Prospects, Analysis and Trends in Global Pharma

Industry Expert Panel Submissions

CPhI Annual Industry Report 2017

Released at CPhI Worldwide, October (24-26), 2017 in Frankfurt
Part 1.

Contract services and outsourcing
PANEL MEMBER
Gil Roth, President of the Pharma & Biopharma Outsourcing Association (PBOA),

CMO/CDMOs: Challenges and Opportunities

Introduction

“All predictions null-and-void if Trump wins the US Presidential election”: That’s how I closed out last year’s ‘Looking Ahead’ piece. Suffice to say, my crystal ball is C-R-A-C-K-E-D, and my backup Magic 8-Ball’s answer to everything is, “Reply hazy. Try again later”. Since the election last November, the pharma industry and US healthcare overall have been on a roller-coaster ride, learning how to work with an unpredictable new environment. I won’t say things are settling down now, but there seems to be less of a tendency by pharma to overreact to presidential tweets than in the first months after the election.

What does it all mean for the CMO/CDMO industry? Good/unanswerable question! Rather than go into “predictions,” I’ll highlight concerns and how they may play out. Sound good?

Protectionism

One of the biggest concerns about the new administration has been what its “America First” ethos would mean for the globalized supply chains of the bio/pharma sector. Will we see a push for economic protectionism that compels drug companies to bring manufacturing in-house and/or to move their production facilities to the US?

The verdict is out on that one, but the Republican leadership in the House of Representatives recently conceded that one of the key tools to promote domestic production – a Border Adjustment Tax (BAT) – is off the table, after pushback from business interests. The BAT would have (in essence) taxed imported goods to the US and removed taxes on US exports, but could also have had serious consequences for consumers if currency appreciation didn’t follow a particular theoretical model of economics. There’s an array of policy tools that could stimulate domestic manufacturing, but they inherently involve penalizing ex-US manufacturing, and would likely be challenged in the World Trade Organization.

There’s an array of policy tools that could stimulate domestic manufacturing, but they inherently involve penalizing ex-US manufacturing
Still, those considerations can be a factor in the CMO/CDMO space. In November 2016, Patheon acquired an API plant from Roche in Florence, SC. In an earnings call, Patheon CEO Jim Mullen noted that the move would serve as a hedge if BAT was implemented, giving Patheon a domestic API facility with room to grow.

BAT would have been part of an overhaul of the US tax code, which hasn’t seen a major revision since 1986. Given how tough it was to come up with a feasible replacement plan for the Affordable Care Act, it may not be realistic to expect enough interests to line up for a true overhaul, but we could still see a repeat of the 2004 American Jobs Creation Act, which gave a one-time tax holiday for US companies to repatriate revenues that were kept overseas.

A massive influx of pharma dollars could cause those big companies to alter their supply networks and spend more on domestic in-house facilities, to the detriment of their CMO/CDMOs, but I think it’s more likely that the money goes to share buybacks, dividends, and acquisitions of US-based targets (this could lead to pharma-layoffs, which is why I renamed it the American Jobs Destruction Act last time around).

Consolidation

Speaking of acquisitions, one of the perennial issues facing the CMO/CDMO sector is consolidation, under the principle that there’s too much capacity overall and that a winnowing out through mergers and shutdowns will lead to more efficient and effective outsourcing.

It hasn’t exactly worked out that way. Some of the biggest deals in the sector – and they were BIG – don’t exactly qualify as “consolidation.” AMRI Inc. was acquired in June 2017 by a pair of private equity firms — The Carlyle Group and GTCR — but neither one has a presence in the dosage form CMO/CDMO sector. A month earlier, Patheon Inc. was acquired by Thermo Fisher in a $5.2 billion deal that shocked the industry. But Thermo doesn’t have a CDMO unit to merge with Patheon -- besides its Fisher Clinical Services segment, and I’ve found that clinical services can be a very different business than development and manufacturing services -- making this more of an additive move than a synergistic play. So, while those were large deals in the CMO/CDMO space, they don’t represent consolidation as we know it. Rather, they’re a sign that these companies – and by extension this sector – have untapped potential. (That said, I should note that AMRI was a serial acquirer prior to this buyout.)

On the other hand, Lonza acquisition of Capsugel was both large (~$5.5 billion) and consolidation-y, as it served to build out Lonza’s one-stop outsourcing model with more integrated service offerings. CDMOs are certainly looking for synergistic deals, but that scale of acquisition is rare in this sector, where we’re more likely to see smaller scale buys and tie-ups. Significant but not break-the-bank, Apotex’ Accucaps unit was acquired by Catalent late in 2016, bolstering the super-CDMO’s softgel offerings (and preventing competitors from adding it to their offerings), and Evotec made a larger move by acquiring Aptuit this summer.

