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Advent Engineering
Life Science Solutions

Applications of Computational Fluid Dynamics in Pharmaceutical Manufacturing

Applying a mature technology in novel ways to understand, predict, and explain fluid problems, so you can save time and bring products to market more quickly.

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Introduction

In 2000, the Clay Mathematics Institute laid out seven math problems so difficult it was willing to award a $1 million prize to anyone able to solve any of them. Known as the Millennium Prize Problems, just one of them has been solved in the years since—the Poincaré conjecture, which Russian mathematician Grigori Perelman proved in 2011 before famously declining the award money.

Among the six remaining prize problems is the Navier-Stokes existence and uniqueness problem, based on equations written down in the 19th century. If solved, the Navier-Stokes equations would significantly improve our understanding of how fluids behave. In theory, this set of coupled differential equations can be solved for a given flow problem by using methods from calculus. In practice, however, the equations are too difficult to solve analytically.

Continuity Equation

$$\nabla \cdot \vec{V} = 0$$

Momentum Equations

$$\rho \frac{D\vec{V}}{Dt} = -\nabla p + \rho\vec{g} + \mu\nabla^2\vec{V}$$

Total derivative = $\rho[\frac{\partial V}{\partial t} + (V.\nabla)V]$

Change of velocity with time

Convective term

Pressure gradient
Fluid flows in the direction of largest change in pressure.

Body force term
External forces, that act on the fluid (gravitational force or electromagnetic).

Diffusion term
For a Newtonian fluid, viscosity operates as a diffusion of momentum.

That's where Computational Fluid Dynamics, or CFD, comes in. CFD uses high-speed computers to solve approximations of these equations, delivering a numerical solution rather than an analytical one. Automakers use it to analyze aerodynamics, thermal heat management, fuel efficiency, and the performance of engine components and cooling systems when optimizing the design of cars, trucks, and other vehicles. In the aerospace industry, it's used to simulate the drag, lift, noise, structural loads, heat transfer, and combustion performance in aircraft systems and subsystems; by enabling engineers to evaluate designs earlier in the development process, it can reduce the number of physical prototypes required during the design process.

But while the value of CFD in these industries is widely known and the technology is mature, fewer people are familiar with its applications in biopharmaceutical manufacturing. Use of CFD is growing by leaps and bounds in other industries due to digital trends and increasing computational power, but adoption in biopharmaceutical manufacturing is hampered by a lack of awareness, a perception that it's an expensive process, and a lack of understanding of the value it brings to the industry.

In this eBook, we'll delve into everything CFD—what it is, what it's used for, and how biopharmaceutical leaders can use it to save time and bring products to market more quickly.

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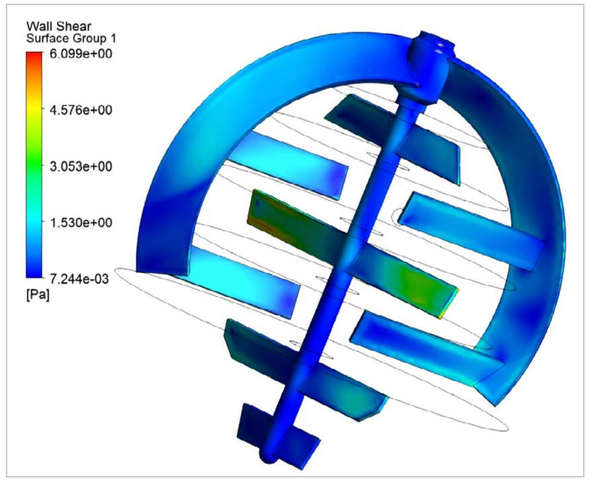
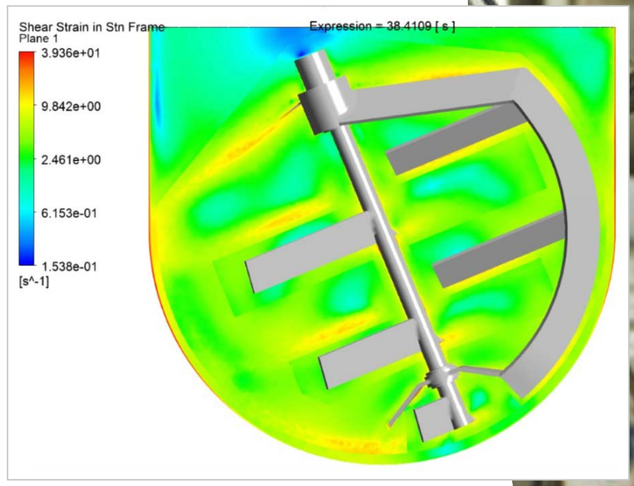
What is CFD modeling?

