SUPPORTING CLIENT PROJECTS FOR CDMO SUCCESS

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The production of increasingly complex small molecule APIs is challenging drug makers. CDMOs with multiple capabilities are needed to develop efficient routes to synthesize these complicated molecules. With expertise in both fermentation (including purification and downstream processing) and synthetic chemistry, BioVectra is positioned to support client projects from early clinical stages to commercial production.

SMALL MOLECULE CHALLENGES

Looking across the global pharmaceutical pipeline, it is clear that small molecules continue to command a very strong presence. Despite the recent focus around biologics, small molecules comprise a larger fraction of commercialized drugs and drugs in early through late-stage development.[1] In addition, the majority of projects outsourced to CDMOs continue to involve small molecules. However, the small molecule projects being outsourced are becoming increasingly complex, as are regulatory expectations. Most of the projects presented to BioVectra involve compounds that are moving into development and require process development, are difficult to manufacture or handle (e.g., highly potent compounds, controlled substances), require a novel route to circumvent existing patents or have associated procurement issues, such as key building blocks that cannot be found and may need to be manufactured.

LEVERAGING FERMENTATION AND SYNTHETIC CHEMISTRY

Microbial fermentation is experiencing a period of revitalization. One of BioVectra's areas of focus is the expression of small molecules via fermentation – including leveraging novel expression systems. We are currently exploring systems that allow the expression of molecules that were previously accessible only through cell cultures, extraction from biomass or chemical synthesis. Aside from presenting a novel approach to complex API drug development, the use of microbial fermentation has cost advantages, as it allows for large-scale manufacturing of complex compounds in a single upstream and downstream process sequence. This process requires fewer solvents and produces less waste compared with traditional chemical synthesis and extraction processes.

BioVectra has been involved in fermentation for more than 15 years. Our systems include microbial (filamentous and marine-based bacteria), *Escheria coli* and fungal platforms. Our site on Prince Edward Island includes cGMP pilot and commercial suites containing equipment tailored for the production of small molecule metabolites and their purification (e.g., resin or media capture), centrifugation, ultrafiltration/diafiltration, lyophilization and spray drying, as well as filter dryers at scales that support fermentations ranging from shaker flasks up to 15,000-L fermenters.

At BioVectra, we specialize in combining synthetic chemistry with fermentation to provide simple and cost-effective solutions to complex problems. We also have expertise spanning a broad range of synthetic methodologies and can perform multi-step synthesis to deliver molecules with complex structures. Our synthetic chemistry capabilities cover all conventional organic chemistry reactions, including asymmetric synthesis and catalysis. We operate cGMP kilo-labs and scale-up facilities that can handle gram through multi-metric-ton products – as well as

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high-potency containment for cytotoxic compounds.

END-TO-END SERVICES WITH PHASE-APPROPRIATE SUPPORT

In addition to combining fermentation and organic synthesis capabilities, BioVectra supports processes from the earliest stages through commercial production. With equipment that can support volumes from glassware to thousands of liters, we are able to tackle projects with a wide range of volume expectations, including low-volume APIs for therapies designed to treat rare diseases and APIs that target large populations.

BioVectra also provides formulation development services, with a particular emphasis on challenging formulations. Production challenges stem from the API itself, which requires special handling. For instance, the highly potent APIs used in antibody–drug conjugates require complex multi-step chemical synthesis or are made from starting materials that are difficult to procure. On the formulation end, we focus on complex intravenous injectables utilizing nanoparticle delivery systems and intramuscular sustained-release formulations. These formulations require a targeted manipulation of the API's physical properties in order to achieve an extended release profile.

DEVELOPING PROCESSES FOR INCREASINGLY COMPLEX SMALL MOLECULES REQUIRES FLEXIBILITY IN CAPABILITIES, CONTINUED INVESTMENT IN ADVANCED TECHNOLOGIES, **OPENNESS TO NEW TECHNIQUES AND AN UNDERSTANDING OF THE MOLECULES INVOLVED.**

Our experience in this area has helped us develop an understanding of the challenges that clients face when formulating their own products. We recognize how physical and chemical characteristics can critically impact the behavior of APIs in various formulation environments, which strengthens our understanding of what is important for API development and manufacturing. Some of our clients are seeking assistance in developing oral forms of existing parenteral oncology drugs, and doing so requires understanding the morphology and characteristics of the API and how they will impact a reaction in different environments.

Our tailored and personalized approach to process development helps our clients reduce the time it takes to move from one development phase to the next. The needs at each phase are considered and addressed without creating unnecessary roadblocks for later development stages. Patient safety issues must be identified early on, while installation of control measures for critical quality attributes and critical process parameters is essential, as the process is developed to ensure that the desired quality is achieved.

Our integrated approach ensures that development is not performed in isolation; it is a joint effort encompassing R&D, manufacturing, quality and procurement. By taking this approach, our goal is to identify an optimal and manufacturable process that provides the highest-quality product in the least time possible.

This high level of commitment to the process does not end when process validation is achieved. Once the engineering and validation batches are completed, continuous monitoring is performed to enable identification of any opportunities to drive more value out of the process.

By offering fermentation and chemical modification within one CDMO, clients can simplify their supply chains and streamline their development processes, reducing costs and time to market. In addition, with over 50 years of experience working with small molecules, BioVectra also brings a depth of knowledge about the behavior of small molecules and an awareness of potential problems that could arise. Our ability to anticipate challenges and rapidly provide solutions is another value-add for our clients.

