

REVIEW

In Silico Methods for Development of Generic Drug–Device Combination Orally Inhaled Drug Products

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The development of generic, single-entity, drug–device combination products for orally inhaled drug products is challenging in part because of the complex nature of device design characteristics and the difficulties associated with establishing bioequivalence for a locally acting drug product delivered to the site of action in the lung. This review examines *in silico* models that may be used to support the development of generic orally inhaled drug products and how model credibility may be assessed.

STATUS OF GENERIC ORALLY INHALED DRUG PRODUCTS IN THE UNITED STATES

In a recent report, the Association for Accessible Medicines estimated that generic drugs produced \$265 billion in savings in the United States in 2017 and accounted for 9 of 10 dispensed prescriptions.¹ However, these benefits were not realized for the multibillion dollar market of complex drug–device combination orally inhaled drug products (OIDPs) because there were no approved generic drug products in the United States during this period. These increased costs are felt both by consumers and insurance providers, where the Centers for Disease Control has estimated that there are currently 27 million people in the United States² with asthma and 16 million with chronic obstructive pulmonary disease.³ A generic drug developer that wishes to enter this market would need to design a product that demonstrates bioequivalence (BE) to the reference product in the multiple *in vitro* and *in vivo* studies currently recommended by the US Food and Drug Administration (FDA) while considering brand-name drug product patent protections that may limit design decisions related to the device constituent parts of the drug–device combination product.⁴ In general, to obtain approval of an abbreviated new drug application (ANDA) for a generic drug, an ANDA applicant first must identify the previously approved drug product it seeks to duplicate, i.e., the reference listed drug (RLD), and must show, among other things, that the generic drug is bioequivalent to the RLD. A reference standard selected by the FDA is the specific drug product that the ANDA applicant must use in conducting any *in vivo* BE testing required to support approval of its ANDA. The reference standard, selected by the FDA, is ordinarily the RLD. For ease of the reader, this article will only use the term RLD when describing regulatory requirements and recommendations relating to BE. For more information regarding the distinction between an RLD and a reference standard, please consult the FDA's draft guidance for industry titled "Referencing Approved Drug Products in ANDA

Submissions." When final, this guidance will represent the FDA's current thinking on this topic.

Considering that the majority of drug–device combination OIDPs are locally acting drug products, the FDA has established a weight-of-evidence approach for showing the BE of these products, which includes a combination of *in vitro* and *in vivo* studies, formulation sameness, and device similarity.⁵ This approach has been deemed necessary because the direct measurement of the drug concentration at the site of action is only possible during a surgical procedure,^{6,7} rendering it impractical for a pivotal BE study. For metered dose inhalers (MDIs), the list of *in vitro* studies includes single actuation content at the beginning, middle, and end life stages; aerodynamic particle size distribution (APSD) at the beginning and end life stages; spray pattern at two different distances from the orifice; plume geometry; and priming and repriming. The *in vivo* studies include a fasting, single-dose, two-way crossover pharmacokinetic (PK) study in healthy adult subjects and either a clinical pharmacodynamic (PD) study in patients or a comparative clinical end point BE study in patients.⁵ The list of studies recommended for dry powder inhalers (DPIs) includes *in vitro* single actuation content at the beginning, middle, and end life stages and APSD at the beginning and end life stages as well as *in vivo* PK and either a PD or a comparative clinical end point BE study.⁵ Considering the device aspect of drug–device combination OIDPs, these products are recommended to provide a user interface that is similar to the RLD with similar operating principles to ensure therapeutic equivalence.⁸ The formulation for MDIs should be qualitatively and quantitatively the same as the RLD; for DPIs qualitative sameness is required, and if it is not quantitatively the same the differences should be justified with additional data.⁹ Taken together, a potential generic OIDP developer has to balance the appropriateness of passing all FDA-recommended studies, producing a generic drug–device combination product that can be substituted for the RLD without additional training prior to use and/or without the intervention of a healthcare provider¹⁰ and observing

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any existing device patents that may exist. Meeting these standards may require many device or even formulation iterations before generating an approvable product.

Considering the challenges that a potential complex generic ODP developer faces, strategies are needed to reduce the expected cost and time of development. *In silico* modeling offers a relatively cost-effective means of accelerating generic ODP development. Computational fluid dynamics (CFD) is a physics-based modeling technique that can predict fluid and particle transport inside realistic geometries. The primary advantage of CFD in the context of generic ODP development is its ability to consider device-related characteristics such as the device geometry itself, APSD, spray angle, spray velocity, and orifice diameter while predicting regional deposition fraction of the initial dose in various regions of interest. As a coarse approximation, regional deposition fraction predictions can provide insight into the *in vivo* performance of a given drug-device combination. However, an additional technique is needed to predict local and systemic drug concentrations. Physiologically-based pharmacokinetic (PBPK) modeling is a compartmental technique that can predict local and systemic PK based on several formulation and physiological input parameters. When CFD and PBPK are combined, it is possible to predict *in vivo* performance of an ODP based on the device and formulation. This review provides an overview of research using CFD and/or PBPK to predict the performance of ODPs, with consideration for how these methods may be useful for generic development as well as how model credibility may be assessed.

CFD MODELING OF ODPs

Conceptually, CFD is a combination of fluid mechanics, computer science, and mathematics for which there is a wide variety of applications, including aerospace, process engineering, automotive, power generation, sports, and biomedical.¹¹ The Navier-Stokes equations of fluid motion are a set of nonlinear, coupled, partial differential equations that form the basis of CFD.¹¹ Because of their complexity, analytical solutions of the Navier-Stokes equations are only available in highly simplified cases.¹² Consequently, to solve most real-world problems, a numerical solution technique is necessary.¹¹ To implement this technique, the domain of interest is decomposed into a set of elements called a “mesh.”¹¹ Most CFD solvers use a finite-volume method in which the Navier-Stokes equations are integrated over each volume, which produces a set of coupled algebraic equations that are then solved numerically.¹¹ Special consideration is given for the handling of turbulent flow regimes, where several different strategies are available that include the less computationally intensive Reynolds-averaged Navier-Stokes (RANS) methods or a large-eddy simulation (LES) method that uses considerably more resources.¹¹ Particle transport may be simulated via a Lagrangian approach in which individual particle trajectories are predicted by using the governing ordinary differential equations or the particles may be treated as a separate continuum using an Eulerian approach.¹¹ Upon completion of a simulation, the results include local predictions of velocity, pressure, and

temperature values as well as other values that may include species mole fractions, turbulence parameters, and particle trajectory data.

