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Do Modeling and Simulation Tools Really Benefit the Biosimilar Industry?

MILI PATHAK, PRASHANT POKHRIYAL, RONAK PATEL, AND LAXMI ADHIKARY

ABSTRACT

The concept of end-to-end adoption of modeling and simulation tools for biopharmaceuticals process development is still seen with mixed views across industry professionals. The lack of standard analytics frameworks leads to suboptimal output and limits their widespread applicability. Additionally, the business impact of these tools are poorly understood because of the dearth of case studies on them. In this article, the authors present a business case study to investigate the returns from these tools. The authors also extrapolate the benefits to the overall drug development timelines and portfolio for the biosimilars industry.

A typical biosimilar process development consists of a production bioreactor producing the metabolites (upstream process development [UPD]) and subsequent purification steps consisting of chromatography and filtration steps, followed by fill/finish. FDA's guidance document, *Process Validation: General Principles and Practices* (1) and the *International Council for Harmonisation* guidelines on pharmaceutical development (2) recommend the stages of process validation and specify activities required for each stage in the product lifecycle. The product lifecycle has been classified into three stages, in which stage 1 defines process design; stage 2 defines process qualification; and stage 3 defines continued process verification. In these defined lifecycle approaches, stage 1 delivers the identification of interactions between process parameters (PPs) and critical quality attributes (CQA) as well as the definition of a control strategy that aims to ensure high product quality. Stage 2 demonstrates the validity of the chosen design (from stage 1) and the capability to produce consistent product quality from a commercial-scale process. Stage 3 takes care of continuous monitoring of defined critical quality attributes and parameters (defined at stage 1 and qualified at stage 2) to which operators should be alerted in case of un-

pected deviations from the state of control. A set of process performance parameters is required to ensure that the process is working as anticipated to deliver product quality attributes as expected.

Thus, based on different stages, the total cost for a biosimilar development has been estimated to be between \$100 million and \$300 million (3–6). The cost of clinical studies is expected to form a large portion (at least 75%) of the overall biosimilar development cost (3,5). The remaining portion can be attributed to activities such as product development, regulatory submission fees, and manufacturing multiple batches of biosimilar products as part of the development. The authors of this study considered that 75% of the overall product development cost goes toward clinical development, translating to a clinical development cost between \$75 million and \$225 million. The remaining 25% was considered to go towards product development, which accounts for approximately \$25 million–\$75 million.

Biosimilar development and commercialization timelines are estimated to be 7–10 years based on published articles (4,7). Excluding approximately one year of the regulatory review period, biosimilar product development can be estimated to be around

Mili Pathak*, PhD, mpathak38@gmail.com, is principal scientist, Process Science, R&D; Prashant Pokhriyal is associate scientist, Process Science, R&D; Ronak Patel is principal scientist, R&D; and Laxmi Adhikary, PhD, is senior vice-president, R&D; all at Intas Pharmaceuticals (Biopharma Division), Ahmedabad, Gujarat, India.

*To whom all correspondence should be addressed.

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six to nine years. The authors considered the following timelines for biosimilar development in line with the previous estimate (7): three years for product development (developing target product profile, upstream development, downstream development, formulation development, stability testing, and analytical and functional characterization); one year for Phase I clinical study to establish a comparative pharmacokinetic study; three years for Phase III clinical study (comparative safety, efficacy, and immunogenicity study); and one year for regulatory review of marketing authorization application or biological license application.

Biosimilar product development covers various activities including, but not limited to, developing the target product profile, upstream development, downstream development, formulation development, stability testing, and analytical and functional characterization. The key activities include parameter screening (early stage development), parameter optimization and process characterization, scale-up and scale-down, and process validation. Several modeling algorithms and tools are available for both upstream and downstream processing (DSP) for biologics development. Though modeling and simulation (M&S) tools have been readily adopted by many industries worldwide, the bio/pharmaceuticals industry is a late adopter of these technologies. The workflows in the bio/pharmaceutical industry are still dependent on empirical data, and lesser emphasis is placed on generating output by implementing M&S tools.

