Physically based pharmacokinetic models and IVIVCs are commonly utilized tools in the formulation development of orally administered APIs. Although these approaches have the potential to help in the formulation development of products administered via other dosage routes as well, in the area of inhaled drugs they are often limited only on effect drug deposition [3-5]. The applications accounting for additional processes affecting the drug disposition are more limited [6-7]. The Office of Generic Drugs (OGD) at the US FDA also expressed interest in these approaches through several funded projects for the development of PBPK models with the focus on generic product development for different administration routes [8].

Several years ago, a mechanistic absorption model for pulmonary administration was developed and included in the GastroPlus software and its ability in first-in-human predictions [9-10], dose evaluation [11], and predictive predictions [12] was shown in number of poster presentations. Here we present a recent study where this model was used to explore the possibility of creating an IVIVC for inhaled products using an example of a fixed-dose combination containing two active pharmaceutical ingredients (API). One of the APIs (API1) is a low-solubility compound (<10 ug/mL) where the dissolution rate will affect the rate and extent of drug absorption into the systemic circulation. The second API (API2) has sufficiently high solubility that the dissolution rate is not expected to be a rate-limiting factor. API1 was thus the focus of the IVIVC development and evaluation while API2 served as general validation of the pulmonary model.

### Introduction

Physiologically based pharmacokinetic models and IVIVCs are commonly utilized tools in the formulation development of orally administered APIs. Although these approaches have the potential to help in the formulation development of products administered via other dosage routes as well, in the area of inhaled drugs they are often limited only on effect drug deposition [3-5]. The applications accounting for additional processes affecting the drug disposition are more limited [6-7]. The Office of Generic Drugs (OGD) at the US FDA also expressed interest in these approaches through several funded projects for the development of PBPK models with the focus on generic product development for different administration routes [8].

Several years ago, a mechanistic absorption model for pulmonary administration was developed and included in the GastroPlus software and its ability in first-in-human predictions [9-10], dose evaluation [11], and predictive predictions [12] was shown in number of poster presentations. Here we present a recent study where this model was used to explore the possibility of creating an IVIVC for inhaled products using an example of a fixed-dose combination containing two active pharmaceutical ingredients (API). One of the APIs (API1) is a low-solubility compound (<10 ug/mL) where the dissolution rate will affect the rate and extent of drug absorption into the systemic circulation. The second API (API2) has sufficiently high solubility that the dissolution rate is not expected to be a rate-limiting factor. API1 was thus the focus of the IVIVC development and evaluation while API2 served as general validation of the pulmonary model.

### Methods

All simulations were performed using GastroPlus v6.0. The systemic tissue distribution and clearance were simulated with a full-body PBPK model. All physiologies were generated using the built-in Population Estimates for Age-Related Physiology (PEAR Physiology™) module to match the subjects’ gender, age and body weight (clinical studies). Pulmonary absorption was modeled using the GastroPlus/PBPK model including built-in lung physiologies.

First, a model accounting for intestinal absorption, first pass metabolism, and systemic tissue distribution and clearance was developed for each API using plasma concentration-time (Cp-time) profiles following intravenous (iv) and oral (po) administration reported in literature. The in vivo dissolution, deposition rate, and lung permeability were subsequently fitted using Cp-time profiles after intravenous (iv) administration of the reference product. The baseline models based on the reference formulation were subsequently refined to fit the total lung deposition and in vivo dissolution rate for each API against Cp-time profiles from simulations of the reference formulation. The refined models were used to explore the possibility of creating an IVIVC for these inhaled products.

The in vivo and in vitro dissolution of each API from different formulations was modeled using a z-factor dissolution model (Eq. 1) [13].

\[
\text{DissolutionRate} = Z \times C \times (C - C_i) \times M_{ss}.
\]

\(Z\) represents a z-factor (fitted in vivo or in vitro dissolution data); \(C\) is compound solubility; \(C_i\) is local dissolved compound concentration, \(M_{ss}\) is remaining undissolved compound amount at time \(t\).

The IVIVC was created as a ratio of fitted in vivo and in vitro z-factor for the reference formulation. The in vitro z-factor values for the formulations were predicted using the IVIVC and corresponding in vivo z-factor values (Eq. 2).

\[
Z_{\text{in vitro}} = Z_{\text{reference}} \times \left( \frac{C_{\text{in vitro}}}{C_{\text{in vivo}}} \right) ^{\text{z-factor}}
\]

\(Z_{\text{in vitro}}\) and \(Z_{\text{in vivo}}\) represent fitted in vivo or in vitro z-factor in the dissolution model, respectively, superscript i and v denote Reference and Test formulations, respectively.

