Computational fluid dynamics (CFD) for pharmaceutical aerosol device development: Simulations and processes to facilitate success

CFD modeling for product development requires knowledge of the capabilities of state-of-the-art software and the adoption of a well-controlled simulation workflow.

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Context

Within pharmaceutical aerosol product development and research, usage and awareness of computational fluid dynamics (CFD) and other predictive numerical simulation tools are increasing. Simulation, prediction and visualization of fluid flow and aerosol behavior have been performed for all stages of the drug delivery process, from inside an inhaler [1] to particle deposition in the lungs [2]. Increased confidence in predictive modeling processes could significantly reduce product development time by facilitating the design and investigative process for devices and formulations. This could drive deployment of CFD within the orally inhaled and nasal drug product (OINDP) sector in the coming years, for example, aiding the transition to propellants with lower global warming potential [3].

This article will review previous work in this area, illuminating CFD capabilities and the processes and considerations required to create a trusted, useful, predictive simulation to support the product development process.

Predictive simulation

Predictive engineering simulation is well established in various industries, (such as automobile product development [4] or design of mechanical equipment [5]) and well accepted, due to extensive validation. There have, however, been barriers to uptake within the OINDP industry, not least the complexity of the physical processes to be modeled. This is despite the success in modeling both pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) some 20 years ago [6, 7]. Modeling was discussed in *Inhalation* in 2008 [8] and 2015 [9], in articles that remain relevant reading for those looking to build a simulation of their product or to develop CFD workflows.

While physical testing and verification remain central to product development, approval and manufacture, the use of a multi-dimensional simulation tool offers possibilities prior to physical tests, including:

- testing of unconventional design ideas and hypotheses;
- insight into the complex fluid dynamics within a device, to better understand its performance;
- rapid performance of parametric design and optimization studies to reduce parameter space before physical testing;
- benchmarking of competitor products.

Types of CFD simulation for pharmaceutical aerosols

CFD simulations can model virtually any fluid-dynamic process between a pharmaceutical device and the targeted treatment area, mirroring the journey of drug molecules towards their intended (or unintended) destination. An article by Ruzycki, et al. [10] is still useful in describing the challenges and successes of pharmaceutical inhaler simulation. Particularly apt is the opinion that CFD analyses are most useful in conjunction with experimental studies. Excellent reviews of most aspects of pharmaceutical aerosol study where CFD can be effectively applied are found in references 11 and 12, and these remain relevant from a simulation perspective.

Device internal flow

The aim of simulating device internal flow is to predict or understand the state at the device exit, for example, the study of phase change and atomization in the two-phase flow through the nozzle of a pMDI actuator [13, 14]. Such flow is difficult to simulate, being complex, 3-D, multi-phase, small-scale and transient, as illustrated in experimental observations [15-17]. For DPIs, there is complex internal flow with different phenomena, as observed in a product development study that used validated CFD to investigate powder aerosolization in a new type of DPI [18].

Near-field aerosol

With this approach, the aerosol closest to the device (the near-field or near-nozzle spray) is modeled, sometimes within the same simulation as the internal flow just described [14]. Modeling only the first few millimeters from the nozzle allows high-fidelity simulation of the dense particle flow, with atomization phenomena predicted. These types of simulation aim to predict initial particle size, velocity distributions and spray angles before an aerosol interacts with its environment (e.g., a patient's oral/nasal cavity or a USP induction port throat (USP-IP)). Results might be used as initial conditions in downstream studies.

Far-field aerosol

The aim of far-field aerosol simulations is to understand where particles of different sizes travel and deposit, accounting for interaction of the aerosol with the patient or testing device. These may involve oral or nasal cavity geometry [19], a model throat or other analytical test device [20], or simply a hypothetical box to visualize the aerosol's behavior. Here, local particle density is lower and particles spend more time interacting with their environment; air flow, temperature and moisture are important, as is the interaction with physical boundaries. In these simulations, the aerosol initial conditions at the device nozzle (velocity, particle size, mass flow rate) may be pre-set or predicted from various physically-based or phenomenological models. These may be time-varying, due to the transient nature of most devices.

It is important to model air entrainment accurately, both that of air into the aerosol and of the smallest particles into any air co-flow. Flow and surface temperatures are important predicted parameters because they indicate the patient's experience. In addition, temperature influences physical properties that govern particle/surface interaction, liquid atomization and break-up, evaporation and condensation rates [21, 22]. Surface interaction models can assess whether particles deposit on surfaces or rebound, as a function of surface properties as well as physical particle properties including size, velocity and angle of impact.

