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

**Ross Walenga, PhD**

Senior Chemical Engineer
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

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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 OIDPs 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 ≥ 5%," that in addition to standard PK metrics applicants evaluate BE according to $AUC_{0\text{-}30min}$.[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*

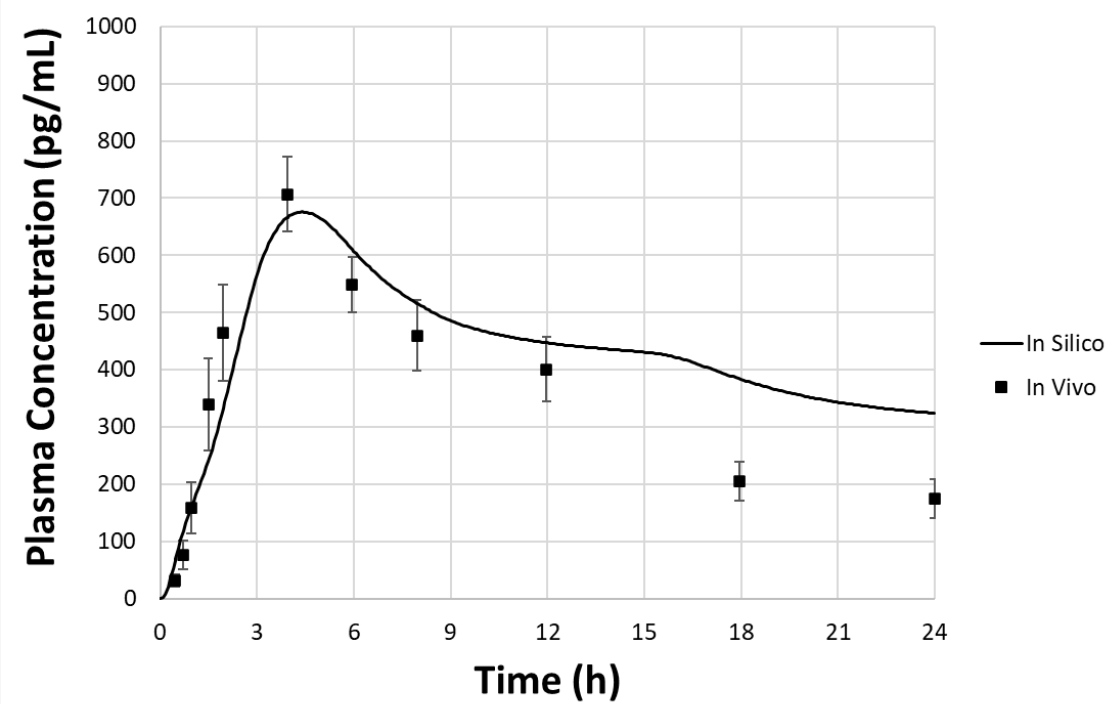
# In Silico Modeling to Evaluate Need for Charcoal Block PK BE Study

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.

| | | $t_{max}$ (h) | | $C_{max}$ (pg/mL) | | |
|---|---|---|---|---|---|---|
| **Route** | **Compound** | **In Vivo** | **Simulated** | **In Vivo** | **Simulated** | **ARD (%)** |
| 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 |

| | | $AUC_{0-t}$ (pg-h/mL) | | | $AUC_{0-\infty}$ (pg-h/mL) | | |
|---|---|---|---|---|---|---|---|
| **Route** | **Compound** | **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.

| | | | | Oral Contribution to: | | |
|---|---|---|---|---|---|---|
| **Source** | **Product** | **Strength** | **Subjects** | **$C_{max}$ (pg/mL)** | **$AUC_{0-t}$ (pg-h/mL)** | **$AUC_{0-\infty}$ (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)

