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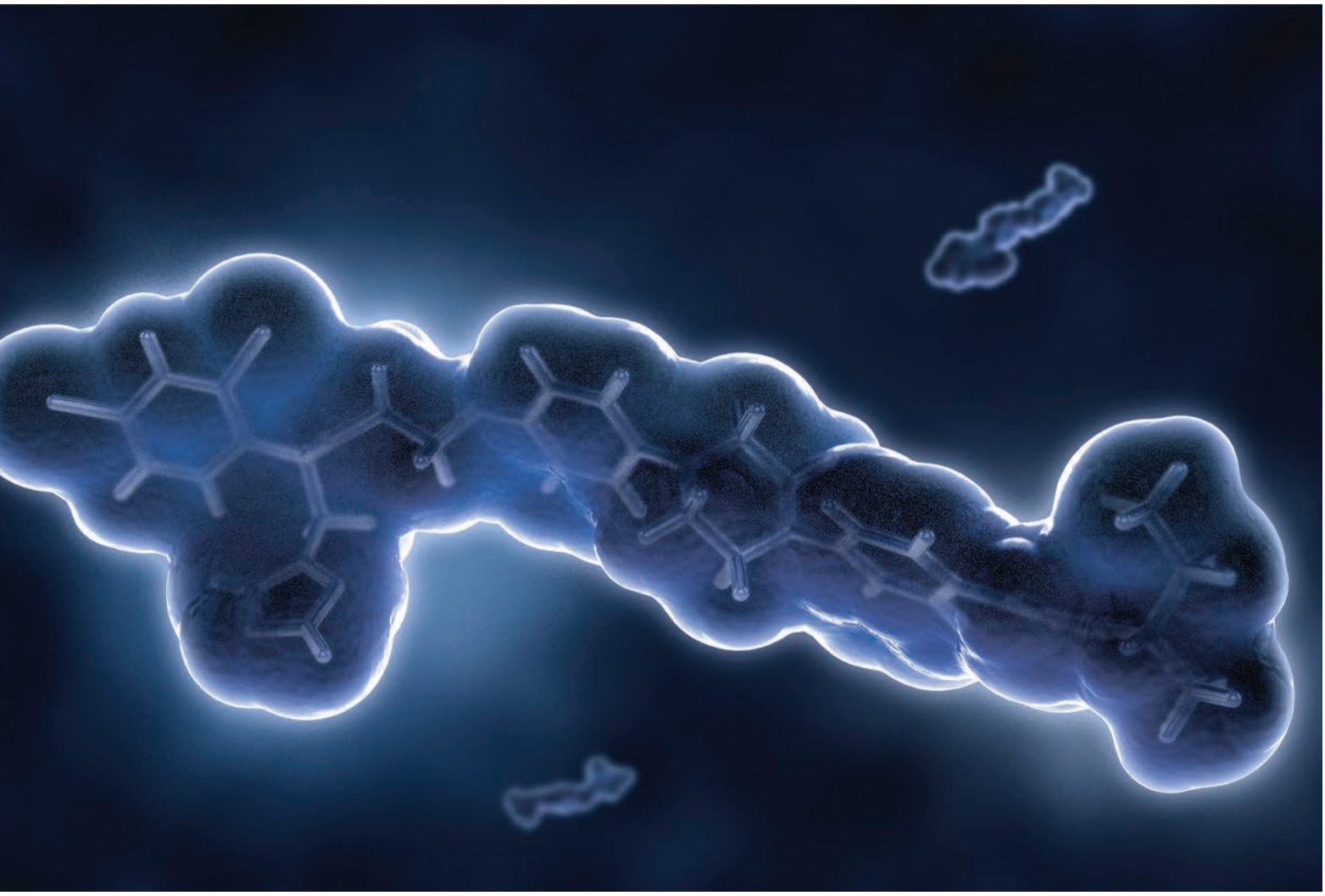

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WHITEPAPER

Synthesizing success: Six principles for getting pharmaceutical development right from the start

