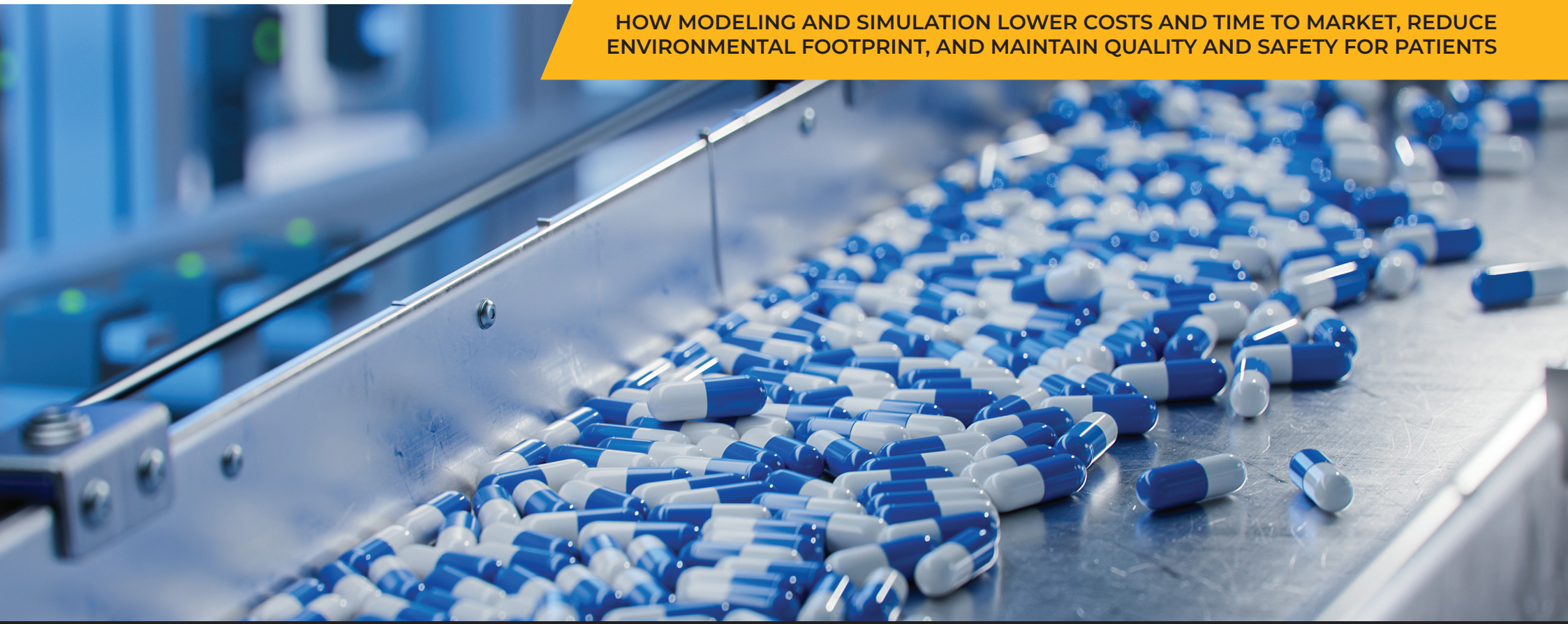
Digital Transformation of the Drug Manufacturing Process

HOW MODELING AND SIMULATION LOWER COSTS AND TIME TO MARKET, REDUCE ENVIRONMENTAL FOOTPRINT, AND MAINTAIN QUALITY AND SAFETY FOR PATIENTS



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Key Highlights

1. Pharmaceuticals can take over a decade to develop and cost billions of dollars to produce.

2. The scaling up of drug manufacturing processes contributes to the cost and delays at the very last stage when the product is ready to generate business.

3. Inefficient upstream and downstream manufacturing processes and packaging activities can further delay time to market, costing companies market exclusivity and limiting potential revenue.

