WHITE PAPER

Leveraging Machine Learning to Accelerate Drug Development

How CDMOs can apply machine learning to help get innovative treatments to patients quicker

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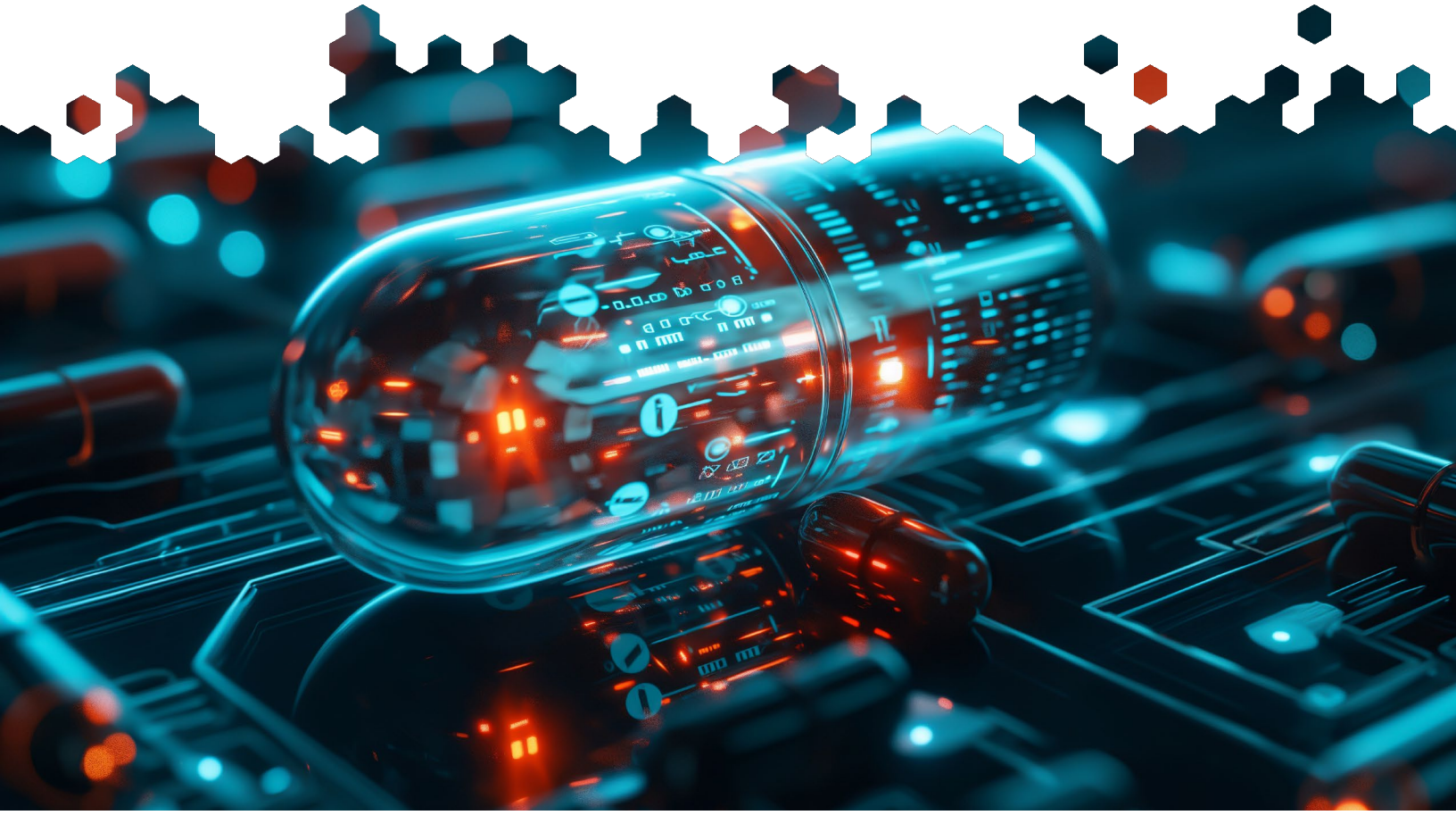

Contents

Executive summary

Contract Development and Manufacturing Organizations (CDMOs) that implement machine learning can expedite the lengthy drug development process, ultimately helping to bring novel treatments to patients more quickly. Discover the ways one U.S.-based CDMO used machine learning to optimize a multi-step process for a drug candidate and enhance analytical method development. With the potential to revolutionize drug development, machine learning can help pharmaceutical companies increase accuracy, reduce costs, speed time to market, improve product yield, and more.