Respiratory deposition and drug delivery

Modeling of airflow, particle flow and deposition inside the lower respiratory system, using 3-D geometry generated from anatomical image data (e.g., a computed tomography (CT) scan) [2, 23], is the final step in predicting the delivery of drug aerosol particles. These simulations seek to assess the probability of deposition of particles of different sizes at various locations. Using image data to generate the CFD modeling domain is often known as image-CFD or image-based CFD modeling [19, 24]. 3-D simulation of vascular systems, including drug transport, is also possible [24, 25], with similar recent advances in ease-of-use, availability, computing power and understanding.

Complex fluid behavior

The fluid formulations present in pharmaceutical aerosols are sometimes non-ideal, highly viscous, non-Newtonian or viscoelastic in behavior, e.g., nasal sprays with added mucoadhesives, recently discussed in *Inhalation* [26]. This altered viscosity can affect spray behavior including nozzle flow rate, atomization and break-up into droplets, and interaction of the liquid phase with the surfaces of the nasal cavity. CFD simulation of highly viscous, non-Newtonian or viscoelastic fluids—e.g., for nasal spray applications—is possible and has been explored [27, 28].

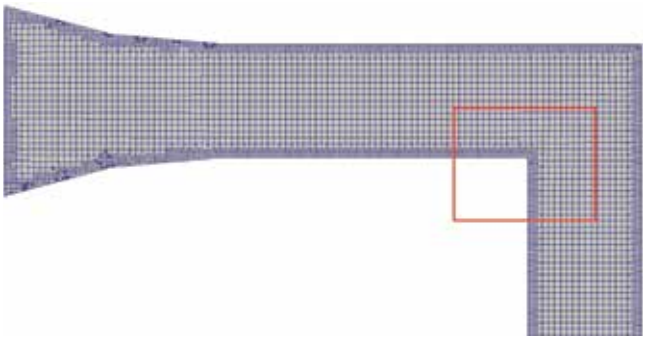
Industrial approach to CFD modeling

A business that utilizes CFD modeling for product development or research may select open-source CFD modeling software or use proprietary software. Open-source software will typically be free at point-of-use and offers full control for users, but training is recommended, as highlighted in reference 8. Product lifecycle management packages in use within organizations may have basic built-in CFD solvers that can be used freely or purchased at lower cost.

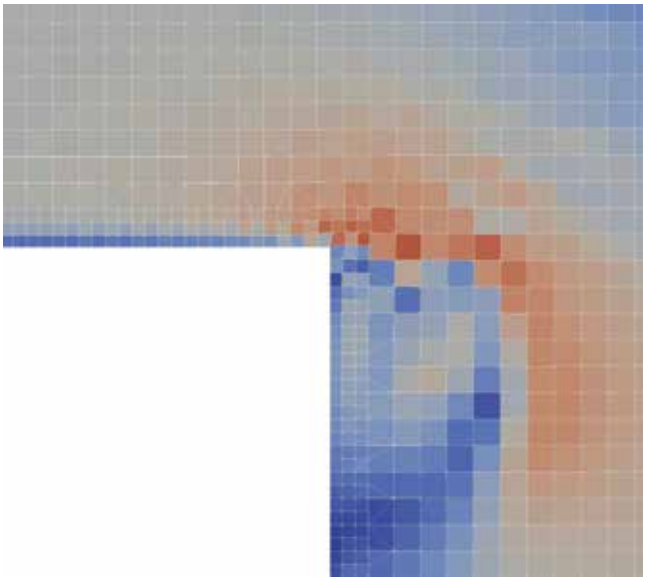
Figure 1

(a) Structured mesh at the center lines of a USP-IP throat CFD model, showing location of results in (b) and (c); (b) CFD-simulated cell values of air velocity magnitude at throat corner; (c) Smoothed air velocity magnitudes at throat corner.