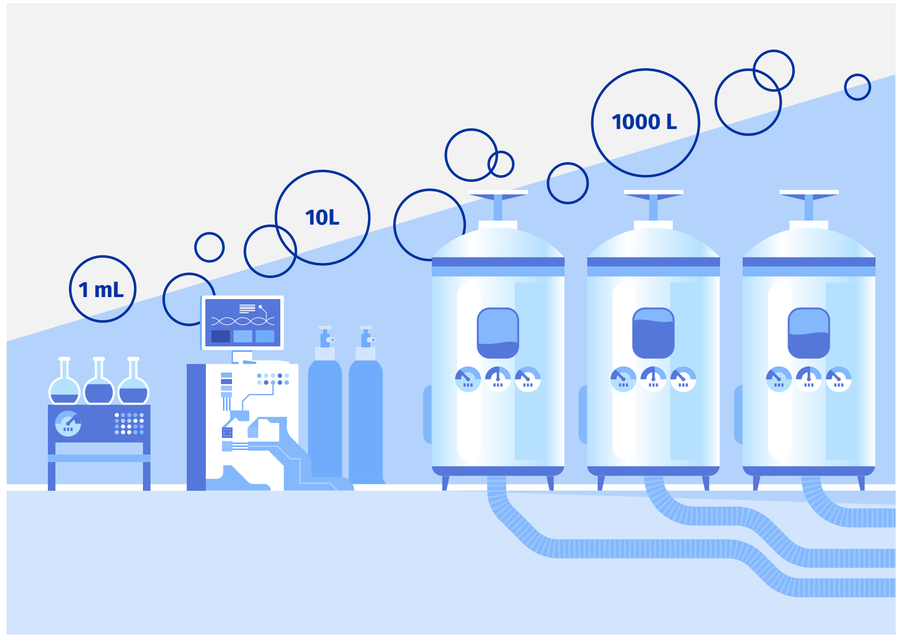
CFD is an engineering tool used to simulate and predict the behavior of liquids with respect to the surrounding environments. Using advanced algorithms and high-speed computers, it solves energy, mass, and momentum balance equations to calculate resulting variables such as velocity, pressure, and temperature. This allows scientists and engineers to analyze complex problems involving interactions between fluids, fluids and solids, or liquids and gases. An alternative to experimentation, which can be time-consuming and costly, CFD delivers visual as well as quantitative results of various fluid parameters.





Why use CFD?

CFD is more economical and faster than experimentation. It can scale up as needed, is always repeatable, and can leverage information anywhere in the model (as opposed to experimentation, where information is harnessed at specific points).



CFD is a versatile tool for understanding and optimizing fluid behavior, delivering results within 10% of reality[1] in a wide range of conditions including:

- Turbulent flow
- Three-dimensional space
- Compressible flow
- Two-phase flow (coexisting gas and liquid phases, no phase change)
- Two or more component flow (liquids or gases or both)
- Gas bubble and bubble interaction
- Steady-state and transient
- Suspended particles (solids)
- Thermally coupled
- Moving boundaries

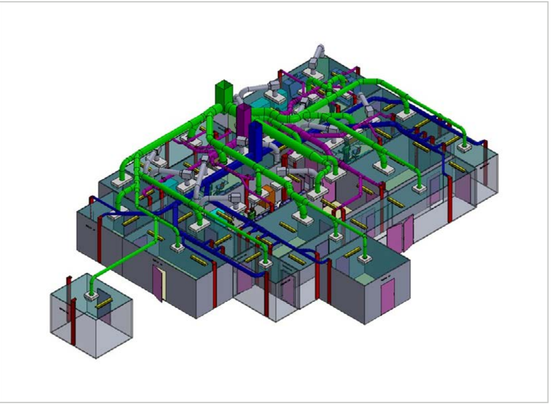
In short, CFD allows engineers to know it before they build it.

1. "Using CFD Multiphase Modeling to Predict Bioreactor Performance." ISPE Magazine, September/October 2020 and "Cleanroom Recovery Study Using CFD Methodology." ISPE Magazine, March/April 2023.

