# THE RIGHT MIX

**CFD simulation saves time and money by validating the ability of a single-use mixer design to scale to 5,000 liters.**

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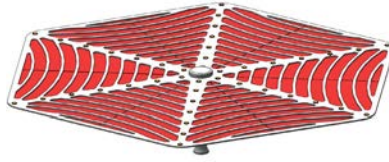
▲ imPULSE single-use mixer

## ASI faces the challenge of providing different sizes of its products for various stages of the therapeutic development process. ▼

**B**iopharmaceutical manufacturers continually need to scale up production as they move from small pilot studies to progressively larger clinical trials, then finally into large-scale production as the drug reaches the market. As a provider of single-use systems and bioprocess equipment utilized in biopharmaceutical manufacturing, ASI regularly faces the challenge of providing different sizes of its products for these various stages of the therapeutic development process. Until recently, biopharmaceutical manufacturing facilities relied solely on hard-piped systems, such as stainless steel bioreactors, tanks and piping. ASI has pioneered development of single-use equipment, designed to be employed once and then disposed of. These systems drastically reduce the need for harsh and lengthy cleaning requirements while improving production speed due to quick changeover between batches.

ASI is a leading global provider of advanced single-use systems for the healthcare and life sciences industries. The company's imPULSE single-use mixing series is a unique system that consists of a stainless steel hexagonal mixing vessel and a matching single-use mixing bag. Together, the system can be
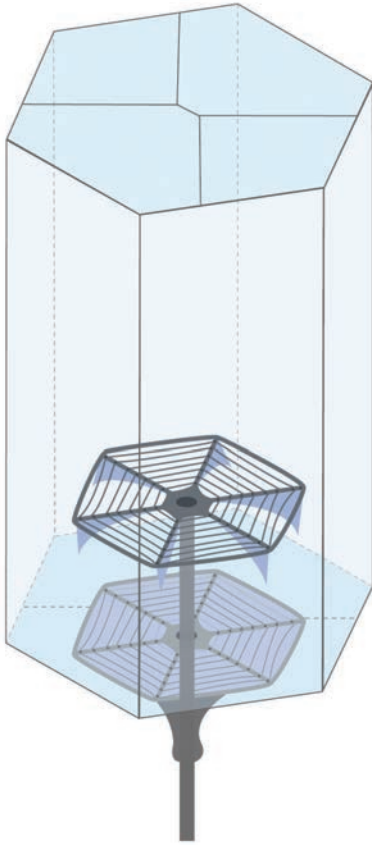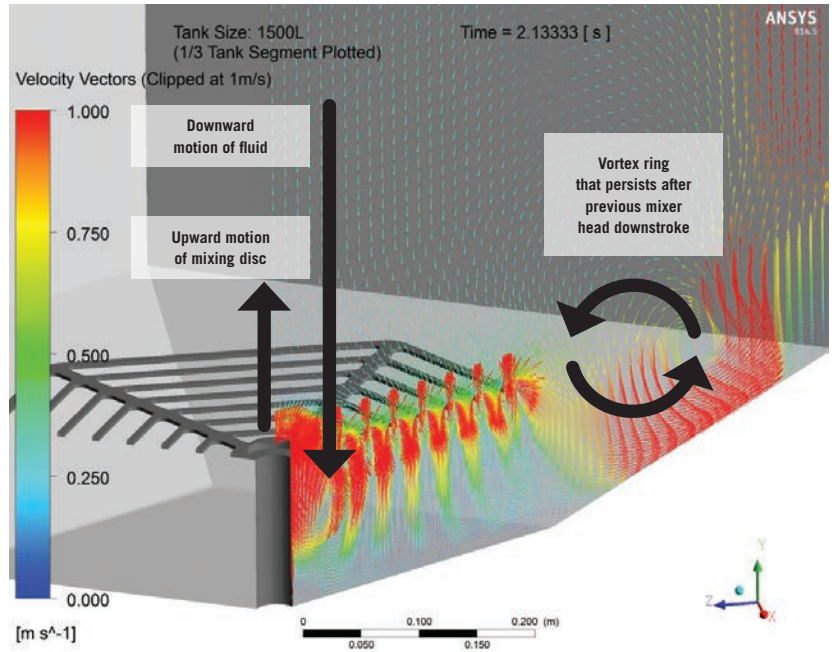
▲ Reusable mixing bag


