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Cutting-Edge Flexibility

CDMOs perfect the art of survival in today's multi-product world

By Karen Langhauser, Chief Content Director

You can't get very far into a discussion of the modern-day pharmaceutical landscape without hearing the word "flexibility." Gone are the days where it was common to find companies relying on blockbuster stars, produced in large quantities in dedicated facilities. Many of today's specialty medicines are produced in higher potencies and smaller quantities. While the price tag may be bigger than traditional drugs, the complexity and business risk of manufacturing is also greater.

Priorities have shifted, and pharma manufacturers are stepping up their focus on increasing efficiencies and maximizing utilization in facilities. Contract manufacturers, however, are veteran players in this department. The nature of their business means juggling multiple clients and products while simultaneously delivering impeccable quality on tight timelines. Flexible production capacity, fast campaign changeovers, and rapid production at different scales are all part of the business model. Combine those demands with tight margins, and efficiency becomes a matter of survival.

Whether it's a business necessity or a chosen mindset — or a combination of both — contract manufacturers have flexibility coursing through their veins. Insight into the methodologies, technologies, and strategies that today's contract manufacturers are prioritizing can benefit the entire pharmaceutical industry as it enters a new era where flexibility is king.

BEST-IN-CLASS EQUIPMENT

Client and project diversity means equipment needs to not only be of the highest quality, but also serve more than one purpose. At Avista Pharma Solutions, a contract development, manufacturing, and testing organization with three U.S. sites, this flexibility is prioritized during equipment selection.

"We make sure all our equipment has the ability to fulfill a wide spectrum of formulation capabilities — from easy simple blends all the way to coated multi-particulates, for example," notes Rich Shook, associate director, Drug Product Operations at Avista.

This flexibility extends to validation as well. Per the FDA's process validation guidance, an Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification is generally performed for each piece of manufacturing equipment. Completing these qualifications means that the equipment can then be used for GMP manufacture of multiple products. This serves to ease the transitions for customers looking to move from early formulation development to larger scale production.

Using the same equipment for multiple products also introduces safety issues for workers and, ultimately, patients. When it comes to selecting equipment, especially with the increased use of highly potent active pharmaceutical ingredients (HPAPI), contract manufacturers prioritize equipment that both provides containment — lessening the chance of employee and environmental exposure — and minimizes contamination risks.

An Avista Pharma manufacturing technician removes the fluid bed multi-particulate coating insert to prepare for a top spray granulation process.

In order to reduce the chance of contamination, establishing a cleaning validation process is critical, and these too must be flexible enough to cover the wide range of equipment used across various contract facilities. Most guidance documents encourage the use of a risk- and science-based approach to cleaning validation.

"Our analytical cleaning methods are validated to cover each of the materials of construction found at our facilities i.e., glass, hastelloy, stainless steel and PTFE. Swab and rinsate samples are tested at every product changeover with individual cleaning limits based on established allowable daily exposure calculations. This provides the analytics needed to rapidly move a product from one production area to another," says Dave Rippon, manager, Project Management at Cambrex's Charles City, Iowa facility. Cambrex is a global CDMO with API development and manufacturing facilities in the U.S., Sweden, Italy, Estonia and Germany.

Many contract manufacturers are reducing contamination risks by investing in single-use equipment. With clear advantages in terms of flexibility, reduced cleaning resources, and lower utilities costs, single-use equipment speeds changeover between products and batches and, in the context of a multi-product facility, can drastically lower the risk of cross contamination.

Just last year, Emergent BioSolutions, in partnership with the federal government, spent $80 million to double the size of its plant near Johns Hopkins Bayview Medical Center. Emergent is a global life sciences company that manufactures specialty products that address intentional and naturally occuring public health threats, as well as provides contract manufacturing services for both bulk drug substances and sterile injectable drug products. Emergent's recent expansion included the purchase of an ABEC 4,000L Custom Single Run (CSR) bioreactor. This is the largest single-use bioreactor size available in the industry by a factor of two.

"We are not buying fancy equipment. Instead, we're using lean principals."

—Sridhar Krishnan, Catalent Pharma Solutions

The use of single-use bioreactors (SUBs) in the commercial market is a relatively new concept, but Emergent BioSolutions believes it is going to be a major factor in the future of manufacturing.

"The use of SUBs saved us a significant amount money on upfront capital installation of cleaning systems and the ongoing

operational burden of utilities, as well as enhanced overall flexibility of our facility. We can now turn over the facility in a matter of one week and have the speed and assurance of no contamination," says Sean Kirk, senior vice president, Manufacturing Operations, Contract Manufacturing Business Unit Head at Emergent.