The high stakes of drug development

According to Pharmaceutical Research and Manufacturers Association (PhRMA),[1] bringing a new drug to market takes on average 10 to 15 years – which significantly delays getting new treatments to patients. That translates to over a decade of waiting for those suffering from illness, potentially delaying relief and impacting their quality of life. For healthcare providers, it means years before they can offer innovative treatments. Only then can pharmaceutical companies begin to see a return on investment. This lengthy process fuels considerable frustration for everyone involved.

Imagine the following scenario: A pharma company has completed patient enrollment for an upcoming clinical trial – a process that, in and of itself, was quite time consuming. The supply of drug substance or active pharmaceutical ingredient (API) has been delayed – and the drug has yet to be formulated. So, the pressure to produce these drugs in a timely manner escalates.

Indeed, timelines are tight because there are so many variables in the overall drug development process. “At every point within the spectrum of pharmaceutical development, there is a lot of pressure to meet those timelines…and that does raise the blood pressure a little bit for everyone,” said Robert Hughes, Research Fellow, W.R. Grace & Co.

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Enter cost into the equation and the aggravation has the potential to multiply exponentially. According to a report from consulting firm Deloitte, the average cost of developing a new drug among the top 20 global bio-pharma companies is approximately $2.2 billion.[2] With these numbers added to the mix, the need to streamline the process and reduce overall costs is blindingly clear.

Pharmaceutical companies are looking to adopt a variety of strategies to compress these timelines, especially as pressures mount on the industry to more quickly develop and provide advanced therapies to patients awaiting treatment.

The role of Contract Development and Manufacturing Organizations in drug substance development

Many small to large pharma companies, for instance, rely on Contract Development and Manufacturing Organizations (CDMOs) to carry out phases of the drug development process, and to bring much needed efficiency into the mix. CDMOs specialize in providing services to help pharmaceutical companies develop and manufacture their drugs.

As such, CDMOs can play an important role in assisting pharmaceutical companies with complex API production processes, from early development to commercial manufacturing. Their expertise enables pharma companies to focus on research and marketing while outsourcing complex drug substance manufacturing processes.

More specifically, CDMOs often focus on:

- **Process development**, which includes optimizing the drug substance production process to ensure consistency, scalability and cost-effectiveness. This includes identifying the best methods for scaling from small laboratory batches to larger commercial productions.

- **Analytical development**, which focuses on developing and validating methods that can accurately and reliably measure the properties of the pharmaceutical compound or product.

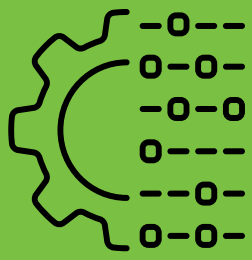
Both of these processes are used throughout the development journey, from early-stage drug development through commercialization. Addressing such processes can, indeed, be especially resource-intensive for CDMO or pharma staff members. For example, "when looking at peak separation in a gas chromatography (GC) or high-performance liquid chromatography (HPLC) chromatogram, it can take a Ph.D. analytical chemist months to overcome various problems, and sometimes the solution is still not 100% to their liking," Hughes said.

"Indeed, such processes are often cumbersome to carry out before the scientist will get to a point where they will say 'yes, this will probably work.' However, when transferring the analytical method to Quality Control (QC), system suitability[3] is a requirement when the method is run and the less-than-ideal separation puts this at risk of failing. So, overall, it can be very complicated and challenging for even the most advanced scientists," Hughes noted.

The end result: Typically, weeks – and in some cases, months – elapse before arriving at an optimal solution. "It always comes back to time. Pharma companies and CDMOs want to solve these problems as quickly as possible. They need to get the process into the plant as soon as possible so they can manufacture an API that will support ongoing clinical trials," Hughes added.