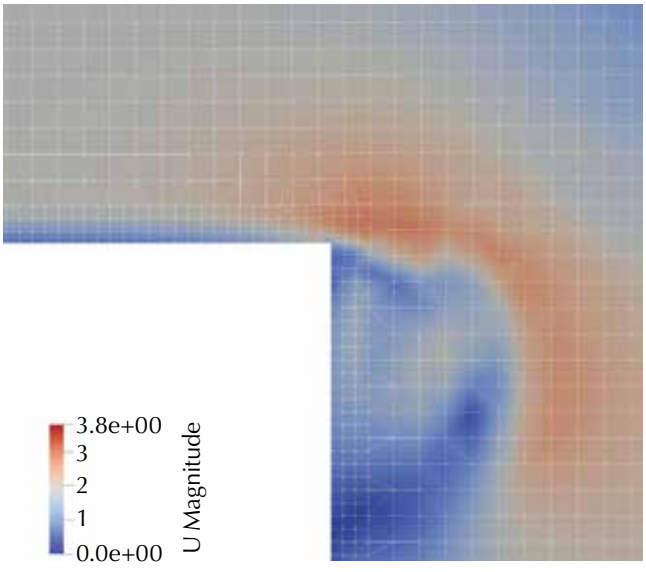
(a)



(b)



(c)



Industry methods

The industry-standard CFD method is the finite volume method (FVM), which solves the transient equations of fluid flow, treating the fluid as a continuum—that is, not attempting to model the motion of individual molecules. Finite element method (FEM) solvers also exist. Equations for conservation of mass, energy and momentum are solved, often called the Navier-Stokes equations. FVM operates by discretizing the entire fluid region into a grid or mesh of small volumes, known as cells.

The simulation proceeds from an initialized fluid state, with the Navier-Stokes equations solved in each cell at a series of small timesteps, each new fluid state dependent on the last. Steady simulations have artificial timesteps, allowing convergence towards a single solution. Simulations involving transient device actuation or patient inhalation are inherently transient, needing an unsteady simulation, where the timesteps represent the passing of time from a known initial state into a simulated future.

Single-phase Eulerian simulation

With this method, each cell is a fixed observation point for the fluid as it flows past—known mathematically as an Eulerian description (after Leonhard Euler). The output from a basic industrial CFD solver can provide the flow velocity and direction, pressure, temperature and fluid composition in each cell as a function of time, which, when viewed as a whole, provides an overall visualization of the predicted fluid flow. Figure 1 shows the mesh for simulation of air flow through a USP-IP throat, the simulated flow velocity at the 90° corner, and a smoothed version with cell interpolation to give a continuous visualization of flow velocity typical of that usually presented.

Multi-phase simulation

Of relevance for simulating sprays and aerosols is the ability of CFD solvers to track particles and interfaces. This allows simpler simulation of multi-phase flow, e.g., bubbly, flash boiling flows within the expansion chamber of a pMDI, particle-laden flows of a DPI or liquid jets of a nasal spray. A standard method for simulating an aerosol is Lagrangian particle tracking, also known as discrete droplet modeling [29]. A Lagrangian description of fluid flow (named for Joseph-Louis Lagrange) moves with the fluid, so each particle is modeled from an observation point that moves along with it.

For aerosol simulations, the ambient gas is modeled in the previously-described Eulerian sense (the 'Eulerian phase') and individual droplets or particles (the 'Lagrangian phase') are tracked from the time of their creation until they disappear. The fate of particles may be coalescence with another particle, break-up under aerodynamic forces into child particles, deposition on solid surfaces, evaporation or exit from the simulated region. Each droplet or particle is assumed

to be spherical, having relevant properties updated at every timestep with respect to position, velocity, size, temperature and chemical composition. Ideally, the particle moves no further than one cell per timestep, otherwise it would miss the opportunity to exchange mass, momentum and energy with all of the air through which it travels.

Coupling equations

Coupling equations are solved to calculate the exchange of mass, momentum and energy between the Lagrangian and Eulerian phases, e.g., causing fast particles to slow down, transferring momentum into the gas; cold droplets to heat up, cooling down the surrounding gas; and volatile droplets to evaporate and reduce in size while transferring their contents into the gas. The coupling can be "one-way" for certain simulations when the aerosol is dilute [10], modeling only the effect of the gas on particles. In Figure 2(a) and 2(b), results from a coupled aerosol spray simulation with the USP-IP throat geometry are shown, illustrating the prediction of the fate of different size particles, where the large particles (> 20 µm) have deposited on the throat walls before the 90° bend. In Figure 2(c), a one-way coupled solution is shown for the same problem: very similar particle behavior is observed, with a 20% reduction in computational time.