According to a 2017 Nice Insight Contract Development and Manufacturing Survey, the top driver for pharmaceutical outsourcing is "access to specialized technologies." For contract manufacturers, this need, paired with an ongoing focus on flexibility and containment, often results in a push to select equipment that is best-in-class in the industry.

"To put it simply, we need to have what clients will need to quickly and safely accomplish their goals in a finished dosage form," says Shook.

FOLLOWING A ROADMAP

On its own, even the best-in-class equipment is not enough to enable facilities to juggle multiple products at once. Implementing new equipment and technologies requires a well-thought-out plan.

Sridhar Krishnan, vice president of Business Analysis & Excellence, responsible for Operational Excellence at Catalent Pharma Solutions, a global provider of drug delivery technology and development solutions with more than 30 global locations, stresses the importance of following a roadmap and progressing in a sequential order.

"Without understanding the process capability and limitations, automating the process does not make any sense," Krishnan explains.

Catalent employs a seven-step process when it comes to implementing new technology. They focus on understanding process capability and optimizing each process step. Rather than rush onboard with new technology trends, they instead lay the groundwork for future technology and expansion, which also assures that facility space doesn't need to be re-engineered after the fact.

"We are investing proactively in areas but doing so in a very sequential way," says Krishnan.

For example, when it comes to continuous manufacturing — an approach that has been heavily discussed in the industry for years but still has few real-world examples — Catalent is taking a methodical approach.

"We are not jumping the gun and buying fancy equipment. Instead we are using lean principles, optimizing the processes, putting semi-automated technologies in place and building the framework for continuous manufacturing," notes Krishnan.

> **"Because you don't know all your customers' needs upfront, you have to design with flexibility."**
>
> *—Ken Domaalski, Avista Pharma*

While it's tempting to always be the first one out of the gate with new ideas, smart contract manufacturers are recognizing that properly preparing facilities for the future lessens the risk of failure when it's time to launch new technologies.

DESIGNING FOR FLEXIBILITY

Planning ahead doesn't just apply to technology implementation. Contract manufacturers are also meticulous planners when it comes to facility and suite design. Open spaces, modular equipment, and equipment on wheels — enabling plant floor operators to put together a new process train without engineers and mechanics — are common.

"Because you don't know all your customers' needs upfront, you have to design with flexibility and the capability to service their needs, not only from a GMP and quality perspective, but from a business perspective," says Ken Domagalski, general manager at Avista Pharma's Longmont, Colo. facility.

"Not designing facilities correctly upfront can cause major infrastructure issues down the road if you try to realign existing facilities to meet requirements," adds Shook.

Avista's recent investment in suite upgrades and capacity expansion at its Longmont site involved upgrading three existing GMP drug substance manufacturing suites and adding a fourth. In addition, Avista has also completed an expansion of new drug product manufacturing facility containing four flexible manufacturing suites for tablet and capsule manufacturing. Flexibility and containment were designed into the suites from the start. The suites have unidirectional air flow patterns — a single pass, single direction air flow of parallel streams — which enables air to flow past potential obstacles with no risk of contamination from outside the zone.

"Each suite can be utilized for a different client at the same time, giving us ultimate flexibility, as well as containment," says Shook.

To ensure that processes and systems were not only flexible, but also designed with containment and safety in mind, Avista

enlisted the help of Safebridge Consultants — safety, health and environmental consultants who focus specifically on the pharmaceutical industry. Safebridge has been involved since pre-construction and Avista works with them on an ongoing basis to integrate suggestions and upgrades.

Emergent BioSolutions is also no stranger to the need for design flexibility. The company's newly expanded Center for Innovation in Advanced Development and Manufacturing (CIADM) at its Bayview Campus in Baltimore is designed to support the U.S. Department of Health and Human Services' strategic imperative to have "nimble, flexible capacity to produce medical countermeasures rapidly in the face of any attack or threat." Because of the government's need to respond to biological and chemical threats, as well as emerging infectious diseases quickly and economically, the 112,000-square foot facility was designed to incorporate flexible, innovative manufacturing platforms that can be used to manufacture multiple products.

"We are working with ABEC to push the boundaries on single-use," says Scott Battist, Emergent BioSolutions vice president, and general manager of the Bayview site. "Now, rather than incur the costs needed to 'scale-out' capacity with multiple 2,000-liter systems, single-use customers can achieve true economies of scale."

"Ultimately, this has helped us to focus on agility and nimbleness and our ability to service a variety of customers with unique needs across multiple platforms," adds Kirk.

EMPLOYEE SKILL AND MINDSET

Of course, no facility can operate seamlessly without the right people. The business of contract manufacturing mandates that employees have a balance of technical skills and the right mindset.

Cambrex's Charles City, Iowa, facility is home to a team of more than 350 employees who understand the specific requirements of multi-product facilities. "We operate our production areas and testing labs on a 24/7 basis. We are staffed with highly trained operations and QC/QA personnel who have extensive experience in rapid equipment changeover," says Rippon.