4. Optimizing scaling up the manufacturing processes with modeling and simulation accelerates timelines without compromising quality, advances equipment performance, and reduces waste throughout the process.

Drug Manufacturers Endure High Costs and Long Delays

Bringing new pharmaceuticals to market is a slow, laborious, and costly process. Studies show that a single drug or vaccine may take 10 to 15 years and up to $2.5 billion to formulate, study, test, and produce — and just one in eight drugs receives regulatory approval. As the COVID-19 pandemic made clear, these timelines, costs, and low approval rates are unsustainable. For companies, it means lost revenue and wasted time, but for patients, it could be a matter of life or death.

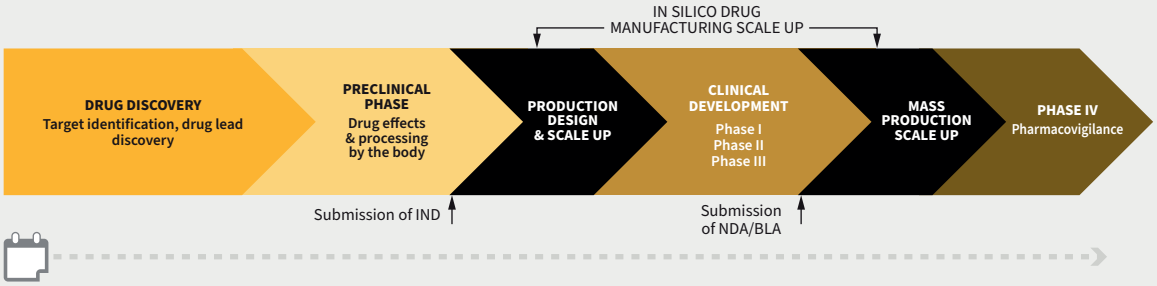
For today's pharmaceutical companies, the drug manufacturing and packaging processes contribute to the high cost and slow pace of getting a product to market. Scaling up production, refinement, and packaging from lab- to industrial-level while maintaining patient safety, product quality, and sustainability efforts is a significant challenge. The traditional method of trial and error may work in other industries, but in pharmaceuticals, conditions must be exact or companies risk wasting expensive product.

Pharmaceutical companies with less efficient manufacturing processes leave patients in need, limit revenue potential, reduce their market opportunity, and increase waste.

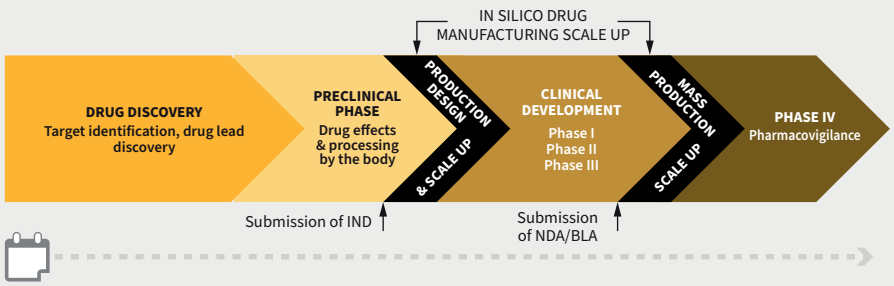
Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA. 2020 Mar 3;323(9):844-853. doi: 10.1001/jama.2020.1166. Erratum in: JAMA. 2022 Sep 20;328(11):1110. Erratum in: JAMA. 2022 Sep 20;328(11):1111. PMID: 32125404; PMCID: PMC7054832.

IN SILICO METHODS SIGNIFICANTLY REDUCE SCALE-UP TIME

(A) THE CONVENTIONAL DRUG MANUFACTURING PROCESS



(B) THE DRUG MANUFACTURING PROCESS WITH IN SILICO METHODS



Overcoming Manufacturing Challenges Is Essential

But the advantages for companies that successfully navigate drug manufacturing challenges are undeniable. Blockbuster drugs deliver billions in revenue, enhance brand recognition, attract investors, and fund future research and development. Meanwhile, more modest drugs fill therapeutic gaps, serve niche markets (e.g. orphan diseases), and build a diversified product portfolio that offers the company long-term financial stability.

