Rising CMO Business Fortunes, by Adam Runsdorf

The current business climate favors forward-thinking contract manufacturing organizations that improve ties with manufacturers for services across the entire value chain, writes WDPrx President Adam Runsdorf in the May 2018 issue of Contract Pharma magazine.

Read the article on the Contract Pharma site .

The relationship of pharmaceutical manufacturers with contract manufacturing organizations (CMO) and contract development and manufacturing organizations (CDMO) is increasingly evolving from one-dimensional product outsourcing into a broad partnership model involving several aspects of development, testing, production and research.

Several developments occurring from within and outside the pharmaceutical industry are converging to promote a favorable business climate for progressive CMO firms that align their corporate strategies to take advantage of the signs and signals occurring around them.

Reasons To Be Cheerful: Two Parts

The growth of the global CMO industry is most clearly observed in the projected increase in revenues, expected to grow from $62 billion in 2016 to $83.9 billion in 2020.

Two sets of factors are shaping the promising fortunes of the outsourced manufacturing business: external factors that are occurring outside the direct control of the CMO industry involve financial, economic, structural and regulatory developments; internal factors are driven from within the industry including continuing breakthroughs in large- and small-molecule formulations, an emphasis on services across the value chain, capital investments in technology and persistent cost pressures on manufacturers.

Consistent quality and reliability are common threads woven through all external and internal factors that manufacturers demand as important measures of project success.

A Little History

The origins of the CMO industry were brought about by lack of production capacity at manufacturer facilities. The relationship began with contractual agreements to produce active pharmaceutical ingredients (API) or finished dosage forms (FDF). The model operated essentially unchanged until internal and external forces set the stage for growth.

Dedicated CMO firms as we know them today began operating around 1996 and were dominated by companies in Europe. Prior to this time, pharmaceutical manufacturers maintained loosely defined ‘gentlemen’s agreements’ to produce chemicals and API for each other in order to discourage competition.

The North American Free Trade Agreement (NAFTA) adopted in 1994 and other similar agreements around the same time opened the floodgates for the CMO industry to derive benefits working with international manufacturers sharing technology across borders.

The Trans-Pacific Partnership (TPP) trade agreement being negotiated without the United States includes 12 countries representing 40% of the global economy. If we stay on the sidelines, U.S. biopharma companies may be negatively impacted by the agreement concerning intellectual property protections.

Biopharma manufacturers based in the U.S. are protected from biosimilar competition for 12 years. Any data collected from clinical trials and other R&D initiatives remain the exclusive property of the manufacturer and cannot be utilized by prospective copy-cat organizations.

The U.S. was the strongest voice in favor of maintaining multi-year protections for data exclusivity. Now that the U.S. is no longer at the negotiating table, the other nations may shorten or eliminate these provisions, increasing competition in the biopharma industry with global repercussions.

Then came an influx of bio-pharmaceutical companies backed by venture capital funding. These companies focused on securing a molecule for promising therapeutic value and relied on outsourcing for most business activities, which in turn supported the rise of the contract research organization (CRO).

These forces built the solid foundation for the fertile business landscape that exists today for the CMO industry.

Dividing The Pie

Currently the majority of revenue in the CMO sector is derived from API manufacture followed by finished dosage forms and then drug and process development including laboratory work. Business from all categories is expected to rise with API maintaining the prominent revenue position in future.

Although the largest slice of the CMO revenue pie is generated by API, the fastest growth vehicle in the international CMO market is finished dosage form manufacturing, forecasted at a 6.9% CAGR through 2026 due mainly to strength of oncology and immunology therapies.

Closely related to the CMO function are CROs, which provide drug discovery and critical data support as well as contract packaging organizations (CPO) for secondary packaging and labeling. Clearly defined lines of responsibility are now blurring.

External Factors Driving CMO Business

The pharmaceutical industry is profoundly affected by external forces that have a direct impact on profitability. All businesses must allow for unforeseen or unexpected circumstances that might disrupt operations. But pharmaceutical manufacturers are in the midst of several developments occurring simultaneously. Leadership of these companies must combine sound financial management with forward-looking strategies in order to prosper.

Key external challenges for pharmaceutical manufacturers involve more stringent government and regulatory compliance, industry consolidation, continued erosion of traditional corporate structures and economic pressures cutting profit margins.

The consensus solution among manufacturers to most of these external considerations is their increased reliance on contract manufacturers.

Regulatory Requirements

Government and other authorities require that manufacturers adhere to stringent standards for regulatory compliance. In some cases, scientific advances in the medical field have occurred faster than the government's ability to keep current with relevant testing to assure patient safety.