Unfortunately, the standard approach to process and analytical development can be inefficient and time-consuming. This approach typically unfolds via one of two modes of operation. Scientists can run experiments where they change the variables one at a time to determine if there is any impact on Critical Quality Attributes[4], for example, impurity levels. Another option for scientists is to change more than one variable by taking a statistical approach under an experimental design.

"There is Design of Experiment software that enables us to do this, but it can be a very complex process. Scientists could be looking at running more than 50 reactions depending on the number of variables that are included in the study. Considering these reactions are frequently run at lab scale, that equates to



Machine learning, however, has emerged as a technology that can help and ultimately move drug and biotechnology development into a new realm, far beyond what can be done with traditional human modes.

time — the more variables included in the study translates into more experiments needed to be run. So, this is not always the best solution when time is of the essence," Hughes commented.

The benefits of machine learning

Improving these processes, unfortunately, is not an easy task. Machine learning, however, has emerged as a technology that can help and ultimately move drug and biotechnology development into a new realm, far beyond what can be done with traditional human modes.

Perhaps most importantly, machine learning can quickly assess large data sets and analyze trends. “So, if there are at least 10 experimental data points, or 10 reactions, it's possible to build an effective machine learning model. This model will excel at looking at every possible interaction you can imagine, and it looks for trends that affect the output," Hughes said.

As a result, scientists can leverage the machine learning tool to produce desired results in a much more efficient manner. For example, imagine that a scientist is working with a compound that has a 2% impurity and wants to reduce the rate to < 1%. “The scientists can enter that requirement as an objective into the machine learning platform. As additional rounds of sequential learning are generated and new data is entered into the platform, the algorithm will look for the trends relative to inputs that minimize the formation of that impurity.

"So it's possible to design a machine learning model specifically to focus on impurities and that could be incredibly efficient," Hughes continued. "We have demonstrated that machine learning can cut down the amount of time it takes to get to a satisfactory outcome from months to weeks."

Machine learning algorithms can be employed to analyze complex datasets generated during the process development phase of drug development. By identifying patterns and correlations that may not be evident through traditional human methods, machine learning can optimize parameters such as yield, purity and scalability. This artificial intelligence-empowered approach accelerates the identification of optimal process conditions, reduces the need for extensive experimental trials and enhances overall efficiency and cost-effectiveness. Furthermore, by predicting potential issues in early stages, machine learning aids in minimizing risks associated with process and analytical development.

Realizing improvements in process and analytical development

Grace, a U.S.-based CDMO, recently leveraged machine learning to study a multi-step process for a drug candidate that was at the clinical stage. The initial objectives of the initiative were focused on optimizing reaction conversion, maximizing isolated yield and minimizing impurities.

Grace scientists started with data from 36 experiments, each examining the impact of a single variable, that were conducted during the initial phase of the laboratory development program. This dataset was used to create a machine learning model from which a series of experimental conditions were recommended. These experiments were executed and after two rounds of machine learning sequential learning (10 experiments), improvements were observed in all of the experimental focus areas. Furthermore, optimal improvements were realized after a third round of sequential learning which involved just three additional experiments.

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The machine learning led to a variety of specific improvements such as:

- Yield improvement from 88-92% to 92-95%
- Key impurity reduced by 20%
- Key raw material charges reduced by 7%, an unexpected, but welcome improvement beyond the original study objectives
- Potential annual savings of up to $2 million at 10 metric ton scale

Machine learning can also bring much-needed advantages to analytical method development. More specifically, these tools can be leveraged to refine techniques, such as gas chromatography. By processing large volumes of analytical data, machine learning algorithms facilitate the rapid optimization of method parameters such as peak resolution and detection limits. This enhances the precision and reliability of analytical methods, ensuring robust performance across different sample matrices. Moreover, machine learning-driven insights support the development of novel analytical techniques that can adapt to evolving regulatory requirements and industry standards.

Deploying machine learning to save time and enhance results

The following case illustrates the advantages that machine learning offers over traditional analysis: Grace recently used machine learning to make improvements to analytical GC method development. The initial challenge was to separate positional isomers on an aromatic ring for a regulatory starting material (RSM). When an experienced Ph.D. chemist conducted this initial analysis through traditional techniques, a method with a resolution between the critical peak pair of 1.7 was achieved. The chemist worked on this initiative for approximately six weeks.