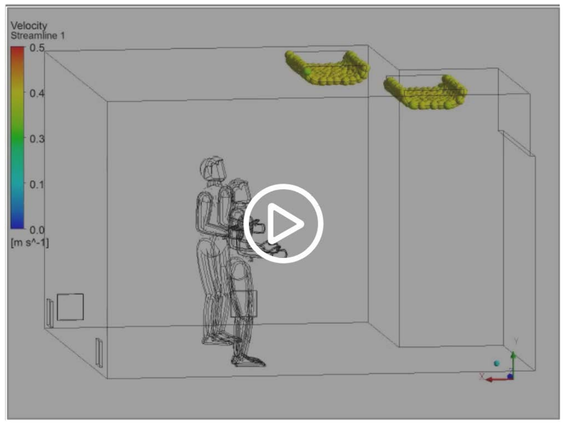
What are the practical applications of CFD in biopharmaceutical manufacturing?

Speed to market is critical in the life sciences industry. With the patent expiration dates looming, the rate at which a new product is brought to market is critical. It is therefore imperative for biopharmaceutical leaders to be able to bring products to market as quickly as possible while complying with all applicable regulatory standards.

To this end, CFD is increasingly being used in biopharmaceutical manufacturing anywhere liquid or gas behavior needs to be better understood, ranging from bioprocess equipment optimization to facility design. Bioreactors are among the most complicated unit operations in a biopharma facility, and their performance is incredibly important to the manufacturing process. As companies try to improve output performance, the bioreactor design needs to be optimized. Robust facility design is becoming ever more critical, especially with novel modalities requiring functional segregation and the desire of manufacturers to operate multi-product facilities. Being able to understand and predict operating performance with strategically located and designed airlocks and efficient process, equipment, people, and waste flows helps industry leaders achieve regulatory compliance, streamline workflows, and ensure that the facility can operate at the capacity it was designed to deliver.



Develop 3D models to run simulations based on design parameters



Click to play a video illustration of particulate movement

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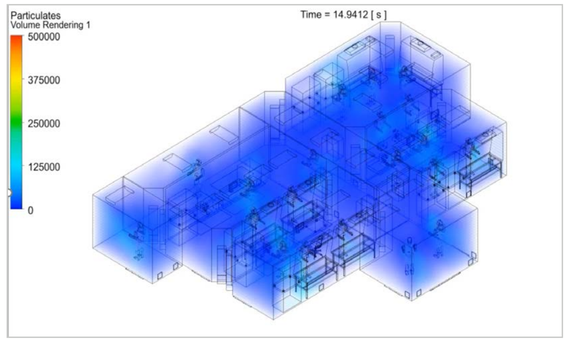
View simulation results of particulate levels:



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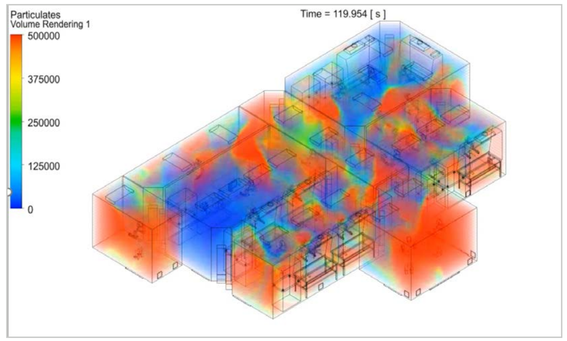

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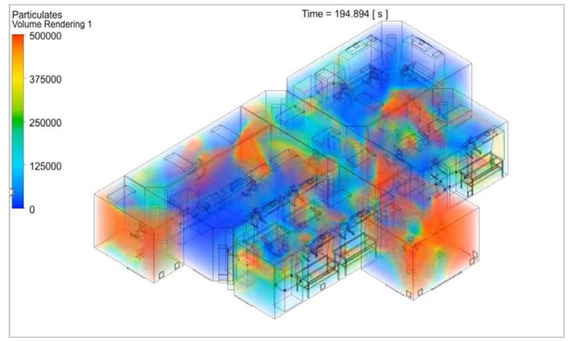

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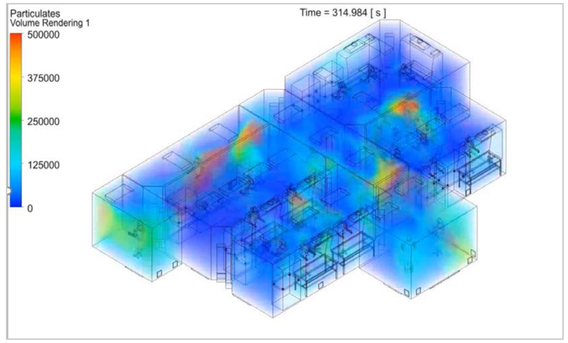

