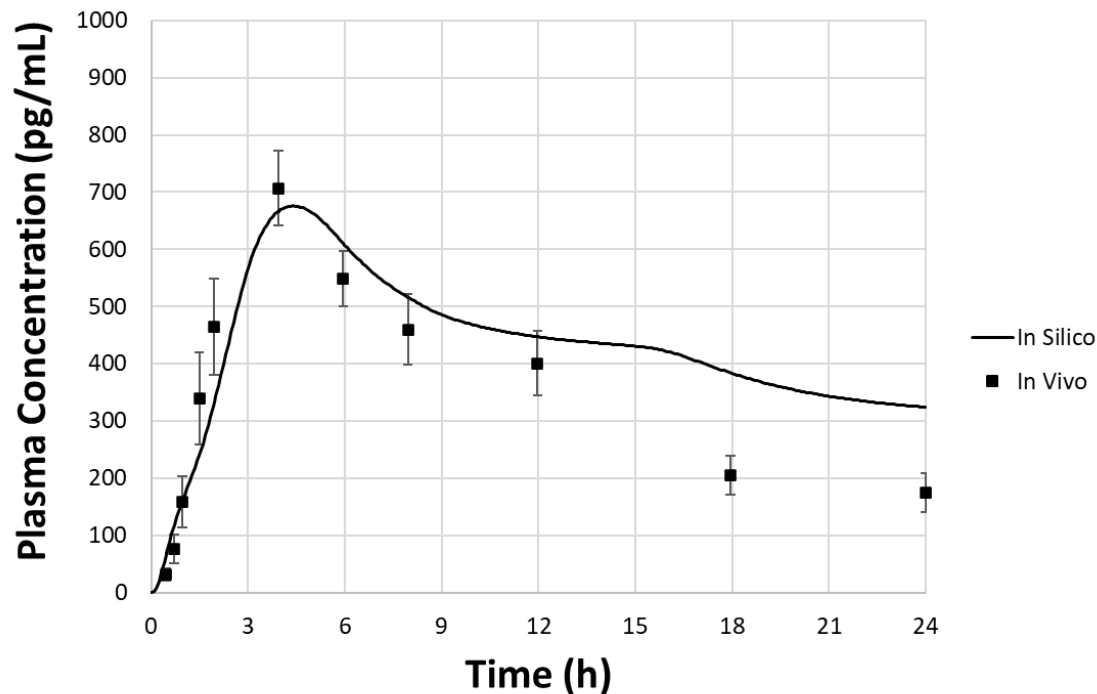


For this study, to help determine whether a PK study with a charcoal block is needed to demonstrate BE for beclomethasone dipropionate (BDP) inhalation metered aerosol (new drug application [NDA] 020911, brand name: QVAR), a PBPK modeling approach was employed.

Specifically, an oral PBPK model was used to predict the contribution of GI absorption to PK, which was then compared with overall PK following inhalation administration without a charcoal block as obtained from a regulatory data source for the reference listed drug (RLD).

The model was built using GastroPlus® 9.9 (Simulations Plus, Inc., Research Triangle Park, NC, USA) and used a whole-body approach to model PK of BDP and the active metabolite, beclomethasone 17-monopropionate (17-BMP).

Oral Administration – Prediction



Predicted mean plasma concentration of 17-BMP following oral administration of 4 mg of BDP, as compared with mean in vivo data (n = 12) from Daley-Yates et al. (2001), where error bars show standard deviation values for each time point.

Model Validation



Observed (from Daley-Yates et al. [2001]) and predicted values for $C_{\max}$, time to $C_{\max}$ ($t_{\max}$), AUC_{0-t} , and $AUC_{0-\infty}$ following IV and oral administration of BDP inhalation metered aerosol, for both BDP and 17-BMP. Absolute relative difference (ARD) values are provided by dividing the absolute difference between simulated and in vivo values by the in vivo value.

Route	Compound	$t_{\max}$ (h)		$C_{\max}$ (pg/mL)		ARD (%)
		In Vivo	Simulated	In Vivo	Simulated	
IV	BDP	0.2	0.17	35356.0	35968.5	2
IV	17-BMP	0.2	0.17	2633.0	9326.9	354
Oral	17-BMP	4.0	4.40	703.0	675.9	4

Route	Compound	AUC_{0-t} (pg-h/mL)			$AUC_{0-\infty}$ (pg-h/mL)		
		In Vivo	Simulated	ARD (%)	In Vivo	Simulated	ARD (%)
IV	BDP	6476.7	9383.8	45	6660.0	9916.0	49
IV	17-BMP	5991.9	5526.5	8	6185.0	6336.3	2
Oral	17-BMP	9032.8	10346.6	15	10158.0	34365.3	238

Oral Contribution



Percentage of contribution to systemic exposure from swallowing the dose orally after inhalation administration as observed in literature and predicted using an oral PBPK model compared with data from a regulatory data source.