Lagrangian parcels

Dense pharmaceutical aerosols contain thousands of microparticles. It is computationally inefficient to model every droplet, particularly given the further reduced timesteps required for fast-moving droplets and particles. A reliable way of greatly reducing computational time is to group hundreds or thousands of simulated particles into parcels. These parcels behave like one particle, with a defined position, size, velocity, temperature, etc., but contain the mass of multiple particles, co-located. In this way, a reduced number of parcels can be simulated, in a reasonable time, to represent the overall aerosol.

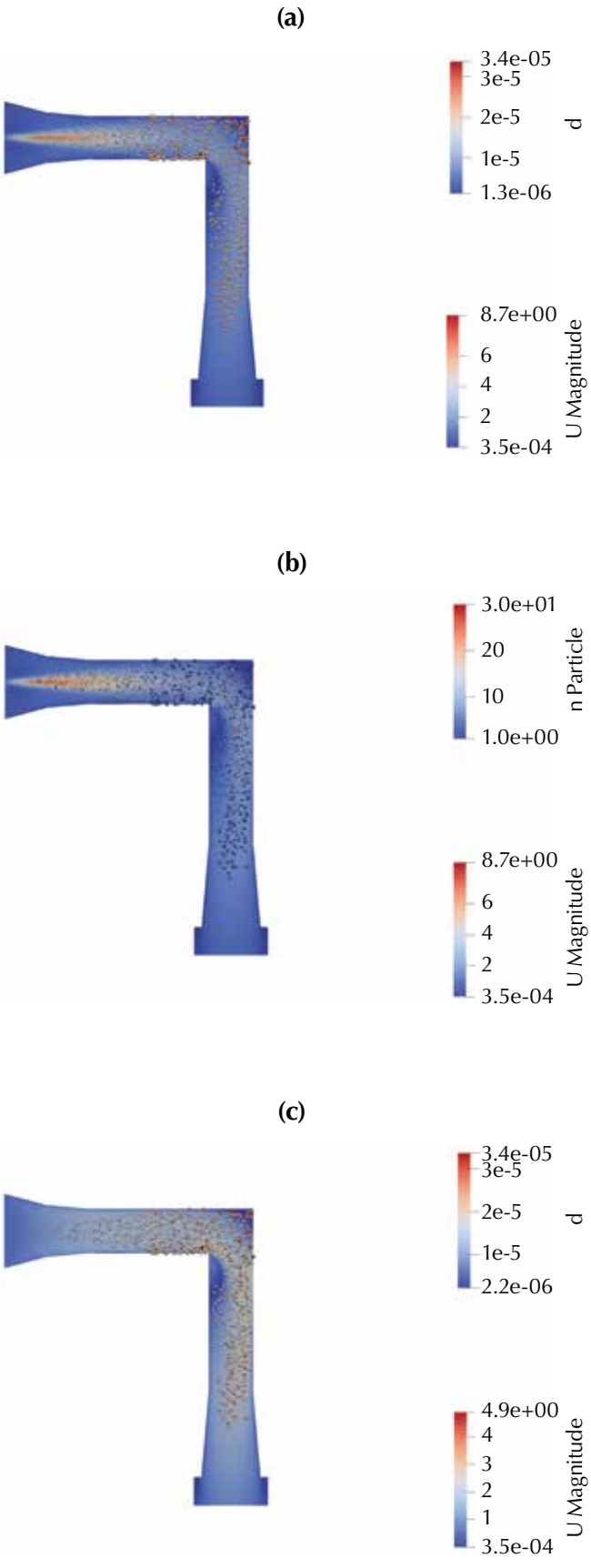
"Engineering-level" simulation and workflow

The "engineering-level" simulation seeks to simulate just enough of the physics of the fluid behavior to provide accurate prediction of trends and relatively accurate prediction of numerical quantities. Typically, engineering-level CFD includes a type of turbulence modeling called Reynolds-Averaged Navier-Stokes (RANS). Turbulent flow is important in several applications relevant for inhaler devices. RANS solvers produce a time-averaged prediction of flow, or an ensemble-averaged version for transient flow events. Although this means some turbulent detail will be missed, it is far more computationally efficient.