▲ Flow during mixing downstroke


▲ Flow during mixing upstroke



Tank Size: 1500L
(1/3 Tank Segment Plotted)

Time = 2.13333 [ s ]

Velocity Vectors (Clipped at 1m/s)

Downward
motion of fluid

Upward motion
of mixing disc

Vortex ring
that persists after
previous mixer
head downstroke

[m s^-1]

▲ Velocity vectors show mixing motion.

configured for a variety of end-user mixing applications. The disposable polymer mixing bag is engineered with an integrated mixing disc that consists of multiple slots and film flaps. The flaps open and close as the mixing disc moves up and down within the mixing bag. On the downstroke, the flaps close, and energy is directed to the bottom of the mixing bag and up the sidewalls. On the upstroke, the flaps open, allowing the fluid to flow through the slots, thus producing one-way flow and very effective mixing. Simulation with ANSYS Fluent helped ASI to eliminate the cost and lead time of prototyping, demonstrating that ASI's design could be scaled up to an

industry-leading 5,000-liter size while providing the same mixing performance as smaller mixers.

ASI first developed the imPULSE design in a 250-liter (L) size and expanded the portfolio to include sizes from 30 L to 1,500 L. As customers further scaled up their batch sizes, they demanded larger mixers. Although it was not difficult to scale up the mixer, it was a challenge to maintain mixing efficiencies and patterns. The time required to achieve a certain level of homogeneity is critical to the efficiency of biopharmaceutical manufacturing. To sell the larger mixers, ASI needed to prove that mixing time would be consistent in both

larger and smaller mixers. The lead time and cost required to build a prototype of the new 5,000-liter mixer was quite high. So ASI investigated the potential for using computational fluid dynamics (CFD) simulation to validate the design of the larger mixer. Besides being faster and less expensive than building and testing a prototype mixer, CFD provides more diagnostic information, such as flow velocities throughout the tank along with shear rate, all of which are useful in diagnosing and improving a mixer design.

ASI contracted with consultants from ANSYS channel partner SimuTech Group, a supplier of engineering simulation software, support, training, consulting and testing services. The team used ANSYS Fluent to simulate the motion of the mixer discs. Fluent's dynamic layering method

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**BSA Volume Fraction vs Time (at a specified probe point)**
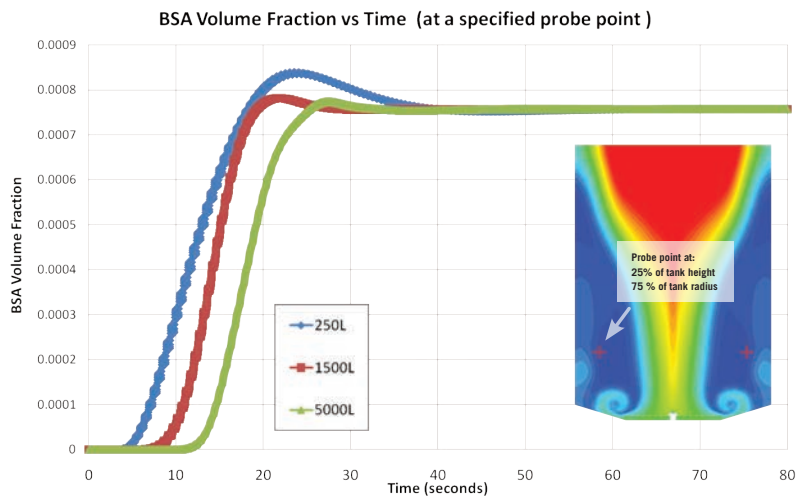
▲ BSA volume fraction versus time for different tank size