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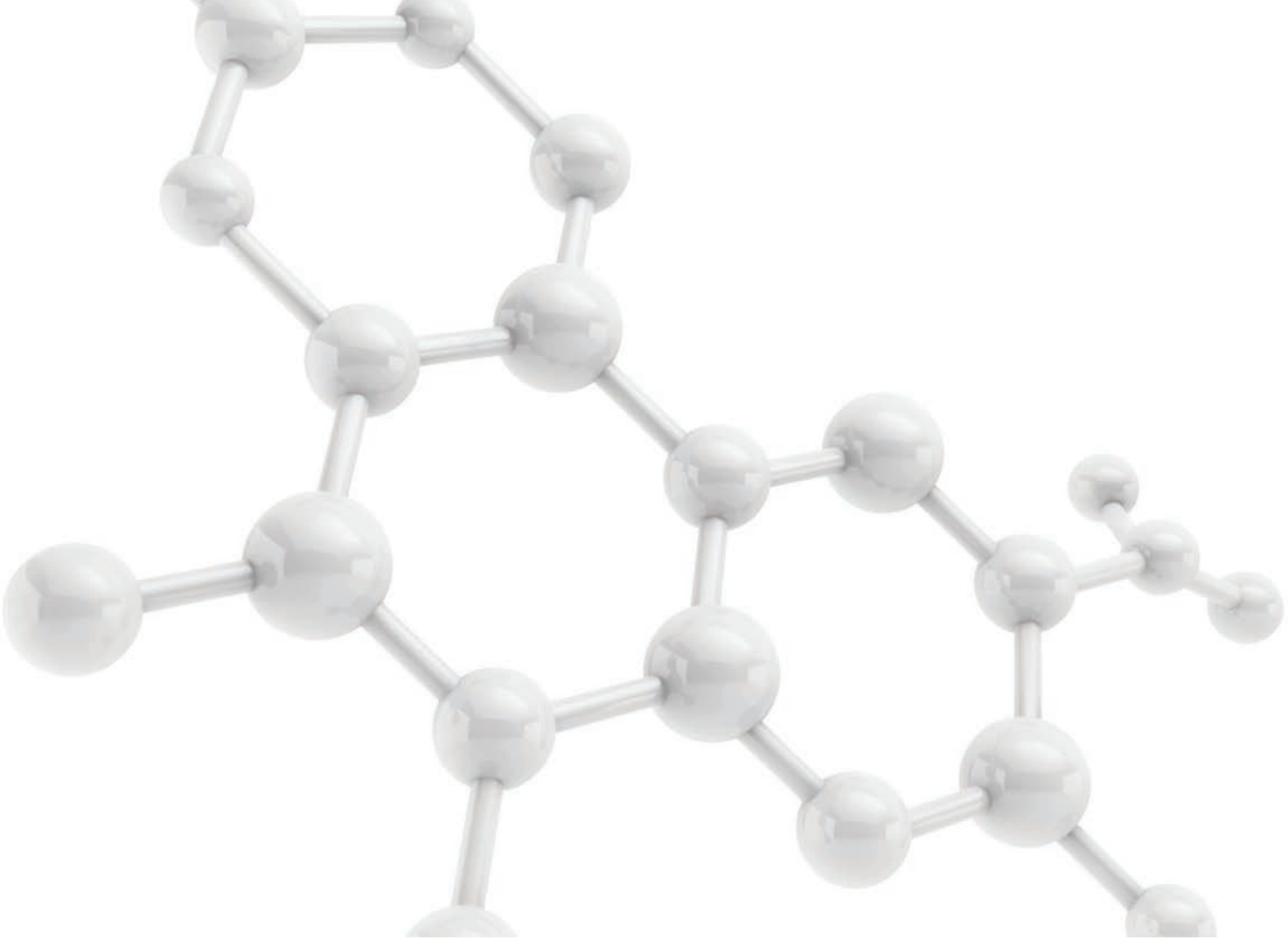

Abstract

Today's market demands speed, flexibility, and innovation to address today's new challenges. As a result, pharmaceutical and biotechnology companies face increasing pressure to bring blockbuster drugs to market quickly and cost-effectively. Selecting the right partner is critical to bringing a drug to market—on time, and on budget. Outsourcing eliminates the need to maintain expensive in-house facilities while providing access to a broad range of different technologies and expertise.