Companies that deliver pharmaceuticals ahead of the competition enjoy market exclusivity and patent protection that can last anywhere from 180 days to seven years depending on the drug type. This can increase their return on investment (ROI) — by hundreds of millions of dollars in some cases — and reduce labor costs and operating expenses, which frees up resources for future drug research.

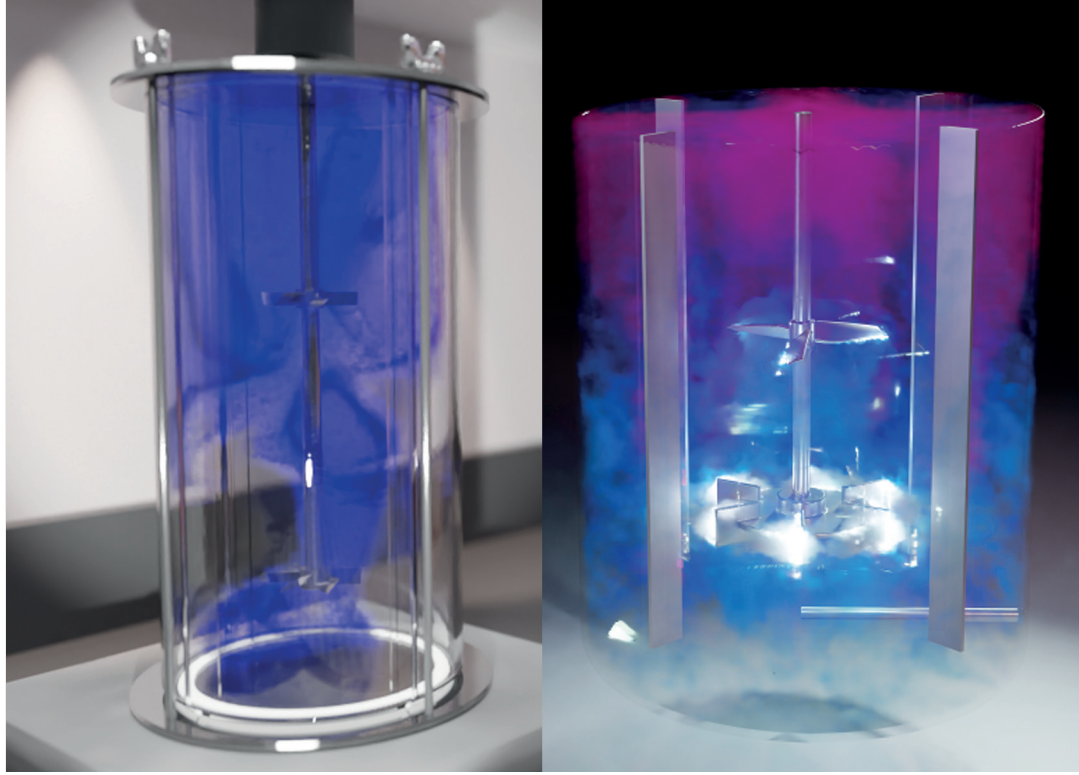
Pharmaceutical companies should embrace digital transformation of their manufacturing and equipment processes with modeling and simulation. Optimizing the upscaling manufacturing processes with modeling and simulation accelerates timelines without compromising quality, advances equipment performance, reduces waste throughout the process, provides patients with much-needed medications, and increases margins and market position.

In Silico Methods Yield Key Advantages

Extensively validated computational modeling and simulation (CM&S) — or in silico methods — are often used by different healthcare sectors throughout the process and product life cycles, including manufacturing processes.

In silico methods provide pharmaceutical companies with a wealth of information at every stage of manufacturing. Companies can use these insights to scale their manufacturing efforts more efficiently and optimize upstream and downstream aspects of the process without relying on costly, time-consuming rounds of trial and error.