## CFD simulation saved hundreds of thousands of dollars, providing characterizations that apply to the overall scalability of ASI's products and significantly reducing the need for building and testing prototypes. ▼

adds or removes layers of cells adjacent to a moving boundary based on the height of the layer bordering the moving surface, which enables simulation of devices with complex moving parts. The dynamic layering method allows users to specify an ideal layer height on each moving boundary. The layer of cells neighboring the moving boundary is split or merged with the layer of cells next to it based on the height of cells in the adjacent layer. This unique approach to simulating a moving boundary eliminates accuracy problems, which are caused by cell shape deformation.

SimuTech engineers simulated performance of the bag in mixing two different particles: salt and bovine serum albumin (BSA). The software enabled engineers to customize material properties to model the properties of each particle type. The simulation showed that the flow traveled up along the outer walls, crossed over at the top of the tank, and returned in a downward moving column. This was expected since the mixing

disc, located in the center of the bag, was designed to push the fluid on the downstroke, but not on the upstroke due to the opening of the membrane film flaps. The result is that during the downstroke bulk flow is accelerated, but on the upstroke a more complicated local mixing flow pattern is formed around the mixing disc. A complicated local mixing flow pattern is evidence of the random and aggressive mixing patterns this disc creates. The aggressive behavior creates a turbulence that generates random patterns, which provide additional paths for the solutions and bulk flow to conjoin.

The simulation showed that localized flow near the mixing disc changes significantly depending on its position in the stroke cycle. On the downstroke, with the membranes closed, the flow is pushed outward toward the tank walls at a high velocity. A vortex ring forms around the periphery of the mixing disc, which is beneficial to mixing and persists even after the mixing disc starts to move up again. The vortex generally follows



**250 L**



**1,500 L**



**5,000 L**

▲ Flow circulation patterns for different tank sizes

the bulk flow, so the circulation pattern migrates toward the walls. When the mixing disc is moving up, the bulk of the fluid in the center column continues to move down, but now the mixing disc opposes this motion. With the membranes/holes open, the flow is free to bypass the mixing disc by moving through these holes, which further agitates flow. The localized vortices illustrated in the CFD results generate turbulence with the ability to mix even difficult powder/liquid solutions at a rate that will enhance conjoining the bulk fluid and powder/liquid product solution. The localized vortices near the disc show that air is not being entrained or pulled in; only unmixed product is pulled in through the submerged disc.

To compare and predict scalability across various sizes, SimuTech engineers compared flow patterns of three different-sized mixers — 250 liters, 1,500 liters and 5,000 liters — to determine whether or not the tanks behave similarly. The results showed that flow patterns were largely unchanged in the larger devices as compared to the 250-liter baseline. Within a few seconds, all the tanks establish the pattern of flow moving up along the outer walls and down through the center column.

The mixing patterns were observed directly through multiphase simulations with salt and BSA particles present in the tank. These results showed that at 6 seconds all three mixers had significantly suspended salt into the fluid. For the smallest equipment size, significant concentrations of salt were present at the top of the tank; even for the largest sizes, significant concentrations were present two-thirds of the way up the height of the tank. The near-neutrally buoyant BSA particles, which started in a thin layer at the top of the bag, were drawn down in the center column of descending fluid, then agitated by the mixing disc and eventually dispersed throughout the entire tank. The simulations showed that within 60 seconds, the concentrations throughout the tank were relatively uniform.

To quantify the mixing of BSA particles over a longer period of time, researchers created a monitor point in the three tanks. This point was placed 25 percent of the way up the height of the tank at a radial position of 75 percent. The results showed that the smaller tanks mixed faster than the larger tanks, but within practical limits, all tanks mixed very quickly. Within 60 seconds, the volume fractions in all of the tanks stabilized at about the same level. Overall, while slight differences were present in time scales in the different tanks, the tanks all scaled well, since they all mixed in less than a minute and displayed similar mixing patterns for the specific CFD testing conditions.