For example, a new requirement of the United States Pharmacopeial Convention (USP), enforced as of January 2018, sets new analytical and validation requirements for measuring elemental impurities. This new standard replaces a test for heavy metals that was accepted for almost a century.

Another example of government compliance: the U.S. Food and Drug Administration (FDA) is charged with implementing Federal laws assuring the safety of medications. The most recent FDA Guidance concerning analytical testing requires greater details about drugs and process development than previously published.

Adding to the administrative obligations, the Drug Supply Chain Security Act (DSCSA) passed into law in by Congress in 2013 imposes many new requirements on manufacturers designed to reduce drug diversion and minimize counterfeit products.

Manufacturers must make significant investments in internal personnel, external consultants, facilities, equipment and machinery to maintain compliance. The development of more complex molecules and the increasingly sophisticated infrastructure required to successfully process them are prompting corporate leaders to constantly re-examine the costs and benefits of maintaining in-house capabilities to fulfill this purpose.

Outsourcing regulatory compliance responsibilities to CMO partners is an increasingly popular solution.

Industry Consolidation and Rationalization

Global investment firms search for industries with a healthy number of profitable players, a diverse supply chain as well as a burgeoning niche of smaller companies exploiting new technologies. The pharmaceutical

industry fits this strategy which has historically resulted in industry consolidation, enabling the acquiring company to create internal efficiencies, expand product offerings and incorporate new technologies that would be more expensive to develop from scratch.

Although 2017 saw fewer mergers compared with preceding years, there were many significant transactions.

The takeover of Patheon by Thermo Fisher Scientific in May 2017 was valued at $7.2 billion. Johnson & Johnson acquired Actelion, a biopharma company based in Switzerland, for $30 billion and Gilead paid $11.9 billion for the privilege of swallowing Kite Pharma.

These examples demonstrate the desire for companies to create a 'one-stop-shop' for pharmaceutical outsourcing with expertise along the entire supply chain from drug discovery, development, API production, formulation and packaging.

Industry consolidation is followed by rationalization of resources to streamline administration and increase profitability of the combined venture. For example, a manufacturer with ten CMO relationships taken over by a manufacturer with the same number of CMO vendors may produce an unwieldy total of 20 possible CMO firms under the same corporate umbrella.

Decisions are made about how best to reallocate the catalog of outsourced products to the smallest quantity of their best-performing CMO partners. This process results in more business spread out among fewer CMO firms, increasing business volume for the most highly regarded partners.

Faster Approval Process

A faster approval process for drug approvals also contributes to more business for the CMO industry.

President Trump made quicker drug approval an issue in the Presidential election. Dr. Scott Gottlieb, Commissioner of the FDA, is capitalizing on recent statements and the passage of the Advancing Breakthrough Therapies for Patients Act of 2012. The Act authorized a new abbreviated approval process for breakthrough therapy drugs to "expedite the development and review of drugs which may demonstrate substantial improvement over available therapy," according to the FDA.

According to the FDA Center for Drug Evaluation and Research (CDER), 46 drugs were approved in 2017 compared with 22 in 2016, 45 in 2015 and 41 in 2014, the most since 1996.

The Commissioner, in written testimony from April 2018 to the House Appropriations subcommittee, further committed to compacting the approval process when he stated is agency will "sharply increase" release of guidance documents designed to assist manufacturers to derive new treatments.

Summary

Outside forces are sometimes detrimental to business. Weather-related disasters including the destructive hurricane season of 2017 create significant damage with little warning and with long-lasting effects.

At other times, outside forces combine to boost business success. Several external circumstances in government and in business are propelling the CMO industry to greater opportunities. Some of the key factors responsible for this business upswing are increasingly stringent regulatory and compliance requirements, financial opportunities creating compelling logic for pharmaceutical industry consolidation and the creation of more efficient drug approval processes resulting in more manufacturing resources being devoted to bringing new products to market.

Internal Factors Driving CMO Business

Internal factors positively affecting the CMO industry are issues within the direct control of pharmaceutical manufacturers. These include technological advancements in processes and equipment, additional service offerings and efficiency enhancements. Unlike external forces, internal factors facilitate long-term planning and they are often developed in response to external factors.

Virtual Reality

Virtual pharma companies reduce fixed costs to a minimum by outsourcing some or most marketing and manufacturing activities to businesses including CMO firms. Typically, virtual pharma companies may employ quality and regulatory professionals and financial and commercial staff. The rise in virtual pharma benefits the CMO industry in several ways.

First, the investor community has pivoted from focusing on company assets to concentrating on project ownership. The lion’s share of investment funds in virtual operations are available for CMO firms to help the project succeed.