Some key benefits of using in silico methods during the drug manufacturing processes include:



Mixing at the lab level (left) and at the production level (right)

Identifying the shortest path to a good mixture:

Simulation aids equipment design to account for adjustments that must be made to accommodate much larger production volumes and ensure a good product mixture no matter the volume.

Ensuring products remain within required paramemeters:

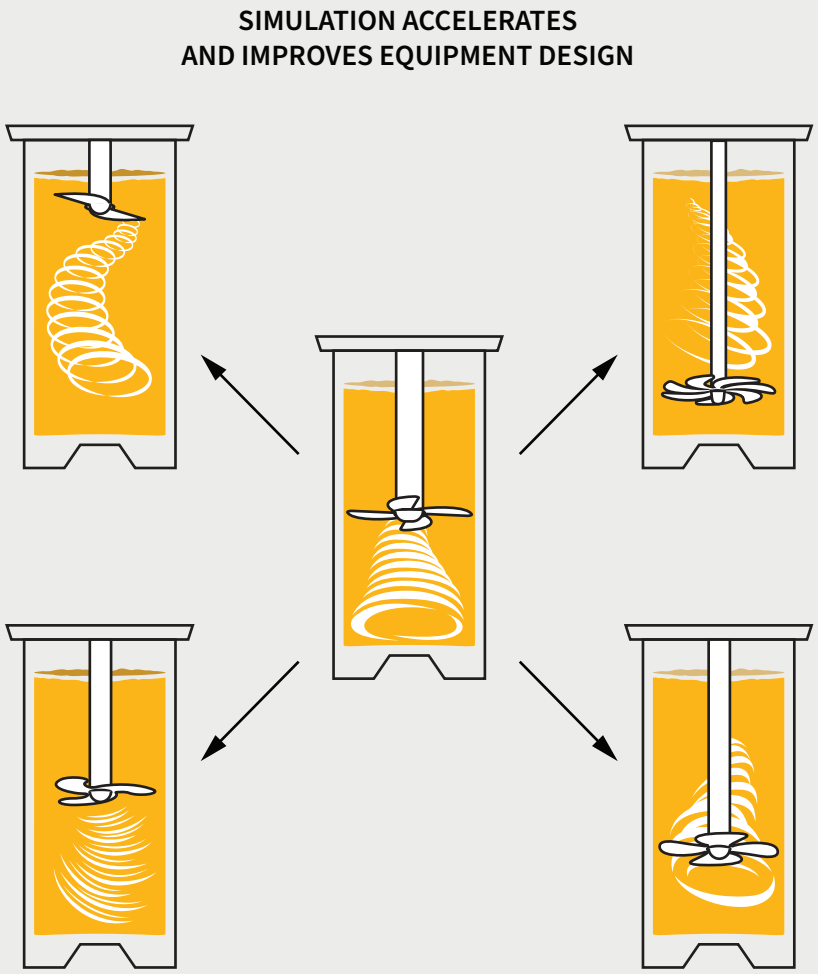
Simulation is key to maintaining ideal production conditions — including pH, oxygen, and temperature levels — throughout the entire bioreactor and at the microbiological level as the line is running. Simulation also ensures that nutrient mixtures remain consistent and that any waste is evacuated properly.

Delivering high-quality, uniform products:

Real-time feedback from a digital twin enables stakeholders to quickly identify and correct issues related to the mixing process before any batches are lost.

Reducing wasted energy and materials:

Modeling and simulation eliminate companies' reliance on repeated physical iterations of equipment and production lines — and corresponding energy and material waste.



Modeling and Simulation Simplify Scaling Up

Drug manufacturing begins in earnest once the medication receives regulatory approval. At that point, the company must scale lab- or pilot-level production up to plant-level manufacturing while ensuring consistency throughout the upstream and downstream processes. But scaling up is not merely a matter of multiplying dimensions and ingredient volumes to match the expected market demand.