I think the sector is still ripe for narrow-focused acquisitions of technologies, while ex-US CDMOs may look to boost their US presence by acquiring either an existing provider or an available pharma facility. CDMOs talk more about expanding their current facilities, adding services and building more integrated suites of services.

Immigration

“America First” carries another concern for the pharma industry overall, and that’s immigration to the US. The new administration’s first major move was an executive order banning immigration and refugees from several countries. It was struck down in court, subsequently modified and is now working its way back through the US legal system. The administration meanwhile sustained its campaign rhetoric about barring illegal immigrants and more recently endorsed a legislation that would cut legal immigration to the US in half, partly based on a points system.
These initiatives may not be permissible or practical, but they could have the effect of making the US appear unwelcoming to potential pharma-employees. This may shift the talent pool – for both in-house pharma and CDMOs – to other nations and create greater opportunities for companies with ex-US operations, while impacting domestic wages.

**Drug Pricing**

Here’s one of the issues where the administration’s approach is simply unknown. When he was a candidate, the President inveighed against the cost of pharmaceuticals and the pharma industry’s use of lobbyists. Leading up to his inauguration, he repeated the charge and implied he had a plan to reduce drug prices. But the administration hasn’t offered up any new strategies beyond getting more generics approved more quickly in order to bring prices down. That’s an admirable goal, and we’re glad the administration hasn’t tried to lower prices by fiat, but at the same time, it’s an example of that roller-coaster I mentioned at the outset; pharma companies and the CDMOs who serve them seem in the dark about policy decisions that could cause major disruption to their business models.

**Regulatory**

One of the bright spots of 2017 was the FDA Reauthorization Act (FDARA), the bill that reauthorizes four of the FDA’s major user fee programs, Prescription Drugs (PDUFA), Medical Devices (MDUFA), Biosimilars (BSUFA), and – the one that’s nearest to me, because I spent 10 months yo-yo-ing on the Northeast Regional train between New Jersey and Maryland so I could negotiate it – Generic Drugs (GDUFA).

GDUFA will include numerous enhancements to improve review times for generic applications, and increase communications with industry regarding complex generics, which have bedeviled the sector and the agency for years. With a significant increase in budget (up 50%, but with a reduced share coming from CDMOs), GDUFA II will help improve predictability for generic companies and their manufacturing partners, while bringing lower prices to patients.

There are plenty of other areas where we’re waiting to see how the new administration will work with the FDA in the years ahead. The new FDA Commissioner, Scott Gottlieb, M.D., has both agency and industry experience, so he understands the role FDA can play in facilitating drug development (be it innovator, generic, biosimilar, drug-device combo etc.).

That said, he works within the parameters of the new administration. Prior to his appointment, the White House barred new federal hiring across the board, although FDA eventually received clearance to add staff. Another early executive order specified that federal agencies would have to rescind two regulations for every one they added, but we’ve yet to see how that will play out.

You see what I mean about not making predictions?
Continuous API Manufacturing – It’s time pharma went with the flow

Introduction

There has been a recent surge in interest for continuous processes in the pharma industry as the benefits have become more widely known. This is due to the availability of more expertise in the area of flow chemistry over the last decade, in combination with the need for the industry to develop safer, faster and more sustainable processes, with higher quality and less expensive products. But the first thing we need to do is define what we mean by continuous processing and flow chemistry. The industry is running two broad types of continuous processing, in finished dosage form and API manufacturing – often commentary in the media has made little effort to separate these, and they invariably get confused. Whilst continuous processing in finished formulations with the potential of on demand dosing is extremely exciting, for the purpose of this article we are instead going to specifically look at the improvements flow chemistry can bring to process development and manufacturing for APIs.

It is time the wider pharma community set aside the decade-old views of continuous manufacturing as a ‘luxury but impractical tool’ and looked at the technology as a practical and valuable approach that can resolve our every day chemical processing issues. Flow chemistry offers a more streamlined and continuous synthesis process as well as a variety of advantages compared to a batch operation. Incorporating a flow operation results in increased production with decreased capital. In terms of safety, flow reactors for pharmaceutical reactions are normally run in much smaller volumes than those of batch reactions, therefore lowering the risk of hazardous reactions. Dealing with toxic chemicals is also safer – cytotoxic APIs can be produced in inexpensive, dedicated, and disposable equipment sets for production of low volumes of these compounds in the laboratory fume hood.
for safe reactions that were previously unstable in batch. Reactions can also undergo superheating, enabling them to be heated above their boiling point, further resulting in faster reaction rates. The flow operation reduces the break time between consecutive steps and can significantly reduce the manufacturing time.