Source	Product	Strength	Subjects	Oral Contribution to:		
				C _{max} (pg/mL)	AUC _{0-t} (pg-h/mL)	AUC _{0-∞} (pg-h/mL)
Daley-Yates et al. (2001)	Beclovent	0.05	healthy adults (n = 12)	25%	-	38%
Singh et al. (2011) ³	Foster	0.1	healthy adults (n = 12)	-1%	46%	-
Rony et al. (2024) ⁴	Trimbow	0.1	healthy adults (n = 63)	21%	43%	40%
Rony et al. (2024)	Trimbow	0.2	healthy adults (n = 64)	12%	41%	40%
Agertoft et al. (2003) ⁵	QVAR	0.05*	pediatric patients (n = 14)	25%	10%	18%
Predicted	QVAR	0.04	healthy adults	5%	14%	14%
Predicted	QVAR	0.08	healthy adults	5%	14%	15%

* - dose reflects loaded dose, which was later changed to reflect emitted dose (0.04 mg/inh)

BDP Evaluation



The PBPK models for BDP and its metabolite 17-BMP were validated using available IV and oral PK data from Daley-Yates et al. (2001) and the oral PBPK model was then used to predict PK due to swallowing of BDP following inhalation administration without a charcoal block.

Predictions showed that GI absorption may contribute to approximately 5% of $C_{\max}$ and 14-15% of AUC_{0-t} and $AUC_{0-\infty}$.

Based on these results, FDA reviewers determined that GI absorption for 17-BMP is sufficiently minimal that a charcoal block PK study is not needed for demonstration of BE for a prospective generic BDP inhalation metered aerosol against the RLD, which helped facilitate approval of a generic product and posting of two newly revised PSGs of BDP inhalation metered aerosol (NDA 020911 and NDA 207921).^{6,7}

Tiotropium Bromide Inhalation Powder

Methods



Research funded by Generic Drug User Fee Amendments (GDUFA)

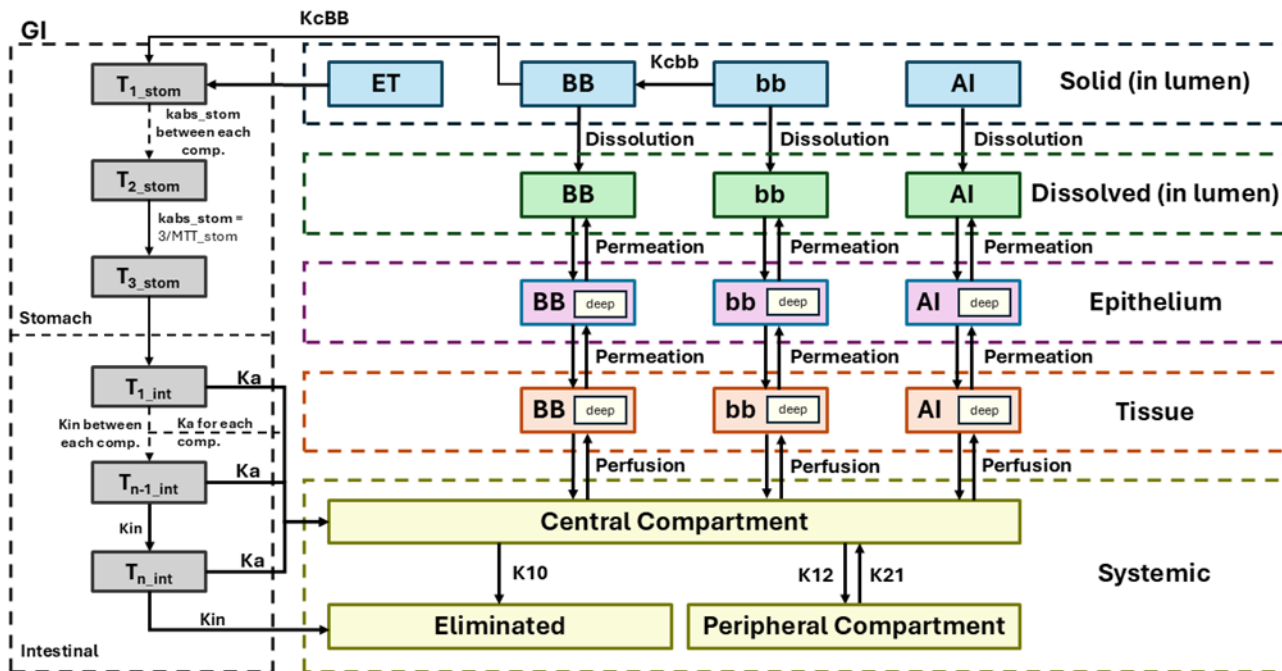
- Grant U01FD007936 (PD/PIs: Jürgen Bulitta and Günther Hochhaus, University of Florida)
- PBPK model developed by Dr. Yongzhen Zhang

Software package: Berkeley Madonna (University of California at Berkeley, Berkeley, CA, USA)

Regional deposition was predicted using a semi-empirical model, Mimetikos Preludium (Emmace Consulting AB, Lund, Sweden) and particle size distribution data obtained from a gamma scintigraphy in vivo study.⁸

Charcoal block absorption and drug binding to charcoal were modeled mechanistically.