Because ASI engineers confirmed the simulation predictions with actual data in three sizes, they can draw a correlation between the actual and simulated data for application across the company's entire portfolio of mixing products. Overall, CFD simulation saved hundreds of thousands of dollars, providing characterizations that apply to the overall scalability of ASI's products and significantly reducing the need for building and testing prototypes. **∧**

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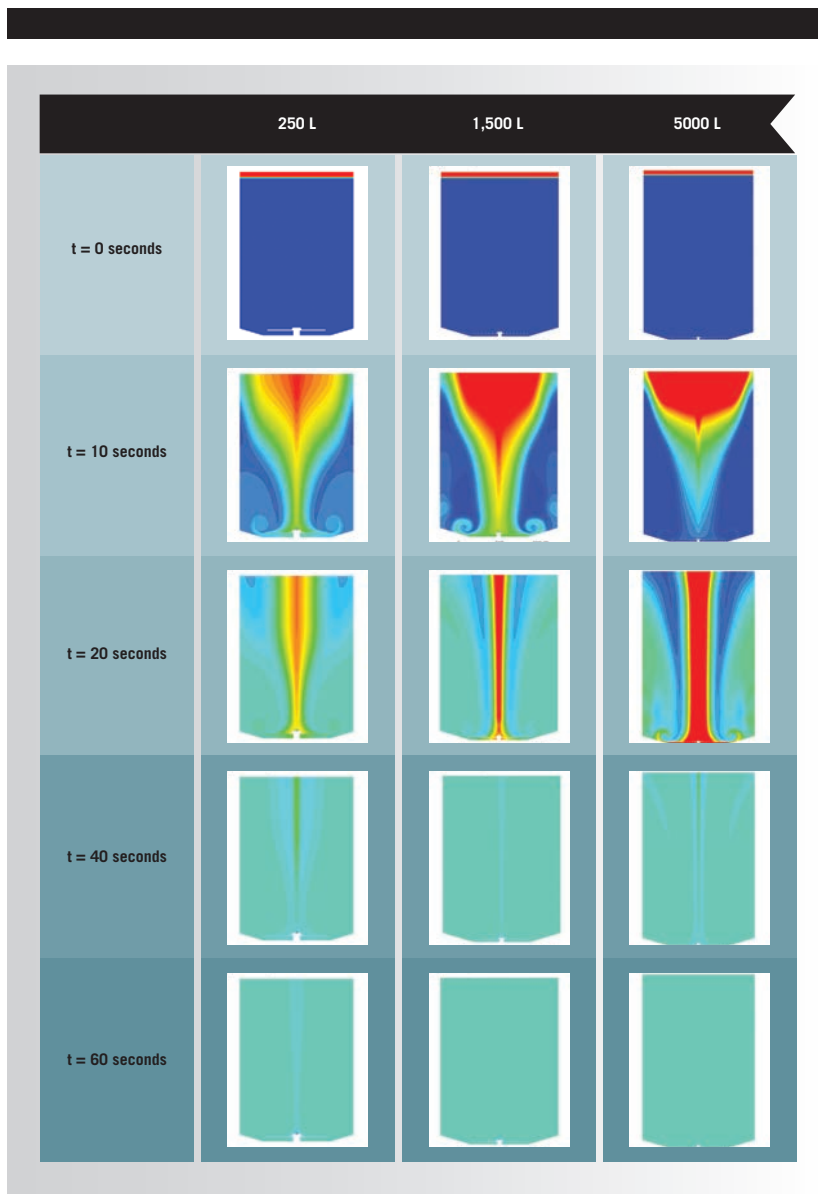


▲ BSA particle mixing patterns for different tank sizes