An important advantage of flow chemistry is the ability to fully control many of the parameters, such as mixing, temperature, and reaction time. By having the capability to add or remove heat almost instantaneously, one could remove the heat generated from a reaction; for exothermic reactions or a reaction requiring hazardous materials, this is an especially important benefit. Flow reactors also allow control over residence time, which is the time that the reaction is exposed to a set temperature, allowing for far more precise reaction times. This is immensely beneficial, particularly if a reaction creates more than one product. There is also continuous monitoring of the quality – such as purity – by online or offline sensors, so parameters can still be fine-tuned during the operation in order to obtain the best product quality. During a batch process, you would need to wait until reaction is completed, by which point it may be too late to make any adjustment.

The intense mixing in flow chemistry is provided by microreactors, which enables scientists to use multiple phase systems, fewer solvents, and produce purer material – reducing unit operation and work up steps. The high-temperature, high-pressure flow reactors reduce reaction time and provide better conversion whilst using starting material more efficiently. This requires tightly controlled Process Analytical Technologies (PAT), and resolution of any Quality Assurance issues related to acceptability of the intermediates. Microreactors can be designed to fit the requirements needed for the reaction, therefore providing customisation opportunities. In addition, microreactors have low maintenance and operational costs without abandoning productivity and efficiency, which provides an economic incentive. These technological advancements are valuable and vital assets in flow chemistry and have expanded the versatility in its use.

Although the advantages are clear, before a flow process can be developed a working small-scale batch process should still exist since, in general, developing a flow step may take much longer than its batch equivalent. However, once a flow step has been developed, its scale up is far easier and encounters fewer issues than in batch. The reason for this is that the sizes of the reactors in the scale up version are normally less than 20 times the size of the lab version. For example, the diameter of lab scale PFR tubing is normally around 1/16" - 1/4", and its pilot plant version is around 3/8" - 1/2" – these are not very different in size. The scale up in the batch process could be 100 to 1000 times bigger than the original lab scale process – this is impractical as mixing and other engineering aspects can complicate such large scale up operations.

The total cost of producing a final product depends on the cost of the process R&D, starting materials and the operational costs – of these, the latter two have the greatest impact on the overall cost. Using the flow operation, cost incentives include the reduction of energy costs and reduction of impurities and waste products. Awareness by chemists of the capabilities of flow chemistry as an enabling technology gives them the power to design shorter synthetic routes, and therefore also reduce the cost once operational. Of course, reducing waste promotes efficiency, enhances purity, and is beneficial to the environment. Companies may realize too late that their drug has an excessive, multi-step process that could have been shortened and since their cost would be unnecessarily high due to a longer synthetic route, this could result in losing substantial amounts of profit.

An important advantage of flow chemistry is the ability to fully control many of the parameters, such as mixing, temperature, and reaction time.

If we assume that flow facilities provide major benefits at larger scales, we could see that later phase and commercial products are more amenable to continuous processing and will see the greatest benefits. Big pharma such as Lilly, GSK, and Novartis are already preparing for launch of their pilot or commercial plant facilities and, at this time, these plants are built within their own companies. However, over time these companies may decide to outsource such operations to CMOs or CDMOs – we have one such flow chemistry partnership with big pharma, but we’re very much in the minority. Our belief is that it’s only a matter of time until much more flow work is outsourced, and we are building up capacity in anticipation of this.
During development, flow steps seem to be more appropriate for early steps of the synthetic route where less expensive raw material are available for process development and the volume of the material to be processed is larger. Perhaps the majority of the APIs currently produced at a commercial stage have the required volume to be turned into flow. However, due to regulatory issues, limited changes can be applied to the existing commercial processes but it can still potentially be achieved with some investment and time.

The transition from batch to flow operation is generally thought of as both costly and inconvenient, but implementing this change in early development is simple and beneficial. Comparing Phase I and Phase III, it is much easier to manage changes in development and regulation if switched at Phase I, but to switch at Phase III could result in a delay in market release and a loss in both time and money.

Yet, the number of flow steps during development currently remains below 5%. The message here is clear: for flow chemistry to deliver on its huge promise, pharma and CDMOs need to build the platform into the phase I process R&D of innovative API programmes. This requires commitment from the beginning of a project, and a wider commitment to running in flow whenever possible. Flow chemistry has suffered slow implementation into the industry – especially as compared to some other industries such as oil and gas – even though more are beginning to recognize its benefits. This is largely due to the increase in demand for flow chemists while there remains a lack of experience and education in the field. With an entirely new manufacturing process people may be reluctant to adopt it as they think it may slow down the manufacturing process. The safety, efficiency, and flexibility of flow chemistry are what drives its high interest and is why it should become an essential component in research, development, and for the future of the industry.

