Tim Wright, Editor
Contract Pharma


Courtesy of Baxter BioPharma Solutions

Parenteral Outsourcing Trends

Contract Pharma asked a roundtable of business leaders from Symbiosis, Grifols, Althea, LSNE and Baxter to discuss key trends in the parenteral dosage development and manufacturing market

DESCRIBE CURRENT MARKET CONDITIONS FOR PARENTERAL DEVELOPMENT AND MANUFACTURING?

Colin MacKay, chief executive officer, Symbiosis Pharmaceutical Services: There is no doubt evidence in the sector of further consolidation in the parenteral manufacturing space, however the market remains relatively fragmented. The demand for sterile manufacturing is directly linked to several industry-wide factors. These include the number of drugs in the collective drug pipeline of the global biopharma industry, the proportion of those drugs that will be administered by injection and the proportion that lie in those therapeutic areas where medicines are traditionally injected for good medical reasons. Fuelling all of these is the amount of finance recently raised to fund biotech in the U.S. in particular. In combination, these are intrinsically positive factors driving demand for sterile manufacturing, particularly on the specialist scale where Symbiosis excels.

Marga Viñes, business development manager, contract manufacturing, Grifols International: Parenteral manufacturing is a complex industry. There are currently many opportunities for growth. It is a growing market particularly in the areas of oncology, anti-infective and cardio vascular drugs. This year a considerable number of acquisitions have taken place, whereas until now the market was highly fragmented. The outlook for the years ahead is for the market to become more consolidated. Companies with a strong area of expertise stand to gain strength and increase market share.

Don Paul Kovarcik, technical marketing specialist, Althea: The parental development and manufacturing market is experiencing healthy growth compared to other dosage form contract manufacturing. Market growth estimates are in the double digits. The main drivers of this growth are an increase in the number of biologics in development and the increased outsourcing of fill

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finish manufacturing by drug developers. Because of this growth, the industry is bringing additional capacity online to meet the demand. To a lesser extent, we also see new entrants into the parental GMP manufacturing space.

Christine Palus, vice president, sales and marketing, Lyophilization Services of New England: LSNE has seen a significant increase in the number of outsourced parenteral products. The market appears to have really turned around from the downturn that we experienced several years ago. Now it appears to be strong and companies are investing in the development of new drugs as well and generics and biosimilars. The propensity toward outsourcing has also continued and fill/finish is one of the fastest growing services to be outsourced.

Benoite Angeline, director of marketing, Baxter BioPharma Solutions: We are seeing a shift from small molecule "blockbusters" to high value/complex molecules such as biologics, immuno-oncology products, and ADCs. As a result, many CMOs need to invest in new capabilities to keep up with the evolving marketplace. For example, CMOs are adding conjugation capabilities, putting in new lines capable of handling biologics, building more lyophilization capacity, and refurbishing lines in order to install isolators or RABs.

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> – Marga Viñes, Business Development Manager, Contract Manufacturing, Grifols International

WHAT ARE SOME KEY TRENDS PUSHING AND PULLING THE MARKET?

MacKay, Symbiosis: Specialists versus large CMOs is one. Specialist CMO players have an operational flexibility to move clients through the clinical development stages quicker than larger, less nimble competitors. In contrast, several of the larger CMOs are looking to extend their service offering to align with the one-stop-shop service provider model. Arguably that is an effort to resurrect the all-under-one-roof organizational model, which the big pharma companies had in-house a generation ago, prior to the advent of modern drug development outsourcing as it we know it now. Ironically those pharma companies moved to dismantle the internal one-stop-shop principally to minimize inefficiency and mitigate fixed cost.

In addition, quality concerns in the sterile manufacturing market have remained a huge issue in the U.S., EU and in traditional low-cost economies over the past few years. The high profile actions from the MHRA and FDA on certain sites illustrate the point. We have seen the regulators become increasingly pragmatic over the past 10 years while ensuring absolute compliance. This will continue to be a major factor in the parenterals market indefinitely, due to the inherent infection risk of administering drugs by injection along with the absolute need for sterile manufacturing to minimize those risks.

Viñes, Grifols: In order to reduce costs many pharmaceutical companies are now concentrating on their core business and tend to outsource the manufacture of other products to companies with a specific area of expertise. The other major tendency is to establish long term relationships with CDMOs that last for many years. These relationships are now starting to initiate in the early stages of development of the pharmaceutical product.

Kovarcik, Althea: According to BioPlan's *12th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production*, single-use and disposable equipment adoption is the most important trend in fill and finish today (*see p.26 and p.54 in this issue*). The use of stainless steel systems that require lengthy change-over times, labor-intensive set up, and costly clean/steam in place (CIP, SIP) procedures doesn't fit with the demands of today's marketplace. Contrast that with single use systems that offer many benefits—reducing contamination risk, increasing operation flexibility, and shortening changeover times—all of which generate tangible cost savings and increase speed to market.

In general, the days of the blockbuster drug are over. As drug developers increasingly focus on personalized medicine and orphan designations, lower-volume products are being introduced to the market. Smaller indications require smaller production batches and this creates a need for flexible, multiproduct facilities. Manufacturers who focus on efficiency and have shorter cycle times will have an advantage in the marketplace.