Model Structure



Abbreviations:

ET – extrathoracic

BB – tracheobronchial

bb – bronchiolar

AI – alveolar-interstitial

Tn_stom – stomach transit compartment

MTT_stom – mean transit time in the stomach

kabs_stom – transit rate constant in the stomach

Tn_int – intestinal transit and absorption compartments

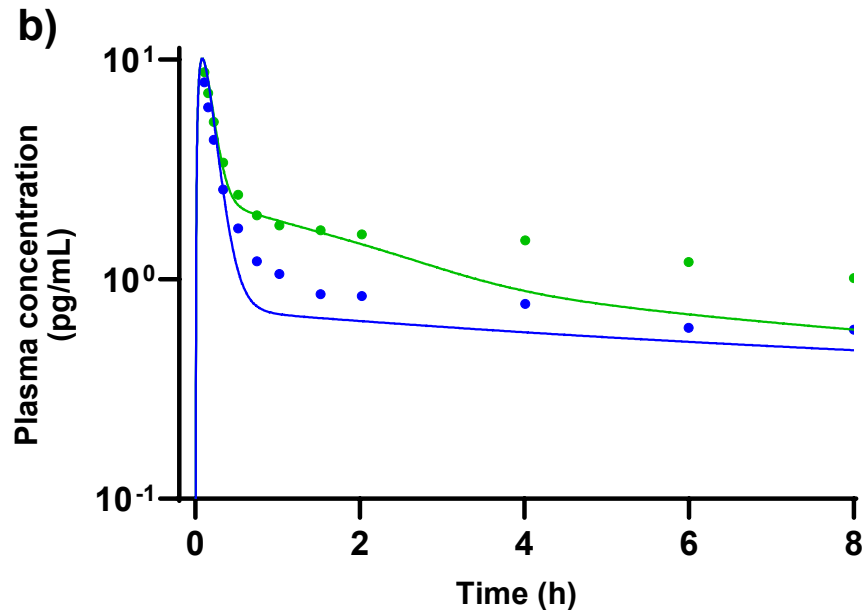
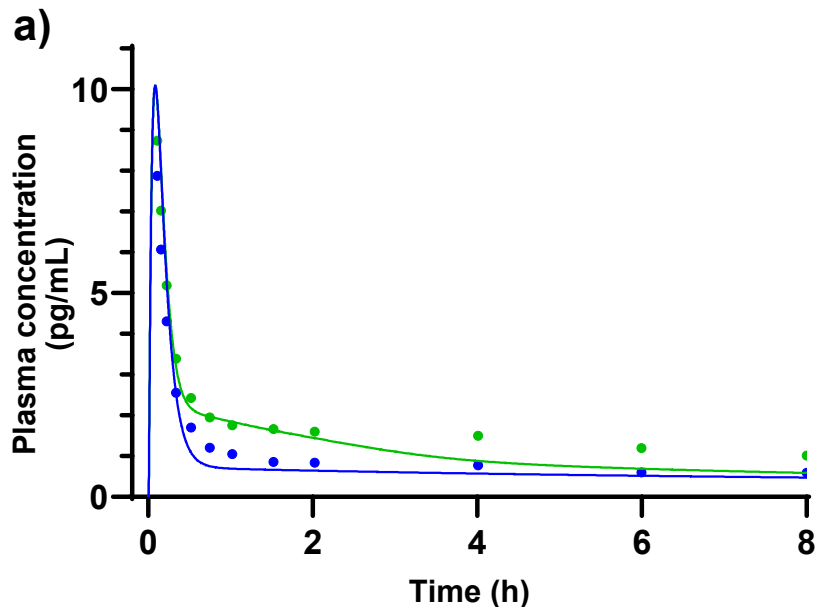
Ka – intestinal absorption rate constant

Kin – intestinal transit rate constant
k10, k12, k21 – distribution coefficients

KcBB – mucociliary clearance rate constant in tracheobronchial region

Kcbb – mucociliary clearance rate constant in bronchiolar region

Model Validation



In silico predictions of plasma concentration following inhalation administration of tiotropium bromide without charcoal (green) and with charcoal (blue) as compared with in vivo PK data from Perry et al. (2019)⁹ on a) ordinate scale and b) log scale. (Figure provided via Grant U01FD007936)

Model Validation



Predicted PK metrics with and without a charcoal block with mean stomach transit time of 15 min, following administration of tiotropium bromide inhalation powder, as compared with observed results.