Q&A on the future of flow chemistry and its industry adoption

**Q) What are the major drivers for the recent surge in efforts within the pharma industry in choosing to use flow processes and investing in greener chemistries?**

The need of the industry to develop safer, faster, and more sustainable processes with higher quality and less expensive products, combined with the availability of more expertise in the area of flow chemistry built up in the last decade are behind the recent increase in the industry using more continuous flow processes. Parallel to major pharma companies, we actively initiated our activities in the area of continuous processing and in the last two years we have had around 40 steps processed in flow in our Jinshan plant (in Shanghai).

**Q) What uptake do we predict over the next 5 years – how and why?**

Currently, many pharmaceutical companies believe that there should be a reaction specific driver to using flow technologies in plant operations, although this might not be the case in the future. At STA, for example, we have great batch plant facilities in Shanghai and Changzhou in addition to many experienced batch scientists to support the PRD and plant operations. It is more economical and meaningful to utilize the existing knowledge and investments in batch operations, and do the chemical steps in flow when there is a driver. In the next 5 years however, more advanced flow technologies will be developed and more dedicated flow companies will be developing continuous processes, while the existing scientists will build up more experience in this area. As a result we should expect a wider range of reactions to be processed through flow, and a lower bar to be established for selecting a process to be operated in flow. During this time, we expect to see more multistep flow processes performed.

For companies with a strong flow team, we should also see more work-up operations steps coupled with the reaction
steps in flow. We expect them to move from the currently 1-2 steps to 5-6 chemical steps in flow. This should be coupled with 1-2 unit operation steps per a chemical step including solvent switch, phase separation, extraction, crystallization, filtration, and dissolution bringing the flow steps to 10-15 steps (including unit operations). This brings the system closer to full flow operations, but it is unlikely that within the next 5 years all of the chemical steps on a project will be carried out using flow technologies.

Q) As a company you not only utilize more efficient processes, but you are currently looking to reduce your PMI (Process Mass Intensity), do you think this is something that will set a trend and we will see more companies moving to flow chemistry in the future with waste management and safety regulations getting tighter?

Yes, environmental regulations including control of PMI are one the industry’s big concerns. The smart design of a flow step process could end up using less solvent mass compared to the batch systems. Flow chemistry can not only be applied to chemical steps, but can also be utilized for unit work-up operation steps. In fact, it makes sense to do the work-ups between two consecutive chemical flow steps to be done in continuous mode.

For example, a more effective work-up is provided if a multi-step counter current extraction system is used to separate the liquid phases instead of using batch mode phase separation; this means less solvent is used in the process. In addition a flow chemical step might generate purer intermediates and less work-up might be needed. Furthermore because the flow reactors are smaller, less solvent is used to wash these reactors after run completion. Additionally, the high temperature accessibility provided by flow may mean less solvent requirements due to the higher solubility for compounds at high temperatures or even going fully green by performing the reactions at melt conditions.

Q) Does using continuous flow techniques allow you produce drugs that you were perhaps unable to make using batch processes?

Experience has shown that the batch chemists can ultimately find routes to develop the final API. Therefore it may not necessarily enable us to produce new drugs, but it allows us to use shorter routes to the final product. The reason for this is that flow chemistry enables us to adopt a reaction path that might not be possible in batch mode due to the safety or quality concerns. As an example, performing azide or ozonolysis reactions usually reduces the length of synthetic steps – these reactions are much safer in flow than in batch mode. Around 30% of the flow reactions we have performed at STA are related to the safety; without flow capabilities we may not have been able to do these steps or may have had to take different and perhaps longer synthetic routes.

Q) How crucial is support from the authorities in ensuring flow chemistry secures a place in the future of the pharma industry?

This is very crucial. Fortunately, the FDA is a strong supporter of converting from batch to continuous. Continuous processing has less manual operations and logistics and disturbances that caused process review concerns with the FDA. However, last year the FDA gave the green light to Johnson & Johnson to produce its HIV drug Prezista in flow mode and then invited other companies to take the same approach. Johnson & Johnson has now said that it may want to produce up to 70% of its highest volume drugs using flow manufacturing. Vertex has also built a continuous manufacturing plant in Boston for one of its drugs.

Q) Why has pharma and the wider industry been slow to adopt flow chemistry and continuous processing?

