AMGEN, USA

MULTIPHYSICS MODELING IN THE BIOPHARMA INDUSTRY

At Amgen, a diverse portfolio of multiphysics simulation apps are used to streamline processes, enhance workflows, and ensure the safety and efficacy of drug products.

by ZACK CONRAD

To deal with multiple drug modalities, functions, and stages of commercialization, the diverse modeling and simulation tools in the biopharmaceutical industry need to provide considerable breadth with sufficient depth.

Amgen, a leading multinational biopharmaceutical company, uses multiphysics simulation as a tool in their arsenal at any point in their drug production processes to ensure drug efficacy and safety. Their various products have treated serious illnesses in millions of people around the world. But behind every product is a plethora of processes, and Amgen employs a diverse portfolio of process models to enhance their workflow. In an industry where process modeling is more prevalent than product modeling, a portfolio such as this is key. Pablo Rolandi, director of process development at Amgen, has overseen the use of the COMSOL Multiphysics® software as a platform modeling tool for his workforce. "COMSOL is a mature platform with modern design principles," Rolandi explains. "With a streamlined and easy-to-use interface and GUI and both single and multiphysics capabilities, we can create a great diversity of tools." As various problems in the development phase arise, Rolandi and his team turn to multiphysics modeling as a solution. In many cases, these solutions are also accompanied by the development of simulation apps, which can be created directly from the model via the Application Builder. By operating a specialized user interface, the end user can still benefit from the insights provided by simulation results, even if they are not experts in modeling. For the last year and a half, they have developed app packages that are streamlined, communicable, and easily deployed to serve corporate functions in process development, operations, and R&D.

⇨ ELIMINATING BOTTLENECKS IN PRODUCTION

The optimization of a drying process serves as a great first example where Rolandi's team developed a custom app to help solve a production workflow issue. This case centered on relocating the manufacturing process of a small molecule drug substance from a contract manufacturing organization (CMO) to Amgen's plant in Singapore. In the midst of this, drying operations, isolations performed by an agitated filter dryer (AFD) in a process similar to the one in Figure 1, were identified as potential bottlenecks in the production facility. Naturally, a bottleneck can pose a substantial risk to meeting product demand, so Rolandi and his team set out to model the drying operations and streamline the process. Because the CMO used a different type of dryer for the first three steps of the process, shown below in Figure 1, they lacked sufficient characterization data from these isolations to accurately model it and identify the impact of changing operating conditions.

Known properties of the system included material properties; geometric properties of the equipment; and operating conditions, including moisture

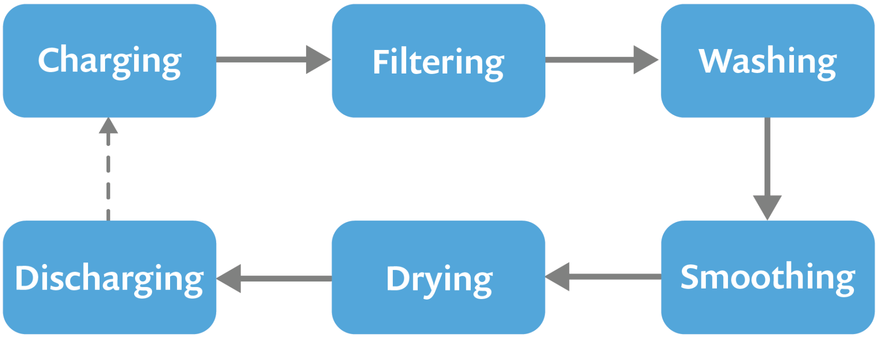

FIGURE 1. Basic steps in a typical batch filtration and drying process for the isolation, or physical separation, of a chemical substance.

content, temperature, pressure, and whether agitation is involved. Rolandi, however, still needed to determine two critical factors: the evaporation rate and the diffusion coefficients of the new AFD. To accomplish this, extensive data acquisition was performed and, using multiphysics simulation, they manually estimated the regressed parameters to characterize the model. Once this was completed, a simulation app that calculates drying times was created and deployed to process engineers changing production sites in the pivotal phase. This played a significant part in giving end users the opportunity to visualize the impact of altered operating conditions, as shown in Figure 2. It was ultimately discovered that the combination of agitation with a heating plate reduced the time to dry, thus helping mitigate the bottleneck and increase efficiency.