Drug discovery is given a greater emphasis in the drug development process than process development, translating to greater industrial innovation in the former. This emphasis stagnates the progress of biosimilar development organizations, which have process development as their core competency. In a cut-throat competitive biosimilars market, the timeline for biosimilar develop-

ment is of utmost importance, because it directly correlates with the organization's profitability. It is estimated that even a minor reduction of three months (i.e., one quarter) in the drug approval timeline can increase the net present value (NPV) of that drug (8). Modeling and simulation tools can provide the leverage needed to reduce timelines and costs as well as improve robustness and regulatory compliance (9).

Despite the perceived benefits of M&S, the quantification of these tools has been notoriously difficult, which makes organizations reluctant to use them. The conventional design-of-experiments (DoE) concept is effective for process development activities and could also be used in conjunction with other modeling techniques. For DSP, mechanistic modeling based on physiochemical phenomenon is well developed, and several tools are available for the same. However, a similar corollary cannot be drawn for upstream processing (USP), because pure-mechanistic modeling principles are too complex to be adopted by the industry. The alternative route is to apply more robust and convenient data-driven or hybrid models in USP and DSP.

This article attempts to provide a clearer picture on this aspect from the process development point of view. In this article, the authors present a case study in which prior knowledge and experience are used to estimate the amount of experiments (cost and time) required for the process development stage, using two scenarios: a traditional approach and an approach employing M&S tools for activities such as parameter screening, parameter optimization, and process characterization.

CASE STUDY: TRADITIONAL VS. M&S APPROACH

The cost contributions of DSP in biosimilar process development can be up to 80% of the total process development cost (10). Out of this, chromatography steps amount to approximately 60% of total downstream cost (11). With such

high stakes, it was imperative that a M&S approach be demonstrated in this case study on a chromatographic unit operation for a biosimilar molecule.

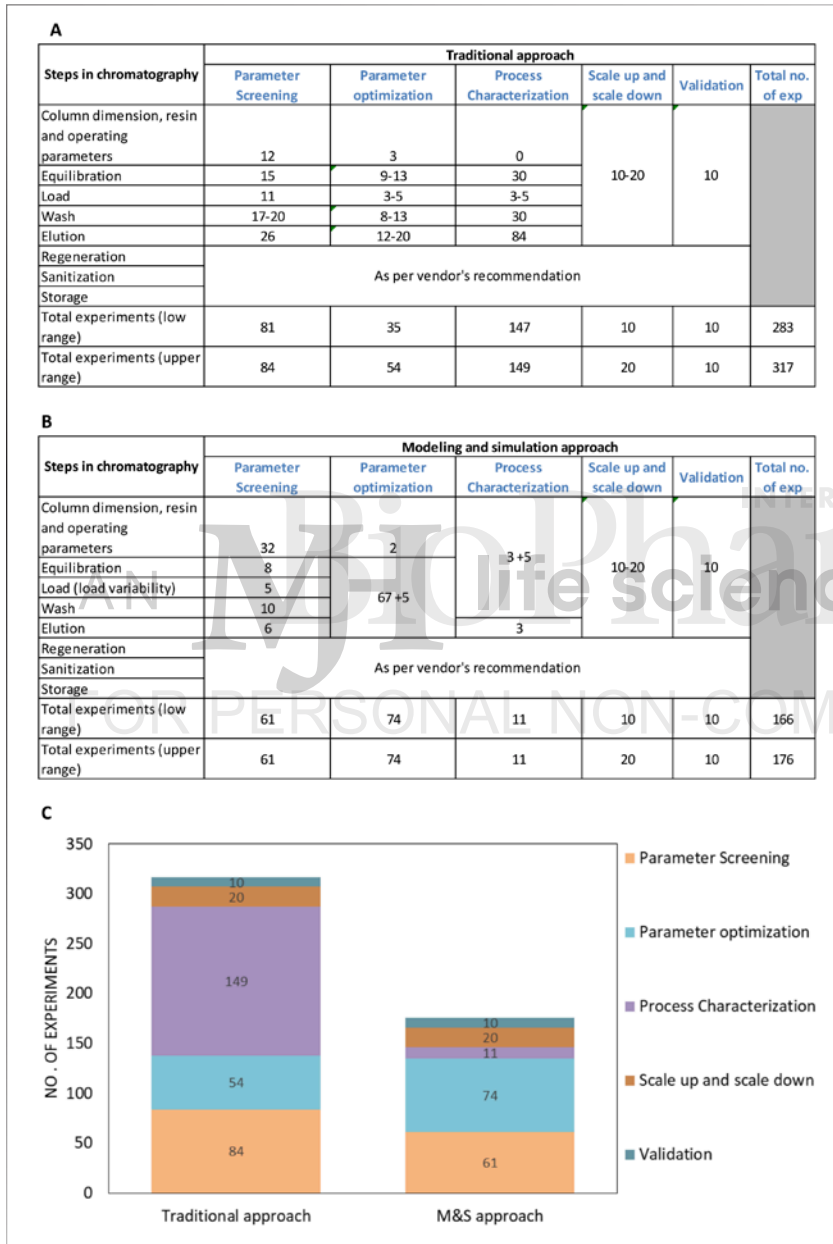
Figures 1A and **1B** list the steps in chromatography unit operations for which different parameters are studied. For example, column dimensions and operating conditions will have parameters such as bed height, bed diameter, packing flow rate, column pressure, type of resin, asymmetry, and height equivalent to a theoretical plate (HETP) range. Similarly, other steps such as equilibration, loading, wash, and elution will have parameters including buffer composition, buffer conductivity, buffer pH, load details, elution column volume (CV), elution gradient type, and peak collection criterion. Though the authors have exemplified the technical details specifically for chromatography, the overall approach can be extrapolated for the development of any biosimilar unit operation.