### Results

The PBPK models developed using Cp-time profiles from literature were able to describe the PK of each API after inhalation administration of the reference formulation from the current clinical study with only the expected changes in the lung deposition and dissolution rates. Despite similar particle sizes of the two APIs (as measured in cascade impactor), API2 required 40% higher total lung deposition to accurately match the observed exposure after inhalation of the reference formulation (Table 1).

The initial IVIVC developed for API1 correctly predicted a significant difference in pharmacokinetics between the test formulations and the reference formulation. However, the overall prediction errors for the test formulations were outside of the IVIVC limits established for oral formulations (Table 2). Closer examination of the predicted and observed average Cp-time profiles showed that, even though the overall exposure was underpredicted, the shape of the Cp-time profile, including the initial peak which would depend on the rate of drug dissolution and absorption, were predicted correctly (Figure 1).

This suggests that the differences in the in vivo dissolution rates of API1 between the formulations were predicted correctly from the IVIVC, but the total bioavailable dose was underpredicted. Considering very low systemic bioavailability of this API after po administration, the underprediction of systemic exposure was assumed due to underpredicted lung deposition for the test formulations. The total lung deposition was fitted for each test formulation (results shown in Table 2) and the relationship between the known formulation parameters and the fitted lung deposition was explored.

### Conclusions

This study demonstrated the potential of using an IVIVC to evaluate the in vivo dissolution rates for inhaled products. However, a sensitive method for predicting the differences in lung deposition is required for more accurate prediction of overall systemic exposure after inhalation administration. The model showed a good correlation between the fitted total lung deposition and dissolution rates for the two APIs resulted in good prediction of systemic exposure (Cmax and AUC) for API2 after inhalation of all three test formulations (Table 3).

The fitted lung deposition for test formulations correlated well with mean aerodynamic diameter (MMD), but not with impactor-sized mass (ISM), or fine particle mass (FPM) as shown in Figure 2.

<table>
<thead>
<tr>
<th>F01 % PE</th>
<th>F05 % PE</th>
<th>F06 % PE</th>
<th>F01 % PE</th>
<th>F05 % PE</th>
<th>F06 % PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
<td>1.28</td>
<td>1.13</td>
<td>0.03</td>
<td>0.10</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Table 1: Cmax and AUC prediction errors for API1 after inhalation of reference formulation.

<table>
<thead>
<tr>
<th>F01 % PE</th>
<th>F05 % PE</th>
<th>F06 % PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.16</td>
<td>1.28</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Table 2: Comparison of Cmax and AUC prediction errors for API1 after inhalation of the three test formulations with different total lung deposition fractions. Both sets of simulations used the same in vivo dissolution rates as predicted from the IVIVC.

Figure 1 - Predicted in vivo dissolution profiles (red) and plasma concentration time profiles (blue) for the three test formulations using the IVIVC built from the reference formulation and assuming the same total lung deposition as fitted for the reference formulation.

The fitted lung deposition for test formulations correlated well with mean aerodynamic diameter (MMD), but not with impactor-sized mass (ISM), or fine particle mass (FPM) as shown in Figure 2.

The fitted lung deposition of API1 were used to predict the total lung depots of API2 from each test formulation. Simulations of both APIs from the reference formulation showed that API2 required 40% higher fraction of the dose to be deposited in the lung than API1. The same ratio of deposition fractions for the two APIs resulted in good prediction of systemic exposure (Cmax and AUC) for API2 after inhalation of all three test formulations (Table 3).

<table>
<thead>
<tr>
<th>F01 % PE</th>
<th>F05 % PE</th>
<th>F06 % PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.16</td>
<td>1.28</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Table 3: Cmax and AUC prediction errors for API2 after inhalation of the three test formulations using the API2 deposition fractions predicted from deposition fractions fitted for both APIs in the reference formulation and the fitted deposition fractions for all test formulations.

This study demonstrated the potential of using an IVIVC to evaluate the in vivo dissolution rates for inhaled products. However, a sensitive method for predicting the differences in lung deposition is required for more accurate prediction of overall systemic exposure after inhalation administration. The model showed a good correlation between the fitted total lung deposition and dissolution rates for the two APIs resulted in good prediction of systemic exposure (Cmax and AUC) for API2 after inhalation of all three test formulations (Table 3).