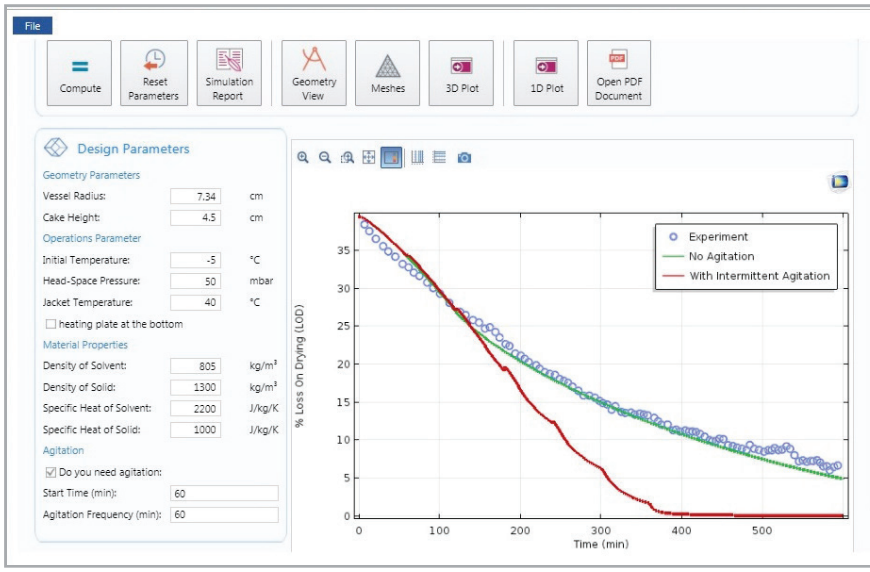

FIGURE 2. Simulation app that calculates drying times for models with no agitation (green) and intermittent agitation (red) and compares them with an experimental result.

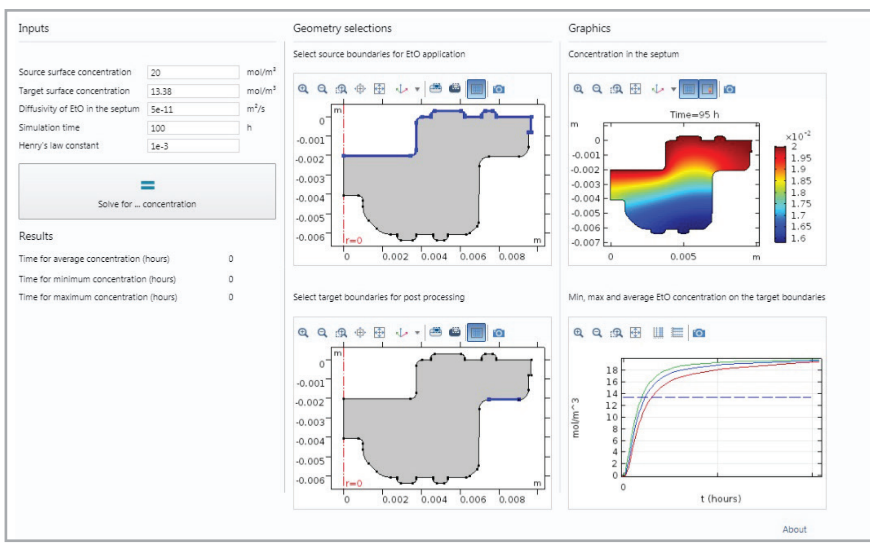

FIGURE 3. This sterilization process app calculates the concentration of ethylene oxide.

⇨ ENSURING STERILIZATION STANDARDS ARE MET

In another situation, one of Amgen's production teams encountered an issue with sterilization. Compounds from manufacturers are transported in primary containers. These are often vials, and must be sterilized to a certain standard to be classified as a novel container, as bacteria in drug products can pose tremendous health risks. However, the standard sterilization protocol, which involves the diffusion of ethylene oxide as the main transport mechanism, was not meeting the requirements for a novel container.

Naturally, the sterilization process needed to be tweaked, but rather than undertake undue experimentation and costly iterations of trial and error, Rolandi and his team took to simulation to model the ethylene oxide's diffusion through the vials.

The app featured options to select permeation and contamination boundaries, input solubility and diffusivity constants, and generate time-dependent concentration profiles of the ethylene oxide, (Figure 3). Process engineers could then use the apps to determine if concentration levels were high enough to warrant sufficient sterilization. As a result, experimentation was either reduced or avoided altogether and the program was accelerated by a number of months. "In the end, it was much more efficient to just create simulation apps," Rolandi said.

⇨ BEYOND SIMULATION

"I'm very keen on thinking beyond simulation about the development and integration of very advanced applications and techniques," says Rolandi. "I think there is a strategic challenge with that and we are just getting started." One of his goals is to incorporate uncertainty into their models. In practice, parameters are rarely exact and operating conditions are variable. Integrating these variations into their simulations can lead to more predictive results that can be better understood in context.

For example, Rolandi and his team are working on an autoinjector, a device that injects medicine into a patient without a physician having to administer it. A critical aspect of injections is the time of delivery; this needs to be controlled very precisely in order for the administered drug to perform as intended. The issue is that the delivery time depends on a number of factors, all with varying degrees of uncertainty, including the container geometry, the viscosity and volume of the drug, the spring constants of the injector, and the friction constants of the plunger. If the uncertainty in these factors is not accounted for, a simulated time of delivery will have an unknown variance, thus giving no information on its potential to be precisely controlled. In process modeling, it is invaluable to create a probability distribution of the expected outcomes in order to better understand how the system will behave.