Traditional approach

The experiments are generally performed empirically and through the one-factor-at-a-time (OFAT) approach. The focus is on getting optimal conditions based on previous knowledge of resins and molecules, which leads to experiments that are more focused around center points and significantly reduced design space. This approach might quickly provide initial optimization results, but it is more cumbersome during the process characterization and process validation steps. For example, during initial screening experiments, 10 different resins are assumed to be screened at a single condition, resulting in 10 experiments. The condition could be based on theoretical knowledge, or it could be based on a platform process that has already been applied for a different molecule.

The resins are selected based on bind and elute and/or separation properties. Similarly, for determining bed height, a standard practice is

Figure 1. Estimation of number of experiments for chromatography steps during parameter screening, parameter optimization, process characterization, scale up and scale down, and process validation using (A) traditional approaches and (B) modeling and simulation (M&S) approach. (C) Comparison for traditional and M&S approach with respect to number of experiments required at every stage (i.e., parameter screening, parameter optimization, process characterization, scale up and scale down, and process validation).



to use a bed height of approximately 15 cm, which makes for a good starting point. An experiment could still be performed even if the standard height is not able to give a good resolution, or the experiment could be

conducted based on a vendor's recommendation for a pressure limit. In the bind and elute mode, a lower bed height (approximately 10 cm) may be preferred to achieve maximum productivity. In a similar way, other

experiments can be designed for various parameters in the initial parameter screening stage (see **Figure 1A**).

Based on the range studies performed during parameter screening, further experimentation is required in a relatively narrower range during the parameter optimization step. Additionally, five to 10 experiments can be done based on scale-up principles, including pilot-scale and at-scale experiments. Because the factors were not methodically evaluated, extensive factorial studies must necessarily be conducted during the process characterization step. A screening design followed by full-factorial or fractional factorial DoE incorporating different process parameters is studied to define the operating range, process acceptance range, and characterized range. A separate OFAT experiment can also be done to evaluate parameter edges.

After completion of the entire process characterization study, independent effects, interaction effects, critical process parameter (CPP), key process parameter (KPP), and non-critical process parameter or non-key process parameter (NCPP/NKPP) are determined and validated. A minimum of five experiments in R&D and five experiments in manufacturing is a probable-case scenario for validation step.

M&S approach

Alternatively, process development can proceed with an M&S approach integrated from the beginning. The focus here is to gain process knowledge to widen the design space as much as possible and to optimize the process along the way. **Figure 1B** presents the list of experiments required with a M&S approach, which is explained with a few examples.