In the contract world, experience counts. Rich Shook and Ken Domagalski had a collective 55 years of industry experience between them — mostly with large pharma manufacturing — prior to joining Avista Pharma.

During Shook's 20 years of experience at Sandoz, he often found scheduling constraints and the inability to fulfill needs on a tight timeline to be the biggest frustrations in large pharma/contract manufacturing relationships.

"I feel their pain," says Shook. "At Avista, we look to alleviate some of the frustrations we've had in the past, and this helps build a trust with our clients."

A contract manufacturer's strong commitment to clients requires a certain type of mindset.

"We hire people who are able to handle a 24/7 commitment, who can think outside the box. Training is obviously important but having experience and a willingness to be flexible is key," says Domagalski.

At Catalent, a flexible mindset when it comes to adopting new technology is also important.

"We have reached a tipping point in the industry. With increasing scrutiny from regulators from a patient safety point of view, the industry needs to realize that if we don't start eliminating manual steps, we will not be able to meet these requirements," says Sridhar Krishnan. "CDMOs are now embarking on an automation journey and this requires buy-in from plant floor employees."

Ultimately, it circles back to employees who can build relationships with clients.

"Clients will ask themselves, 'Who am I signing up to work with and do I trust them to deliver?'" says Battist.

"The cornerstone of any successful CDMO is establishing trust — having clients know they can rely on us to help them accomplish their goals," adds Shook.

TAKING CUES

As pharma manufacturers pursue success in a landscape that demands flexibility, taking cues from those whose business model relies on their ability to efficiently accommodate different products, on a wide range of delivery platforms, with a variety of batch sizes, can help refine the art of multi-product manufacturing.

Deciphering what it takes to become a multi-product master is "the million-dollar question contract manufacturers must address," says Krishnan. And for contract manufacturers, it appears that continually working to find the right balance between a multitude of techniques and technologies — all with flexibility at their core — is paying off.

Biopharma CMO Consolidation: Opportunity or Obstacle?

M&A may dominate the 2018 biopharma contract manufacturing landscape and the future will depend on the industry's response to consolidation

By Eric S. Langer, President, BioPlan Associates, Inc.

Outsourcing to contract manufacturers can be a valuable, even critical, option allowing companies to focus their resources and talents on their primary objectives. In some cases, having others do operations that otherwise could not be done efficiently, or at all, in-house is a rational manufacturing strategy. These can include certain R&D or manufacturing tasks where the skills, equipment, or talent are not available in-house. In the biopharmaceutical industry, contract manufacturing organizations provide capacity reservoirs for companies to tap as needed, and the value proposition offered by CMOs can be compelling.

BioPlan Associates' 14th Annual Report and Survey of Biopharmaceutical Manufacturing[1] includes findings on several key aspects of the contract manufacturing industry's role in biopharmaceutical R&D and manufacturing. For example, less than half of biomanufacturers surveyed (only 44 percent) now report their facility does all their production in-house (see Exhibit 1). In other words, 56 percent outsource at least some of their manufacturing; further, 19 percent report outsourcing more than half of their total production operations. These numbers have been steadily increasing over the past decade. But the increasing trend toward CMO consolidation may create problems, as there may be fewer outsource suppliers and less competition, which may decrease options for some companies. This may also lead to constricted capacity, and likely higher prices, as those seeking CMO services tend to bid up the increasingly scarce capacity and project slots.

There also continues to be strong expectation that the future of bioprocessing will involve significantly greater outsourcing. When we compare the percent of respondents to our Annual Report who project their five-year forecast for outsourcing, we find this year's respondents predict nearly 71 percent of biomanufacturers will be outsourcing at least "some" of their bioprocessing by 2022.