Bulk chemicals industries such as fertilizer, sugar, and oil are at least 50 years ahead of pharmaceuticals in using flow technologies. There are at least two reasons for this: the first and most important reason in this difference is the volume of the commodities they are dealing with. The other reason is hidden in the structure of pharmaceutical industry. Prior to the 1990’s, chemists were almost the only lab scientists developing chemical processes, and management of process R&D centres was also done by chemists. By end of the same decade, chemical engineers had been hired as research staff to deal with chemical reaction kinetics and unit operation steps including crystallization and distillation. The same engineers later expanded their scope of work into flow chemistry. By around 2004, several major
companies had flow teams. By 2010, almost all major companies and many intermediate size companies had either expanded into or at least touched the area.

**Q) How much money across the entire industry do you think could be saved using flow chemistry and/or how much money do you think will be invested into it over the next 5 years?**

Perhaps it would be difficult to put a number for saving across the entire industry, but MIT scientists estimate a saving of 15-50% by switching to flow. The wide range of these numbers indicate uncertainty in the estimation, which perhaps depends on what items are counted in the estimation.

**Q) Do you believe that technological advancements over the next few years will allow flow chemistry processes to become more accessible on a global scale?**

More technologies will certainly be invented and more processes will be amenable to flow systems. The MIT flow system sponsored by Novartis inspired Novartis and other companies to perform multi-steps or full steps including formulation in flow. We have heard that Novartis renewed the sponsorship for the second time for another 5 years term of the MIT setup, which is good news for flow chemistry.

**Q) What challenges does the industry as whole face over the next 5-10 years when it comes to using flow chemistries?**

The existence of experienced batch scientists combined with lack of experts in flow chemistry makes traditional process development very tempting. In addition, flow chemistry has put forward some new questions for quality of the products. For example, we can clean and validate a multi-purpose batch reactor using established methods, but those are not valid for a plug flow reactors as the access to the internal walls of the tubing is restricted. These are not very difficult obstacles to overcome, however there are very limited opportunities for drug development companies to learn from each other due to the restricted access of information, the reality is that most companies have to face and resolve these challenges on their own.

**Q) What needs to be done to speed up the adoption of flow chemistry processes?**

To move faster in the direction of flow, more chemical engineers should get involved with the development. The speed of development is crucial for Pharma and with current infrastructure and expertise, batch processes still win this competition in most cases. “Think in flow” is yet not the mentality in pharmaceutical companies’ management. The industry needs to see more successful commercial cases to be convinced that applying flow offers significant advantages over traditional batch processes.
PANEL MEMBER
Vivek Sharma, CEO of Piramal Pharma Solutions

Integrated projects bring benefits and challenges, but there will be no stopping industry adoption in the long term

The Need for Integrated Pharmaceutical Outsourcing

In today’s pharmaceutical industry, innovation and speed-to-market are more critical than ever. The life sciences industry is moving towards more complex molecules, niche therapy areas, targeted delivery – all of which require a wide range of expertise, capabilities, and scale, in both development and manufacturing, a number of which may not be present in-house. In parallel, there has been an increase in virtual biotech firms with a willingness to externalize clinical development and manufacturing to focus on their competencies and to reduce costs.

Figure 1: Novel Drug Approvals over the past 7 years

Figure 2: Small Molecules in Clinical Trials
Additional drivers for externalization include the impact of drug approvals – in 2016, thirteen (13) New Chemical Entity (NCE) were approved compared to thirty two (32) in 2015 (Fig.1) - that has led to large pharmaceutical firms redefining their core internal activities. Consolidation and cost rationalization in the industry mean reduced capabilities and capacities, and fewer internal people to manage programs. Access to capital post financial crisis, could be one potential reason for the observed increase in later stage clinical programs around 2013. The gap between the internal need and demand for resources is hence further exacerbated by the need to drive more programs (Fig. 2), to alleviate the impact of clinical attrition and reduced approvals.

These drivers have all led to the interest from pharmaceutical firms, both big and small, for strategic, integrated partners, who can seamlessly deliver on multiple verticals – such as both drug substance and drug product. By forming strategic alliances with Contract Development and Manufacturing Organizations (CDMOs), both innovators and biotech firms can focus on their core competencies, access specialized expertise, reduce costs, and significantly accelerate timelines towards successful commercialization of their molecules.

Who is an Integrated CDMO?

A CDMO that is "integrated" provides a seamlessly interconnected supply chain, across more than one part of the discovery and development continuum. For example, they could begin with assisting in discovery of New Chemical Entities (NCE), through supporting the clinical development of the active and the formulated product, and culminating in the commercial manufacturing of the Active Pharmaceutical Ingredient (API) and the final drug product. The spectrum of services that the contract partner provides may include a combination of Discovery Services, Drug Substance and Drug Product (Formulation) development and manufacturing, and Clinical Trial Supplies and Packaging. These CDMOs are also often referred to as “one-stop shops” or as “end-to-end solution providers”.

