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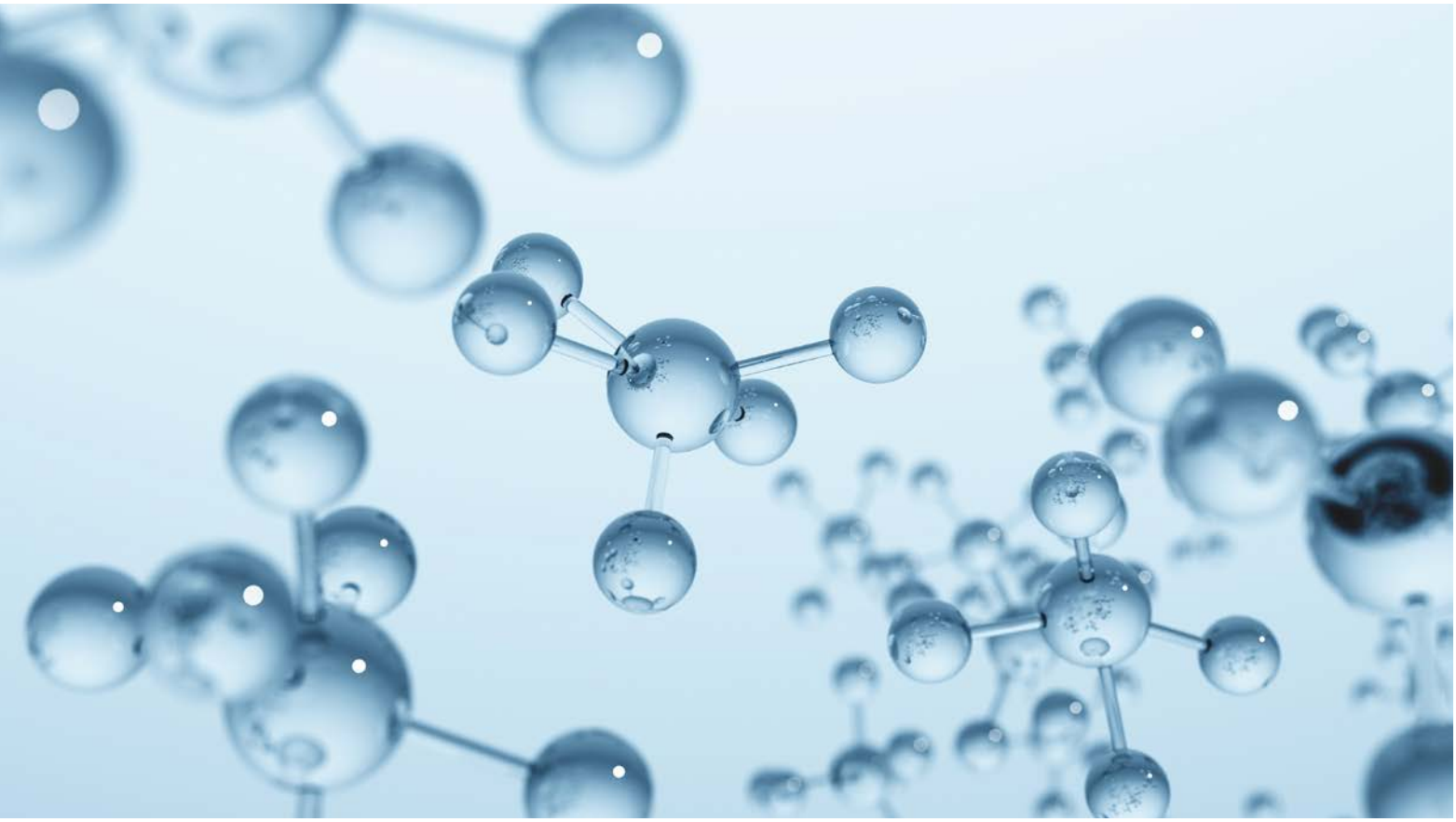

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COLLABORATION & COMMUNICATION

WHITEPAPER

Accelerate complex molecule development by optimizing chemical synthesis and formulation