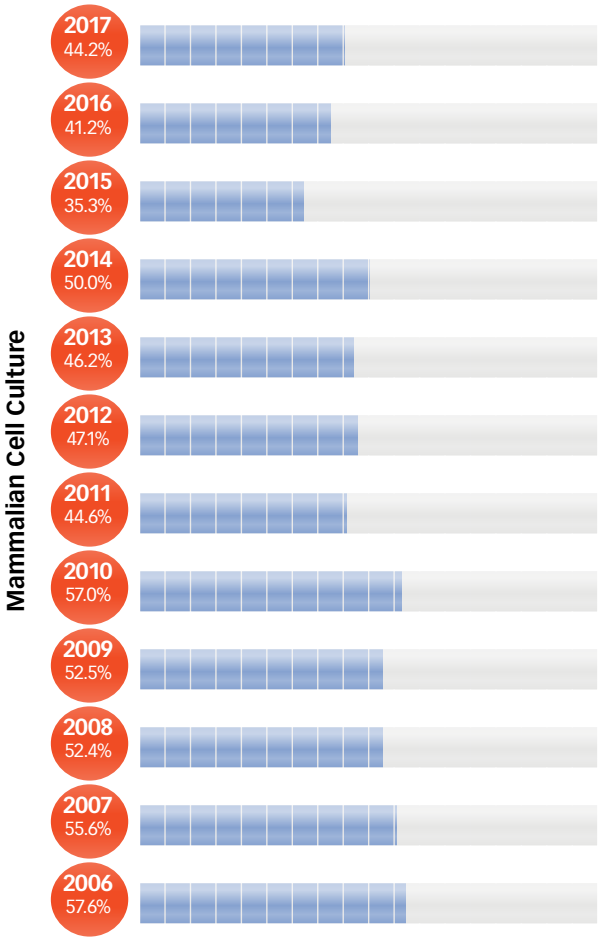
The biopharmaceutical industry has continued its consolidation among CMOs. And while a certain amount of consolidation — mergers and acquisitions — is normal in most every industry, biopharmaceutical CMOs have recently been particularly active. Both investment firms and existing CMOs are finding the market to include readily sellable commodities/investments, and have been busy merging and acquiring various biopharmaceutical-related CMO assets. This has largely started from the top down, with many of the biggest and most of the mid-tier CMOs having recently been involved in M&A activity.

The CMO industry is highly stratified, with a few major players generating most of the revenue from commercial manufacturing (e.g., billing $100s millions/year); slightly more mid-sized players (e.g., billing up to $100s millions/year); and many smaller clinical-scale CMOs (e.g., billing <$20 million/year). Commercial manufacturing is by far the major revenue source for CMOs, but is restricted to the few mostly largest CMOs, with this involving more resources, larger scales, etc. than pre-commercial projects.

The biopharmaceutical CMO industry has and remains stratified by company size, based on revenue, capacity, projects, clients and, particularly, commercial manufacturing competence. This, in particular, differentiates the largest CMOs from the rest. The biggest international CMOs offer

Exhibit 1

Biopharmaceutical Manufacturing Facilities Outsourcing NO Production, 2006-2017



Source: 14th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity, April 2017

essentially everything conventional product developers would need, from R&D through commercial manufacturing and fill-finish. They necessarily have considerable technological and regulatory expertise, often more than their clients, the Big (Bio)Pharma companies that account for most of their billing. An estimated ≥30 percent of biopharmaceuticals in major markets are commercially manufactured by CMOs, by just a few of the very largest having long been involved in commercial manufacturing. These include Lonza, Boehringer Ingelheim, Sandoz/Novartis and Patheon, each involved in manufacture of marketed biopharmaceuticals, including those with blockbuster status (≥$1 billion/year revenue). Several newer CMOs with super-sized facilities are starting to establish major facilities internationally, including in the U.S. and Europe, while other leading CMOs generally already have facilities in these major markets.

A major factor promoting CMO consolidation, particularly larger CMOs, is that Big (Bio)Pharma clients are making presumptions that larger CMOs are best for their needs. If only due to their size, large CMOs will be expected to have sufficient staff, available capacity, and facilities on multiple continents to address concerns over single-source operations. The largest, affluent biopharmaceutical developers, including the successful innovative product developers, often seek the largest international CMOs. There is good reason for this. The big clients can generally obtain larger discounts and bundle services they may need into large, multi-year contracts. Big clients can reserve large blocks of CMO project time years ahead and not be concerned about having projects to fill these slots. Small biologics developers, on the other hand, lack a critical mass of outsourceable projects and need to do more transactional contract negotiations.

2017 CMO MERGERS AND ACQUISITIONS

Large CMO consolidation deals in 2017 included:

- Thermo Fisher paying $7.2 billion for Patheon, a top-tier and one of the largest international biopharma industry CMOs
- Catalent, a top-tier CRO with significant biopharma CMO operation, acquired Cook Pharmica, a mid-sized biopharma CMO, for nearly $1 billion, significantly expanding its capacity
- Asahi Glass (Japan) acquired one of the few unacquired mid-sized CMOs — CMC Biologics — for about $500 million
- Lonza acquired Capsugel, a fill-finish company, for $5.5 billion, and other CMOs, e.g., Micro-Macinazion
- Recipharm acquired Kemwell, a major CMO in India
- KBI, a mid-sized CMO which was acquired by JSR, a Japanese chromatography supplier, acquired Opexa Therapeutics to expand its cell/gene therapy services
- 2017 also brought more large-scale partnering among Big Pharma companies and

larger CMOs, and more investments in CMO expansions. For example:

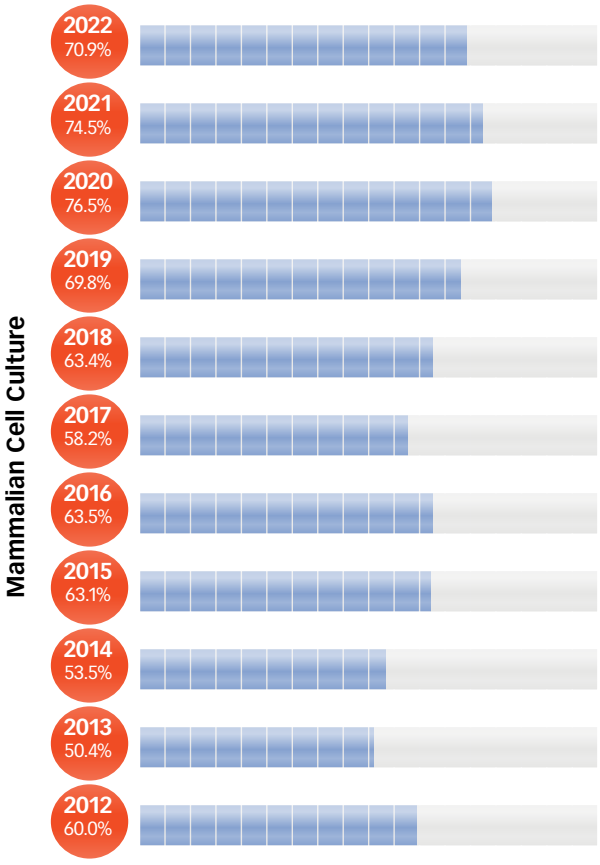
- Sanofi and Lonza are jointly constructing a new monoclonal antibody manufacturing facility in Switzerland
- GE is investing $184 million in a new facility in Ireland to manufacture for several clients
- Lonza is adding 150,000 sq. ft. to its recently completed 100,000 sq. ft. cell and gene therapies manufacturing facility in Texas
- Vetter is investing $320 million, and Fresenius Kabi is investing $250 million in various new U.S. sterile injectables facilities

Many, if not most, existing CMOs are continuing to report bioprocessing capacity expansions, most involving addition of single-use production bioreactors and process lines. This is besides a growing number of new and established CMOs entering and/or expanding services in new technology areas that are just starting to become more mainstream, notably cell and gene therapies and antibody-drug conjugates (ADCs).

Patheon is perhaps a model of industry consolidation to date and may foreshadow the future. Already one of the largest international biopharmaceutical CMOs, Patheon was acquired in 2017 for over $7 billion by Thermo Fisher, one of the largest sellers of bioprocessing supplies. Recall that originally Gallus, then already a large CMO including

Exhibit 2

Five-year Projections: Percent of Biotherapeutic Developers Planning to Outsource at Least Some of Their Future Production; *Projections made 2007-2017*



Source: 14th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity, April 2017

commercially manufacturing several biopharmaceuticals, acquired Laureate Pharma, a mid-sized CMO; DPx Holdings, an investment company jointly owned by Ridgemont Equity and DSM, a large chemical company with biopharma CMO capacity, acquired Gallus and merged it into its large, primarily small-molecule oriented Patheon, forming a very large international biopharmaceutical CMO; and Thermo Fisher subsequently acquired Patheon. Owning one of the largest CMOs will obviously provide Thermo

Fisher with a wide variety of options for combining and bundling diverse products and services, including using its CMOs as test beds for new products and technologies, and perhaps offering discounts for bundling of both supplies and services. With Patheon, we see not just CMO M&A activity, but acquisition by non-CMO investors — the former Patheon investment/holding company and Thermo Fisher, a diversified high-tech mostly hardware supplier. Presuming the Thermo Fisher integration of Patheon works out, we may well see other pure investment firms and companies not primarily involved in the biopharmaceutical industry acquiring biopharmaceutical CMOs.

Multiple other current leading bioprocessing suppliers also have their own but smaller biopharmaceutical CMO operations, e.g., MerckMillipore/SAFC and GE Healthcare each have multiple facilities worldwide. Several other leading bioprocessing suppliers, notably Pall and Sartorius Stedim, currently do not own any CMOs. Presuming cost-savings from these acquisitions can be realized, clients will likely find such integrated bioprocessing suppliers that also provide full CMO services to be attractive. These cost savings and other benefits could well happen, leading to more mergers. But this is largely dependent on the future prospect of mergers such as Patheon with Thermo Fisher. Further, not every bioprocessing equipment suppliers can also manage services businesses. And some services business have suffered from acquisition by product-oriented companies. Services businesses can require very different operating and marketing philosophies. If not managed well, the unique nature of services businesses can create integration problems, where the client, and ultimately the bottom line can suffer.