In case of parameter screening, resin screening can be performed by integrating the test with a mechanistic model. If, for example, 10 resins are evaluated, then a total of 30 experi-

ments are required to evaluate binding and elution coefficients across three different pH conditions. The model will also help to build correlations for binding and elution coefficients for the target product and both process- and product-related impurities. Furthermore, the optimizer function of the model can give a good range for pH and conductivity, which are to be used during further studies.

Similarly, for process residence time, the mechanistic model generated during resin screening will be useful in deriving the association (binding) and dissociation (elution) constants. Thus, two breakthrough experiments, the first at maximum loading capacity and the second derived from using the previously constructed mechanistic model, are sufficient at this stage. The mechanistic model will subsequently be updated with new data obtained at every step of experimentation and will thus provide a deeper insight. The experimentations for other process parameters at each step are also determined with a M&S approach during initial screening.

Because all the parameters are well understood during the initial screening experiments, a combination of DoE experiments could be applied during the parameter-optimizing stage. Because the model is already developed during the parameter-screening step, the parameters are already screened down to lower levels while doing DoE. The newly generated experimental data can then be further merged with the previously built mechanistic model to get both the mechanism- and data-driven relation of CPP and KPP to CQA and productivity. Moreover, as the model is already calibrated up to the optimization step, the predictions from the model can be used to experimentally check the two best- and worst-case scenarios during the process characterization stage.

Few OFAT experiments could be carried out to nail the operational

range (OR), process acceptance range (PAR), and characterized range (CR), and, additionally, five to 10 experiments each for scale-up and scale-down. A total of five experiment runs in R&D and five experiment runs at-scale is a probable case scenario for the validation step.

The mechanistic model is updated at each step using the new data for better parameter estimation and robustness. A multivariate model can be built in parallel, which would evolve and incorporate potential CPPs along the process development lifecycle. The mechanistic/multivariate model can be combined with the empirical/machine learning model to form a hybrid model. This hybrid model should be more robust for different feeds, impurities, and experimental conditions and could be extrapolated for new molecules. A chemometrics model (e.g., partial least squares, ordinary least squares) can be used for scale-up/scale-down and validation. Load variability of chromatography input should be covered before scale-up/scale-down for both traditional and data analytics approaches.

As defined in previous sections and depicted in **Figure 1C**, the M&S approach can reduce the experimentation by around 30% to 60%. Even with more experimentation during the parameter screening and optimization step, a well formulated M&S approach covers most of the design space, is more robust, and has better predictive power.

OVERALL IMPACT OF DATA ANALYTICS

Taking an estimate of approximately 30–60% reduction in total experiments in process development through the application of M&S tools, the total process development cost of a biosimilar is expected to be around \$10 million–\$52.5 million, which is a savings of about \$15 million–\$37.5 million for one product (**Figure 2**). Assuming a similar reduction in the

product development timelines, the modified timelines would be 2.8 to 4.9 years for one product (**Figure 2**).

Based on published estimates (8), this saving of two to six calendar quarters in time-to-market can increase the NPV of a drug from about 8% to more than 26%, depending on the market uptake, which can generate additional revenues for the organization. Early market entry will also enable organizations to capture the markets faster than competitors. These types of analyses can be easily combined with existing models for more accurate R&D cost estimations.