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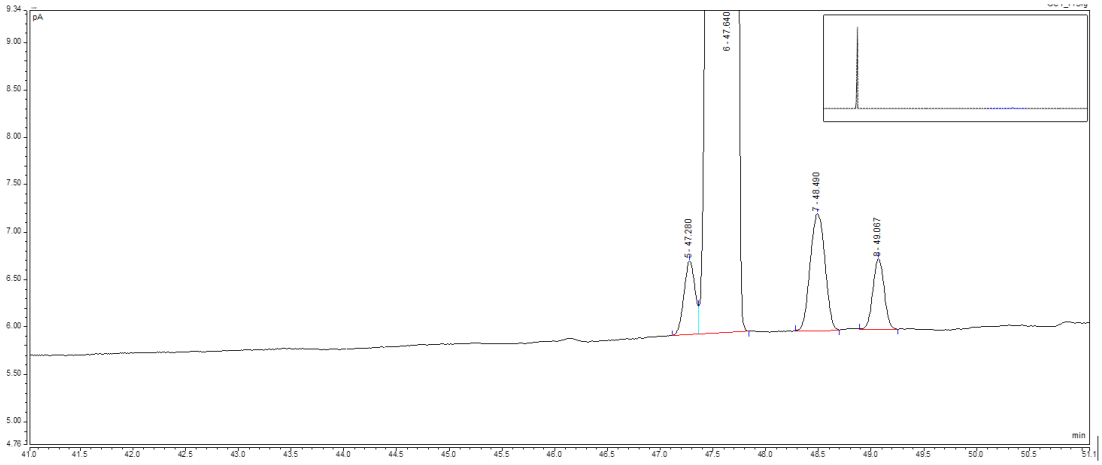
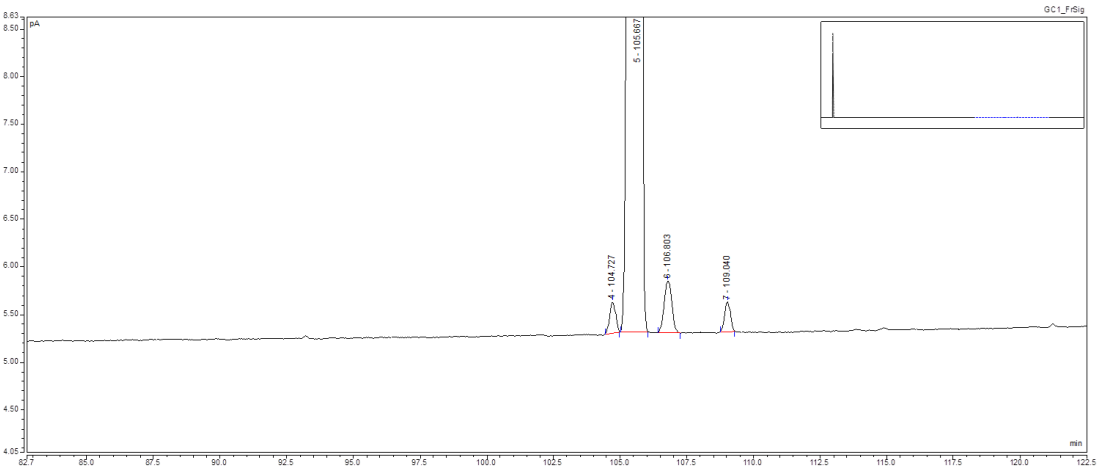
When machine learning was deployed, however, the results were significantly improved. Three sequences of iterative machine learning resulted in an improvement in peak resolution of 2.2. What's more, this optimization procedure took less than a week. A comparable regulatory starting material method development in the past has taken as long as six months. This new method has since been successfully validated and transferred to Quality Control (QC) for the RSM that is used in a product currently at the process validation stage, and system suitability has routinely passed.