Palus, LSNE: Three key trends are the influx of biosimilars, oncology products and lyophilization to improve stability and reduce the need for cold chain storage. Potential for cross contamination is also a concern for a lot of our clients and LSNE has implemented a number of internal systems and procedures to protect our facility, operators and clients. We have all incoming products reviewed by a toxicologist and we utilize disposable and product dedicated material as well as containment system for power API. There are no shared product contact surfaces in our facilities.

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Angeline, Baxter: The increasing demand for more complex manufacturing such as highly potent drugs/cytotoxics is one trend. This demand translates into a need for flexible compounding areas, containment technology and dedicated facilities with experienced operators and sophisticated equipment. Building these capabilities and facilities can be very costly, resulting in more companies turning to outsourcing for this type of manufacturing.

In addition, more "fragile" molecules (biologics), as well as high-value, niche products often driven by immuno-oncology and orphan drug needs are also driving the market. This translates into a need for novel packaging systems like premix bags, and filling technologies that protect the integrity of these fragile molecules, which can optimize yield of these costly APIs. Technologies include 100% in-line, non-destructive weight checking, advanced cold-chain filling, dual filling technologies and high-yield process design.

WHERE ARE THE OPPORTUNITIES FOR GROWTH?

MacKay, Symbiosis: We believe the opportunity for growth in the global parenteral sector is significant provided that as a CMO you can leverage a source of differentiation, which the client defines as truly value-adding. The substantial barriers to entry and increasing quality requirements ensure it's not a market to consider lightly, hence the number of companies who have shifted their focus away from sterile manufacturing in recent years or who have been closed down. Very few parenteral manufacturers consistently get it right given that the nature of the work is complex and includes a range of inherent technical, regulatory and service-delivery challenges. The probability of succeeding in the parenteral manufacturing market is most likely for those companies that see niche sterile manufacturing as its core service. We believe it demands that level of business focus and commitment.

Viñes, Grifols: In order to extend product lifecycles, companies are reformulating their existing products. One clear example is the growth in pre-mixed formulas in detriment to concentrated formulas. These new products also bring other advantages in the area of safety and ease-of-use.

In addition, drug delivery options are becoming more sophisticated and this is an excellent opportunity for growth particularly in the area of pre-filled syringes, in the field of oncology, and biological products.

Kovarcik, Althea: Over the last few years there has been tremendous growth in sales and units of pre-filled syringes versus other injectable dosage forms. We anticipate that many of the biosimilars coming onto the market in the next few years will be in this format as well. Althea prepared for this favorable market condition by investing in a new syringe line a few years back, which is now commercially approved and ready for business.

Palus, LSNE: As the parenteral industry grows, there are some areas that are growing faster than others. These areas include cytotoxic filling, lyophilization and the movement towards personalized medicine, which necessitates smaller batch sizes.

Angeline, Baxter: We are seeing continued strong growth in immuno-oncology, resulting in stronger demand for lyophilization services, including formulation development, optimization and container compatibility.

WHAT ARE THE MAJOR CHALLENGES IN THE MARKET?

MacKay, Symbiosis: Change regulations and quality standards remain a major challenge for many CMOs. Given quality issues elsewhere in the industry, clients are rightly vigilant when placing their projects with sterile CMOs. By demonstrating robust and continuously improving quality systems and a strong regulatory track record with the MHRA, who are regarded globally as a gold standard, clients are reassured when dealing with our team, knowing our operations absolutely comply with prevailing regulations.

Viñes, Grifols: One of the major challenges lies in effectively communicating the importance of product quality and purity to our customers at a time when the market is particularly sensitive to price.

Kovarcik, Althea: Biologics are large, complex molecules that are technically challenging to manufacture. Drug developers typically work with multiple specialized partners to make the end product. As a result, the supply chain is often complex and any disruptions can cause significant delays in the timelines. For example, delay in delivery of API (bulk drug substance) or key components to the drug product manufacturing partner could cause delays in manufacturing and final releases.

In addition, increases in drug prices, including some very high profile examples in the news recently, have come under intense scrutiny from politicians, patient advocacy groups, and the general public. The pharmaceutical industry is under pressure and will be looking to reduce production costs, simplify supply chains, and optimize manufacturing networks and infrastructure. Some of the burden will be passed on to its development partners to implement new technologies to increase yields, reduce waste, speed up development and keep cost of goods low.

Palus, LSNE: The main challenge that we see in the market is the trend of outsourcing to overseas CMOs. Many companies are choosing fill sites in Asia to cut cost of their product(s), especially for generics. Another potential challenge is the uniqueness of the different products that clients are developing. Many of the projects that we are seeing have very specific formulations or require dedicated equipment. As a CMO we strive to remain adaptable and creative and we have been able to successfully manufacture many complex projects. The fill/finish business is no longer a one size fits all industry and flexibility is critical.

Baxter: Pharma and CMOs operate in a complex and dynamic environment that requires strict attention to meeting new regulatory standards. And CMOs must constantly monitor industry trends and market developments to ensure they are ready to meet the needs of their clients. **CP**

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