	C_{max}		AUC_{0-30min}		AUC_{0-8h}	
	Predicted value (pg/mL)	Simulated-to- Observed Ratio	Predicted value (pg-h/mL)	Simulated-to- Observed Ratio	Predicted value (pg-h/mL)	Simulated-to- Observed Ratio
With charcoal	10.08	1.22	2.37	1.22	6.73	0.88
Without charcoal	10.09	1.28	2.58	1.28	10.29	0.86

Model Results



Predicted ratio of inhalation absorption to oral absorption 20 minutes and 30 minutes after inhalation administration of tiotropium bromide inhalation powder for mean stomach transit time (MTT_{stom}) of 15, 20, and 25 minutes.

Inhalation-to-Oral Absorption Ratio	MTT _{stom}		
	15 minutes	20 minutes	25 minutes
@ t=20 minutes	13.59	20.42	29.73
@ t=30 minutes	6.25	8.23	10.85

Table prepared by Dr. Steven Chopski

Tiotropium Bromide Evaluation

Results suggested that PK metrics $AUC_{0-20min}$ and $AUC_{0-30min}$ may be viable substitutes for a charcoal block PK BE study for tiotropium bromide inhalation powder based on the predicted ratios of inhalation to oral absorption.

The PSG for tiotropium bromide inhalation powder was revised to include an option for demonstrating BE using a partial AUC approach with $AUC_{0-30min}$ in lieu of a charcoal block PK BE study.¹⁰ Although both $AUC_{0-20min}$ and $AUC_{0-30min}$ were considered valid, $AUC_{0-30min}$ was selected to foster harmonization with EMA.

Conclusions

1. Recent FDA PSGs include recommendations to conduct a charcoal block PK BE study for certain generic ODPs.
2. Two case studies describe the use of PBPK to better understand the need for a charcoal block PK BE study for beclomethasone dipropionate inhalation metered aerosol or the viability of a partial AUC approach for tiotropium bromide inhalation powder.
3. FDA will continue to work toward identifying instances where a partial AUC approach may be used in lieu of charcoal block PK BE study for relevant ODPs.

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Closing Thought

Consider using MIE to support alternative approaches in lieu of a charcoal block PK BE study



References

1. European Medicines Agency. Guideline on the requirements for demonstrating Therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD). 2026.
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-demonstrating-therapeutic-equivalence-between-orally-inhaled-products-oip-asthma-chronic-obstructive-pulmonary-disease-copd-revision-2_en.pdf. Accessed on 23 Jun 2026.
2. Daley-Yates PT, Price AC, Sisson JR, Pereira A, Dallow N. Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. British journal of clinical pharmacology. 2001;51(5):400-9.
3. Singh D, Collarini S, Poli G, Acerbi D, Amadasi A, Rusca A. Effect of AeroChamber Plus™ on the lung and systemic bioavailability of beclomethasone dipropionate/formoterol pMDI. British journal of clinical pharmacology. 2011;72(6):932-9.
4. Rony F, Cortellini M, Guasconi A, Mathews KS, Piccinno A, Poli G, Vanhoutte F, Klein J. Evaluating the pharmacokinetics of beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide delivered via pressurised metered-dose inhaler using a low global warming potential propellant. Pulmonary Pharmacology & Therapeutics. 2024;85:102299.
5. Agertoft L, Laulund LW, Harrison LI, Pedersen S. Influence of particle size on lung deposition and pharmacokinetics of beclomethasone dipropionate in children. Pediatric pulmonology. 2003;35(3):192-9.
6. Draft Guidance on Beclomethasone Dipropionate (NDA 020911). 2025.
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020911.pdf. Accessed on 23 Jun 2026.
7. Draft Guidance on Beclomethasone Dipropionate (NDA 207921). 2025.
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_207921.pdf. Accessed on 23 Jun 2026.

References



8. Brand P, Meyer T, Weuthen T, Timmer W, Berkel E, Wallenstein G, Scheuch G. Lung deposition of radiolabeled tiotropium in healthy subjects and patients with chronic obstructive pulmonary disease. *The Journal of Clinical Pharmacology*. 2007;47(10):1335-41.
9. Perry J, Trautman B, Takher-Smith J, Kramer S, Kane K, Silverman M, Tan L, Haughie S, Richter W, Kirkov V, Arsova S. Particle size and gastrointestinal absorption influence tiotropium pharmacokinetics: a pilot bioequivalence study of PUR0200 and Spiriva HandiHaler. *British Journal of Clinical Pharmacology*. 2019;85(3):580-9.
10. Draft Guidance on Tiotropium Bromide (NDA 021395). 2026. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021395.pdf. Accessed on 25 Jun 2026.