End-to-End Development and Manufacturing in Support of Small Volume Commercial Products

Pharmaceutical companies of all sizes are often challenged to identify a CDMO partner that can truly grow with their candidates from early development through commercialization, particularly for small molecule API manufacturing. Technology transfers between vendors are perceived as a predictable step to scale as clinical trials progress. However, predictability is never guaranteed in drug development.

As clinical results emerge, additional indications may be added, and forecasts recalculated. Increased API demands may begin to outstrip their partner's capacity. Faced with uncertainty, the sponsor might consider adding additional CDMO partners, or a transfer to a larger CDMO, both of which will impact the development timeline.

For sponsors developing and commercializing orphan drugs, continuity of CDMO partners proves to be equally, if not more challenging. In 2021, 52% of CDER-approved drugs held the orphan drug designation, many of which also had fast-track status. To keep these therapies on their development timelines, CDMOs must be able to scale quickly within their facilities to help therapies progress from early clinical development to validation and commercial launch. An unexpected technology transfer can have major implications for these sponsors.

Cambrex has recognized the lack of market options for true end-to-end (pre-clinical to commercial launch) CDMO support for orphan and small-volume drugs. Our vision is to support early API development and small-scale commercialization under one roof, backed by our large-scale manufacturing network support, should the sponsor need to scale as indications grow and API demands rise.

To make this vision a reality, Cambrex recently invested $30M to upgrade the High Point facility with new, state-of-the-art process chemistry, engineering, and analytical laboratories, and a production plant expansion that will double our clinical production capacity, which includes new small-volume commercial capabilities.

These changes empower Cambrex to deliver right-sized solutions for each client's needs. We strive not only to enable the next clinical delivery — be it first in human, API delivery, or preparedness for Phase II clinical trials — but to facilitate the fastest possible pathway toward commercial launch.

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,300 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.

Building a Process for Small-Volume Success

Sponsors spend considerable time and resources on process development and validation to create a launch-ready manufacturing process, which might require minor refinement. More often, however, significant process refinement is needed when adding additional CDMOs in preparation for process validation and commercial launch. Our goal is to ensure the sponsor process is optimized and prepared for commercial scale across any site in the Cambrex network.

In High Point, Cambrex's engineering R&D team is intentionally embedded into the chemical R&D group. By design, we want our engineers to have full access to the process chemistry, working alongside the chemical R&D group to not only move projects along more efficiently, but to add sufficient scrutiny to safety and hazards analysis. However, the primary focus of the engineering R&D team (and one of the driving factors for constructing a new lab for that team) is continuous flow processing, an alternative to traditional batch chemistry. So, we dovetailed our engineering R&D and continuous flow efforts into our traditional batch paradigm.

This becomes increasingly important for sponsors developing low-volume clinical batches that will progress to small-scale commercial. In this scenario, there are specific actions that clients might take to lessen the impact of the higher COGS, depending on the complexity of the manufacturing process. For example, maximizing batch volumes at early steps of the process and stockpiling intermediates allows clients to build economy of scale into the process. Additionally, enabling technologies that can bring down processing time and cost, such as continuous flow chemistry or process analytical technology (PAT) can help to streamline the development cycle.

The capacity offering from Cambrex High Point is well-suited for this approach. With a target sweet-spot of approximately ~200 to 500 kg/year of API per commercial program, High Point is in a position to support small volume commercial needs for clients seeking that flexibility. As clients seek to add additional indications, and may require larger annual API volumes, the team might consider validating the approved process at one of our larger-scale commercial sites. Cambrex inherently designs processes to perform optimally on equipment at any of our sites — ensuring services can be tailored to each client's needs, transfers between sites proceed smoothly, and high quality is never compromised.

Enhancements and Expansion

Cambrex has made its largest investment in the company's history, $100 million over 3 years, to dramatically expand our capacity and capabilities across our drug substance manufacturing network. To deliver on quality and speed for our clients, our investments include modern equipment and enabling technologies to accelerate drug development and commercialization.