Aerosolized medicine deposition in human lungs has been investigated using CFD methods for nearly 3 decades, with early work focusing on deposition predictions within a single idealized lung bifurcation.^{13,14} Several recent reviews have summarized much of the work that has occurred since the early efforts of Gradon and Orlicki¹³ and Hofmann and Balásházy,¹⁴ which include a comprehensive review by Longest and Holbrook¹⁵ of all *in silico* models used to predict lung deposition. Recently, Longest et al.¹⁶ followed up the previous review¹⁵ with updates in whole-lung modeling capabilities using CFD, a discussion on the role of CFD with inhaler design, the use of CFD for development of new respiratory drug-delivery studies, CFD studies in special populations, and a discussion on the merging of CFD and PK models. Reviews by Wong et al.¹⁷ and Ruzycski et al.¹⁸ focus on the role of CFD within inhaler design, where as Wong et al.¹⁷ also describe discrete element modeling (DEM), a computational technique that considers particles as three-dimensional (3D) domains as opposed to the standard Lagrangian method, which considers particles as point masses. A combined approach using CFD and DEM is particularly useful for predicting DPI product performance, where DEM is capable of capturing agglomeration and deagglomeration processes because of the interactions of carrier and active pharmaceutical ingredient (API) particles, as summarized in recent reviews by Tong et al.¹⁹ and Yang et al.²⁰ In addition to the use of CFD for characterizing device performance, some recent reviews have focused on methodologies for capturing the influence of lung anatomy and physiology on particle deposition from ODPs. The status of conducting airway modeling methodology as well as the application of local ventilation boundary conditions and turbulence model selection was reviewed by Lin et al.²¹ It was noted by Lin et al.²¹ that although some studies have used RANS turbulence models for the prediction of aerosolized medicine deposition, several studies using an LES method have demonstrated good predictive capability, including a study by Jayaraju et al.,²² in which deposition predictions were improved by using an LES method as compared with a RANS model. Hofemeier et al.²³ reviewed subacinar models and their use in predicting deposition of aerosols in the deep regions of the lung. Altogether, considering the breadth of reviews available that describe the use of CFD for predicting lung deposition, the portion of this review that addresses CFD models will focus on recent developments not included in these reviews, with a special focus on the utility of CFD for generic inhaler design and considerations of lung models for capturing intersubject variability.

PREDICTING THE INFLUENCE OF DEVICE AND FORMULATION PARAMETERS ON REGIONAL LUNG DEPOSITION USING CFD

To adequately compare a potential generic MDI to the RLD, a CFD simulation must be able to accurately characterize the spray, which requires consideration of the potential impact from all device and formulation differences. Spray

characterization of MDIs using CFD is challenging because of the several physical processes that include droplet formation,²⁴ the large temperature gradient at the device orifice,²⁵ high initial velocity values,²⁶ and rapid evaporation of the propellant.²⁴ Several studies have considered MDI delivery to the lungs using CFD, with varying physical treatments.^{27–37} Proper characterization of an MDI spray requires the careful selection of orifice boundary conditions because this process is crucial to understanding device differences. There are no known studies that directly simulate the fluid behavior inside the MDI canister through atomization. One group has used theoretical mathematical formulations to produce both velocity and APSD boundary conditions at the orifice, indicating good agreement with experimental values using this approach.^{27,28} Recently, this same group has developed a theoretical method for predicting velocity and APSD boundary conditions for mixtures of ethanol and 1,1,1,2-tetrafluoroethane (HFA-134a), as illustrated in **Figure 1**.³⁸ The method is based on work by Fletcher³⁹ and Clark,⁴⁰ where the behavior of constituents in the metering and expansion chambers, as shown in **Figure 1a**, is modeled using a homogeneous frozen flow model that does not permit evaporation in these regions but rather allows isentropic expansion.^{38,41} Upon exit from the spray orifice, atomization is predicted using the model developed by Gavtash *et al.*⁴² as displayed in **Figure 1b**, where the initial output is treated as a flat sheet using the linear instability sheet analysis framework as developed by Senecal *et al.*,⁴³ which predicts growth of the wave-induced stabilities that are responsible for droplet breakup. Further development and application of methods such as these will be beneficial for future CFD studies seeking to compare a

generic MDI to the corresponding RLD because they may directly capture the influence of device and formulation changes on APSD and other *in vitro* metrics.

Most CFD studies that model MDI behavior have applied experimentally measured values to some or all of the orifice boundary conditions, which include spray velocity, spray angle, and APSD.^{29–36} However, experimental spray velocity measurements are not available directly at the orifice but ~20–50 mm downstream of the orifice, where some assumptions need to be made to specify orifice boundary conditions. For example, Farkas *et al.*²⁹ used several downstream experimental spray velocity measurements to extrapolate to the orifice. Most groups have used theoretical formulations to estimate spray velocity.^{27,28,31–37} Where reported, spray angle is either taken from experimental measurements³⁵ or varied to capture its influence on particle deposition.³⁶ Experimental APSD values have either been specified using measurements from an impactor^{29–34} or from a laser diffraction instrument,^{35,36} where impactor measurements are typically taken downstream of an US Pharmacopoeia induction port attached the inhaler outlet, whereas laser diffraction is capable of measuring APSD near the actuator outlet.

In addition to orifice boundary condition selection, certain aspects of model selection are expected to significantly affect MDI spray behavior directly downstream of the orifice and may be important for accurate comparisons of device performance. The expected large temperature gradient at the orifice²⁵ and the rapid evaporation of propellant²⁴ may significantly affect aerosol behavior and subsequently drug deposition, but there is no consensus in the literature for the manner in which these processes are modeled. Several