To scale manufacturing effectively, stakeholders must understand precisely how the transition will affect the final product and calculate the adjustments required to increase output with no loss of quality or efficacy. Traditionally, companies scale up manufacturing by iterating on potential setups, equipment, and processes until they find a solution that ensures effective production without deteriorating the active pharmaceutical ingredient (API). But this traditional approach requires numerous time-intensive physical iterations: manufacture the equipment, test a production line, measure the quality, and repeat until the desired quality is met.

In contrast, modeling and simulation enable pharmaceutical companies to actually see the flow in the mixing tank, the biological reaction in the bioreactor, or the coating process for each tablet. Then they can optimize manufacturing parameters, ensure stable product quality regardless of production variability, and minimize waste, all without the need for extensive physical experimentation.

Optimizing the Upstream Process With Simulation

The upstream process, in short, is everything related to the scalable production of medicines. Two of the biggest factors throughout this process are proper mixing tanks and bioreactors.

Mixing Tanks

When scaling up production, it's essential that pharmaceutical companies develop mixing tanks with the optimum design configurations. A poor design can cause uneven mixtures and other issues that undermine batch quality and efficacy. Manually iterating on blade and tank design or mixing processes is time-consuming and quickly increases costs. It also provides little insight into equipment failures away from embedded sensors. In contrast, modeling and simulation enable companies to iterate virtually, optimizing designs far more rapidly and accelerating an otherwise expensive, laborious process.

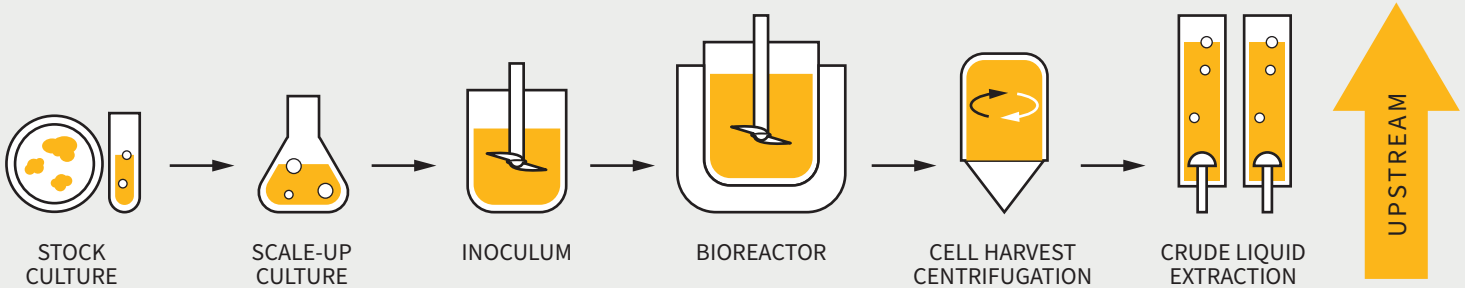
Bioreactor

Similarly, ensuring optimal conditions inside a production line's bioreactors is a significant challenge during the scaling process. Traditionally, companies have relied on trial and error to establish ideal pH and temperature levels, nutrient density, and other operating conditions and geometries. But this approach is as cost- and time-intensive here as it is in mixing tank design. CM&S, however, enables stakeholders to identify the best conditions for bioreactors of any size in less time — and without the waste inherent to manual iterations.

Digital Twin

Building and validating digital twins of mixing tanks and bioreactors is also made simpler by these in silico methods. When a conventional prototype fails, organizations often have little to no insight into why the failure occurred, leaving them without a clear understanding of what to adjust or change. In contrast, digital twins of such equipment use sensor data fed into simulation models to accurately mimic conditions inside the equipment during production. The digital representation provides rich insight into failures. This offers stakeholders a clear path to quickly — and sometimes automatically — address any production hiccup, improving equipment design and performance while reducing waste.