At the Cambrex High Point site, the first phase of evolution was completed in Q3 2022 – which adds analytical and chemical development laboratories totaling 30,000 square feet and provides future workspace for 85 chemical development, engineering, and analytical scientists. These laboratories will support the development of APIs to be manufactured in the facility's current clinical manufacturing area, as well as the future expanded clinical manufacturing and commercial manufacturing suites.

The newly commissioned engineering R&D lab features large walkthrough hoods designed to accommodate fully custom carts/skids built to perform a single, focused chemistry step in a continuous flow paradigm, or perform end-to-end chemical synthesis for multiple steps. The approach works extremely well for both existing and novel processes, and has been demonstrated for proof-of-concept studies, clinical GMP API production, and transfer to our largest-scale commercial facilities.

Similarly, buildout of a spacious new chemical process R&D laboratory has increased the total number of hoods for the chemical R&D team (mix of traditional, walk-in, and walk-through hoods) from 35 to 80, and will allow addition of at least 25 additional process chemists at the High Point site. Each hood has been outfitted to include the latest in laboratory technology and has been personalized by individual chemists to suit their needs. Most of these hoods are outfitted with jacketed glass reactors that function as scaled-down versions of pilot plant reactors, and many have been installed with cutting-edge development tools such as Mettler Toledo EasyMax platforms and in-situ reaction monitoring probes (Raman, ReactIR, Lasentec, etc). This technology ensures that the transition from the lab to the plant is representative and predictable, further reducing the timetable to successful scaleup.

Finally, addition of a new state of the art analytical R&D lab has provided increased space for newly purchased analytical equipment and technology (HPLC, GC, ICMS, a 2nd XRPD), and has provided generous footprint for further growth of the High Point analytical team. All this equipment is qualified for GMP use with an eye toward developing more robust processes in a shorter timeframe. Using the same equipment for analytical development that we use for QC release means no differences exist between development work and live samples from the plant — resulting in fewer issues, investigations, or quality concerns.

Phase 2 of the project is ongoing and will approximately double the facility's manufacturing capacity, adding 9 clinical and commercial reactor trains to complement the existing stable of 8 large scale clinical manufacturing reactors. The newly added reactors will essentially mimic their existing counterparts, which means that processes developed and optimized in the existing clinical space can smoothly transition into the commercial reactor trains for validation activities with minimal additional development.

The new commercial area will provide an ideal scale for the manufacturing of orphan drugs and niche therapies, while larger volume products developed at the facility can continue to grow in capacity at one of Cambrex's larger commercial scale facilities in Iowa and Sweden.

Quality Platform

Cambrex offers process flexibility across a range of clinical and commercial settings, creating a tactical advantage for our clients. By taking advantage of our nimble and aggressive early development capacity, clients can shorten the timeline leading up to commercial launch. During that phase, Cambrex employs a flexible but comprehensive early development quality system built to be phase appropriate. But as a product nears commercialization, Cambrex implements a more robust and rigid later-stage commercial platform that satisfies more stringent regulatory demands toward commercial launch, focusing on analytical and process validation with applicable quality support. With this approach, Cambrex is able to fine tune the quality needs for any program spanning from early clinical development through full commercial readiness.

Final Thoughts

Large pharmaceutical companies and emerging biotechs alike will continue to push the cutting edge of orphan drug development and small-volume therapies. In doing so, they will seek to partner with a CDMO partner whose experience and capability engenders full confidence in its ability to implement their process on its equipment, regardless of changes, while facilitating an accelerated development timeline and ensuring regulatory adherence each step along the way.

Cambrex, from its High Point site outward, is uniquely positioned to serve such clients. Whether sponsors begin the process with a dream and a molecule, or an existing process in need of refinement on scale, Cambrex can help.

Authors


Dan M. Bowles, Ph.D., Senior Director, Chemical Development, Cambrex High Point


Mike Johnson, Senior Director, Quality, Cambrex High Point


Brian Swierenga, VP Operations and Site Director, Cambrex High Point