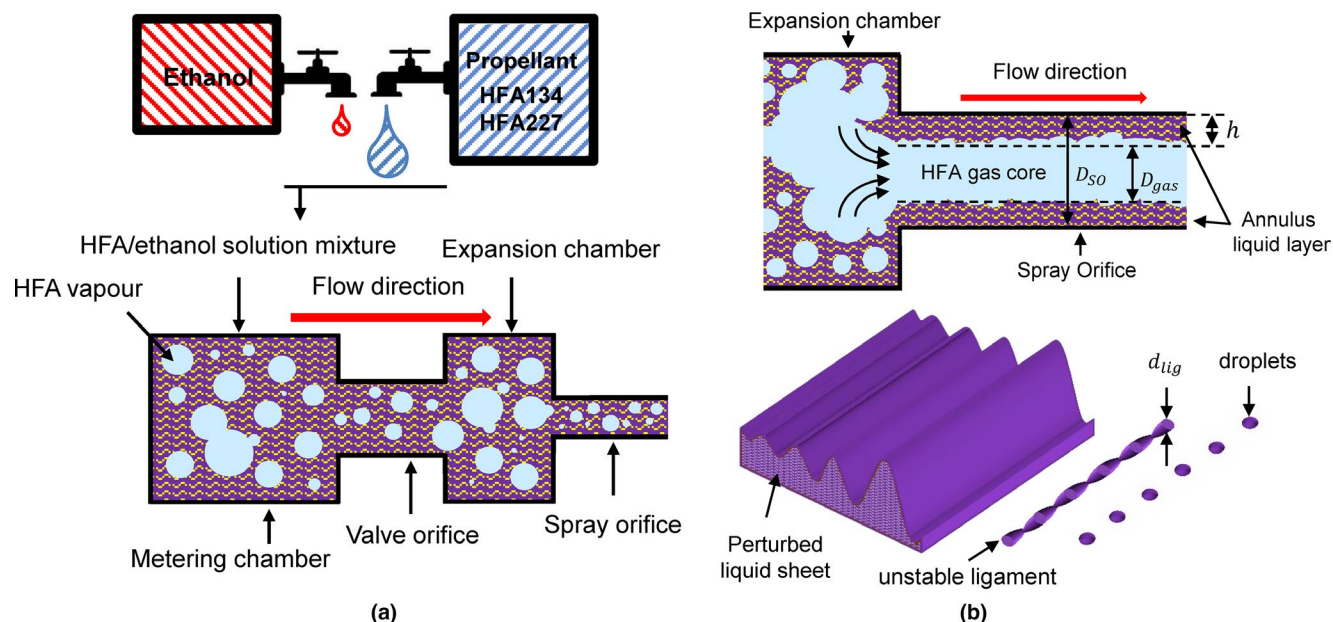


Figure 1 Methodology used by Gavtash *et al.*³⁸ to predict (a) fluid behavior in the metering and expansion chambers of ethanol/propellant mixtures and (b) transitional behavior through the spray orifice into an annular sheet exiting the orifice followed by droplet formation. HFA, hydrofluoroalkane; DSO, spray orifice diameter; H, annular liquid film thickness; Dgas, vapor phase diameter; Dlig, unstable ligament diameter; HFA134, 1,1,1,2-Tetrafluoroethane; HFA227, 1,1,1,2,3,3,3-Heptafluoropropane. Reprinted with permission of Taylor & Francis. Copyright © 2018 Taylor & Francis.

studies have assumed that the temperature at the orifice is at the boiling point of the propellant, and conservation of mass was used to estimate the initial density.^{29,31,33,34} Oliveira *et al.*³⁵ specified a value of 215 K to the injected droplets, which subsequently cooled the surrounding air. For several studies, it is unclear what, if any, treatment for heat transfer was applied.^{30,32,36,37} Studies conducted by Gavatash *et al.*^{27,28} considered heat transfer but did not describe the method. Regarding evaporation, several studies that model MDI delivery treat the initial aerosol state as a dry particle, with the inherent assumption that propellant evaporation is so rapid that it does not affect drug deposition.^{29–34,36,37} Longest *et al.*³¹ showed good agreement with *in vitro* regional deposition data using this approach with a suspension-based MDI. However, for studies that model solution-based MDI delivery,^{29,30} it is unclear whether this assumption is appropriate considering that ethanol, a common cosolvent in solution-based MDIs, evaporates more slowly than the propellant.²⁴ A few studies did consider evaporation,^{27,28,35} but details on model implementation were few.

The Respimat Soft Mist inhaler (Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany) is a relatively new type of inhaler that is similar in some ways to MDIs with some fundamental differences. The energy for atomization of the solution-based aerosol is provided by a spring-loaded mechanism, which simultaneously avoids the need for patient effort to generate the aerosol and for a propellant.⁴⁴ The lack of propellant allows for aqueous solution formulations.⁴⁴ Other features of the device include a high fine particle fraction (FPF) and a greatly reduced aerosol velocity, which in turn increases the jet duration to ~1.5 seconds from about 0.2 seconds (for an MDI).⁴⁴ The FPF is the percentage of particles that are smaller than 5 μm. In a general sense, a reduction in velocity and high FPF are desirable because they tend to reduce aerosol deposition by inertial impaction, whereas increased spray duration tends to improve patient coordination. Considering the relative novelty of these design features when compared with MDIs, it is expected that CFD may be useful for better understanding the impact that differences in device design may have on spray velocity and duration.

A few studies have used CFD to model drug delivery from Respimat products.^{45–48} Similar to most MDI studies, the device orifice APSD is specified using experimental data.^{45–48} Longest and Hindle⁴⁵ recognized that based on experimental data of stopping distances from Respimat-generated aerosols, the droplet–air interaction should be considered two-way coupled. A two-way coupled interaction is when the fluid medium influences the dispersed phase while the dispersed phase also significantly influences fluid behavior. However, considering the long spray duration and available computational resources, a one-way coupled approach with an effective velocity applied at the inlet was used that showed good agreement with experimental results.⁴⁵ Predictions from Longest and Hindle⁴⁵ indicated a loss of 23.7% of the drug, albuterol sulfate, in the device, which was much greater than the predicted loss of 5.1% in the attached US Pharmacopoeia induction port. In a follow-up study, Longest and Hindle⁴⁶

explored the impact of different excipients in an aqueous budesonide solution on hygroscopic growth with a capillary aerosol generator and a Respimat device using experimental and CFD techniques, where the one-way and two-way coupled CFD results both showed good agreement with experimental particle size measurements at the system outlet. In a later study from the same group, Tian *et al.*⁴⁷ predicted the deposition of a fenoterol solution from a Respimat device in a realistic lung model developed by this group (described in Walenga *et al.*³⁴), which used a stochastic individual path method developed by Tian *et al.*⁴⁹ to predict small-airway deposition and a correlation developed by Khajeh-Hosseini-Dalasm and Longest⁵⁰ to predict alveolar deposition. Using a similar method as in previous studies,^{45,46} Tian *et al.*⁴⁷ showed predictions of mouth–throat, central lung, and peripheral lung deposition, as shown in **Figure 2**, that were close matches with available *in vivo* data from Newman *et al.*,⁵¹ who had measured deposition values using radiolabeled aqueous fenoterol solution in a Respimat device and a gamma scintigraphy technique. In a recent study from a different group that was sponsored in part by Boehringer Ingelheim, Ciciliani *et al.*⁴⁸ compared regional deposition from a Respimat device and from three DPIs in which the drug for each drug product was different than the others. Predictions by Ciciliani *et al.*⁴⁸ showed that the Respimat