Second, the rise of the virtual business model shifts more responsibility to the CMO to perform more work compared with a conventional manufacturer. For example, laboratory work including analytical testing and additional services, plus clinical trial management provide expanded opportunities for the CMO to develop deep, long-term relationships with virtual manufacturers.

Cost Pressures Create Bold CMO Initiatives

The search for profits in a world of shrinking margins is not unique to pharmaceutical manufacturers. However, there are many issues weighing on industry profitability that favor entrepreneurial CMO leaders.

Pharmaceutical manufacturers face stiff challenges to success including price pressures, raw materials shortages, government oversight, litigation and insurance liabilities. In a nod to the virtual model, the solution for many conventional manufacturers is to reduce operational expenses to achieve greater profit potential. Focusing on core capabilities, primarily marketing, research and development, necessitates the downsizing of internal manufacturing capabilities at traditional manufacturers to trusted CMO firms.

A related development spurring transition to CMO operations is high capital expenditures required for equipment and facilities to meet testing and manufacturing requirements for large molecule APIs, high-potency APIs, biopharmaceuticals and other new molecules. As an example, expensive new high-resolution

accurate-mass instruments and other technologies allow for the necessary testing and measurement of biologics. Existing testing equipment may not be able to be upgraded to new standards.

Conventional manufacturers that have previously spent large sums to upgrade facilities and build new infrastructure based on finite projects or over-enthusiastic sales forecasts are more reticent to make those investments themselves. Entrepreneurial CMO companies offer a solution for risk-averse manufacturers by committing to absorb capital costs up front for new production capacity, strengthening the business relationship with priority manufacturers over a longer contract term. This includes increasing capacity for production of highly potent APIs (HPAPIs) to satisfy increased demand for biologics.

Ultimately, prudent reliance on reputable CMOs returns additional benefits to traditional manufacturers including a stronger risk management position by producing product at multiple external sites and also reducing potential shortages with advance preparation for manufacturing drugs in short supply at multiple CMO facilities.

Continuous Manufacturing

Harnessing technology is enabling CMO firms to increase revenues with more cost-effective alternatives to current production methods. To further improve the existing efficiencies for manufacturers, more CMO firms are investing heavily in continuous manufacturing methods in addition to conventional batch processing methods.

Compared with batch processing, which creates a finished dosage form (FDF) after preliminary phases are performed by multiple parties all converging at the production line, continuous manufacturing involves a single end-to-end production line beginning with the raw materials and ending with a final product or packaged unit ready for sale.

Batch processing is better suited for smaller runs with multiple products, while continuous manufacturing is designed for production of a specific drug. Compared with batch processing, continuous manufacturing increases speed to market, reduces risk because fewer people from fewer facilities are involved in the manufacturing process and requires a smaller footprint.

With continuous manufacturing, quality assurance protocols must be adjusted to consistently test and monitor the production line. Progressive CMOs are transitioning to automated testing solutions to meet the requirements of these new production methods.

Arriving Early and Staying Late

To spur growth, the CMO industry is taking on capital projects and investing in new technology to share risk with manufacturers. The outcome of these strategies creates a mutual dependence for CMO and client that helps assure long-term and profitable relationships.

As manufacturers shed non-core business practices, preferred CMO firms take on responsibilities at the earliest stages of the chain that may begin with formulation development and pre-clinical studies, then move

on to main business lines of drug development, API production and formulation. As industry consolidation continues, efficiencies may be found in the same CMO becoming involved with end-stage operations that may include packaging responsibilities.

The results include stronger partnerships and increased involvement between CMO and manufacturer that benefit both parties.

Conclusion

Developments within the pharmaceutical industry are creating a favorable environment for CMO growth. The continued popularity of the virtual pharma business model, cost pressures on conventional manufacturers, the ascendency of continuous manufacturing and the efficiencies gained from relying on CMO partners at every stage of the value chain, all point to continued prosperity.

External factors outside the industry bolster the optimistic outlook. The challenge of adhering to changing and expanding regulatory requirements, disruptive M&A activity from global financial interests and the accelerated pace of drug development and approval all work in favor of broadening ties between manufacturers and the CMO industry.

One foreseeable challenge to future growth concerns global biopharma companies that are building their own infrastructure to produce their own technologically advanced formulations. New drugs often are produced in very small quantities as specialty pharmaceuticals to treat specific rare conditions. The high profit margins that are realized from these therapies provide justification for these manufacturers to control production internally.

Another situation with potential effects on future business is the outcome of the Trans-Pacific Partnership (TPP) negotiations, which may jeopardize U.S. interests related to intellectual property rights concerning data collection and results for pharmaceutical development.

Despite these potential pitfalls, the outlook remains positive for continued rise in business performance for progressive contract manufacturers.

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