



Small Molecule APIs: aligning drug strategy with partnering strategy

A review of the trends and market dynamics
driving outsourcing decisions

Getting drugs to market faster and more economically is prompting new drug product development strategies to support better business and patient outcomes. Development of critical drug substances, particularly novel small molecule active pharmaceutical ingredients (APIs), is now being turned over to outsourced partners who have become the integral, primary drivers of the product's overall development and go-to-market strategy.

To meet the incredible rise in global demand for drugs of all kinds, as well as leverage the opportunities presented by advancing pharmaceutical science, pharma's leaders have become fully invested in strategic outsourcing to bring their innovations to patients.

Demand for outsourced services of all kinds, including APIs, has risen on this tide. Currently there are hundreds of potential partners that drug owners can choose from to develop and manufacture small molecule APIs – which can make choosing the best partner all the more challenging.

In this white paper, we explore pharma's most significant drug development market trends and the importance of aligning overall drug development strategy with partnering strategy. We also review how increasing development of novel drugs are also impacting the industry's go-to-market efforts, driving new demand for expert small molecule API suppliers.

Lastly, we consider how small molecule API development projects can be executed by leveraging the experience of embedded contract development and manufacturing (CDMO) partners.

Pipelines filling with sophisticated novel APIs

Experiencing significant growth, the highly potent API (HPAPI) market is being driven by demand for compounds to treat cancer, organ rejection and conditions treated with hormone products. According to MarketWatch analysts, the HPAPI market is expected to exceed more than US \$28.0 Billion by 2024 at a compound annual growth rate (CAGR) of 8.5 percent in the given forecast period.¹

In terms of small molecule API development and manufacturing, there is also a trend towards green chemistry and API synthesis using bio routes. More specifically, there is a rise in manufacturing using fermentation to shortcut long synthetic routes.

FDA takes a novel approach, industry responds

Since about 2008, the pipeline has steadily filled with New Drug Applications (NDAs) followed by a flood of FDA approvals. In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) was enacted by Congress which accelerated the trend.²

The law created the Breakthrough Therapy (BT) designation to identify promising new drugs with the potential to demonstrate substantial improvement over existing therapies treating serious chronic and life-threatening disease states.

The BT designation provided an alternative regulatory pathway to allow the FDA to expedite and accelerate the approval process. With FDASIA came three other "fast-tracks" to approval: Accelerated Approval Pathway, Fast-Track Designation and Priority Review Designation.

The program is proving to be quite successful. In 2017, the FDA approved 46 novel drugs under FDASIA, either as new molecular entities (NMEs) under NDAs, or as new therapeutic biologics under Biologics License Applications (BLAs).³ Apparently that was just a prelude. In 2018, the FDA approved 59 novel drugs.⁴ Novel drug development is generating billions in investment because it offers a faster and (perhaps) a less risky path to market. Novel drugs are clearly dominating recent drug development pathways, and as noted, most recent approvals have been for highly potent novel drugs. Many have likely been developed with the help of small molecule API suppliers.

Novel drug projects are challenging developers and their strategic outsourcing partners like never before, compressing development timelines and increasing the pace of regulatory filings to secure key early development approvals and Scale-up and Post-Approval Change (SUPAC) validation.

For CDMOs, especially embedded ones, their internal experience successfully managing compliance in early development may never be a more valuable commodity than it is today. For CDMOs with the right capabilities and experience, the novel medicine trend will continue to generate hundreds of projects for years, if not decades to come.

Neurosteroids potential large and small

Strategic outsourcing has also become the business model for pharma to launch their mainstream Investigational New Drug (IND) strategies as well as executing their program's drug substance commercial manufacturing plans. As pharma's focus on new, underserved and existing patient groups continues to grow, so will the complexity and risk of manufacturing the sophisticated APIs for these therapies.⁵

For example, neurosteroids are now in development to treat a range of central nervous system (CNS) conditions including epilepsy and Alzheimer's. These bio-synthetic compounds are difficult to ferment, synthesize and scale successfully. Drugs in this category are demonstrating great therapeutic potential for fast-track status and standard IND filings.

For the foreseeable future though, complex small molecule products will make up a significant proportion of drugs in the pipeline destined for approval. While there is clear growth in biotech-based drugs, more than half (60 percent) of the therapeutics in the current R&D pipeline are small molecule.⁶

Here, drug substance partners need talented teams, great science and flexible facilities to commercially manufacture these compounds. Why? Because patient groups for neurosteroids can start small, but post-approval have the potential to grow tremendously and fast.