To gain a better grasp of how the uncertainty of these parameters propagates, Rolandi and his team used multiphysics simulation to run a global sensitivity analysis on the system and rigorously quantify the effect of factor variability. The analysis determines a sensitivity index for each parameter, which is a fractional attribution of the variance in response to that parameter. What they found was that the viscosity of the product, the spring constants, and the needle geometry accounted for 90% of the variance in injection time, allowing them to greatly simplify their model. Because only a few parameters have significant impacts on the injection time, it is much easier for them to manage uncertainty and risk through robust specifications to component providers.

Similar to their other solutions, the injection time model was packaged into a user-friendly and easily deployed simulation app. The app, shown in Figure 4, features user-defined input distributions, runs an uncertainty and sensitivity analysis, writes an automated report, and displays model documentation. The app has delivered cost savings and speed gains and fostered more effective management of uncertainty throughout the entire process.

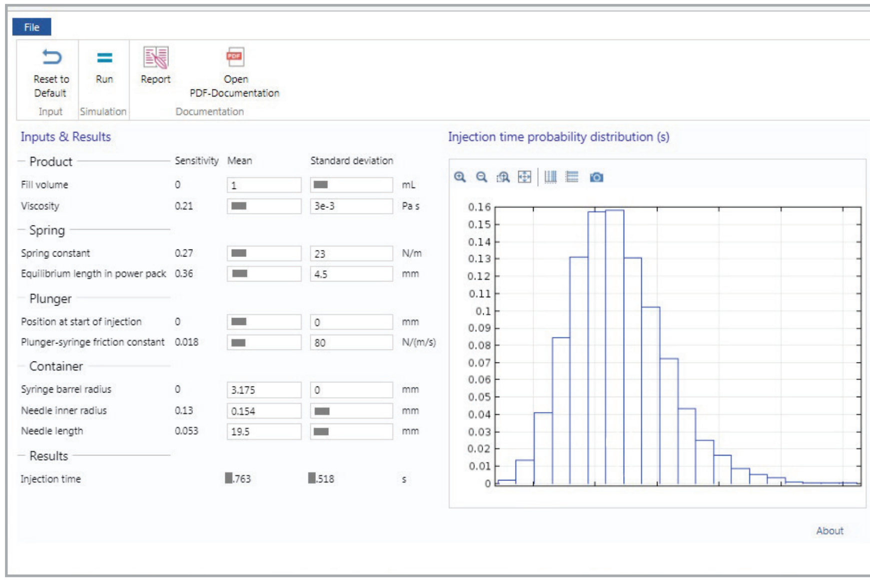

FIGURE 4. Autoinjector model simulation app that shows an injection time probability distribution. Proprietary data have been hidden.

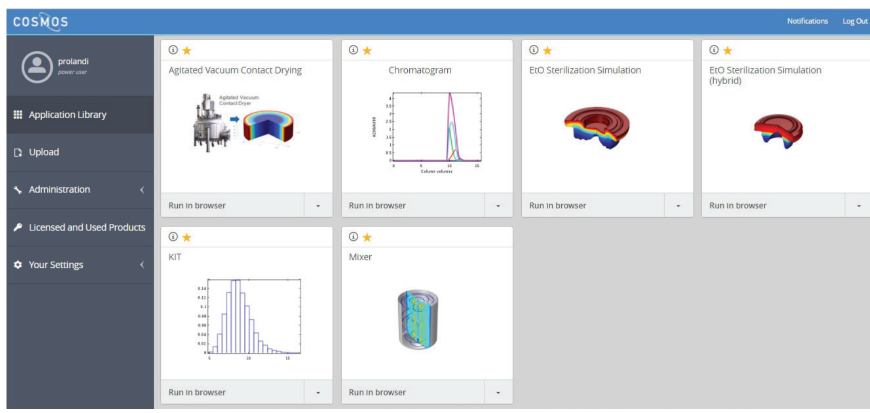

FIGURE 5. Amgen has personally branded their COMSOL Server library, naming the system COSMOS.

➪ APP DEPLOYMENT

Amgen also takes advantage of a local installation of the COMSOL Server™ product to increase accessibility for their employees. "We have an array of applications that we really want to deploy to everybody at Amgen," Rolandi says. "At the moment, there are about a dozen applications and those are being used today across the organization in a way that I am quite proud of, and COMSOL enabled us to do that." With COMSOL Server, app deployment is trivial and lifecycles can more effectively be managed. Users can simply log in via a web browser to access the application library developed by Rolandi's team. They also have plans to increase the sophistication within their system by moving away from manual entry and thinking of COMSOL models as "compute kernels." These can be repurposed with the help of advanced algorithms in a number of high-impact model-based studies, which would mark a major step in implementing enterprise-level modeling that delivers true business value to a large user base and many stakeholders. ❖

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