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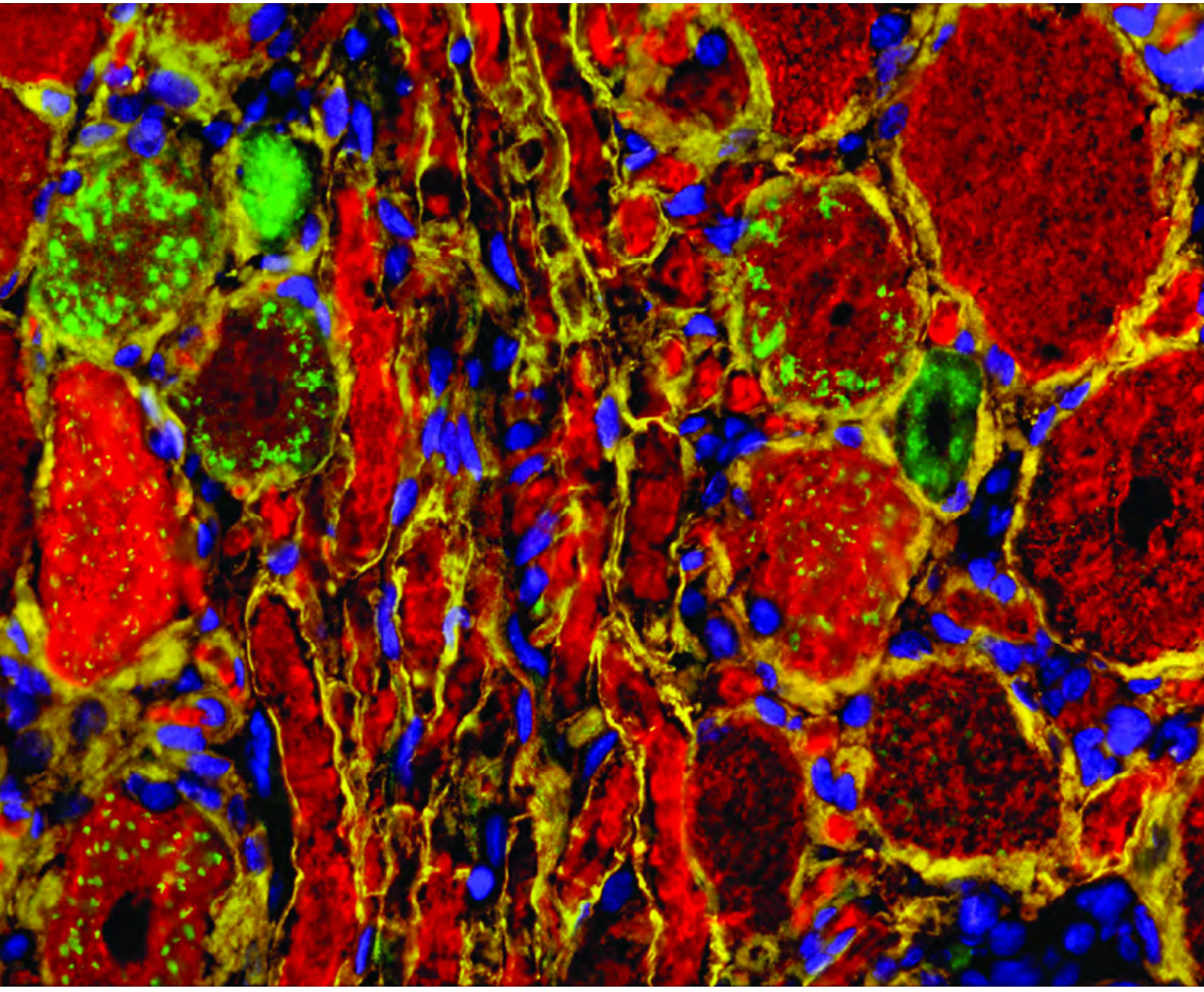

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Courtesy of Lonza Biologics, Inc.

Buffer Preparation suite in Lonza Biologics'New Hampshire, USA facility

Biopharmaceutical Contract Manufacturing: An Overview

BY DAVID SHERWOOD

The revolution in biotechnology has led to 133 biotechnology-derived medicines being approved by 2001 with sales of $22 billion. This is less than 10 percent of today's total pharmaceutical market, but it is a rapidly growing sector. Biologics are predicted to grow to nearly $50 billion by 2008.[1] Marketed biopharmaceuticals include several blockbuster products with multibillion-dollar sales. In recent years, biotechnology-derived therapies represented 10 percent to 20 percent of all new approved molecular entities and hundreds more are in development,including nearly 200 proteins in late-stage trials.