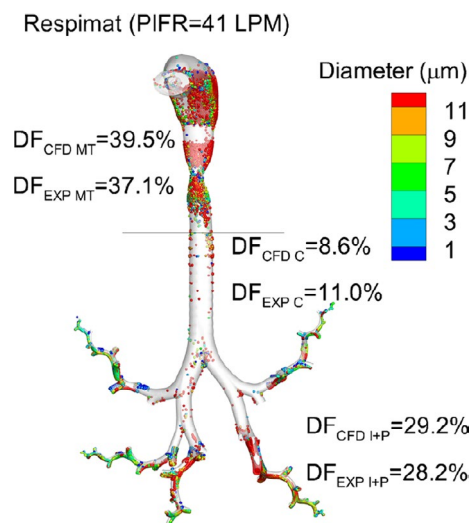


Figure 2 Predictions by Tian *et al.*⁴⁷ using computational fluid dynamics (CFD) for mouth–throat, central lung, and peripheral lung deposition of an aqueous fenoterol solution as delivered by a Respimat Soft Mist Inhaler (Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany), where predictions are compared with *in vivo* gamma scintigraphy results from Newman *et al.*⁵¹ $DF_{CFD\ C}$, CFD predictions of deposition fraction in the central region; $DF_{CFD\ I+P}$, CFD predictions of deposition fraction in the intermediate and peripheral regions; $DF_{CFD\ MT}$, CFD predictions of deposition fraction in the mouth–throat region; $DF_{EXP\ C}$, Experimental measurements of deposition fraction in the central region; $DF_{EXP\ I+P}$, Experimental measurements of deposition fraction in the intermediate and peripheral regions; $DF_{EXP\ MT}$, Experimental measurements of deposition fraction in the mouth–throat region; LPM, Liters per minute; PIFR, Peak inspiratory flow rate. Reprinted with permission of Springer US. Copyright © 2015 Springer US.

device delivered the most drug to the small airways and the least amount to the mouth–throat.

When compared with MDIs and RespiMat products in which spray atomization is generated using energy from internal mechanisms, DPI aerosolization is accomplished by a patient-generated flow rate that induces shear fluidization of the particles.⁵² Typical DPI formulations consist of the API particles and significantly larger carrier particles, which are usually lactose.⁵³ Because typical patient flow rates are not sufficient to entrain smaller API particles, carrier particles are usually necessary.⁵² Once API-carrier combination particles are entrained, deagglomeration occurs mainly as a result of device impaction.⁵² DPI performance is significantly affected by the efficiency of the deagglomeration process because carrier particle diameters are generally about 100 μm ,⁵² which is too large to bypass the mouth–throat region.⁵⁴ In contrast, API particles are ideally between 1 and 5 μm in diameter.⁵⁵ Altogether, to understand the full impact of device and formulation changes on DPI performance, their impacts on the efficiency of deagglomeration and on the ability of a typical patient-generated flow to entrain API-carrier combination particles need to be well characterized.

As reviewed by Tong *et al.*¹⁹ and Yang *et al.*,²⁰ the combination of CFD and DEM is capable of modeling particle–particle, particle–wall, and particle–fluid interactions, which affect agglomeration, entrainment, and deagglomeration of API-carrier and API-API combination particles. Early development of these models focused on mathematical relationships to characterize particle–particle and particle–wall phenomena such as van der Waals, electrostatic, capillary, and contact forces as well as particle–fluid interactions, whereas some models that actually modeled DPI drug delivery were newly available at the time of those reviews.^{19,20} Since 2015, when those reviews were published, several studies involving CFD-DEM based models that consider DPI delivery have been published.^{56–62} Leung *et al.*⁵⁶ investigated the effect of two mouthpiece grid mesh designs on FPF of four different albuterol sulfate formulations from an Aerolizer DPI using an *in vitro* method. By switching from the original grid mesh to a cross-grid design, FPF was reduced for drug-only and 1:5 and 1:10 API-carrier ratio formulations, but not for a 1:100 API-carrier ratio formulation, where corresponding CFD-DEM simulations were able to describe the complex relationship between flow and impaction differences caused by the switch in mesh designs that explained differences in

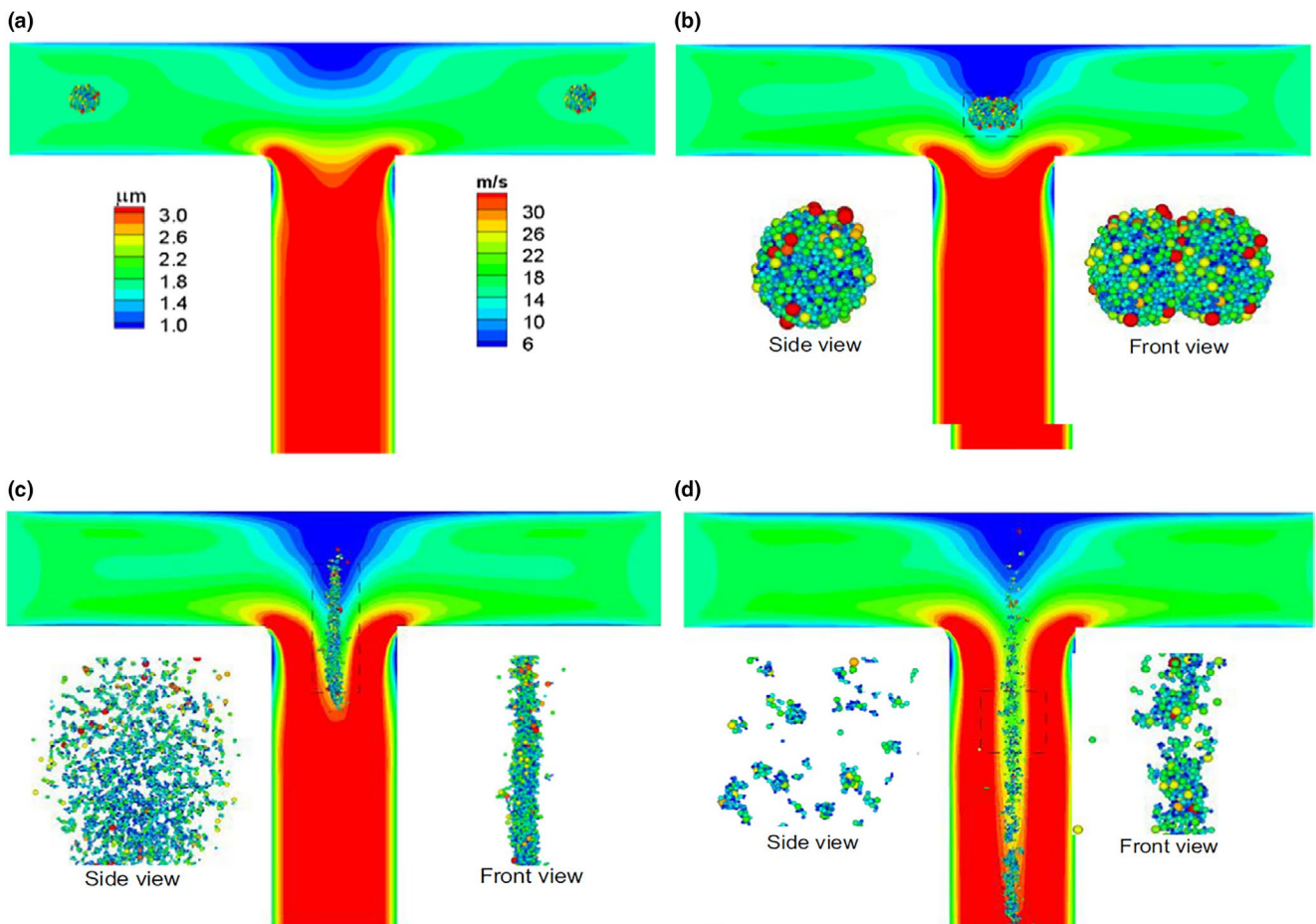


Figure 3 Velocity contours and breakup patterns of agglomerate–agglomerate collision as predicted by Tong *et al.*⁵⁹ at times of (a) 0, (b) 0.15, (c) 0.26, and (d) 0.33 seconds after particle release. Reprinted with permission of Elsevier. Copyright © 2016 Elsevier.