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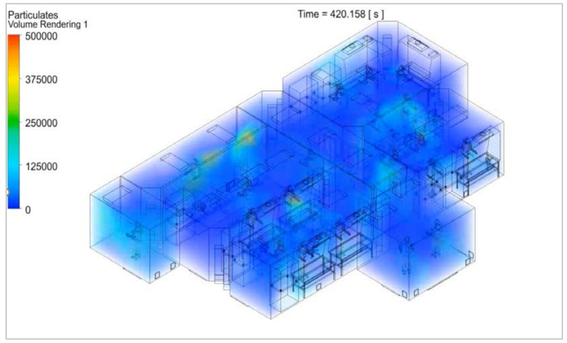

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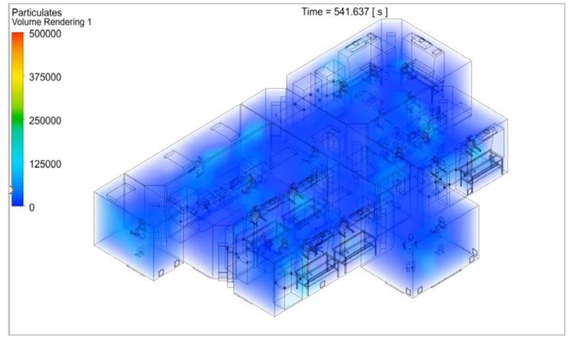

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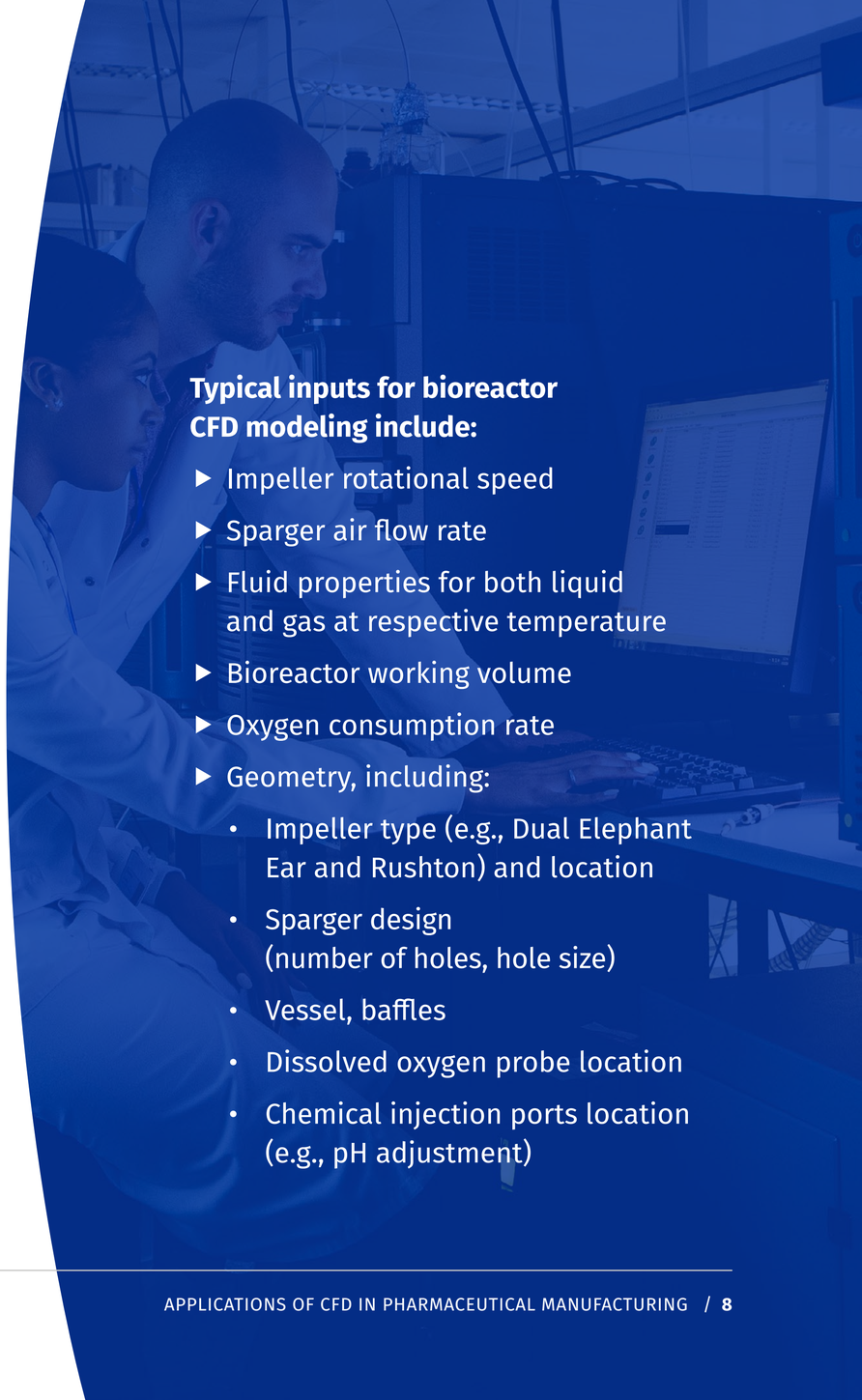
How is CFD used with bioreactors?