IMPACTS OF CMO CONSOLIDATION

Acquisitions and more centralized control of significant CMO capacity may not be good for CMO clients and the industry in the long run. Will reduced competition result in lower costs? Will smaller clients find their projects pushed out of the queue? Based on experience, especially with fewer competitors and higher demand, there is little precedent for prices ever going down among bioprocessing suppliers.

Whether these super-sized consolidations are good for the biopharmaceutical industry, and for CMO clients is not clear. And whether Big Pharma preference for partnering with fewer, larger suppliers will continue remains to be seen. However, we expect the mergers and acquisitions in recent years will likely also affect remaining independent lower-tier CMOs, as CMO consolidations, largely driven by capturing outsourcing from Big Pharma companies, moves downscale. Further, it is possible the costs of M&A related financing will put some CMOs in a weaker position, making it more difficult

to invest in needed expansions, such as in cell and gene therapy sectors.

The largest CMOs, each with multiple world class-size facilities, are particularly attractive to large clients because larger CMOs can offer broader, large-scale manufacturing infrastructure, and more specialized bioprocessing and regulatory expertise. These clients are increasingly looking to outsource much of their less innovative R&D and products, such as conventional antibodies and proteins, biosimilars, etc. to large, commercial scale CMOs. In many respects, the largest CMO facilities and expertise often surpass that of their Big (Bio)Pharma clients. These CMOs generally handle all, from cell line through fill-finish and packaging, and can do this at geographically-distributed facilities, often offering better access to local/regional markets and providing 2nd-source backup commercial manufacturing at geographically-distributed facilities.

However, a common complaint among smaller and mid-size clients is that they are ignored by large CMOs. Their smaller single projects often do not fit well within the largest CMOs. Smaller clients and projects often get delayed, besides services costing more than at smaller but less capable CMOs. Mergers create larger CMOs that often are not perceived as suitable partners for smaller clients.

The largest CMOs generally have well-developed proprietary in-house manufacturing platforms, including those used at commercial scales, often for multiple products. These platforms can provide benefits, as CMOs plug clients' products into their established platforms and practices, saving time and potentially costs. Leading CMOs are also likely to have already licensed any needed third-party technologies. This works well for product developers with conventional bioprocessing, such as mainstream recombinant monoclonal antibodies and proteins with conventional structures. However, established CMO technology platforms often do nothing for clients with more innovative or newer classes of products, such as novel antibody structures, cell

A common complaint among smaller companies is that they are ignored by large CMOs.

and gene therapies, antibody-drug conjugates, live microorganisms as therapeutics, etc. Many of these prospective clients complain that the largest CMOs primarily want to do production their way using established platforms. This particularly affects smaller developer companies, which are often forced to go to smaller and less experienced CMOs more willing to adapt and accommodate unique technology needs.

Large CMOs' size and established platforms allow increased efficiency and economies-of-scale, compared with smaller CMOs, with their commercial manufacturing providing higher billing and margins (vs. R&D support) over long periods. Large CMOs often charge higher prices due to their capabilities, and established track records. However, many smaller companies, which tend to have more innovative products, must often adopt development strategies involving different, smaller CMOs for R&D and clinical needs, and then consider hiring yet another CMO to handle commercial manufacturing.

Smaller CMOs, of which there are many, and mid-sized CMOs, of which there remain relatively few not merged/acquired, are needed by the biopharmaceutical industry to fill niche segments. In our prior studies, we have found that smaller CMOs can often be better partners. Smaller CMOs can provide preclinical and early clinical phase support comparable in quality, time, etc. to that of the largest CMOs, while generally lacking in facilities and experience for commercial manufacturing. For many smaller biologics developers, smaller CMOs can do what is needed pre-commercially in comparable timeframes. However, for some clients and projects, smaller CMOs may come up short in terms of manufacturing, regulatory and other expertise.

FUTURE OF BIOPHARMACEUTICAL CMO SECTOR

Pressures and good rationale for outsourcing to CMOs persist, and CMOs of all sizes will continue to grow, as this sector is tracking with the ~10 percent annual growth in biopharmaceutical products revenue. But much of the future of the biopharmaceutical CMO sector and broader industry will be dependent on near-term responses to consolidations so far, including perceived needs for consolidation among CMOs and their owners.

REFERENCES

1. *14th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, April 2017, BioPlan Associates, Inc. Rockville, MD*

Leaders of the Pack

Contract packagers accelerate pharma packaging innovation

By Doug Bartholomew, Contributing Editor

Complexity is everywhere in today's fast-changing world, but outside high tech, there are few industries where the ground rules, the products and the markets are shifting as fast as in pharmaceutical packaging.

Bursting the envelope — er, blister pack — is an exploding array of new drugs and drug delivery formats, many of which need new ways of presentation and packaging. At the same time, regulators in the United States and Europe are taking a more active stance in deciding how drugs can be packaged and shipped to domestic and global markets.

