GEN Genetic Engineering & Biotechnology News

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Custom Manufacturing Accelerates Time to Market

As the life science industry faces increasing competition—as well as global regulatory and pricing pressures—outsourcing portions or all of manufacturing is becoming increasingly prevalent. A custom or contract manufacturing partner can help eliminate bottlenecks reducing a product's time to market.

An off-the-shelf product may not exist, or existing products may not fit a process workflow. Custom manufacturing allows suppliers to not only continue to produce standard products, but also to add value and manipulate their designs in order to produce a unique product for a specific customer. Custom manufacturing should not be confused with original equipment manufacturer (OEM) products. In this scenario, a company rebrands an existing product from another company.

A subset of custom manufacturers, contract manufacturing organizations (CMOs) typically focus more on helping pharmaceutical companies with comprehensive services from drug development through drug manufacturing. Regardless, if

a custom manufacturer or CMO is used, potential customers evaluate prospective partners in a similar fashion and expect competitive pricing, regulatory compliance, flexibility on production capability and on-time delivery.

As stated earlier, in custom manufacturing, unique products are developed or packaged to order for a specific application. It is not a 'one size fits all' operation. Applications run the gamut from simple to complex, whether producing a single component or the complete, final product.

Simple examples include repackaging an existing product in a different size, concentration or company-branded container. More complex examples include customizing an existing product for a specific work flow, developing and/or producing a proprietary formulation or product, or developing a new product, including therapeutics, from the ground up based on supplied specifications.

Not a One Size Fits All

Genedrive plc provides a compact PCR platform that enables rapid nucleic acid amplification and detection from plasma, sputum and buccal swabs for rapid point-of-care diagnosis of infectious diseases, such as tuberculosis and hepatitis C (HCV), to address large unmet global health challenges. For example, over ninety percent of people with HCV are undiagnosed. Pressure exists to identify these individuals and to immediately start treatment in the hopes of eradicating the disease globally.

Automation of product finishing contributes to rapid turnaround and helps the client meet critical deadlines. [Promega Corporation]

As a company of 40 employees, producing GMP-grade biologics is not part of genedrive's business supply-chain strategy; they decided to turn to industry experts and to develop custom manufacturing partnerships.

"Early in the HCV assay development we needed to select enzymes, a Taq polymerase and a reverse transcriptase, that had the required quality and performance to work with blood and plasma, not just purified nucleic acids. These enzymes need to withstand some severe inhibitors because of the sample composition. Addressing this performance requirement was a top priority," explained Gino Miele, Ph.D., R&D director at genedriveplc.com.

"Cost and performance needed to be balanced. Our assays must be affordable in developing countries. This puts extreme pressure on the price, which is driven by the component costs."

In another case, Tocagen is developing first-in-class broadly applicable product candidates for the treatment of cancer using their cancer-selective gene therapy platform built on retroviral replicating vectors (RRVs). Their lead product candidate is a two-part cancer-selective immunotherapy comprising an investigational biologic, Toca 511, and an investigational small molecule, Toca FC.

Toca 511 is a RRV that selectively infects cancer cells and delivers a gene for cytosine deaminase (CD).

Through this targeted delivery, only infected cancer cells carry the CD gene and produce the enzyme. Toca FC is an orally administered prodrug, 5-fluorocytosine, which is converted into 5-fluorouracil (5-FU) by CD. 5-FU kills cancer cells and immune-suppressive myeloid cells resulting in anti-cancer immune activation and subsequent tumor killing.

According to Carlos Ibañez, Ph.D., vice president, product development and manufacturing, Tocagen, tocagen.com, a decade ago, CMOs had minimal experience with manufacture of RRV products; therefore, the company leveraged in-house expertise to develop a proprietary and scalable production process for its newer generation of gene therapy products. They

then searched and transferred the process to contract manufacturers that could perform the process and had ambitions to move from clinical trial supply to global commercial supply.

Partners, Not Simply Suppliers

The scorecard must be balanced; cost is important but equal or greater service levels, quality program adherence, project management and adaptability must be factored in. In the custom field, things change or evolve more commonly than not, and manufacturers need to be flexible and able to respond.

A custom manufacturer is a partner, not merely a supplier. An experienced manufacturer will set expectations early on in terms of capability, meeting timelines, costs and deliverables and provide open interactions between scientists and other departments on both sides of the equation.

Genedrive's assay reagents are lyophilized, which generates some bespoke enzyme requirements. Enzymes need to be provided glycerol-free in high concentrations in order to be incorporated into the core formulation and freeze dried.

"At an earlier phase of the business when we began looking for a custom manufacturer that understood our growth path – we wanted a company who made it their business to get down on the ground and to work with us as an active collaborator. After triaging several enzyme suppliers, we selected a manufacturer who could not only give us the tools, modeling and forecasts that we needed to persuade our management but was poised to grow with us long term," said Warren Berry, operations director, genedrive.

"Early on our partner made it clear they would work with us to get the right formulation. Currently, one enzyme is provided ready to use and the other one in a format where we do some downstream manipulation. These formats were acceptable during assay development; in the future we may elect to have the manufacturer perform the downstream manipulations. Flexibility was an important component in our decision making; we wanted options to evolve as the assay progressed through release and commercial scale-up."