This whitepaper outlines the vital six-point criteria that pharmaceutical and biotechnology companies should follow when looking to select the ideal partner to synthesize an their API and ensure their drug development process stays on the path to success.

Introduction

The pharmaceutical industry must constantly evolve as companies race to develop the next blockbuster drug. As they face pressure to bring new drugs to market more quickly and at minimal cost, pharmaceutical and biotechnology companies are increasingly outsourcing various parts of the drug development and manufacturing process, explains analyst Kate Kuhrt from Clarivate Analytics. Outsourcing eliminates the need to maintain expensive in-house facilities while providing access to a broad range of different technologies and expertise.

A Nice Insight survey published in January 2017 found that the synthesis of a drug's biologically active component—the active pharmaceutical ingredient, or API—is the most frequently outsourced part of drug manufacturing. A 2016 survey by the same agency found that 56% of pharmaceutical and biotechnology companies outsourced the synthesis of small-molecule APIs at the clinical scale, and about one third of the companies outsourced commercial small-molecule API production. The reverse trend is being reported for biological products, such as vaccines and cellular therapies, Kuhrt says. "In the area of biologics, we're seeing that outsourcing is decreasing due to the complexity and the promise of developing new intellectual properties." Nevertheless, a recent Transparency Market Research report predicted that the global API market would expand from $134.7 billion in 2015 to $219.6 billion by 2023.

Mirroring the acquisition and merger trend among their clients, there has been significant consolidation among contract manufacturing organizations (CMOs) and contract development and manufacturing organizations (CDMOs). Acquiring companies with specific expertise allows vendors to rapidly offer a broader range of services and manufacturing scales to potential clients. This integration can be advantageous for the pharmaceutical and biotechnology companies, too. "Some pharma companies have a preference to reduce the number of companies they work with," Kuhrt says. "One of the ways to contain costs is by working with fewer suppliers."

Patheon, for example, is a leading global CDMO working with approximately 400 pharmaceutical and biotechnology companies. Founded in 1974, it has undergone numerous mergers and acquisitions in its quest to offer a broader range of services to its clients. During the past five years alone, Patheon acquired Banner Pharmacaps, Gallus BioPharmaceuticals, Irix Pharmaceuticals, Agere Pharmaceuticals, and Roche Holding. It also merged with DSM Pharmaceutical Products.

These acquisitions and merger allowed Patheon to offer new or expanded manufacturing services in areas such as soft-gel capsules, difficult-to-manufacture small-molecule APIs, and solid-state chemistry. In August 2017, Thermo Fisher Scientific acquired Patheon. Adding Patheon's CDMO capabilities to existing clinical trial services and bioproduction technologies means Thermo Fisher now supports clients throughout the entire pharmaceutical and biotechnology life cycle.

In May 2017, at CPhI North America, the president of PharmSource Information Services, Jim Miller, told the audience that there are now approximately 25 CDMOs focused on supporting innovation and new drug developments and launches. Thermo Fisher, for example, helped clients earn 112 New Drug Application approvals between 2006 and 2016, the most of any CDMO. There are also more than 400 CDMOs and CMOs that work mostly with generics or late in a new product's life cycle, Miller said.

Even with all the acquisitions and mergers, a pharmaceutical or biotechnology company looking to outsource its API production still has a lot of choices. Kuhrt says the market has changed from one in which companies had a short-term focus, making fresh outsourcing decisions at each step in the process (preclinical, Phase I, and so on), to one in which companies plan for success by looking at the entire development cycle.

The growing desire to select one API partner to work with throughout the drug development process, and to potentially also synthesize commercial quantities, puts an increased importance on the selection process.

This white paper highlights six key points that pharmaceutical and biotechnology companies should keep in mind when looking to select the ideal partner to synthesize an API for them—and ensure their drug development process stays on the path to success.