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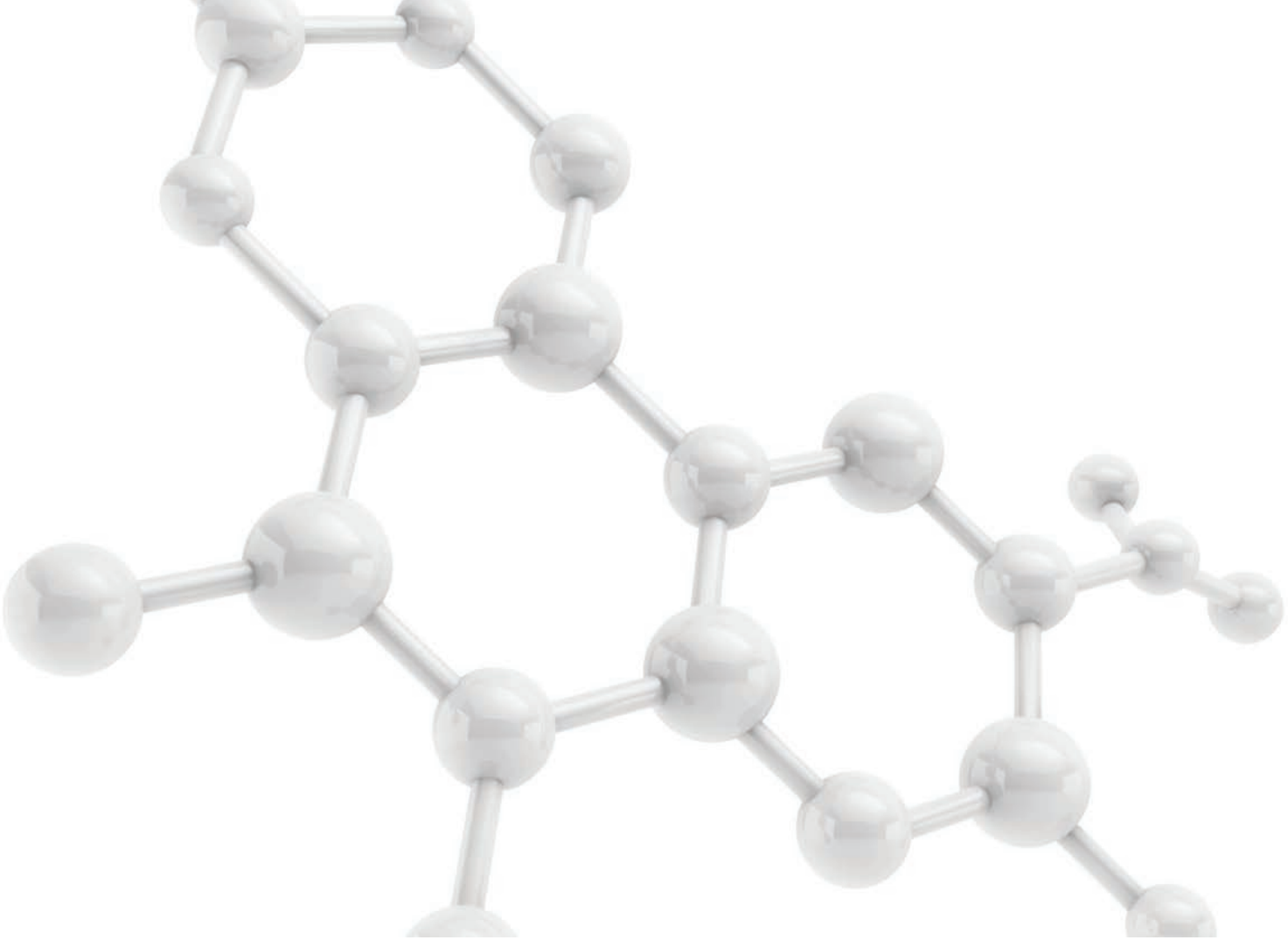

Abstract

Innovations in science and technology over the last few decades enable scientists to create far more advanced pharmaceuticals for today's industry.