What if you could understand why your large-scale bioreactor performs poorly compared to your small-scale bioreactor? What if you could predict when and where vortices form or local impeller flooding occurs? What if you could predict levels of shear or the size of eddies throughout your bioreactor? And what if you could explain anomalous behavior in your process? By enabling us to understand, predict, and explain fluid problems, CFD answers all of these questions—and more.

CFD can reduce or eliminate the need to perform bioreactor scale-up studies by simulating full-scale manufacturing bioreactors—specialized vessels that play a critical role in the cultivation and propagation of cells, microorganisms, or biological entities for commercial-scale production of biological products, including therapeutic proteins, antibodies, vaccines, and other biotherapeutic agents.

Bioreactor scale-up is an important step to commercial-scale biopharmaceutical manufacturing, as it intends to reproduce process performance at large scale that has been optimized at small scale. It's not as simple as linearly scaling, though—as batch sizes increase, properties will change, making it important to validate the process at each scale to ensure that the quality of the final product is not compromised.



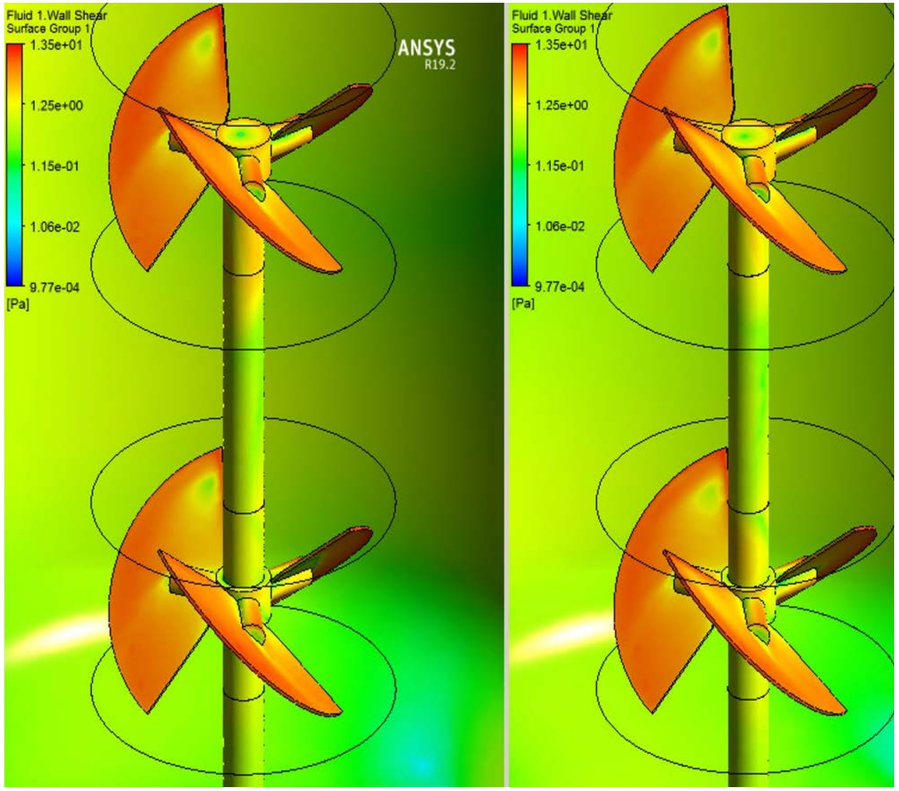
Typical inputs for bioreactor CFD modeling include:

- Impeller rotational speed
- Sparger air flow rate
- Fluid properties for both liquid and gas at respective temperature
- Bioreactor working volume
- Oxygen consumption rate
- Geometry, including:
  - Impeller type (e.g., Dual Elephant Ear and Rushton) and location
  - Sparger design (number of holes, hole size)
  - Vessel, baffles
  - Dissolved oxygen probe location
  - Chemical injection ports location (e.g., pH adjustment)

CFD unlocks the ability to:

- Simulate multiphase gas/liquid (sparging)
- Simulate gas mixtures
- Simulate aqueous solutions with dissolved gasses
- Model multiple sized gas bubbles and bubble interactions
- Model free surfaces and the formation of a vortex
- Predict potential for flooding
- Predict locations of high shear
- Predict eddy size and location

In doing so, CFD provides a faster, more economical alternative to experimentation, which requires building a small-scale bioreactor, conducting small-scale experiments, analyzing results, then changing parameters (and repeating as needed to model different conditions, not all of which can be isolated).



Quickly model different conditions to view simulation results... without building a small-scale bioreactor in the lab.

When compared to experimentation, CFD also enables biopharmaceutical leaders to apply a more comprehensive range of output parameters in the scale-up:

OUTPUT PARAMETERS	CFD	LABORATORY
Velocity field for both gas and liquid phase	✓	
Agitator fluid torque	✓	✓
Fluid volumetric power	✓	
Shear stress	✓	
Gas holdup	✓	
Overall and local kLa	✓	✓ overall
Gas phase volume fraction distribution	✓	
Dissolved oxygen and carbon dioxide distribution*	✓	✓ at probes
Mixing time*	✓	✓ sampling
Bubble residence time	✓	

** Transient simulation*

CFD modeling also provides detailed visual data that can complement or exceed experimental methods. This allows engineers to find a suitable operating match between the target bioprocess and the bioreactor without having to undergo extensive experimentation.

In short, CFD enables biopharmaceutical manufacturers to compare and optimize the design of bioreactors before they are built, mitigating risk while improving speed to market.

How is CFD used to optimize GMP facility design?

The design of a facility has a determinant impact on the efficient and compliant production of biologics, vaccines, and other biopharmaceutical products. The design and layout of a facility affect a wide range of factors, including workflow, equipment placement, cleanroom ingress/egress, and environmental segregation. Proper facility design is also essential for meeting regulatory requirements, optimizing workflows, and avoiding product contamination.

CFD plays a significant role in optimizing facility design by providing insights into the pressurization, airflow, and environmental conditions within the manufacturing space. It minimizes the need for assumptions and guesswork while focusing on the user requirements for each operational area.

With traditional approaches to facility design, particulate levels and room recovery are not fully understood until environmental monitoring qualification, well after the facility is built and operating.

Traditionally, the design of biopharmaceutical facilities has involved facility programming to develop an understanding of product and process requirements. Design teams:

- Determine personnel and material movement and operation transitions based on area classification
- Develop a conceptual layout based on programming, equipment arrangement, movement, and operation transition
- Establish HVAC parameters to supplement facility design, including determining the location of supply, return, and exhaust registers and establishing desired environmental conditions (e.g., air changes per hour, pressurization, temperature, and relative humidity)

But while designs are based on using industry best practices, this traditional approach makes it difficult to answer some key questions with confidence, like: Where is the best place to install supply diffusers and exhaust grills to promote unidirectional air flow? Can I reduce air changes per hour while maintaining compliance for particulate levels? Will I be able to recover my cleanroom to its stated classification within a reasonable time after an upset condition?

In contrast, CFD takes an iterative approach to optimizing facility design:

- Define room layout based on user requirements, with input design parameters that include room layout (e.g., personnel, equipment, and furniture) and HVAC and facility parameters (e.g., ACH, location of supply/return/exhaust registers, desired particulate level, target pressurization, number of people in each room)
- Develop a 3D model of the layout, for example using SOLIDWORKS, AutoCAD, or Revit software
- Run a CFD simulation based on design parameters and review the results to determine whether desired conditions have been met
- Revise design parameters as required and run the simulation until design conditions are met

This iterative process delivers a wide range of benefits by enabling facility designers to:

- Predict particulate levels in a clean room during "at-rest" and "in-operation" conditions to meet regulatory requirements set for a Good Manufacturing Practice (GMP) facility
- Predict room recovery times (to comply with ISO 14644-3) based on particulate challenges to the model
- Confirm integrity of the containment boundary within a cleanroom suite, providing science-based data to empirically demonstrate compliance to regulatory standards
- Optimize air changes per hour for each room while maintaining room cleanliness to meet desired particulate level, recovery rates, and pressurization
- Help size air handling unit (AHU) capacity effectively, for lower operational expenditure (OPEX) and lower capital expenditure (CAPEX)
- Optimize supply and return/exhaust diffusers to promote airflow laminarity and visualize airflow patterns, minimizing turbulence at operational areas as well as cross-contamination and deviations
- Verify appropriate room pressurizations and differential pressure to adjacent classifications during "at-rest" and "in-operation" conditions
- Predict airflow pattern for gas sterilization (e.g., vaporized hydrogen peroxide, chlorine dioxide, and ethylene oxide) to room suites, chambers, isolators, and more, allowing for confirmation of sterilization
- Predict hot and cold spots of environmental chambers (e.g., walk-in coolers, freezers, and incubators), demonstrating and validating design before construction
- Determine particulate level impact of adjacent rooms or facility upon a room or facility upset (e.g., AHU failure)

In short, CFD enables biopharmaceutical manufacturers to simulate and analyze fluid flow, temperature distribution, and containment within facility designs, allowing them to optimize ventilation systems and cleanroom layouts—before the facility is built—to ensure regulatory compliance and efficient biopharmaceutical production processes.

What are some real-world results using CFD modeling?

Studies comparing CFD modeling to real-world results have shown that CFD is highly accurate—within 10% of real-world performance for the kLa of a bioreactor[2] and within 10% of real-world performance for particulate mitigation for cleanroom recovery.[3] Our client engagements have included:

- **CFD for bioreactor performance scale-up studies:** A biopharmaceutical corporation needed to predict the performance of manufacturing-scale bioreactors under various operating conditions and evaluate different design options to optimize production. Trinity Consultants' Advent Engineering Life Science Solutions team used CFD to simulate the fluid dynamics and the working parts of the bioreactor, quickly and cost-effectively answering key questions related to the design and performance of the bioreactors. The analysis allowed the Advent team to optimize the design of the bioreactors before they were built, mitigating risk while improving speed to market.
- **CFD for facility design:** A client asked Advent to help estimate room recovery time for a Grade B cleanroom to minimize operational risk. Advent used CFD to predict that the particulate concentration level would be reduced by a factor of 10 in 10 minutes (90% reduction). The CFD simulation also enabled the team to design a room with the number of air-changes-per-hour much lower than that produced by relying on standard rules of thumb. Once the model was developed, the client was able to use it as a baseline for making further facility modifications.

2. "Using CFD Multiphase Modeling to Predict Bioreactor Performance." ISPE Magazine, September/October 2020.
3. "Cleanroom Recovery Study Using CFD Methodology." ISPE Magazine, March/April 2023.

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What's next? How to get started with CFD

CFD is incredibly fast, effective, and accurate, but it can be difficult to know how to get started—and how to apply the insights it delivers. Advent's team of industry veterans can help guide you along the way. An industry leader and innovator with extensive experience in the application of CFD to support our clients in compliant production of novel therapies, we can help you reduce the time and cost of trial-and-error experimentation and minimize the need for "rule of thumb" based designs in favor of data-driven design decisions. We serve as a partner throughout three key steps that are integral to using CFD:

1 Understand

The first step is to define the problem you are trying to solve; Advent can help in this foundational stage. We start by listening, so we can gain a deep understanding of your unique situation, the challenge you face, and the key parameters involved. Once we understand the critical and key process parameters of your equipment and facility layout, we can work together to gather inputs. Your teams probably have most, if not all, of the information you need; our team of experienced industry veterans can generate estimates for any missing parameters or perform a sensitivity analysis for any uncertain input parameters.

2 Predict

Using the latest CFD software, the Advent team excels at all types of CFD simulations—no matter how complex or critical your project. We'll help you leverage CFD modeling to simulate and predict the behavior of fluids with respect to the challenge you are trying to solve.

3 Explain

We'll show you how to use the results of the CFD modeling to communicate and explain processes and conditions. With visualizations and pictures worth 1,000 words, you can easily communicate with senior management, non-technical stakeholders, and regulators to explain processes, conditions, and the root cause of the challenge you are addressing.