As importantly, there is a high level of employee retention at BioVectra and our clients can be assured that the same team that works on the initial process development effort will be available to support a project all the way to commercialization and beyond. Observing projects as they mature through the entire development life cycle educates our team about the different problems that may potentially arise. With this knowledge, we are often able to foresee potential difficulties and tailor our development programs with these issues in mind.

UNIQUE APPROACHES

Developing processes for increasingly complex small molecules requires flexibility in capabilities, continued investment in advanced technologies, openness to new techniques and manufacturing paradigms and an understanding of the molecules involved. Over the last 18 months, BioVectra has been building out its analytical capabilities, in addition to investing further in HPLC and UPLC, CAD detection, X-ray diffraction, mass spectrometry, particle size analysis and thermal characterization. As molecular complexity increases, it is essential to be able to fully characterize the physical and chemical properties of APIs in order to gain an understanding of their potential behavior in formulated products and upon administration to patients.

BioVectra continues to apply our skills to produce unique molecules – such as PEGylated products – after observing more demand for PEGylation reagents that move away from the traditional high-molecular-weight linear polymer molecules to very specific, well-controlled, lower-weight species and multi-branched variants. These projects also often require the ability to develop production routes that do not infringe on existing patents.

On the manufacturing side, BioVectra is committed to improving the efficiency and productivity of our processes. To that end, we have begun to provide process analytical technology (PAT) and continuous processing for our clients. The use of PAT enables real-time monitoring and analysis of trends for enhanced process control, while eliminating the time required for iterative sampling and testing. These include UV-Vis and near-infrared spectroscopy analysis, which contribute to the production process and multivariate analysis – these are key to understanding the process and keeping it under statistical control.

BY OFFERING FERMENTATION AND CHEMICAL MODIFICATION WITHIN ONE CDMO, CLIENTS CAN SIMPLIFY THEIR SUPPLY CHAINS **AND STREAMLINE THEIR DEVELOPMENT PROCESSES, REDUCING COSTS AND TIME TO MARKET.**

INVESTED IN CLIENT PROJECTS

BioVectra has proactively worked with our clients to provide services beyond our current offering, in order to respond to demands of increased volumes or to provide a service that was not widely available in the market. Our medium-sized organization has the speed and nimbleness to quickly respond to such requests. This approach can require significant capital and human resource investment (which has been successfully demonstrated over numerous examples) and allows our clients access to material and greater control of their supply chain.

The success of our clients is our success, which is why we have repeatedly expanded our capacity and capabilities to specifically support the commercialization of client products. Indeed, BioVectra became involved in fermentation at the request of a client. We were performing chemical modification on a metabolite when the client's offshore supplier ran into regulatory difficulties. We were asked to take on the entire scope of the project, and, 15 years later, we have attained strong expertise in fermentation.

BioVectra has also invested in specialized technology for the isolation and filtration of metabolites captured on a resin surface to improve a client's process. A single process operation took more than a week to complete; however, once the new technology was installed, the process time was reduced to less than one day. Similarly, we invested in a fraction-collection system that allows for the collection, transfer and concentration of fractions containing highly potent compounds in a contained environment. Isolation, filtration and packaging are also performed in the unit. This investment was made for a particular client, for whom BioVectra now produces more than 40 kg per year of a highly potent compound.

Beyond developing processes and scaling them up in our multipurpose equipment, we are committed to engineering and designing specific plants for clients that drive efficiency and value as they achieve commercial success. In fact, a 200-metric-ton site is currently being purpose-built for a client – this mutually beneficial construction will thus help us serve more clients.

BioVectra's core competency in microbial fermentation of small molecule APIs led to our expansion into fermentation of large molecule biologics. We now provide process development, analytical support and cGMP manufacturing for proteins, enzymes, antibody fragments, peptides and attenuated virus vaccines. We are currently bringing a dedicated biologics site for the production of large biomolecules online. In addition to providing entry into this exciting market, this new capability will enable BioVectra to leverage our small molecule capabilities in PEGylation and conjugation chemistry to support clients with ever more complex needs. BioVectra provides its experience as a market-leading supplier of high-quality reagents to the pharma and biopharma industries from research to manufacturing scale, including bioprocessing, diagnostic and molecular biology reagents and MPEGs, to support any partnership. P

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Marc joined BioVectra in 2006 as an Analytical Research Chemist. He quickly transitioned to Analytical Research Group Leader and then Analytical Services Group Leader, followed by roles as Manager and Director of Analytical Services. In 2014, he was appointed to the position of Vice President, Research and Development. Marc received a B.Sc. in organic chemistry and an M.Sc. in physical chemistry from the University of Oldenburg and a Ph.D. in physical chemistry from the University of Basel, Switzerland.

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Mark has over 20 years of experience with BioVectra, during which time he has contributed as a team member toward the development of fine chemicals, advanced intermediates and active pharmaceutical ingredients. During his time at BioVectra, Mark has held the positions of Research Scientist, Product Manager, Custom Synthesis Project Manager and Manufacturing Manager, Special Projects. He was appointed to the position of Vice President, Manufacturing in 2014. Mark received an M.Sc. degree from Memorial University of Newfoundland.

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