Microbial and mammalian expression systems are typically used to produce biotherapeutic proteins (many companies are also working on transgenic expression systems). Microbial cultures (typically, *Escherichia coli* or yeast) are used to produce smaller, less-complex proteins or those where specific modifications,especially glycosylation,are not required. Examples of licensed biotherapeutic proteins produced in microbial cultures include interferons, insulin, growth hormone, and hepatitis B vaccine. Mammalian cell cultures, such as Chinese hamster ovary (CHO) cells or mouse myeloma cells, are usually grown in either batch or

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continuous perfusion cultures. These are commonly used to make large, complex, glycosylated proteins such as monoclonal antibodies.[2–4] Mammalian cells are capable of glycosylating proteins, and this can be essential for therapeutic activity. Erythropoeitin, tissue plasminogen activator, factor VIII, and monoclonal antibodies are a few of the recombinant proteins produced in mammalian cells. Approximately the same number of products are made in each type of expression system.[5]

The use of microbial and mammalian cell systems with the appropriate manufacturing capabilities and technology has enabled a variety of proteins to be economically produced with purity and quality levels sufficient for therapeutic use in humans. Given that developing and manufacturing biopharmaceutical products require significant technical expertise and capital investment together with high operating costs, many companies (both large and small) have developed outsourcing strategies to manufacture biologics for clinical trials and the commercial market. As a result, the biopharmaceutical contract manufacturing industry has grown dramatically.

In the late 1980s, several contract manufacturers were supplying services (at small scales by current standards) to the pharmaceutical industry, particularly in the area of mammalian cell culture. However, the lack of products severely hindered the growth of contract manufacturing. Several products, especially monoclonal antibodies, took longer than expected to go through the clinical programs and then to market. In addition,some production processes did not lend themselves to the scale-up required for commercial manufacturing. Many contract manufacturers did not have the capital funding required to do business in a GMP environment. A large-scale facility can cost several hundred million dollars to build and validate.

Looking Back

Biopharmaceutical contract manufacturing has developed significantly during the last 10 years. Many companies are now able to offer small-scale manufacturing for preclinical and clinical studies. Some of these companies can scale up to production volumes suitable for in-market supply supported by all the necessary services (such as regulatory affairs, validation,analytical capabilities, and formulation). The most common products made by contract manufacturers are monoclonal antibodies and recombinant proteins using mammalian cell culture and microbial systems.[6] Contract manufacturers now work with companies of all sizes — from virtual and discovery-based companies to large pharmaceutical companies — to provide product development and manufacturing for preclinical, clinical, and in-market use. During the last five years, contract manufacturers have evolved from small independent companies to being part of larger businesses that serve a wide range of contract manufacturing needs within the life sciences industry. Companies such as Lonza, DSM, Avecia, Diosynth, Boehringer Ingelheim, Cambrex Bio Sciences, and Dow are expanding their services, especially manufacturing capacity (for example, Lonza will have 60,000 L of stirred tank capacity in early 2004 and Boehringer Ingelheim will have 90,000 L of stirred tank capacity by 2005).[7,14]

Why Outsource?

When considering the manufacture of a biopharmaceutical product, companies need to decide whether to develop expertise "in-house" and build or acquire their own manufacturing facilities, or look at services provided by a contract manufacturer. A model was developed to enable decision making based on what would be the best strategy given a company's situation, product profile, product demand, and control requirements.[8] Sponsor companies must be able to protect their technology (IP), seek appropriate development and manufacturing capacity, monitor the remote manufacturing site through audits (cGMP compliance) and technical and project reviews, ensure that timelines are met, execute efficient technology transfer (when appropriate), and document all aspects of the project.[6] Using a contract manufacturer reduces the risks that sponsor companies face. For example, outsourcing

- avoids capital investment in a manufacturing facility before the safety and efficacy of the drug product is proven,
- eliminates long lead times (typically three to five years) to build and validate a manufacturing facility,
- accesses contract manufacturers' expertise (e.g., Lonza created more than 200 high-yielding cell lines and developed more than 300 GMP processes over the last 20 years), and
- provides project management experience that improves overall project timelines and reduces time to market.