FPF.⁵⁶ A follow-up study by Tong *et al.*⁵⁷ used a CFD-DEM approach to further investigate the impact of API-carrier ratios on the FPF of albuterol sulfate formulations, where it was concluded that by increasing API-carrier ratio the aerosolization efficiency was increased, but the improvement was dependent on carrier size. Recently, Nguyen *et al.*⁵⁸ measured the FPF from two devices with the same budesonide formulation using *in vitro* techniques, where CFD-DEM simulations used a semiempirical approach to provide apparent surface energy of a given formulation to provide predictions that were reasonably close to the measured values of FPF. The efficiency of agglomerate–agglomerate collisions was investigated by Tong *et al.*⁵⁹ using a CFD-DEM approach, as illustrated in **Figure 3**, where a correlation based on the ratio of collision to cohesion energy was able to describe differences in FPF according to differences in air inlet velocity, the Hamaker constant, and collision angle, which may be useful for guiding device design. Several other recent studies have provided insights on the influence of collisions on particle–particle momentum exchange, the relative difference in time required for API and carrier particles to leave the device, the influence of the Hamaker constant, the quality of a dry-coating process based on certain parameters, and the influence of impact velocity, impact angle, and carrier rotation on the dispersion process.^{60–62}

In addition to current work using a CFD-DEM approach, several recent studies have used CFD with the more traditional Lagrangian approach for particle tracking to investigate DPI performance.^{33,47,63–70} The use of CFD with Lagrangian particle tracking for the investigation of DPI performance was also recently reviewed by Sommerfeld *et al.*,⁷¹ who also included some discussion on CFD-DEM models. A good example of the utility of CFD with a Lagrangian approach comes from Shur *et al.*,⁶³ who made modifications to an existing RLD device, Multihaler (Cipla Limited, Mumbai, India), and tested eight different formulations of fluticasone propionate in the modified devices with the intent of producing a drug–device combination with comparable *in vitro* performance to an existing drug–device combination, Flixotide Accuhaler (GlaxoSmithKline UK Limited, Brentford, UK; fluticasone propionate DPI). A CFD method with Lagrangian particle tracking was used to characterize the differences in pressure drop, particle residence time, and normal particle velocity at the time of impact between Multihaler and Flixotide Accuhaler, where two modifications to Multihaler were designed based on these results.⁶³ *In vitro* characterization of impactor sized mass, fine particle mass, and mass median aerodynamic diameter from the modified devices with the eight formulations showed that the second modified device when combined with the formulation that included sieved lactose and the API with the least adhesion to lactose was most similar to Flixotide Accuhaler.⁶³ Suwandecha *et al.*⁶⁴ made three modifications to Cyclohaler (Pharmachemie B.V., Haarlem, The Netherlands; albuterol sulfate DPI) based on design elements from another commercially available device (Rotahaler, Cipla Limited, Mumbai, India), where CFD with Lagrangian particle tracking was used to understand how the different modifications affected metrics such as pressure drop and number of impacts per particle. The third modification of Cyclohaler was predicted by CFD to have the best performance, which was

confirmed via *in vitro* experiments that measured FPF and mass median aerodynamic diameter (MMAD).⁶⁴ Several different alterations of Turbuhaler (AstraZeneca plc, Cambridge, UK; budesonide DPI) were investigated by Milenkovic *et al.*⁶⁵ using CFD with Lagrangian particle tracking, where predictions indicated which design produced the highest FPF and the lowest device deposition. Several recent papers by Kopsch *et al.*^{72–74} have taken a different approach to others by using an Eulerian particle tracking method rather than a Lagrangian approach to predict particle behavior. This new method has been used to predict powder entrainment from three custom DPIs, where experimental measurements of drug-release profiles showed reasonably close matches to predicted values.⁷⁴

In addition to its ability to model effects of device and formulation changes on ODP drug delivery, CFD may also be useful for characterizing effects of intersubject variability according to healthy and diseased lung structure, which are pertinent to understanding the BE of two drug products. Disease modeling is covered by Longest *et al.*¹⁶ in some detail and is not repeated here. A recent review by Martin *et al.*⁷⁵ included a discussion that highlighted the ability of *in vitro* and analytical methods to predict mouth–throat and total lung deposition on a population basis. However, as Martin *et al.*⁷⁵ pointed out, there is no current method for assessing small-airway intersubject variability because little is known about structure in this region as the result of insufficient resolution in current computed tomography scan technology for imaging in this area. Although it is true that this limitation applies to CFD as well as other methods, CFD is currently more suitable for studying small-airway intersubject variability when compared with *in vitro* or analytical methods because of its ability to couple small-airway predictions with validated large-airway predictions and then vary small-airway dimensions to investigate sensitivity.

As reviewed by others, several methods have been developed to allow for the prediction of regional drug deposition from the extrathoracic region all the way to the alveolar region.^{16,21} However, although there are several studies that have investigated small-airway deposition using a variety of CFD methods,^{21,34,46,76,77} very few have addressed the effects of small-airway variability. A technique developed by de Backer and colleagues uses four computed tomography scans for each of several subjects to define upper-airway geometries, where scans are taken after normal expiration at functional residual capacity and after deep inhalation at total lung capacity before and after treatment.^{76,77} The scans at functional residual capacity and total lung capacity are segmented on a lobar basis to determine airflow distribution, whereas the upper airways are segmented to provide geometric models for CFD analysis, where pressure outlets on the resulting upper-airway models are chosen to represent airflow distribution measured via lobar segmentation.^{76,77} This method, which has been termed *functional respiratory imaging*, can then be used to predict central and peripheral depositions for all subjects in the study, where this method was used to predict central to peripheral ratios for both APIs of a combination product (Flutiform, Bard Pharmaceuticals Limited, Cambridge, UK; fluticasone propionate/formoterol

fumarate MDI) for several different inhalation conditions in six subjects with asthma.⁷⁷