Branded and generic developers are also outsourcing APIs at a growing rate. Demand for general commercial scale API supply by outsourced partners is also rising. Sub-segmented into branded API manufacturing and generic API manufacturing, analyst firm Research and Markets notes that generic API manufacturing accounted for the largest revenue gains in 2018 and is expected to grow at mid-single-digit CAGR from 2018 to 2025.⁷

This growth, explains Research and Markets, will stem from patent expiries of branded drugs and the affordability of generic medicines. For now, the branded API segment is projected to grow at a CAGR of 4.0 percent from 2018 to 2025.

Outsourcing APIs showing no signs of abating

It's clear contract developers and manufacturers of small molecule APIs are now playing an even more fundamental role in contemporary drug development strategies.

Established pharmaceutical companies, for instance, have reduced their manufacturing footprints to match their R&D and capital plans, opting for strong collaborators with the experience and expertise to fulfil their drug strategies and complete their projects successfully.

According to Result Healthcare's *Pharma & Biotech 2017 – Review of Outsourced Manufacturing*, in light of burgeoning demand for APIs, CDMOs face the real challenge of capturing more value from drug product supply chains. "Overall, the level of outsourcing is 24.6 percent at present, and this is expected to grow," the report states. They predict outsourcing will rise to over 26 percent by 2021.⁸

Equally dependent on strategic outsourcing partners are small-to-midsize drug innovators pursuing their go-to-market plans via virtual company routes. According to the FDA, more than half of all the novel drugs approved in the last 10 years came from companies with fewer than 500 employees.⁸ Research and Markets forecasts that the overall pharmaceutical contract manufacturing market is growing rapidly, achieving revenues of \$96 billion by 2025 at a CAGR of about 5 percent.

Breaking it into two segments, API manufacturing and Drug Product manufacturing, Research and Markets analysts find the API manufacturing market held the largest share in 2018 and is expected to grow at a mid-single-digit CAGR from 2018 to 2025.

There is plenty of evidence that the trend to outsource API manufacture is growing at an accelerating pace. Coherent Market Insights projects that the global API market will exhibit a CAGR of 6.8 percent in the forecast period (2018 – 2026), causing it to surpass \$274.9 billion by 2026. That's a significant jump from current levels; for reference, Coherent Market Insights notes the API market in 2017 was valued at \$153.4 billion.⁹

Taking drugs to market is challenging. It takes deep, established resources and operational expertise to accomplish successfully. To ensure that success, pharma has compartmentalized its development risk and is putting it in the hands of the most capable outsourcing partners it can find. Depending on the compound and market plans, an embedded CDMO may offer an even better project risk profile.

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The ingredients for a successful outsourcing strategy

For the reasons outlined above, pharma's developers need strong, experienced CDMOs to produce APIs for their fast-track novel drugs, as well as their increasingly hard-to-make formulations for treating cancers, infections, CNS disorders, allergies and other chronic, debilitating conditions. But what are the ingredients needed to formulate a successful collaboration?

A drug's commercial development and speed to market hinge on creating effective working relationships with API outsourcing partners. Finding and selecting the best supplier to manage a small molecule API project and launch a drug's commercialization strategy from a position of strength has become mission number one for most contemporary drug sponsors.

Aligning drug substance outsourcing effectively with commercial drug product strategy requires concerted effort and a highly choreographed dialogue between all parties.

It is also important to assess and evaluate if potential partners have the necessary industrial expertise making specified APIs at scale to feed commercial supply requirements and demand targets.

Ingredient one: Partner commitment

Critical to assuring an API project's success is recognizing how potential suppliers demonstrate commitment to their customers. Regardless of what a drug's market agenda might be, it is likely plans call for long-term commitments.

Customer commitment can be measured by the time, money and resources contract partners consistently invest in their people and facilities. Partners focused squarely on operational excellence and the development of their people, set the foundations on which collaboration can be built upon.

Processing API, batch-after-batch, month-after-month, year-after-year, may introduce complacencies and issues related to creeping status-quo in processing. There's an old industry rule of thumb offering a cautionary tale: "The most expensive batch of API you will ever pay for is the one you can't use or sell."

If an API supplier is not continuously focused on process improvement, they may not be the strategic partner a successful API project requires.

Ingredient two: Flexibility and agility

A supplier's technical acumen, capacity and operational resources must be flexible enough to meet the many known and unknown challenges drug manufacturers face ramping up API manufacture. Experience equals strength here as well. How well an organization responds to challenges is closely related to the number of campaigns they've completed – embedded API suppliers offer this value proposition, by integrating the experience of the parent and employing that to the benefit of their contract partners.