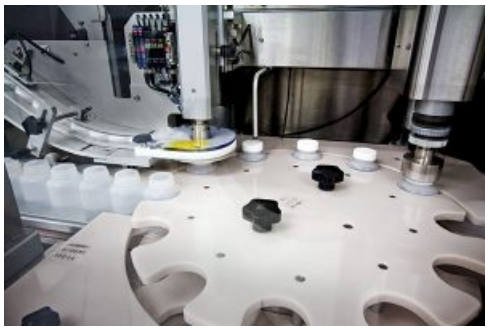
Partners must be aligned on clearly stated goals so that both parties stay the course and expectations are met. For Tocagen, flexibility was also paramount. Their partners required an understanding of both the need for ongoing process adjustments while meeting clinical supply demands and also the rigor and understanding of generating and following the rigid requirements for commercial manufacturing that satisfy global regulatory agencies.

"These requirements necessitate a different mind-set and base of knowledge and experience, and we established critical success factors for the manufacturing partnership: first, to understand each other's needs, capabilities, and vision for success; second, to ensure that all of the necessary resources are available to sustain the partnership long term; and third to facilitate and encourage open, honest and constant communication between all levels of the companies so that everyone was on-board with the vision," discussed Dr. Ibañez.

Tocagen wanted to avoid unrealistic expectations on both sides, procedures that were without some form of precedence and limiting themselves to a process that would be difficult to scale further. A collaborative approach to process optimization, automation, scaling and validation planning was also critically important to them.

"I look at whether a business is shaped to help you achieve your goal, and can become a long-term partner. We needed to have a relationship in which the provider understood the trajectory of the business and that would take the time and attention to understand more deeply the journey we were about to embark on. Also that our needs may change rather than this is the product and price," added Mr. Berry.

"As we scale up and implement our launch plans we continually find that the flexibility the manufacturer provides to modify and adapt to meet our business needs is invaluable for a company at our stage of development."



Automation of product finishing contributes to rapid turnaround and helps the client meet critical deadlines. [Promega Corporation]

Long-Term Outlooks

The market may change, expectations and technologies will change; adaptability is crucial. Setting realistic expectations prior to embarking on a custom manufacturing relationship ensures everyone is on the same page in terms of deliverables and timeline.

There must be a spirit of partnership; the relationship is more than a short-term project. A decision should not be made on a promise without vetting it thoroughly inserted Mr. Berry.

Dr. Ibañez advised to decide early if you want the contract manufacturer to own the process or have the flexibility of a portable proprietary process. If the latter is selected, ensure there is internal expertise to develop a process that can be commercially ready. If not, maintain excellent in-house expertise to follow the partners' course and developing capabilities.

He suggested that a company develop as deep an understanding as possible of the partner's picture of the relationship and how it would and should develop, and to talk to several prospects. It can be worth considering different early-stage and later-stage manufacturers. In this case, technology transfer agreements need to be in place up-front, and the phase 1 process must be compatible with development into phase 3.

Custom processes are unavoidable when developing and manufacturing a novel type of technology such as RRVs. Such processes are also valuable and are expected to form a competitive advantage, both in proprietary know-how and affording more control of the outcomes.

From many points of view, timely investment in custom processes for a novel type of product should give a rapid pay-off, for example in timely and appropriate product development, internal confidence, regulatory body interactions and product partnering. However, at the same time, it is important to understand your partner's position and their desire to use routine procedures. They must have a sufficient level of confidence in the company and product to appreciate the value of investing time and resources to learn and validate new processes.

Collaborative Relationships Lead to Unique Solutions

Selecting the best custom manufacturing partner can be a challenge. Key considerations include depth of scientific expertise, ongoing technical support, and compliance with regulatory requirements. It is also critical that manufacturing and logistics capabilities can scale to meet future needs.

The Promega manufacturing facility in Madison, Wis. maintains certification to ISO 9001, ISO 13485, and ISO 18385 standards. [Promega Corporation]

Promega offers a range of custom manufacturing services, from simple changes in dispensed size to uniquely designed products specifically adapted for individual client needs. Each client works with a lead scientist and dedicated custom manufacturing team. Where needed, the team consults with subject matter experts to ensure that specifications are captured and the team is delivering the best product that addresses the client's requirements. Flexibility is a key part of the relationship—products and processes can be adapted to meet the changing needs of every client.

With more than 450,000 square feet of manufacturing space, including cGMP facilities, Promega has invested in the development and maintenance of state-of-the-art, high-quality manufacturing facilities. These facilities include environmentally controlled spaces, separation of pre- and post-amplification processes, semi-automated filling, and automated packaging of ambient kits with 100% inspection of components and label content. The Promega manufacturing facility in Madison, Wis. maintains certification to ISO 9001 and ISO 13485 standards, as well as ISO 18385, which focuses on minimizing the risks of human DNA contamination in products. Currently, 15 Promega facilities around the world are certified to ISO standards.

Built on over 40 years of serving the life sciences industry, Promega's scientific expertise encompasses protein engineering, cell biology, bioluminescence, and nucleic acid purification and amplification. Despite the company's rapid growth, it continues to maintain personal relationships with all its custom manufacturing clients. Based on feedback from current clients, that's a small detail that can make a big difference when choosing a custom manufacturing partner.