BPBK MODELING COUPLED WITH CFD TO PREDICT DRUG ABSORPTION IN THE LUNGS

It is widely considered that regional deposition values for locally acting ODPs provide a good estimate of drug delivery. However, the precise characterization of the rate and extent of drug delivered to the site of action for these products requires lung tissue concentration measurements. Although it is possible to directly measure unbound drug in lung tissue interstitial fluid using a microdialysis technique, it must be done during open chest surgery, making it an impractical technique for comparing two drug products in a BE study.^{6,7} In the absence of direct lung tissue concentration measurements, PBPK modeling is useful for understanding the differences in drug product performance because it is capable of predicting lung tissue concentrations for locally acting ODPs. A PBPK model is a compartmental approach in which various tissues in the body (e.g., brain, lung, kidney, etc.) are represented by separate compartments with corresponding tissue volume and blood flow rate values, and it represents a more mechanistic approach when compared with a simple two-compartment PK model.⁷⁸ When paired with accurate regional deposition data, a PBPK model may be capable of predicting lung tissue concentrations with enough accuracy that results may be useful for drug development. In addition, PBPK is capable of simultaneously predicting pulmonary and gastrointestinal tract absorption, which is useful for understanding the competing effects of absorption from these two regions on systemic plasma concentration values. When paired with a validated CFD model capable of predicting regional deposition with a reasonable amount of accuracy, the combination of CFD and PBPK represents a fully *in silico* approach to ODP development. This may be especially useful in early drug development, when many device and formulation changes are expected yet the firm may not wish to invest too much because of the perceived risk.

Lung PBPK modeling for delivery of locally acting ODPs is a relatively unexplored area when compared with PBPK modeling of solid oral dosage forms. PBPK modeling from a pulmonary toxicology perspective has a somewhat longer history, with published work available as early as 2008⁷⁹ and with several studies published afterward. A recent review by Bäckman *et al.*⁶ provides an overview of available lung PBPK models for pharmaceutical drug delivery and of those developed for private use by industry. Key considerations according to model structure and parameterization for the models described were divided into aerosol deposition, dissolution, nonabsorptive clearance, and absorptive clearance.⁶ The only commercially available PBPK software that was capable of addressing all four of these areas as identified by Bäckman *et al.*⁶ was Gastroplus (Simulations Plus, Rochester, NY), where other available packages such as the SimCyp Simulator (Certara USA, Princeton, NJ) and PK-SIM (Bayer AG, Leverkusen, Germany) reduced dissolution to first-order processes, which limited their ability to model region-specific absorption. One notable example of a

custom PBPK model was developed by Boger and Fridén,⁸⁰ who used PBPK combined with PD modeling to predict values of forced expiratory volume after 1 second after the administration of albuterol sulfate using either an ODP or an oral tablet, where the predicted values of forced expiratory volume after 1 second show reasonable agreement with the clinical data.

Only a few studies have used the Pulmonary Compartmental Absorption & Transit (PCAT) model in Gastroplus to model absorption from ODPs.^{70,81–83} The effect of different carrier properties on systemic PK was investigated by Wu *et al.*⁸¹ who measured APSD from two formulations of albuterol sulfate using the Cyclocaps capsules Teva UK, Harlow, UK in an Aerolizer device, where glass beads were used as carrier particles as opposed to lactose because of the ease of surface modification. Values of maximum plasma concentration (C_{max}) and FPF were increased by factors of 1.20 and 1.36, respectively, for the formulation where the glass bead surface was modified as opposed to the formulation with the unmodified glass beads.⁸¹ The predictive power of deposition and permeability estimates provided by the Gastroplus PCAT model when compared with *in vivo* deposition data and experimentally determined alveolar permeability data was tested by Salar-Behzadi *et al.*,⁸² where predictions of C_{max} and area under the time-concentration curve from time 0 to time t from Turbuhaler (budesonide DPI) when compared with available PK data were greatly improved by the addition of experimental data. Bäckman *et al.*⁸³ used Gastroplus PCAT to model the exposure of a poorly soluble investigational compound, AZD5423, using a number of delivery methods, including different nebulizers and DPI devices, where it was found that total lung deposition values from an *in vitro* model were not alone predictive of differences in PK metrics, but when deposition pattern and dissolution were also considered, the predictions matched well with available PK data.

Although most studies have used empirical or simplified analytical models to predict lung deposition for lung PBPK modeling of pharmaceutical drugs, two have used CFD.^{70,84} A CFD model using a Lagrangian particle-tracking method was used to predict emitted dose, MMAD, and FPF of four amiloride hydrochloride (HCl) formulations from an Aerosolizer device, where predicted values showed reasonable agreement with impactor-based emitted dose data, although MMAD values were underpredicted.⁷⁰ These predicted values were used as inputs for a Gastroplus PCAT model of nebulized amiloride HCl, where the predictions agreed reasonably well with available PK data⁸⁵ in terms of C_{max} and time to maximum plasma concentration, as illustrated in **Figure 4**, especially for the case in which the absorption rate constant in the pulmonary region was reduced by 50%.⁷⁰ However, the model did overpredict area under the time-concentration curve from time 0 to time ∞ ($AUC_{0-\infty}$) because of its inability to capture the trough between the double peaks, where the double peaks are present because of competing absorption processes in the lung and the gastrointestinal tract.⁷⁰ After the validation case with nebulized amiloride HCl, the model was used to predict PK profiles for the four DPI-based formulations, where significant differences were observed.⁷⁰

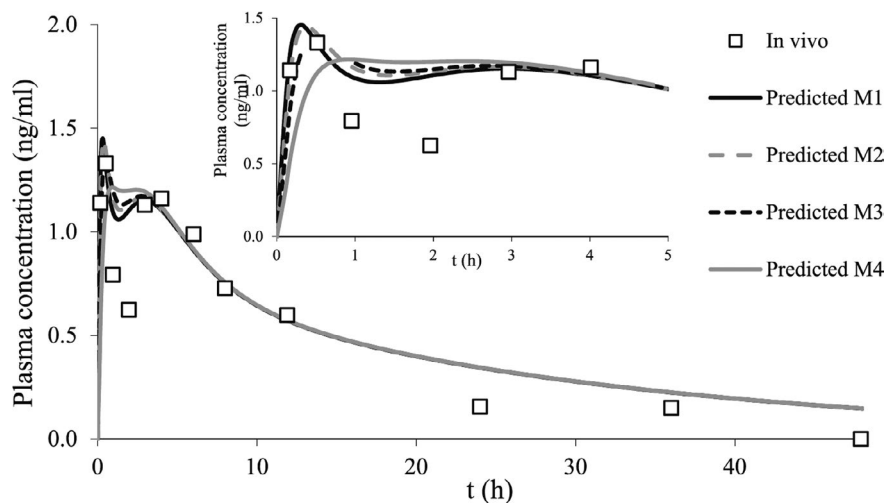


Figure 4 Plasma concentration predictions as provided by Vulović *et al.*⁷⁰, given as function of time (*t*) in hours (h), after administration of nebulized amiloride hydrochloride when compared with *in vivo* data from Jones *et al.*⁸⁵ where the pulmonary absorption constant values are either the default provided by Gastoplus (M1), 75% of the default value (M2), 50% of the default value (M3), or 25% of the default value (M4). Reprinted with permission of Elsevier. Copyright © 2018 Elsevier.