CDMOs brand themselves as integrated providers when they possess more than one capability across a product life cycle, and can seamlessly blend them together, thereby increasing the value for the customer. For example, in high growth areas such as oncology, there is a need for facilities that can handle high potency drugs safely and efficiently, where CDMOs can provide both development support and commercial manufacturing expertise in drug substance and drug product. A typical end-to-end service provider for oncology could have a service offering from discovery, high potency API and formulation development, through to commercial manufacturing and Antibody Drug Conjugation (ADC) (Figure 3).

Figure 3: A Typical End-to-End Service provider for Oncology
Key Criteria for selecting an Integrated Partner

The right CDMO with an integrated offering can provide a smooth transition from the laboratory to commercial manufacturing, by reducing complexity, streamlining processes and may also create new intellectual property. There are several factors to consider when choosing an integrated partner.

- **Domain expertise & presence across the value chain:** Consider whether the CDMO has significant experience and expertise in the specific drug class of the molecule. Outsourcing an oncology product to an experienced CDMO with integrated High potency Drug Substance and Product capabilities creates value for the innovator in terms of both timelines and costs.

- **Capability & Capacity:** In order to match current and future requirements, it is important to assess CDMO size, equipment and product handling experience to ensure that the CDMO can meet your potential requirements as the candidate molecule moves from development to commercial manufacture.

- **Regulatory Accreditations & Certifications:** Owing to constant changes in the regulatory environment, the CDMO must have a proven regulatory track record and compliance with global regulatory agencies such as the US FDA and UK MHRA. To facilitate drug launches across the globe, CDMOs must integrate their regulatory function, ensuring central governance and local execution. By setting central standards, CDMOs can develop tools to evaluate quality health at a site level, such as monitoring Data Integrity or measuring audit readiness. This ensures a shift from mere compliance to quality as part of internal culture.

- **Control on costs & supply chain:** The CDMO must be able to adhere to budgets, control supply chain costs and be flexible to modify development/manufacturing processes to address any potential issues that may occur during the project.

- **Service & Delivery Track Record:** Select a CDMO with a proven history of success for safely and effectively managing projects and delivering timely results. This includes the number of innovator products the CDMO has helped launch, the existing pipeline, and its experience in carrying out integrated programs.

**Working with the CDMO allows companies access to the technology and talent pool, to move programs forward to meet patient needs and investor expectations.**

Integrated partnerships: Benefits and risks for the customer and the CDMO

**Benefits to customers**

The right integrated development and manufacturing partner can accelerate clinical development and drive value by standing out in the following areas:

- **Improved time to market:** Aligning internal capabilities and capacity, to transfer between Drug Substance (DS) and Drug Product (DP) accelerates product delivery to the market. Integrated service providers ensure seamless tech transfer, thus safely and efficiently transferring development/manufacturing information internally.

- **Access to Differentiated Technology:** Companies can gain a competitive advantage and access to specialized technical and operational expertise by forming strategic partnerships with CDMOs experienced in niche areas such as Antibody Drug Conjugation or High potency development and manufacture. By accessing turnkey, world class assets at the CDMO, pharmaceutical companies save in capital expense, expertise development, while reducing the time to get the program into the clinic. In some of these niche areas, for example, the talent pool with domain expertise on...
the differentiated technology may be limited. Working with the CDMO allows companies easy access to the technology and talent pool, to move programs forward to meet patient needs and investor expectations.

- **Optimization of time and costs:** Working with an integrated CDMO with a global network of sites, at scale, provides significant cost and time benefits. An ideal ‘integrated’ CDMO partner, for example, will adjust its drug product capacity availability to any delays in drug substance manufacturing, ensuring that the clinical development program is not delayed. Due to dearth in capacity in the Sterile Injectable segment, clients are often obligated to pay a penalty to CDMOs for unutilized capacity in case there is a delay in API supply from an external source. However if the same CDMO is providing both API and Formulation services, this penalty clause may be waived/reduced, as the CDMO adjusts for internal supply delays, allowing for a benefit in both time and costs for the customer.

- **Efficient program management:** When running an integrated program, the CDMO typically assigns a Single Point Of Contact (SPOC) to liaise with the customer. This SPOC coordinates all activities at the CDMO thereby minimizing the management time required by the customer. In biotech firms that run a lean organization, this is viewed as a significant value addition.