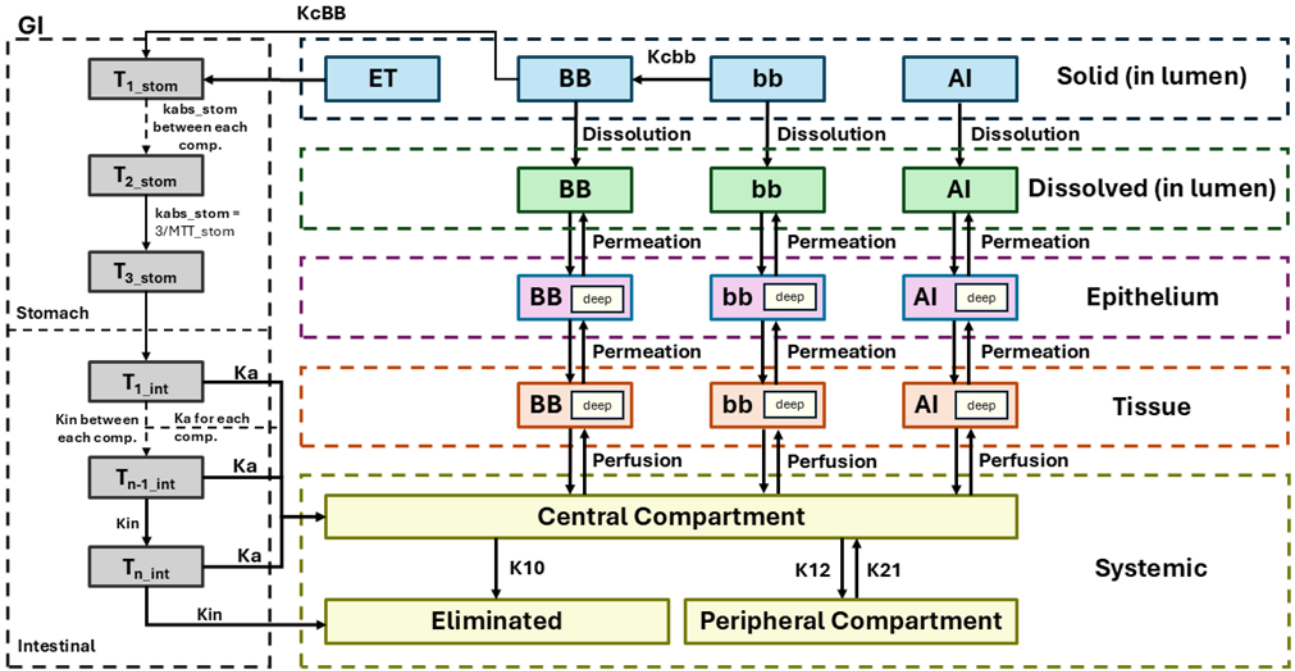
- Grant U01FD007936 (PD/PIs: Jürgen Bulitta and Günther Hochhaus, University of Florida)
- PBPK model developed by Dr. Yongzhen Zhang

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]

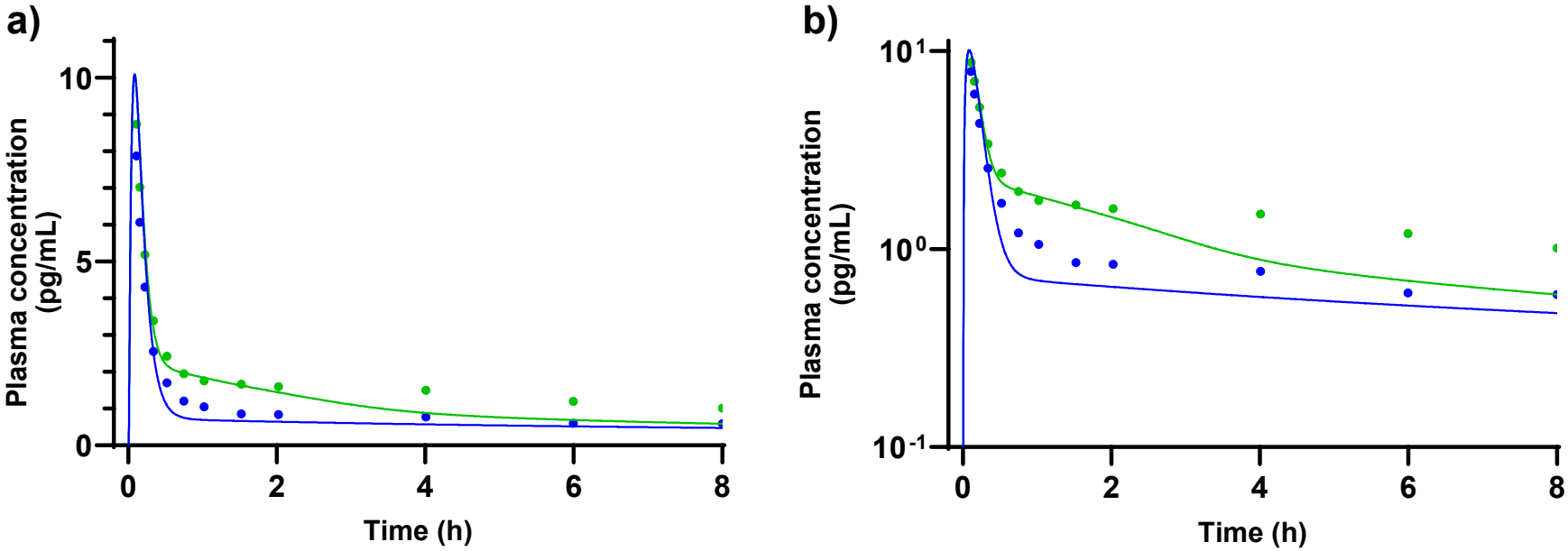
Charcoal block absorption and drug binding to charcoal were modeled mechanistically.

# 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.

| | $C_{max}$ | | $AUC_{0\text{-}30min}$ | | $AUC_{0\text{-}8h}$ | |
|---|---|---|---|---|---|---|
| | **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 |

Table prepared by Dr. Steven Chopski

# 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 $AUC_{0\text{-}20min}$ and $AUC_{0\text{-}30min}$ 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 $AUC_{0\text{-}30min}$ in lieu of a charcoal block PK BE study.[10] Although both $AUC_{0\text{-}20min}$ and $AUC_{0\text{-}30min}$ were considered valid, $AUC_{0\text{-}30min}$ 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 OIDPs.

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 OIDPs.

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# Closing Thought

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

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