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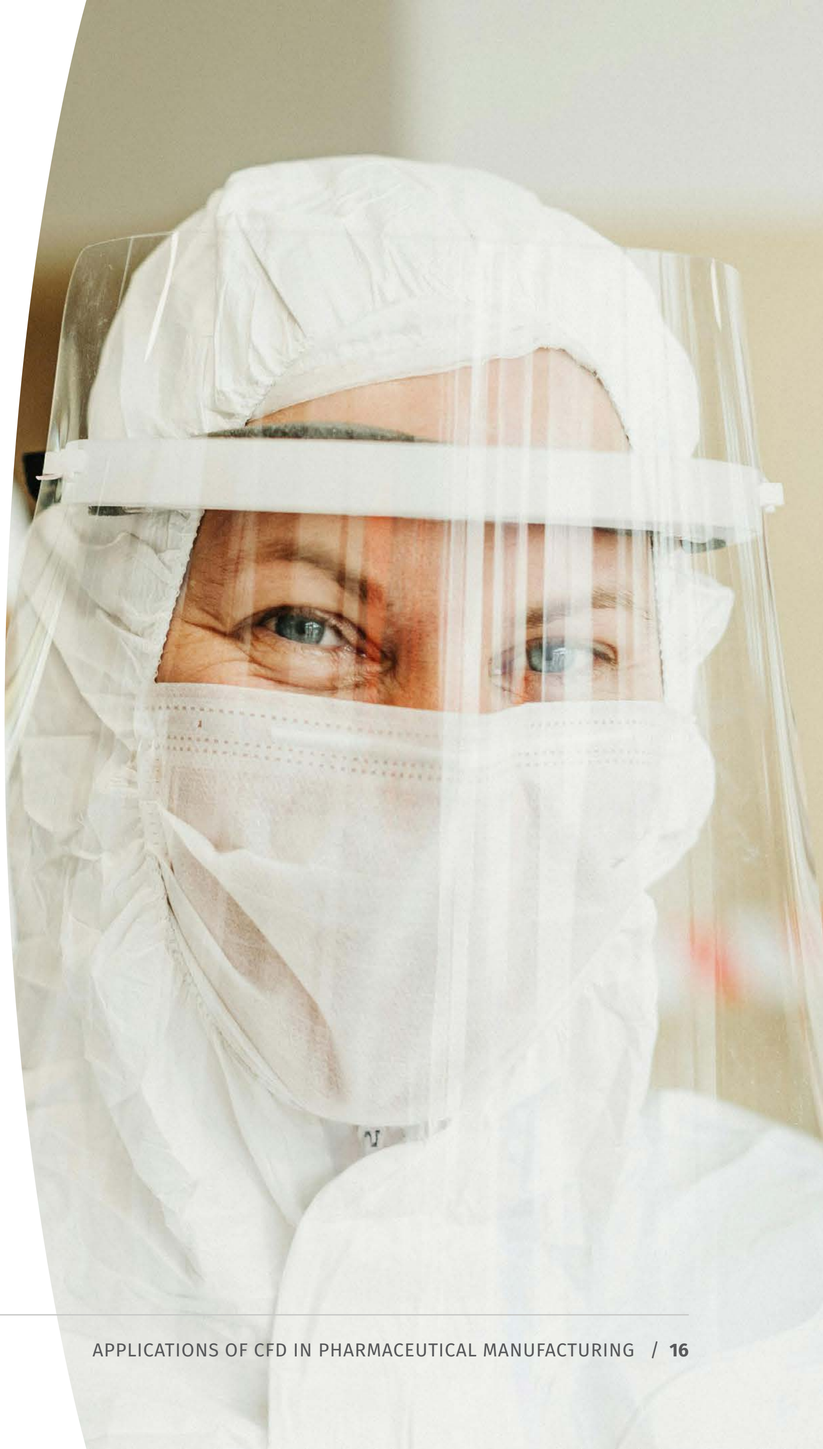
It's often stated that time is money, and nowhere is this more true than in biopharmaceutical manufacturing. In an industry where time-to-market is the holy grail for reaching patients and saving lives, CFD delivers a significant advantage by enabling leaders to move away from experimentation and get high-quality, innovative products in the hands of doctors and consumers more quickly.



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WHY CHOOSE TRINITY

Trinity's Life Sciences division provides optimal solutions to highly complex pharmaceutical development, process, safety, and facility design challenges, with personnel located in the United States, Canada, the United Kingdom, and Asia. For assistance, contact us at 919.313.7234.

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