These changes, combined with the growing trend of pharmaceutical firms to outsource nearly everything but R&D and marketing, have opened the door for contract firms to take a lead role in packaging innovation.

Contract packagers are providing much of the innovation in how many new drugs — as well as traditional remedies — are brought to market. "As manufacturers shift more volume to contract packagers, they are going to be looking for their partners to bring more innovation to packaging," says Matt Rayner, executive director of operations at Legacy Pharmaceutical Packaging, a contract packager based in St. Louis, Missouri.

Also contributing to this contract packaging boom is the move toward smaller, more flexible production lines in response to demand for personalized medicines and smaller batch sizes. "With big pharma

Sharp Packaging Solutions' in-house design team is regularly challenged to meet the specific needs of pharma clients. This assignment required designing a kit that included components of drastically different sizes while communicating effectively the steps needed to administer the drug in the precise order required.

increasingly outsourcing R&D, process development and manufacturing, including packaging, the entire contract arena is growing," says Jerry Martin, pharmaceutical and life sciences consultant for the Association for Packaging and Processing Technologies (PMMI). Still another factor is the reliance on contract manufacturing by small biotech firms, which tend to have limited investment in infrastructure.

In many instances, the contract packagers' role has expanded to include designing and manufacturing the packaging, filling the packages and shipping the finished product to the pharmacy, HMO or other buyer. In effect, they've become the hired gun of the industry, taking on a host of challenges that pharmaceutical manufacturers would prefer to off-load, allowing them to both reduce costs and concentrate on the business of developing and bringing new drugs to market.

"As a contract packager, we provide a full turnkey operation for our customers by sourcing all of the components from our vendors, packaging the drug into its primary and secondary packaging, and when required, serializing the product to track and trace it through the supply chain," says Joe Luke, vice president of sales and marketing at Reed-Lane, a midsize contract packager. "We work with virtual customers to design a package that matches their ideas with what our packaging engineers know our lines are capable of."

INDUSTRY EXPERTISE FOR HIRE

Ultimately, contract packagers must confront largely the same battery of challenges as the pharmaceutical industry overall — only they must be able to shift on a dime to accommodate the varying packaging needs of manufacturers whose drugs range from self-administering biological treatments in prefilled syringes to glass vials to pills in blister packs.

As a by-product of having to deal with all manner of product developed by the industry, contract packagers tend to have built up extensive expertise in dealing with issues

Legacy Pharmaceutical Packaging brought design innovation to its Ecoslide-Rx child-resistant pack by adding a daily dosing reminder on the box to ensure patient compliance.

such as serialization, anti-counterfeiting measures and tamper-evident packaging — all capabilities attractive to big pharma.

"The anti-counterfeiting activities — primarily tamper-evident packaging and serialization — fall directly in the domain of contract packagers for expertise," Martin asserts.

"Pharmaceutical companies are taking more advantage of contract manufacturers as a way of reducing costs and expanding their capabilities to take advantage of the new packaging technologies the contract manufacturers are developing," Martin explains. "The big pharma companies are not set up to deal with these emerging markets, and they are going to avail themselves of the packaging and distribution chain that the contract companies already have in place and available on a global basis."

There are obvious cost savings. Revamping a packaging line every time a new drug or family of drugs is introduced can be far more costly than outsourcing the new product from the get-go. "A lot of manufacturers are looking to outsource more and are relying more on contract packagers because they don't want to invest in modernizing an older packaging line," Rayner says.

The contract packaging market had revenues in 2016 of about $9 billion, Martin says, and it's growing at about 7 percent per year, with a projected revenue total of $15 billion by 2022. The global expansion of the drug market is one factor spurring this growth. The other big factor driving contract packaging is the cost pressures facing pharmaceutical makers. "By contracting out manufacturing and packaging, it's a lot cheaper — you don't have to invest in all the equipment yourself," he adds.

Such emerging trends as single-use or modular manufacturing that enhance the flexibility of manufacturing operations often are best suited to the new, smaller-volume vaccines and other biological treatments. "Companies are looking at adopting single-use manufacturing because it allows them to produce at whatever scale they need," Martin points out. "For formulation, filling and packaging, these flexible operations allow them to contract out at the scale they need. It gives the drug companies the flexibility to concentrate on their core competencies and avail themselves of the new technologies in packaging from contractors."

SERIALIZATION ON DECK

Serialization continues to loom large, although most contract packagers have their hands full meeting today's regional market requirements. "Serialization is not an immediate requirement, because much of the marketing is regional," says Martin. "Nonetheless, it still has many technical and regional challenges."