Improving yield and delivering better quality in the face of uncertainties must be an element of a strategic API outsourcing relationship and must be addressed early. Many challenges begin only after agreements have been signed and projects begin in earnest. That's another reason partner selection has become such an important success factor fuelling pharma's most ambitious drug development plans.

Ingredient three: Regulatory expertise

Regulatory can be a minefield of risk. With many hard-to-make APIs, managing the Chemistry, Manufacturing and Control (CMC) portion of regulatory filings and submissions in an effective and timely fashion is yet another source of anxiety, especially in early API development. Increasingly drug developers' product plans are global. A more strategic partner will know the regulatory territory backwards and forwards around the world, and therefore will be better able to navigate customers' products successfully through the hurdles.

Drug development waypoints are intrinsically linked to meeting regulatory milestones. Key (CMC) studies, filings, applications and tech transfer documentation all have to be prepared accurately, comprehensively while maintaining flexibility.

In the paper "CMC Considerations when a Drug Development Project is Assigned Breakthrough Therapy

Status," Genentech's Earl S. Dye, et-al, explain that due to accelerated clinical programs, the designation can trim up to two years off the timeline of a "conventional" development program.⁹

Key challenges include:

- Addressing compressed stability testing time frames; developers will need to leverage established stability data.
- Having enough manufacturing experience at commercial scale.
- Dealing with limited data sets to derive specification acceptance criteria.

Intelligent collaborations are essential

Small molecule API suppliers are likely to meet more of their customers' drug strategy goals when the relationship is based on experience and a thoughtful, collaborative approach. Part of this comes from the talent and resourcefulness of the people the company hires, and the way they "deploy" this talent to meet project goals and customer expectations.

This extends to the abilities of professional and scientific staff to leverage all resources and technologies at hand to assure the best outcomes. These attributes support creating an environment that is accessible, proactive, responsive, and agile, capable of performing effectively over the course of the project. Experienced partners should be able to bring smarter approaches to small molecule API development including:

- Instituting optimal scale up strategies
- Innovating better, more efficient synthesis and cleaner chemistry methods
- Mitigating process variability and understanding stability issues
- Achieving raw material economies

If reliance on outsourcing partners to supply small molecule APIs is growing, you will want to ensure you're getting the development support you need. As with any important business relationship, it's important to start with a focused, structured dialogue with your contractors, to quickly set expectations and uncover in the earliest stages of the program opportunities for optimization and process timeline economies.

Better APIs and finished drugs begin with more insightful collaboration. It's clear the sooner both partner and sponsor can combine their knowledge and expertise, the more successful an API project will likely be.

Summary

The rising global demand for drugs of all kinds is prompting great innovation by pharma's leaders. But this innovation is coming at great cost and pharma is turning to more effective business models to develop and manufacture their medications more cost-effectively. For the most part, pharma is looking to address gaps in their own capabilities and core manufacturing competencies while seeking collaborators to make their drug substances and drug products.

In an effort to shed risk and realize better development and business outcomes, drug developers have turned to outsourcing critical segments of their drug strategy to contract partners. This has become especially true for API development and an earmark of many of the newest drugs to be approved and treating patients today.

Demand for specialized outsourced API services have followed trends in drug development. Pharma's R&D pipelines are filled with high-potency and hard-to-make formulations. Specific expertise is needed now more than ever by pharma. With hundreds of potential small molecule API contract suppliers offering services, choosing the best partner is challenging.

In light of pharma's most significant drug development and market trends, it's become extremely critical for drug owners to be scrupulous about choosing their partners and carefully align drug development strategy with the capabilities of their partners.

Executing successful drug strategies with contract manufactures will never be "simple" in relative terms. However well API development plans are aligned with a given contractor's operational and technical capabilities, project success and the reliability of these relationships is often dependent on so much more. Project success is often based on the quality of collaboration, how well contractors anticipate issues and opportunities in addition to how accessible they are to their partners.

To deliver today's high-demand APIs, the most experienced partners are required. Embedded CDMOs may offer reliable access to the best resources, talent and technology contemporary drug developers need to make the sophisticated APIs their drug product strategies demand.

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Whatever your product's market strategy might be, API owner and API maker often have to build a common base of knowledge and do it in a timely and prescribed manner. Making more successful APIs begins with a more intelligent collaboration and the sooner both parties can achieve a true and transparent meeting of the minds, the better.

Let's collaborate and discuss your needs today.



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PC1-19-0009/Apr2021-V2