As a result, patients rightfully expect medication with fewer side effects and physicians anticipate new and better cures for formerly untreatable diseases. These expectations require new pharmaceuticals to offer an advantage over existing therapies, one that sponsor companies must be able to prove in clinical trials. However, they also increase the difficulties of drug development, due to the added complexity of the active pharmaceutical ingredient (API) and the delivery system needed for these drugs.

Introduction

Finding a balance between a complex API, its formulation, and its synthesis requires equipment, knowledge, and processes more extensive than those typically required for traditional drug development. It also calls for collaboration across several teams in order to break down the silos that can interrupt the flow of open and clear communication.

Therefore, while the complexity of these molecules begins with their chemistry, any company entering this space is likely to discover the challenges extend well beyond that. Not understanding and preparing for them early in development could result in bottlenecks that significantly slow production and delay a drug's time to market.

Chemistry and beyond: Defining the complexity of today's pharmaceuticals

Chemistry

Once a compound shows efficacy, scientists must come up with an acceptable synthesis route. This is especially challenging with today's pharmaceuticals due to the complex chemical structure of new APIs. Their synthesis includes more chemical steps and potentially unstable intermediates, hazardous reagents, and/or demanding reaction conditions. Initially, the focus of a small innovator company pursuing one of these molecules is to establish a lead structure in an organism that delivers a certain pharmaceutical effect. They ask questions like: Is the lead structure correctly absorbed and distributed in an organism? How is the metabolism working? How is the excretion working?

As they start optimizing leads, they come up with a drug candidate with certain structural features and a substitution pattern that achieves the desired effect. Up until then, though, all efforts went into figuring out how to show efficacy. The chemists have probably synthesized only minute amounts of the material (i.e., milligrams), likely using elaborate methods to do so.

Little consideration has been put into formulation and scale-up, where some of the greatest challenges and costs exist. Because clinical results from material produced by an earlier route cannot be seamlessly applied to material resulting from a large-scale route, the result is a redesign of the chemical syntheses late in the process. This ultimately slows down the supply of quantities required for the clinical trials.

While the complexity of these molecules begins with their chemistry, any company entering this space is likely to discover the challenges extend well beyond that.

Drug substance properties

Because today's drug substances are complex, they may have demanding physical properties that may be hard to control. Physical characteristics, such as solubility and rate of dissolution, have to be determined very early, and they have to be determined under various circumstances. Regulatory authorities will also look to you to show that you are in control of the desired chemical and physical quality attributes of the product as received by the patient. Furthermore, the properties of these new APIs create new risks in handling procedures, as many have "high potency."

This means they are active in very small doses, so people manufacturing them have to be protected to avoid any contact with the drug substance. A potential lack of stability (i.e., durability) causes the APIs to easily degrade when in contact with certain environmental conditions, such as moisture and heat. Therefore, special care must be taken when processing them during formulation.

Once a compound shows efficacy, you should complete route scouting to ensure the synthesis is scalable across all phases of the project.

This is why, once a compound shows efficacy, you should complete route scouting to ensure the synthesis is scalable across all phases of the project. This can be challenging, as the foundation for an efficient, scalable, and reliable process is laid at a time when it is uncertain whether the drug will ever see the date of launch. Considerations such as sustainability of the drug should also be made at this stage. This includes an analysis of how efficiently the raw materials are used and whether they are environmentally acceptable (e.g., avoid halogenated solvents, if possible). From the profitability end of sustainability, you must also make sure the product is fit for the future. In other words, how can it remain competitive after patent expiry and how can it be made to meet healthcare cost targets? While API costs during clinical trials are extremely high, they are typically not a focus since the volumes produced are very small. Once the product is launched, though, the originator company will have to ask a hefty price for the drug product in order to pay for any failed developments. The price drops significantly, though, when the drug becomes a generic and continues to drop until it becomes a commodity, at which point the price is reduced even more. By analyzing its sustainability early, you can establish a process that allows your company to stay in business for the lifetime of the drug.