Initial GC chromatogram (resolution 1.7):



Final GC chromatogram (resolution 2.2):



Pushing the machine learning needle forward

With all of these capabilities, machine learning holds significant potential for pharma companies and CDMOs. The technology, however, could do even more as it continues to mature. To demonstrate its potential, Grace, along with its parent company Standard Industries, sponsored "The $1 Million Standard Industries Chemical Innovation Challenge," an ambitious initiative aimed at transforming small molecule synthesis through the integration of artificial intelligence/machine learning based tools.

The primary goal was to stimulate research in creating retrosynthesis tools imbued with chemical intuition. Retrosynthetic analysis is a problem-solving technique chemists use to plan how to make complex molecules. Instead of starting with available materials and figuring out how to build the target, it works backward from the desired molecule, mentally 'disconnecting' bonds to more simplified building blocks. This process identifies potential starting materials and reactions that could be used to build the target molecule step-by-step. Chemists consider efficiency, cost and safety when designing a synthetic route, and often leverage known chemical reactions to predict new ways to create complex structures. It also involves leveraging reported chemical reactions and reactivity patterns to predict altogether new transformations and chemically reasonable disconnects that have yet to be experimentally validated.

Indeed, the challenge ultimately aims to create a retrosynthetic tool that can propose novel chemistry and is able to display chemical intuition for the development of synthetic routes to complex organic molecules. If successful, this solution would be transformative for organic chemists, resulting in access to novel chemical spaces, more efficient syntheses, enhanced scalability and enhanced sustainability through the reduction in the

use of expensive or toxic reagents. More importantly, it could serve to construct a more effective tool for what has been largely an empirical endeavor for over two centuries.

Entering a world of new capabilities with machine learning

These case studies illustrate just how powerful machine learning can be in the drug development process – we've only just begun to scratch the surface of possibilities. While machine learning can never replace the domain knowledge and critical expertise of a Ph.D. chemist, it serves as a complementary tool that chemists can use to speed up development. With continuous refinement and expert scientists driving the models, CDMOs and pharma companies applying machine learning could see marked improvements over traditional methods. "This is particularly noteworthy as there's been no significant change to timelines in the 30-some years that I've been involved in drug development," Hughes noted. Indeed, machine learning can help:

- Increase the accuracy and reproducibility of pharmaceutical analyses, ultimately supporting better decision-making in drug development and quality assurance processes
- Reduce costs by improving yield and cycle time and reducing raw material charges
- Speed time to market by reducing timelines for process and analytical development
- Improve product quality by introducing better impurity control
- Reduce risk of delays in quality control
- Better process knowledge results in fewer failures during commercial scale up
- Enhance regulatory compliance

"Machine learning is a very powerful tool that enables us to get the solution to a chemical problem or reaction that doesn't work as desired more quickly. In the next five to ten years, I hope to see a reduction in the time it takes to get a new medicine to market, and I believe that the application of artificial intelligence and machine learning in all areas of drug development represents our best hope for shortening the average to under 10 years," Hughes stated.

He concluded: "We've seen how machine learning can significantly reduce the time it takes to realize a scalable manufacturing process. While artificial intelligence is unlikely

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to reduce the lengthy clinical trial and regulatory review phase in the near term – and as tools improve and become more integrated into all stages of drug development – the cumulative impact could become more significant over time. We have only scratched the surface when it comes to artificial intelligence and machine learning applications in the drug development and manufacturing process."

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1. PhRMA. Research and Development Policy Framework. https://phrma.org/policy-issues/research-development

2. Deloitte. Drug development cost pharma $2.2B per asset in 2024 as GLP-1s drive financial return: Deloitte. https://www.fiercebiotech.com/biotech/drug-development-cost-pharma-22b-asset-2024-plus-how-glp-1s-impact-roi-deloitte

3. According to the USP, system suitability tests are an integral part of chromatographic methods. These tests are used to verify that the resolution and reproducibility of a chromatographic system are adequate for the analysis to be performed. System suitability tests are based upon the concept that the equipment, electronics, analytical operations, and samples constitute an integral system that can be evaluated as a whole. General Chapter <621> "Chromatography," in United States Pharmacopeoia (United States Pharmacopeial Convention, Rockville, MD, 2022).

4. As defined by the International Council for Harmonisation (ICH) guidelines, a Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product.