As opposed to Vulović *et al.*,⁷⁰ where the CFD model served to provide parameter inputs to the PBPK model, a new modeling approach detailed in Kannan *et al.*⁸⁴ uses a quasi-3D (Q3D) CFD approach to model the transport and absorption of a deposited drug in the lungs. The first step in the proposed process is to simulate drug deposition using a fully 3D CFD model, where deposition locations are then translated to the Q3D model.⁸⁴ The Q3D model is a simplified version of the 3D model, where the realistic 3D geometry is decomposed into a series of cylinders.⁸⁴ Using the Q3D geometry, flow and deposited drug transport may be solved in a one-dimensional manner.⁸⁴ Details on how the Q3D approach may be used to model fluid transport are available in Kannan *et al.*⁸⁶ The primary advantage of using the Q3D approach to model absorption is that mucociliary transport of the undissolved and dissolved drug in the mucus lining may be modeled with much greater precision than with a compartmental approach. It is possible that this enhanced precision will allow the PBPK model to simultaneously capture pulmonary and gastrointestinal tract absorptions with greater accuracy.

MODEL CREDIBILITY—VERIFICATION AND VALIDATION

Although CFD and PBPK are useful tools for understanding the mechanisms associated with ODP delivery, model credibility should be established for these tools to be used effectively, particularly for regulatory decision making. Validation for PBPK models typically involves comparing systemic PK end points, such as C_{max} and area under the time-concentration curve from time 0 to time *t* after administration of ODPs. If PK data from an intravenously administered drug are available, this can be useful for predicting clearance parameters. Wu *et al.*⁸¹, Salar-Behzadi *et al.*,⁸² and Bäckman *et al.*⁸³ used intravenous data to estimate clearance, whereas others did not, presumably because they were unavailable.^{70,84} Some studies used data

from an oral dosage form of the same drug to build an oral model with the purpose of increasing confidence in the lung model.^{70,81} A primary limitation for validating lung PBPK models is that there is a lack of lung tissue concentration data, so it is generally not possible to validate the model against the true metrics of interest. Until this issue is solved either via collection of human lung tissue concentration data or some other approach, lung PBPK model validation will likely be limited to comparison with systemic plasma concentration values, which does not ensure that local concentration predictions are accurate.

For CFD, several studies have validated the model via comparison of predicted regional deposition values with *in vitro* or *in vivo* data.^{29,31,34,47,69,87–89} For comparison with *in vitro* data, a replica of the computational geometry may be generated using rapid prototyping, and regional deposition after actuation of the device into the geometry may be quantified using high-performance liquid chromatography.³¹ Validation with *in vivo* data uses data collected via gamma scintigraphy with radiolabeled aerosols, where two-dimensional images of deposition locations are used to estimate central and peripheral deposition amounts.^{47,69} As shown in **Figure 3**, the regional deposition predictions of the Respimat Soft Mist inhaler drug delivery from Tian *et al.*⁴⁷ were compared against gamma scintigraphy data. Another approach has been to use particle image velocimetry to experimentally measure local velocity values in an *in vitro* replica of the *in silico* model and then to compare the *in silico* predictions to the *in vitro* data on a qualitative basis.^{68,90} Validating against particle image velocimetry data may be especially useful if deposition predictions are also validated against experimental deposition data.

FUTURE DIRECTIONS

The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research at the FDA has funded two grants

related to the *in silico* modeling of ODPs prior to fiscal year 2018 using funds obtained from the Generic Drug User Fee Amendments regulatory science program.⁹¹ In 2014, a grant titled “A Predictive Multiscale Computational Tool for Simulation of Lung Absorption and Pharmacokinetics and Optimization of Pulmonary Drug Delivery” was awarded to CFD Research Corporation for the development of an integrated CFD-PBPK lung model, which has been previously described in this article.^{84,86,91} The key gap that this grant addressed is the lack of PBPK models for ODPs that take full advantage of CFD for its ability to both predict deposition and to capture the effects of mucociliary clearance. In addition, a grant titled “A Cluster-Based Assessment of Drug Delivery in Asthmatic Small Airways” was awarded to the University of Iowa in 2016.⁹¹ This grant is currently ongoing, and the purpose of the project is to use CFD to explore intersubject variability of small-airway delivery to asthmatic patients from ODPs using a cluster-based approach to identifying different asthma subgroups.⁹¹ As described earlier in this article, because *in vitro* and *in vivo* methods are unable to measure drug-delivery variability in the small airways, it is believed that CFD may be a useful tool for quantifying this variability, where the results of this grant are expected to advance this capability.

There are several examples in the literature demonstrating the usefulness of CFD for ODP development, especially with respect to guiding device changes.^{63–65} However, several issues remain unsolved and must be addressed if CFD is to be capable of fully capturing the effects of device differences on ODP performance. The definition of orifice boundary conditions remains a key challenge for MDI models because experimentally measured values of velocity, temperature, and APSD are only available downstream. If possible, a mechanistic model of atomization using CFD or another modeling strategy may be useful for solving this problem, where work by Gavtash and colleagues may represent a key step in this direction.^{27,28} Further refinement of heat-transfer modeling approaches may improve the accuracy of CFD-based MDI models, especially for solution-based MDIs, where the evaporation of ethanol in droplets from these formulations is sensitive to local temperature changes. Although not discussed at length in this review, evaporation model selection is another key issue for solution-based MDIs, for which a key consideration is the characterization of nonideal mixture behavior.^{92,93} With respect to ODPs that use the Respimat Soft Mist inhaler device and for any potential generic ODPs that reference that device, the modeling approaches described in the literature have shown promise for accurately predicting regional deposition.^{45–48} From the perspective of generic ODP development, future work to characterize the differences in device characteristics such as orifice diameter and chamber volume and device metrics such as spray angle, spray velocity, and spray duration would be useful for understanding how product differences may influence regional deposition. For DPIs, several studies have used CFD with a Lagrangian particle-tracking approach to demonstrate how such models may be used to guide device changes.^{63–65} However, Lagrangian particle tracking requires several assumptions to account for agglomeration and deagglomeration of API and

carrier particles. The combination of CFD and DEM modeling is capable of directly modeling these processes and with further validation may allow for the enhanced precision of formulation change effects on deposition and FPF. To this end, the OGD has recently funded two grants using funds obtained from the Generic Drug User Fee Amendments for the development of CFD-DEM methodologies applicable to DPIs.⁹⁴ Improvements in this area are expected to involve the refinement of models, especially with respect to the complete characterization of electrostatic forces and the generation of experimental data that may be used to validate the accuracy of agglomeration and deagglomeration modeling on a more direct basis than deposition-based validation is capable of. In addition, as noted in the review by Yang *et al.*,²⁰ a study by Kaiyal *et al.*⁹⁵ has demonstrated that particle shape can affect DPI performance. Both new grants will consider the effect of particle shape on various performance metrics by using DEM to model either cylindrical particles or several spherical particles packed together to approximate irregular shapes. Another area of improvement to be addressed is the effect of humidity, where one grant will explore the effect of humidity on the triboelectric charge of dry powders.