Drug product formulation needs

New APIs require specific knowledge during formulation that can be used to identify and prevent adverse reactions that may shorten the shelf life of a pharmaceutical later. A new API may not withstand the conditions as applied in a conventional formulation process, and its proper action in a patient may require specific drug delivery systems that drive an API to its intended location, such as a targeted tissue or tumor. By the end of Phase II, the synthesis and formulation route must be locked and API costs have to be substantially reduced, as this will be the process used to launch the material. All data your scientists create in Phases 0-II should not change during development; otherwise, you could enter a situation where certain studies have to be repeated. For example, changes in polymorph may cause changes in solubility and thus pharmacokinetics, which may force repetitions of studies. One way to manage the complexities of these molecules is to have multiple and different disciplines involved in development to ensure the most critical factors are taken into consideration from the beginning.

Collaboration and communication: The keys to long-term success

There are many different types of expertise involved in drug development, and these teams of experts often work in silos. Additionally, many small companies that discover a new therapeutic concept are not familiar with regulatory filings, due to their limited experience with a new active substance. The missteps that can occur by trying to take their discovery from concept to commercial supply can be avoided by combining drug substance services and pharmaceutical development. By working together, a formulation team and the chemists can collaborate and exchange knowledge to develop a formulation that allows a safe supply of material during clinical trials. Timelines can only be met if a company employs state-of-the-art techniques of API manufacturing, analytics, and formulation (e.g., continuous flow synthesis or large-scale chromatographic separation techniques).

This requires teams working in parallel with many different disciplines contributing their expertise. Many new drug developers ask for a “fast track” approval process as their APIs may respond to an urgent pharmaceutical need (e.g., a cure against multidrug-resistant bacteria found in hospitals).

A new pharmaceutical may fail at any time during clinical trials. Therefore, the developers of new medicines, many of which are small enterprises, are reluctant to spend a lot of time and money while the fate of their clinical candidate is still uncertain.

Nonetheless, formulation problems of currently developed products are arising with greater frequency, and the complexity could jeopardize your development timeline. Your team must learn as much as possible about an API and new drug product early, regardless of the high chance of failure in the initial stages of drug development.

Deficiencies in the new drug, such as unexpected side effects or insufficient stability, may become visible fairly late in development. The drug candidate either then fails or costly rework or repetition of clinical trials is required.

Time is especially precious at this stage as every single week, even day, that a newly launched drug is under patent protection allows the originator to ask a much higher price (to pay for development cost, including candidate failures) than after the drug becomes generic.

If a company does not seek outside expertise to help develop its complex molecule, it should look to resources such as International Council for Harmonisation (ICH) guidelines to recognize and prepare for the related challenges.

There are also industry whitepapers by regulatory authorities describing and proposing ways to handle certain obstacles. Webinars and conferences that include parties sharing their experience handling these issues should also be considered.

However, if a company decides to partner with a CDMO for drug development, look for one that has state-of-the-art infrastructure to perform both drug substance and drug product manufacturing as well as the competencies needed to meet these challenges. This type of expertise and experience provides the capabilities needed to recognize potential showstoppers early in development and offer novel ideas to overcome them.

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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Dr. Stolle serves as General Manager for Linz site and leads a global team responsible for process development, project management and small-scale manufacturing for clinical supply of small molecule APIs. Dr. Stolle is responsible for the global API research and development strategy as well as innovation in API synthesis and manufacturing with the objective to expand Thermo Fisher's ability to continuously meet the unique technical challenges posed by new drugs and the needs of clients. Dr. Stolle joined Thermo Fisher in 2015 and has more than 20 years of experience in pharmaceutical research and development. Before joining Thermo Fisher, held various leadership roles for companies such as Bayer AG, Saltigo GmbH, and Lanxess Deutschland GmbH. Dr. Stolle received both his BS and his PhD in Organic Chemistry from the University of Hamburg in Germany.

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Dr. Poechlauer joined Thermo Fisher Scientific in 1990 and possesses more than thirty-five years of experience in biocatalysis and oxidation chemistry. He is an expert in the application of innovative technologies, such as process intensification and microreactor flow chemistry, to small molecule API process development. A frequent presenter at industry conferences, Dr. Poechlauer has authored forty-seven patent applications, sixty publications and several book chapters. He received his doctorate in Natural Sciences in organic chemistry & pharmaceutical chemistry from Innsbruck University in Austria.

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