- **Availability of documentation through a single source:** The Regulatory Affairs team of an integrated CDMO can provide expert clinical & regulatory support across all phases of drug development. This includes regulatory support for both API and Finished dosage formulations, including New Chemical Entity (NCE) development, Clinical Trials and Marketed products. A single entity for regulatory filing enables the submission of a robust dossier with data consistency.

### Benefits to the CDMO

For a CDMO with a ‘One-Stop-Shop’ offering, an integrated value chain can serve as a differentiation strategy from competitors. CDMOs with integrated approaches improve ‘customer stickiness’, as customers doing multiple parts of the program at one partner are less liable to leave. In addition, CDMOs also maximize ‘Customer Lifetime Value’, as customers tend to work with such providers from clinical development through commercialization.

By forming strategic partnerships, CDMOs can align their investments in facilities and technologies to the customer’s long term plans resulting in a win-win arrangement. Customers are also now more willing to co-invest with the CDMO – when capital requirements are high – in order to meet their future needs. For example, in 2017, Sanofi and Swiss CDMO Lonza struck a deal to co-build a site in Lonza’s Swiss facility to expand their biologics capacity, thereby sharing the €270 million financial burden. The deal provided Sanofi with the capacity and security of supply to meet its pipeline needs, 60% of which were focused on biologics such as monoclonal antibodies. In parallel, Lonza could use the unutilized capacity for other companies, increasing its top line and customers.

### Risks to the Customer and the CDMO

Conversely, Pharmaceutical companies must be wary, as over exposure to a single partner could potentially put the full clinical program at risk. The customer must ensure that the chosen CDMO is world-class in multiple business verticals. The customer must convince themselves that the CDMO of choice has contingency plans ready for adverse events such as operational issues, geo political challenges, among others.

The CDMOs on the other hand, must carefully analyze the segments they expand into to create integrated value chains, as inaccurate capacity estimation can lead to over-
capacity and resource under-utilization. CDMO’s may also consider the risk of having really large customers, the loss of who will lead to significant revenue gaps on exit.

As Integrated CDMOs develop a smaller set of customers they can provide more services to, these select customers could lever the relationship to reduce overall price, resulting in pricing headwinds. As an example, a CDMO offering both Drug Substance and Drug Product, may need to lower its formulations margins to attract the business. This may lead to non-optimal performance in some sites and a lower return on assets. In this example, a single site may have sacrificed its returns to ensure overall CDMO profitability. CDMO’s must plan to ensure that they have a right combination of projects, services, and products to ensure optimal return those investors seek.

Future Trends

As CDMOs continue to optimally fine tune offerings, allowing them to provide more services to a smaller customer base, we expect the integrated CDMO model to continue to grow. Despite some challenges this model is attractive for CDMOs as they can develop strategic, symbiotic relationships with pharmaceutical companies that may involve shared Capital and Risk, allowing them to move from a vendor transaction to a strategic partnership. This can particularly hold true for global large pharmaceutical companies, where integrated CDMOs can develop new service models focused on resource flexibility, shared risk, with upsides on wins.

With pharmaceutical companies continuing to rationalize costs and biotechs becoming more virtual, we expect the need for integrated service providers to also increase. For Venture Capitalists (VCs) funding virtual biotech companies, the integrated CDMO model is attractive as the biotech has ready access to niche technology and diverse manufacturing capabilities, without additional Capital. This may provide VCs with a longer runway for these investments, and a potential for faster returns, while reducing risk.

We expect that the CDMO sector will continue to consolidate, focusing on innovative technology to strengthen their service offerings. CDMOs in niche areas might forward and/or back integrate, to offer more integrated value chains to customers. Recent transactions—Lonza’s acquisition of Capsugel for oral delivery technologies and Fresenius Kabi’s acquisition of Akorn to strengthen its sterile injectable capabilities – reflect this trend.

As oncology continues to grow from a customer interest perspective, one can expect consolidation in niche areas such as high potency API manufacture, Lyophilized/injectable products and Antibody Drug Conjugation. A standalone ADC provider, for example, may want to manufacture the active ingredient, execute the conjugation, and complete the offering by providing fill-finish services.
Piramal’s Integrated Offering

Piramal Pharma Solutions has created a global network of 11 development and manufacturing facilities located in North America (3), Europe (2) and Asia (6) that offer a multitude of services spanning the entire drug life cycle. These range from Drug Discovery & Development, manufacturing and packaging of Clinical Trial Supplies to Commercial Manufacturing of Active Pharmaceutical Ingredients and Finished Dosage Forms. Piramal offers a fully-integrated global supply chain and has a long history of successfully launching 34 products, including blockbusters such as Velcade® and Ninlaro®. With 10 additional launches scheduled for this year and expertise in areas such as high potency API manufacture and Antibody Drug conjugation, Piramal is ideally positioned for continued growth.