While ensuring protection against counterfeiting and tampering, serialization also will help bring about a level of supply chain security on a global basis that so far has yet to be achieved. "Supply chain security is going to be required," Martin says, "so being able to provide it will be critical. Pharmaceutical manufacturers unable to address serialization and product track and trace requirements ultimately are not going to be in business."

Of course, many of the larger contract packagers already are gearing up for serialization's eventual global requirement. "We invested in serialization early on, so we're well equipped to meet upcoming regulatory requirements for unique identification of drug products," says Gaurav Banerjee, director of technical services & enterprise applications at Sharp Packaging Solutions.

The major global contract packaging companies all have the technological capability to implement serialization at least regionally. Global serialization will be established once harmonized standards have been approved by the appropriate regulatory agencies for different markets, Martin says. "The big packaging suppliers will become broader in their offerings and maintain their global approach," he adds. For example, Sharp Packaging Solutions, as part of a global firm, UDG Healthcare, Plc, operates facilities in the U.S., UK, Belgium and the Netherlands.

Martin believes it may take a while longer before global standards have been fully adopted and implemented. For example, he says, serialization poses challenges, "both from the physical space the information requires on the label to differences in national/regional standards.

"We're still in the innovation stage, but perhaps in 5 to 10 years there will be harmonized international packaging and

labeling standards so products can be shipped anywhere in the world," Martin continues. "Right now, serialization and other labeling requirements have to conform to where the product will be shipped. But the big producers want to be able to sell on a global basis, and they don't want to have to be changing labeling because of regional differences."

production capabilities and supply chain networks needed to bring new products to market in innovative packaging.

"The packaging challenges become even greater for virtual pharma companies and biotech, with the need for multi-component kits comprising vials, prefilled syringes and auto injectors that must be presented in a

In some cases, the innovation of a new drug can spawn an innovative approach to packaging.

DESIGN AND INNOVATION

With change being the name of the game, contract packagers must be capable of not only responding to the needs of pharma companies, but taking a lead role in creating new forms and styles of packaging. This kind of innovation in packaging is one way contract packagers can gain a leg up on the competition. "We have a well-developed design service offering that provides options to our customers for compliance and counterfeiting prevention," says Banerjee.

Having a design capability in-house is essential for contract packagers when dealing with the small, fast-growing biotech firms that often lack the various skillsets,

staged format," Banerjee adds. "Our design team is regularly challenged by clients for designs that are intuitive to use for physician and patient, are commercially viable to produce and that enhance patient safety."

As examples of innovation in packaging, Banerjee points to Sharp's child-resistant packaging and its five-level aggregation of serialized product, from individual blister cavity on a card, to blister card, to carton, to case, and finally to pallet.

However, innovative packaging alone does not, by itself, ensure widespread industry adoption. "Given the regulatory issues and the fact that a new technology has to be approved by the FDA in the U.S. or other

regulatory body overseas, there is a reluctance on the part of drug manufacturers to implement a new technology if it's going to take longer to get the product to market," Martin adds. "It will cost more and take more time to get that drug to market with an innovation in packaging."

In some cases, the development of a new drug or family of drugs in itself can help spawn an innovative approach to packaging. "Innovation in packaging is largely tied to formats and dosing," Banerjee says. "As there are new ways of getting effective treatments to patients, there will have to be new packaging methods to go along with those advancements."

"Innovations are coming from the packaging material, equipment and software suppliers — coordinating laser printed labels with filling lines, post-fill secondary packaging and labeling," adds Martin.

"We are an extension of the manufacturer," says Rayner. "For example, we have to be able to connect with their IT systems for serialization. We are always trying to find an innovative solution for the customer," he says, adding that the company has an engineering group that works with customers to develop packaging designs.

"There are a lot of innovative packaging designs and concepts, but the difficulty is in making them cost-effective," says Brad Rayner, vice president of sales and marketing at Legacy Pharmaceutical Packaging and the brother of Matt Rayner. "We were the first to launch our Ecoslide-Rx package, a child-resistant compliance pack that helps ensure patient compliance" with a daily dosing reminder on the box. Another new design was the company's dispensing carton, a prepackaged aid to the pharmacist that enables faster, more accurate dispensing of the prescribed number of tablets in a bottle or carton.

From an innovation standpoint, Martin envisions advances in packaging designed to ensure greater stability of protein drugs. "We're already seeing a switch from siliconized glass vials and rubber stoppers to new glass formulations and fluoroelastomeric coatings that eliminate silicon and glass contamination, reduce leachables from stoppers and minimize protein adsorption/desorption interactions."

An updated standard for extractables and leachables from pharmaceutical packaging has been published for polymeric primary packaging by USP (661), Martin notes, and a new standard for determination of extractables from polymeric process equipment (USP 665) will be published later this year.

In other words, stay tuned, you haven't seen anything yet...