THE UPSTREAM PROCESS FOR BIOLOGICS

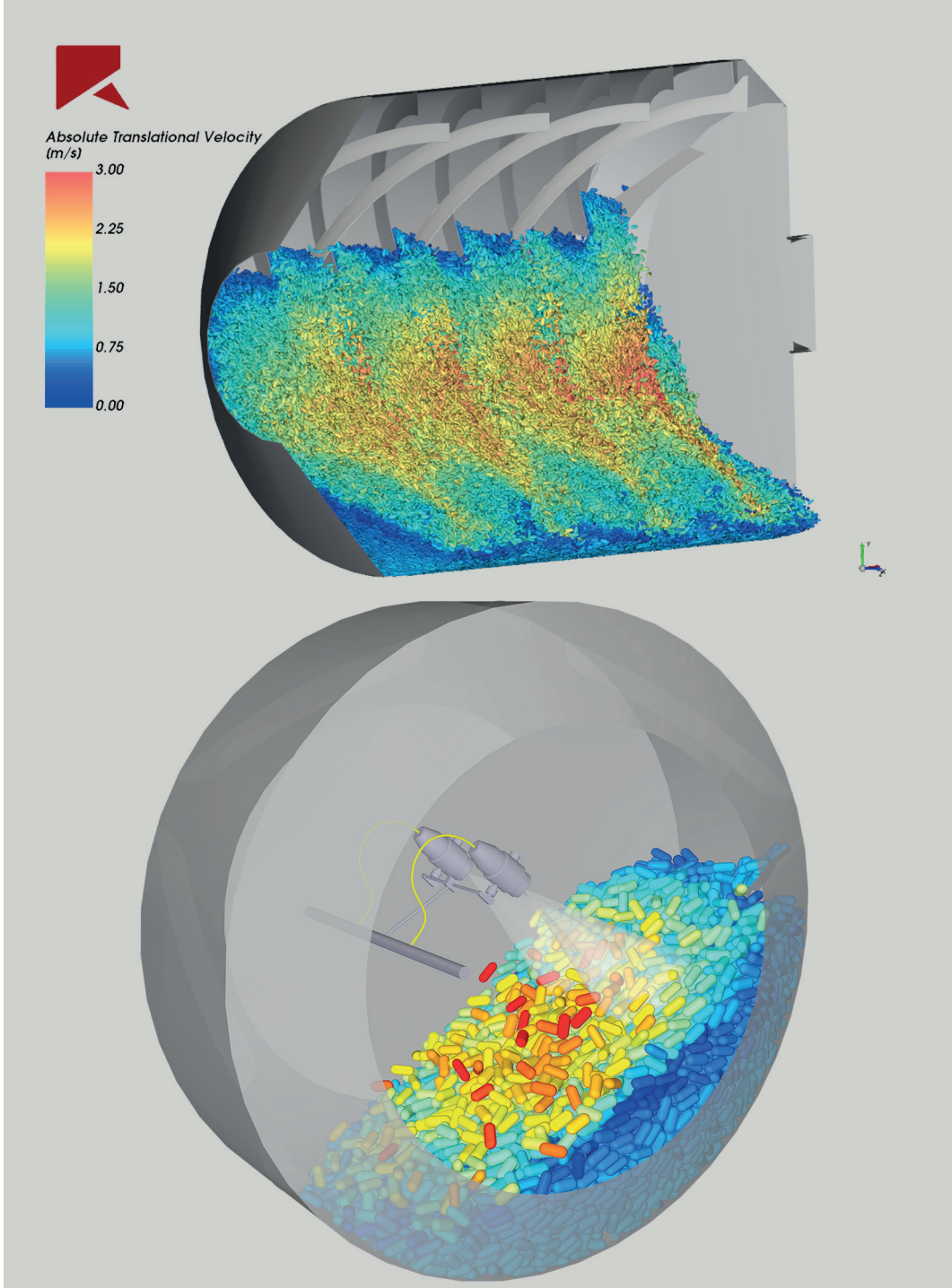


Navigating Complex Downstream Processes Is Easier With Simulation

The downstream manufacturing process primarily involves purification and formulation.