By contrast, simulations in a research environment may use a more complex turbulence-modeling

Figure 2

(a) USP-IP center line air velocity and particle size, simulated with a coupled aerosol and 30 L/min gas flow; (b) as image (a) with particles colored by parcel size; (c) as image (a) with a one-way coupled solution—shown by absence of gas jet at throat entry.



approach, typically large eddy simulation (LES) to resolve large turbulent flow structures. Better representation of the flow allows for greatest insight into underlying physics and subsequent development of new models and computational processes. LES modeling requires much more computational time. Reference 14 notes that "each calculation requires 15,000 to 35,000 CPU-hours (3-4 days of run time) depending on the grid size. This yields 0.16 seconds of a simulated pMDI spray." Therefore, several hundred CPU cores were used, running in parallel.

In selecting software to analyze problems relevant to specific products, the usual questions of cost and availability will be important, as well as consideration of the software's modeling capability. Study of aerosols requires solvers for Lagrangian particle tracking that allow phase change and particle temperature variation. Internal flow studies require incorporation of compressible flow solvers within the software. User-defined function may be a necessity, as employed in references 18 and 19, and as discussed in the section "Solver physics and sub-models" in this article.

The following sections describe the typical CFD workflow. As with experimental or analytical processes, adherence to a proper procedure can help ensure confidence and traceability of CFD results and any decisions made on the basis of these.

Model geometry preparation

The fluid volume ("domain") to be simulated can be generated using the following approaches:

- From a 3-D computer-aided design (CAD) model of a device or product—at a well-known, recorded state of development. The negative of the solid model can be used to create the fluid inside/around it for simulation.
- Created manually within the CFD software. Care must be taken to ensure that it is representative of the real situation to be simulated.
- From 3-D data from computed tomography or magnetic resonance imaging (MRI) scans. Manual/automated manipulation may be needed to smooth or patch image data into a usable closed volume for CFD.

The mesh

Once the fluid volume is created, it must be discretized into cells. This procedure has great impact on the simulation's accuracy and the computational time [30], so care must be taken. Guidelines are available about mesh style for airway models [30]. An automated mesh generator within a CFD package or stand-alone package can create cells of hexahedral or tetrahedral shape, in either a uniform ("structured") or semi-random ("unstructured") pattern. At curved edges, hexahedral cells may have one face reduce in size to zero so that the curve may be accurately followed. In addition:

- Some understanding of the expected flow is important. The mesh should be refined so that the cell size is small where the local gradient in velocity or another variable is large. High refinement facilitates good resolution of changes in the parameter. This can provide good results in this vicinity and elsewhere because the fluid flows around the domain. However, the more cells used, the greater the computational time.
- A mesh dependence study should be undertaken. Scale the cell size up and down to see the effect on the simulated results, and to find the size below which any decrease in cell size has no effect on results in the relevant part of the simulation. This supports the identification of the fastest possible accurate analysis.
- The mesh may take several iterations to perfect; large gradients may appear in the CFD solution in unexpected places, requiring an updated mesh and a re-run of the solver.
- Automatic mesh refinement (AMR) is the term used to describe changing of the mesh during the simulation. Cells are subdivided automatically when and where the solver detects a high gradient of any variable, to provide more accurate results, then returned to a larger cell size when the gradient reduces. This aims to create a compromise between high simulation accuracy and short run time.

Solver physics and sub-models

Once a suitable mesh is created, the solver must be chosen and physics models set. These can include models for turbulence; models for particle or droplet behavior including temperature change and evaporation, collision/agglomeration/break-up, and surface interaction; and models for heat transfer at surfaces. Default choices in software may not be relevant for the situation studied. Due to these varied and complex physical sub-models, at different scales, CFD is referred to as a multi-physics simulation. Some choices that require particular care are discussed below:

- Physical properties (such as density, viscosity and thermal conductivity) must be chosen and set. For multi-component mixtures in formulations, the properties set by the built-in packages found in CFD models may not be accurate enough to represent real, non-ideal behavior. If necessary, user-defined functions that implement temperature-, pressure- and composition-dependent physically-based models [22] can usually be included to define fluid properties.
- Turbulent flow and appropriate turbulence models for CFD represent a complex field of study in any application area. For inhaled aerosol applications,

the ambient gas flow could be laminar—but rapid expansion of formulation from an inhaler could induce turbulent flow. Correct modeling of turbulence within the aerosol will greatly influence the predicted penetration rate and spreading angle, consequently controlling the rate of break-up and agglomeration with knock-on effects on the particle size distribution. Investigation and recommendations for the upper airways are made in reference 31, with the low Reynolds number k-ω turbulence model recommended, as also used in reference 19.