1. Put quality first

The CDMO must have an outstanding track record of identifying and developing synthetic routes to consistently produce APIs to a high standard. Its process development chemists will need to be able to (re)assess, tweak, and potentially completely change the synthetic route the medicinal chemists used to initially synthesize the target compound. Medicinal chemists and process development chemists have different goals, explains Craig Dixon, Senior Business Manager at Thermo Fisher. “The primary goal of medicinal chemists is to make compounds,” he says. “They’re not necessarily focused on how they get to the compounds.” Process development chemists need to be able to consistently make APIs that meet strict quality and regulatory requirements both efficiently and safely.

An important point is the need to ensure that the CDMO is capable of developing and understanding a manufacturing process that consistently produces the same impurities at the same very low levels. “If your chemistry’s out of control, you’re going to see variations in the levels of known impurities, and unknown impurities might begin to appear at times too,” Dixon says.

It’s also important that the CDMO is able to think ahead and ask: Will the route being designed for the first small, preclinical study batch also perform well on a commercial scale?

Optimizing or changing a manufacturing route as batch size increases can lead to questions about the preclinical toxicology study results. “The impurities can change as the chemistry changes,” Dixon says. “There is a toxicology impact of changing the chemistry late in the game.” This can mean redoing early safety studies, which will cost time and money.

A late change will also affect any analytical chemistry techniques required to assess the drug’s quality. “Analytical methods can be very specific to certain impurities,” Dixon says. “New impurities resulting from a route change may not be detected by existing analytical methods.” It may be necessary to go back and redevelop, or revalidate, analytical methods. “Getting the route of synthesis right early on minimizes those headaches down the road,” he adds.

2. Toe the regulatory line

The CDMO must have a solid reputation for compliance with all necessary regulations in the countries where the drug is going to be tested and, eventually, sold. “We reach out to the FDA [U.S. Food & Drug Administration] to make sure the labs are on their list and that they’ve already been toured and approved,” explains Craig Lindsley, co-director at the Vanderbilt Center for Neuroscience Drug Discovery. The center used a broad host of vendors in developing an Alzheimer’s drug that entered Phase I clinical trials—without an industry partner—in July 2017. “I’m also a real big believer in getting references from clients labs have worked with in the past,” Lindsley says.

FDA regulatory hurdles have increased over the past few years, partly because improved analytical methods make impurities easier to spot at lower levels than before. The FDA now demands additional data, using these new techniques, and a deeper understanding of quality to demonstrate products are safe for patients. There has also been a crackdown on the quality of APIs imported from overseas. In 2008, a supplier in China tampered with an API used to make the anticoagulant drug heparin.

This adulteration was linked to 81 deaths in the U.S. There is a long list of API producers temporarily banned from importing into the U.S. listed on the FDA website.

A CDMO that applies the necessary regulatory discipline throughout the drug development process will smooth a drug's path to market, Dixon says. "Running into a regulatory issue can set companies back significantly, if not irreparably."

Over the past nine years, Thermo Fisher facilities have undergone approximately 250 FDA inspections; nearly one-fifth of these went so well that they resulted in no observations or warning letters.

It is also vital that a CDMO is able to recognize when intellectual property needs to be captured. It's a factor that James Bruno, president of consulting firm Chemical & Pharmaceutical Solutions, considers when he's looking for a CDMO for an innovator company. "We'll think highly of a company that'll come in and say, 'We've come up with a synthetic pathway which we should be able to patent,'" he says.

It is equally important that a CDMO does not infringe on other people's intellectual property, Dixon says. "A CDMO partner should be aware of the relevant patent landscape to ensure any route under development does not infringe on another company's patents." Bruno agrees: The launch of a drug will be delayed if it is discovered that a product or process used in its API manufacture infringes on another company's patent, he says.

3. Look for sustainability

The CDMO should embrace the growing global trend toward the sustainable and green manufacture of pharmaceuticals. When designing a synthetic route and manufacturing process, a CDMO should ensure it is not doing more chemistry than needs to be done and should plan for low energy consumption, limit the use of harmful solvents, and source supplies sustainably.