The benefits start with the purification process, during which filtration, chromatography, spray drying, and granulation equipment work in concert to extract a drug's API. This equipment must be finely tuned to manage the complex physics of the purification process. Without a clear understanding of how their equipment will perform, however, companies are left to struggle through the same drawn-out, costly cycle of manual iteration. Modeling and simulation eliminate that struggle by enabling companies to quickly optimize purification equipment designs and processes to ensure consistent results.

The formulation process — wherein a drug's API is combined with other ingredients to create a safe, effective dosage form — is similarly complex. The powder mixing, coating, extrusion, and lyophilization processes must result in a uniform product, which means the equipment that executes them must maintain consistency across millions of units. Achieving that kind of accuracy in a timely, cost-effective fashion simply isn't possible without insights from modeling and simulation. With those insights in hand, pharmaceutical companies can optimize equipment performance in much less time at a much lower cost, which both eliminates significant amounts of energy and material waste and ensures that the ten millionth tablet is indistinguishable from the first.



Simulation Fuels Successful Digital Transformation

The short- and long-term benefits of modeling and simulation represent a sea change in drug manufacturing. Equipped with the right tools, pharmaceutical companies can scale from lab- to industrial-level production more rapidly than ever while minimizing corresponding costs and delays.

Design optimization:

Traditionally, scaling up to plant-level manufacturing is a lengthy, expensive process that requires multiple rounds of physical prototyping and testing. Modeling and simulation shorten that process and make it far less expensive by enabling stakeholders to iterate rapidly and validate an optimized design virtually before committing to a physical

Improved troubleshooting:

At every stage of the drug manufacturing process, modeling and simulation simplify troubleshooting and improve its outcomes. Rather than taking days to identify issues related to equipment design, prototype failures, and production lines and processes, stakeholders can do so in hours or even minutes. Then they can address issues before they affect product quality, increase costs, or create unnecessary delays.

Establishing a digital twin:

As pharmaceutical companies use modeling and simulation to improve their manufacturing efforts, they accumulate a wealth of knowledge about everything from equipment design and performance to product chemistry and process effectiveness. This information can be leveraged to create a digital twin of the manufacturing process. That digital twin can be used to gain insight into the behavior of the physical components of that process — and how they might be improved further. That knowledge can then be used to inform future manufacturing planning to ensure that costs stay low, output and quality remain high, and waste is minimized. Accumulated simulation data can also fuel the use of artificial intelligence (AI) to speed up or even automate aspects of the manufacturing process, lowering costs and improving outcomes even further. This keeps valuable institutional expertise within the company even if employees leave.

Summary and Recommendations

Today's drug production process, from development to manufacturing to release, often takes more than a decade and costs hundreds of millions, if not billions, of dollars.

To meet the world's evolving healthcare needs, pharmaceutical companies must find ways to accelerate the drug manufacturing process and get medicines to the patients more quickly.

Modeling and simulation, which reduce costs and shorten the process of scaling up manufacturing efforts, are the keys to achieving these outcomes. Companies that continue to rely on conventional approaches to drug manufacturing delay their products' much-needed arrival in the market. They will then fall behind competitors that make use of these technologies — and put their bottom lines at risk.

Pharmaceutical companies should take the following steps to make their manufacturing processes more efficient and deliver products to market more rapidly:

- Assess the organization's scale-up processes, including the design and fine-tuning of mixing tanks, bioreactors, spray dryer, and other essential equipment, to gain a clear understanding of the time and cost involved.
- Identify the impact that accelerating drug manufacturing by 50% would have on costs and product release timelines.
- Determine how modeling and simulation can improve the organization's drug manufacturing outcomes and adopt solutions that meet its needs.

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