The intersubject variability of ODP regional deposition in human airways has been considered,^{21,34,46,76,77} but a key challenge is the difficulty in establishing model credibility, especially with respect to small-airway deposition predictions. Future work is needed to enhance confidence in the predictive capability of these models. In addition, to fully understand how device and formulation differences may affect ODP performance, the interaction of these differences with intersubject human airway variability must also be understood. Several studies have combined ODP device and realistic human airway geometries,^{29,33,34,36,45,76,77} but these studies tend to have a strong focus on either device or human airway differences without much consideration for interactions between the two geometries. A study that considers how device and formulation differences affect not only the mean regional deposition values but also the intersubject variability would be useful from a generic perspective. Another consideration for future models that consider human airway intersubject variability is the appropriateness of the rigid airway wall assumption applied by

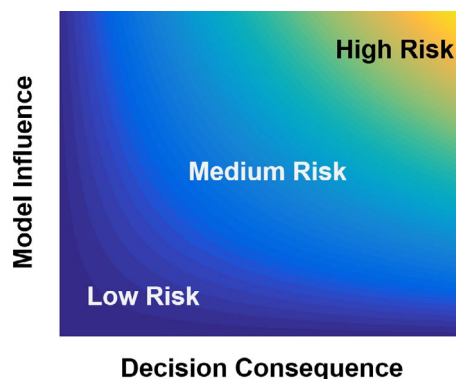


Figure 5 Qualitative description of the interaction between model influence and decision consequence on model risk.

most models because it is known that human airway diameter and length change dynamically during inhalation and exhalation. Although several models have considered the effects of moving airways either indirectly^{76,77} or directly,⁹⁶ the impact of this assumption for regional deposition predictions as it relates to device type (i.e., MDI, DPI, etc.) is not well understood.

Several promising PBPK models of locally acting ODPs have been developed that have shown the ability to predict systemic plasma concentration values with reasonable accuracy. However, examples of lung PBPK modeling in the literature are few, and more examples are needed to explore the potential utility of these models with respect to guiding formulation and device changes. Validation based on systemic absorption is the current approach, which is particularly useful if the purpose of the model is to assess the probability of passing a PK study with a proposed generic ODP and the RLD. However, if the purpose of the model is to assess the local BE of a generic ODP in relation to the RLD, the key metric of interest is lung tissue concentration at different regions of the lung. In this scenario, the ideal experimental data for validation would be unbound drug in human lung tissue interstitial fluid. The difficulty of obtaining this type of data via microdialysis is very challenging because it may only be collected during a surgical procedure, rendering the regular use of such data for validation impractical. However, a few limited data sets may still prove useful for establishing overall credibility of lung PBPK modeling. Another area of potential improvement for lung PBPK models is mucociliary clearance methodology, where most models use a compartmental approach. Kannan and colleagues have addressed this issue in part by developing a Q3D methodology that is capable of local absorption prediction with much greater precision.^{84,86} A Generic Drug User Fee Amendments-funded continuation of this work has recently been announced by the OGD, which will involve the expansion of the Q3D model to include respiratory airways and the application of the Q3D methodology to other lung geometries.⁹⁴

To date, CFD and PBPK models have generally established model credibility via comparison of predicted values with experimental data. However, there is no currently accepted standard for assessing how closely predicted values should match experimental data for a given application. One proposed methodology is verification, validation, and uncertainty quantification, as described by Pathmanathan *et al.*⁹⁷ and Pathmanathan and Gray.⁹⁸ A key concept described by this group is context of use, which refers to the level of evidence required to establish model credibility.⁹⁷ The level of risk for a given model is an interaction of the model's influence in a given decision-making process and also the consequence of the decision,⁹⁷ which is illustrated in **Figure 5**. Higher risk models would require higher evidentiary standards if model credibility is to be reliably assessed. Once the level of evidence required is established for a given application, the group proposes that the model be assessed according to verification, validation, and uncertainty quantification.⁹⁸ As defined by Pathmanathan and Gray,⁹⁸ *verification* refers to the numerical accuracy of the model with respect to the mathematical formulation of the problem of

interest, *validation* refers to accuracy of the model as compared with reality, and *uncertainty quantification* explores the influence of parameter sensitivity of the results of interest. Many of the ideas described by Pathmanathan *et al.*⁹⁷ and Pathmanathan and Gray⁹⁸ are echoed in the recently published standards released by the American Society of Mechanical Engineers (ASME) for establishing the credibility of medical devices, which have been referred to as ASME V&V 40.⁹⁹ The ASME V&V 40 standards provide more specific details on how verification, validation, and uncertainty quantification methodology may be applied.⁹⁹ Although none of the ideas expressed in the literature described here^{97,98} or in ASME V&V 40 are specifically endorsed by the OGD or the Center for Drug Evaluation and Research for the review of ODPs, they provide a useful means for developing a rigorous model that may prove useful for ODP development.

CONCLUSIONS

There is a current lack of generic ODPs on the US market, where increased costs and a reduction in accessibility are associated with this situation. To aid with the development of generic ODPs, CFD and PBPK modeling may be useful for reducing the number of device and formulation changes by quantifying the influence of specific modifications. Research involving the CFD modeling of ODPs has been ongoing for several decades, with much of the focus on the development of geometric lung models and improvements in regional deposition prediction accuracy. More precise modeling of device-specific and formulation-specific influences on ODP performance with CFD is more recent, where most studies have focused on modeling device and formulation effects of DPIs. Other efforts have investigated the influence of orifice boundary conditions on MDI performance and have developed an experimentally validated model for products using the Respimat device. CFD models may also be useful for assessing intersubject variability of small-airway deposition, but only limited work in this area has been completed thus far. PBPK models have been recently developed for the delivery of locally acting ODPs to the lung, with a few examples in the literature. The current models may be useful for predicting the probability of passing a PK study that compares a potential generic ODP with the RLD. Further enhancements in model precision and credibility may be needed to use PBPK models for comparing the local deposition of two ODPs. To establish model credibility for both CFD and PBPK, researchers have typically used experimentally derived *in vitro* and *in vivo* data to compare against model predictions. The more rigorous verification, validation, and uncertainty quantification methodology may be useful for enhancing the credibility of CFD and PBPK models to be used during the ODP development process. As model credibility and predictability are continually improved, it is expected that CFD and PBPK will increasingly occupy a more significant role in the generic ODP development process, where expected benefits include reductions in time and cost.

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