It should also dispose of by-products- hazardous or otherwise-safely and appropriately, without damaging the environment. Subscribing to the ethos of green manufacturing isn't just a case of wanting to be seen to be doing the right thing, Dixon says. The bottom line matters, too: A short, energy-efficient synthesis will be less costly than a longer, inefficient synthesis.

Pfizer has recently introduced environmental sustainability goals for both its internal drug manufacture and the CMOs and CDMOs it works with, explains Thomas Niemeyer, Pfizer's director of global external supply. "Sustainability is very important to us." Pfizer manages a pool of vendors that synthesize some APIs and regulatory starting material on its behalf. "The current work that we have ongoing regarding sustainability could potentially mean that some vendors drop out of our pool if they are not able to achieve certain sustainability targets," Niemeyer says.

4. Prioritize speed

Not only should the CDMO be able to do all the above, but it should also be able to do it quickly. Delays can occur for a number of reasons, Dixon explains. The CDMO may not have the required physical capacity or the required assets, meaning it has to run multiple batches to make the desired quantities. "Getting a partner that has the right technical horsepower as well as the right-size assets to run your chemistry quickly is very important for timeline," he says. With five API manufacturing sites spread across Europe and North America, Thermo Fisher has the capability to rapidly manufacture batches from just 1 kg to thousands of tons.

5. Avoid growing pains

A CDMO should also be able to grow with the drug as it advances through clinical trials to full-scale production. "You don't really want to go to somebody at the start who's not going to be able to handle this product for its whole life cycle," Bruno says. "It's a regulatory nightmare and you've got to transfer the technical process. Things go wrong when you're doing that."

When selecting a CDMO to make an API or regulatory starting material, Pfizer will always have one eye on the future, Niemeyer agrees. “We make sure that any vendor we select would be able to sustain and continue to manufacture at scale, consistently, as the product launches.” That said, the company does sometimes switch CDMOs during the development process. “In our experience very few vendors are truly one- stop shops. They’re very good at early-phase development, being very nimble and fast and really jumping into problem solving quickly, or they’re very good with late- stage development, where they’re really refining and optimizing the process and really getting it to a promotion state,” he says. Thermo Fisher has both capabilities under a single banner, with sites specializing in quick, early-phase development as well as sites that specialize in late-stage optimization.

6. Consider the ultimate bottom line

Cost should never be the key driver when picking a CDMO. The company should be able to achieve all the above goals at a reasonable cost that allows the final product to be produced with an adequate return on investment. But cheap is often cheap for a reason. Missed intellectual property capture means a loss of income, and delays caused by regulatory compliance issues or intellectual property infringements will reduce a drug’s potential income. “You’ve got a limited amount of patent exclusivity,” Bruno says.

It can also be expensive to keep changing CDMOs, Dixon says. “Many of our customers have transferred in from other CDMOs-usually because they have run into issues relating to capacity constraints or the regulatory experience required to advance their project along the clinical trial path,” he says. “Transferring a project from one CDMO to another costs time and money. They probably end up paying more than they would if they’d come to Thermo Fisher from the start.”

Conclusion

Small pharmaceutical and biotechnology organizations starting out on their drug development journey can find a large organization, such as Thermo Fisher, a little intimidating, Dixon says. But they shouldn’t. “We work with a variety of companies from one [person] and a molecule up to multinational pharma companies,” he says. Eighty percent of Thermo Fisher’s clients are emerging and midsize pharmaceutical or biotechnology companies.

More than 40 years of experience and innovation mean Thermo Fisher offers clients expertise and a range of facilities to produce even hard-to-manufacture APIs to a high quality. Its big picture approach ensures a scientifically sound foundation for commercial success. And its ethos of regulatory compliance will become ever more vital as the trend of increased governmental regulatory rigor continues. “Regulatory rigor is growing while timelines for development continue to shrink,” Dixon says. “Many of the new drug discoveries today are being done by the small biotechs, where stakeholders desire a return on investment sooner rather than later.” The risk associated with compressed development timelines is managed by working with a CDMO that has the expertise to get it right the first time and the assets to take projects the distance.

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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