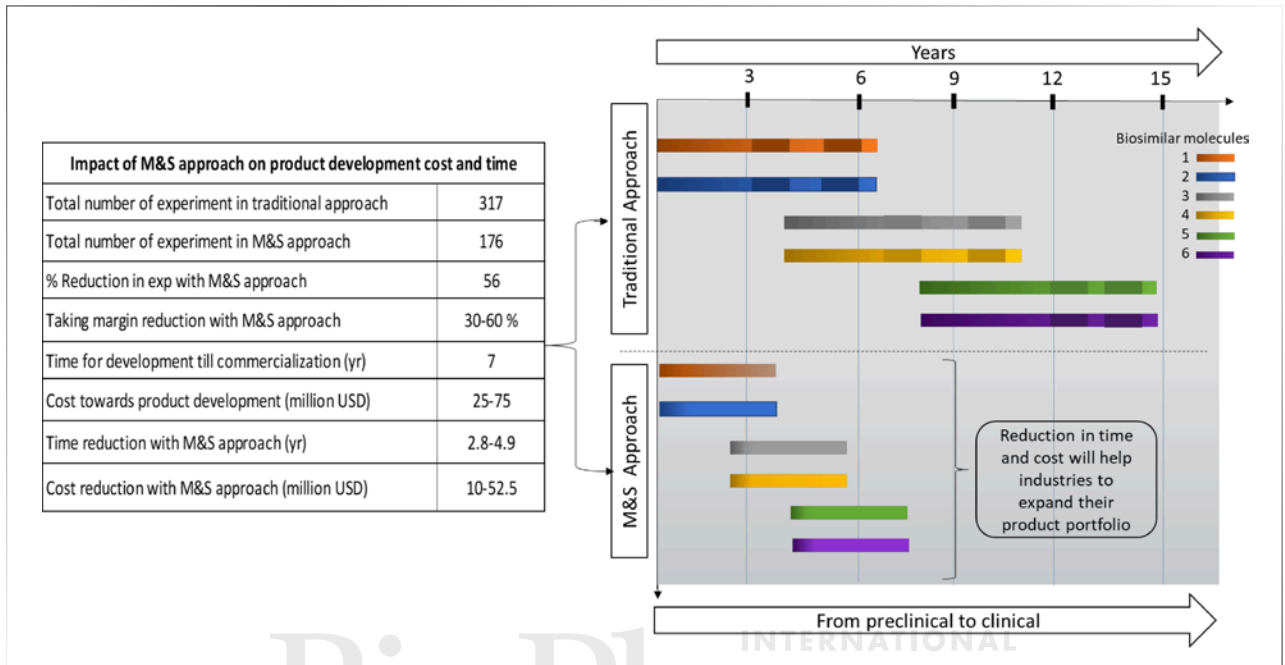
PORTFOLIO OPTIMIZATION WITH M&S

Biosimilar companies tend to simultaneously have multiple molecules in their pipeline, each at different stages of development. As outlined in the previous sections, the application of M&S reduces the development lifecycle, which gives scope for the organizations to accommodate new molecules in their pipeline. In this section, a case study will illustrate how M&S improves the business capabilities of an organization and its impact on short- and long-term goals.

The base case considers an organization with two molecules in the process development pipeline simultaneously. At the end of seven years, these molecules enter the regulatory filing and review stage. After four years, the molecules enter the clinical stages, and the organization is again ready to take up two new biosimilar molecules and start with early stage development. Thus, with this model of workflow, at the end of 16 years, the organization will have six biosimilar molecules ready for market.

Assuming similar human resources and cost of goods are available at the disposal, in the modified scenario with M&S, the development time takes between 2.8–4.9 years (as discussed in the previous section) for a single mol-

Figure 2. Impact of modeling and simulation approach on total process development cost and time in comparison to traditional approach. M&S is modeling and simulation.



ecule. In this scenario, the organization can launch the same number of molecules (six biosimilars) in around eight to nine years, thereby reducing the timelines by nearly half. For ease of understanding, the same calculations are being presented in **Figure 2**, where it is shown that the total time for a single biosimilar molecule is considered to be four years, excluding one year of regulatory filing time. In some cases, organizations might not prefer handling these many molecules in the clinical trials simultaneously. These situations can be resolved by the increased involvement of contract research organizations.

CONCLUSION

The impact of M&S tools goes beyond cost and timelines. The number of molecules in the pipeline are expected to increase by 12% (12). An organization with any kind of biosimilar commercial model can benefit from these tools. However, such efforts require a cultural shift and wholehearted support from employees (13).

The biosimilar industry as a whole would significantly benefit from M&S integration because this would lead to better process robustness, control, and understanding, thereby creating a product with improved quality and bringing a new product a step closer to patients safety and efficacy. The M&S integration with processes would also increase productivity and reduce costs and timelines, translating to quicker patient access to therapies. This will ensure that patients in developing economies, which are dependent on therapies from biosimilar companies, get better healthcare facilities.

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