- Turbulent dispersion models exist for RANS simulations, which simulate the outward spread of particles because they are influenced by turbulent eddies generated within an aerosol. This effect would otherwise be missed in a RANS simulation, as only average flow is predicted.

Initial and boundary conditions

Quantitative initial conditions and boundary conditions must be set for all fluid parameters. Special wall functions are available for turbulence parameters. Ideally, these should be based on measured data or otherwise be the output from other simulations or calculations. Simplifications for rapid transient simulations might be appropriate, such as zero heat transfer through solid boundaries. Sensitivity to these assumptions should be tested before they are adopted wholesale.

Solving and storing solutions

Solutions should be stored at regular time intervals for transient simulations. During development, where storage capacity allows, each new simulation should be saved as a fresh solution "case" with a description. This means changes to the simulation set-up can be easily tracked and their effects understood, en route to the final version.

Post-processing

Generation of visualizations and extraction of data allow interpretation of CFD results and support decision making. Often only the images are generated, which can help view the prediction qualitatively and make comparisons between cases. However, data for target parameters should be extracted at important points, along 1-D traverses through the domain and on 2-D surfaces, for quantitative or statistical analysis. Of particular interest are particle size distributions and deposition statistics, both of which require some post-processing to calculate. Alternatively, relevant metrics can be calculated in cells or on surfaces as part of the simulation, such as the Sauter mean diameter in the near-nozzle pMDI simulations in reference 14.

Validation

Where experimental or validation data exist, these must be properly compared with CFD results. This can build trust in the software, the set of results, the selected mesh and the chosen solver and sub-model set-up. It also can allow variations on the model (e.g., altered geometry) to be run with confidence. Validation data for aerosols and sprays can include high-speed images of a plume emerging from a device nozzle. Comparing these (with correct scaling) side-by-side with CFD simulation results is a good start for monitoring the shape and evolution of the aerosol. Quantitative data, such as local particle size distribution, particle velocity and flow velocity measurements, are invaluable in validating an aerosol simulation. Particle data can be measured using laser diffraction or phase Doppler methods and flow velocity from particle image velocimetry (PIV) methods. Comparison with analytical particle size distribution measurements taken with an impactor can be useful, provided the actual flow geometry before the impactor is modeled in the simulation.

Design optimization

The final potential step in the CFD workflow is the incorporation of the simulation within an optimization process, which is typically available in proprietary CFD packages. These optimizations seek to either:

- optimize the design of a product/device within some constraints to a set of goals;
- select the best set of sub-model options to represent some experimental validation data as closely as possible.

Recommendations for critical evaluation of CFD studies

In analyzing CFD studies, look for quantitative claims of either cell size or number of cells, with evidence of refinement in areas of high velocity gradient. Ideally, there should be evidence or claim of a mesh-dependence study. With Lagrangian particle tracking, look for quantitative data on the total number of parcels tracked (and a parcel number dependence study would be optimal). Both dependency studies are conducted in reference 19. In regions of dense aerosol, the cells should be small enough so that the volume fraction is not unrealistically large, i.e., that the droplets inside the parcels in those cells do not have a packing volume larger than the cell itself. This could result in excessive (i.e., non-physical) transfer of force or energy between the Lagrangian and Eulerian phases in these cells in a coupled simulation and would likely skew the predictions.

In addition, consider whether the code used has been validated for a similar problem, in the study under scrutiny or in works referenced. Consider too the values of fluid system properties and non-dimensional numbers, i.e., the ranges of validity of the model used and whether the current study falls within those.

Conclusions and next steps for deploying CFD

This article has shown some of the capabilities of industrial CFD for pharmaceutical aerosol applications, from the perspective of implementing CFD modeling within a product development process. The fundamental workings of the standard finite volume method with Lagrangian particle tracking have been explained in context, with the requirements and suggested processes for successful modeling.

Looking to the future, those with relevant "CFD skills" may be attracted to careers in the pharmaceutical sector and development of these skills are typically core to most mechanical, aerospace and biomedical engineering graduates. Knowledge of and experience with CFD sub-model selection, such as turbulence, atomization and particle/surface interaction, as well as programming ability and understanding of relevant validation data, is often acquired at the postgraduate/PhD level or via equivalent intensive R&D. Industry access to more advanced CFD packages, bespoke capabilities and personnel with training and experience can come through partnerships with research organizations and universities, which often retain their own high-performance computing facilities.

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