Sponsors' expectations can be extremely high. Contract manufacturers must customise the manufacturing process to sponsors' needs, deliver on time, provide process scale-up knowledge, run cost-efficient processes, and be at the forefront of regulatory compliance.

Outsourcing is a complex process and must ensure that the unique needs of each sponsor company are met as closely as possible by the contract manufacturer. Relationships are key — built on experience, confidence, communication,and trust. In the last five years,differentiation between contract manufacturers has become based on relationship aspects and expectations are high. Lessons learned from working with contract manufacturers are documented and clearly emphasize the need for the sponsor companies to thoroughly define their expectations (including cGMP and regulatory) throughout the projects by using agreements with clear milestones and quality agreements.[9] The interaction can be seen as a learning process for both parties and as a truly collaborative relationship.

Regulatory Changes Equal More Outsourcing

Before 1996, the U.S. regulatory environment provided significant barriers to contract manufacturing of biopharmaceutical products. FDA regulations required that Phase III clinical

trial material be produced by a commercial manufacturing process in a commercial facility. In addition, two license applications were required: the Product License Application (PLA) and the Establishment License Application (ELA). The regulations dictated that both the PLA and the ELA be submitted by the same company. In order to hold the Establishment License (EL), companies had to either perform significant manufacturing steps themselves or be responsible for the product clinical testing and perform the final manufacturing steps of the process. The Product License (PL) and EL were company-specific; any changes to who held the PL and EL, the products they applied to, or the manufacturing site often required submitting a new license application, reapproval,and in some cases,new clinical trials. Linking the PL to the EL and the risks associated with change discouraged small biopharmaceutical companies from using contract manufacturers because the implications meant relinquishing responsibility for their product licenses.

In May 1996 (following the Clinton administration's November 1995 report, "Reinventing the Regulation of Drugs Made from Biotechnology"),FDA eliminated the requirements for ELAs and lot release, thus encouraging the use of contract manufacturers.[10] After that, companies without the financing to build manufacturing facilities could use contract manufacturers without compromising their regulatory control.

Demand for Biopharmaceutical Products

Biopharmaceutical proteins are traditionally low volume (typically kilograms per year) but high value. However, recent years have seen an increasing demand for products such as monoclonal antibodies and fusion proteins, which require higher doses than many earlier biotechnology-derived products. In some cases, demand for these products is greater than 100 kilograms a year.

This situation has put pressure on world manufacturing capacity, especially in mammalian cell culture.[1,11–15] The anticipated increase in demand is driving the introduction of new capacity by both pharmaceutical companies and contract manufacturers. It is estimated that mammalian cell culture capacity will increase from approximately 0.5 million L to 1.5 million L by 2006.[7] This capacity increase is driven by investment from the pharmaceutical and biotechnology sectors as well as contract manufacturers (who hold about 25 percent of the capacity). In addition, it was estimated that, due to new approvals and increased demand for approved biopharmaceutical products,most manufacturing facilities were operating at or near full capacity at the end of 2001.[14]

What is the key to success for contract manufacturers? Sponsor companies need to access a full spectrum of services, in addition to manufacturing capabilities. For example: cell-line construction, high yielding expression systems, access to analytical and process validation services, product formulation services, and regulatory documentation as well as in-market manufacturing expertise for the major global markets (such as the United States, Europe, and Japan). Flexibility is key — the ability to work with many cell lines, product types, and processes ensures that customised processes maximize yield and quality. Sponsor companies need to develop their product as rapidly as possible. This can be achieved by smarter ways of working; for example, using new technology when creating and selecting cell lines and in novel approaches to process development. All of these services enable customers to bring early phase projects for development and clinical supply, using production technologies that can be scaled-up to match increased demand. As products progress through the clinic, the ability to validate both products and processes and provide data packs for regulatory submissions means that established contract manufacturers can partner with sponsor companies to achieve product license status. These capabilities mean that contract manufacturers can now support a customer with late clinical phase product requirements looking to secure in-market supplies.

The Future Landscape for Contract Manufacturing

Contract manufacturers must be flexible and responsive to industry changes and shifting customer needs. This flexibility may be required on many fronts including commercial arrangements.[12] Contract manufacturers must focus on communication and building relationships (and partnerships) with customers. This develops mutual understanding, trust,and confidence. Above all,the contract manufacturer must focus on meeting customers' requirements and must keep in mind that the success of their customers will be reflected in success for themselves.

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