Piramal’s leading capabilities in both drug substance and drug product development and manufacturing, has resulted in over 60 successful integrated projects between discovery, drug substance, drug product and clinical packaging. With innovative business models, a focus on customer centricity, and a stellar quality track record, Piramal is now a ‘partner-of-choice’, for firms from large pharmaceuticals to virtual biotechs, in North America, Europe, and Japan.

Leveraging Fermentation Science to Develop Advanced Therapies

Introduction

Fermentation is one of the earliest forms of biotechnological processes. Human beings have been making fermented foods since Neolithic times. The discovery of microbes in the 14th century led to the application of fermentation for industrial scale manufacturing of bread, beer and wine. Early in the 20th century, fermentation science led to the production of enzymes and antibiotics.

Some decades later, when the growing number of people with diabetes around the world prompted the search for a viable commercial technology to manufacture insulin, fermentation provided an answer. The breakthrough came when Genentech produced human insulin in the laboratory using recombinant DNA technology in 1978. Four years later, human insulin was the first recombinant protein to be approved by the FDA for use in humans as a biopharmaceutical product. Recombinant human insulin (rh-insulin) replaced the old technology of extracting insulin from the pancreas of pigs and cows and significantly boosted production levels. The success of rh-insulin heralded the approval of other key biotherapies such as interferons and growth hormones, and eventually, monoclonal antibodies.

The invaluable role of biologic therapies in treating serious illnesses such as diabetes, anemia, cancer and renal diseases led to them increasingly dominating global development pipelines. Two-thirds of the products approved for commercial use in the world in 2015 were biologics. The trend is expected to intensify with biologics projected to contribute up to 50% of the value of the Top 100 drug products sold globally by 2022.
Fermentation and Biopharmaceuticals Production

Given the growing global disease burden, fermentation offers an efficient and scalable technology to produce advanced therapies. Microbial and mammalian cell culture-based fermentation technologies are key to the manufacture of a range of products, from small molecules (statins, immunosuppressants) to biopharmaceuticals such as recombinant proteins (human insulin) and monoclonal antibodies, which are being used to treat medical conditions including metabolic and immunological disorders, as well as cancers.

Most innovator companies that have made big investments in the future of advanced biotherapies like antibodies and insulins, such as AstraZeneca, AbbVie, Eli Lilly, GSK, Merck, Novartis, Novo Nordisk, Pfizer, Roche, and Sanofi, currently use fermentation technology. Thus 36% of the global biopharmaceutical manufacturing capacity is concentrated in North America, according to the latest data from BioPlan’s Top 1000 Global Biopharmaceutical Manufacturing Index.

Most innovator companies that have made big investments in the future of advanced biotherapies like antibodies and insulins

Of Asia’s 24.6% share of global biopharma manufacturing capacity, India accounts for 7.6%. Biocon, as the largest biotech company of India, has built global scale fermentation-based biopharmaceuticals manufacturing capabilities, including the country’s largest biotech park in Bangalore. Intas Pharma and Zydus Cadila are some of the other players in this field in India.

Fermentation & Drug Affordability

Fermentation has been an integral part of commercial vaccine development and production for many years. In the 1990s, Indian vaccine producers demonstrated their ability to innovate by developing high quality yet affordable fermentation-derived vaccines at a fraction of the cost of western drug makers. At the time, large multinational pharmaceutical companies held monopolies on the recombinant Hepatitis B vaccine, which was priced at over (USD) $25 a dose and was thus unaffordable for most Indians. Shantha Biotechnics, founded in 1993, saw an unmet need domestically and invested in innovation that led to India’s first recombinant Hepatitis B vaccine that cost less than (USD) $1 per dose. In time, Shantha was joined by others such as Bharat Biotech, Serum Institute and Biological E. in producing and supplying low-cost vaccines worldwide. Today, ‘1 in 3’ children globally are immunized with a ‘Made in India’ vaccine.

Similarly, Biocon, which had long experience in manufacturing enzymes, leveraged its capabilities in fermentation technology to develop a portfolio of fermentation-derived statins at the turn of the millennium. When Lovastatin went off patent in 2001, Biocon was the only company from India and among the only three companies in the world to get US FDA approval to supply the API for the drug. Since then Biocon has emerged as a leading producer of statins and immunosuppressants. Biocon subsequently has used its strengths in fermentation technology to build global scale capability to manufacture complex biologics.

Fermentation: An Evolving Field

While fermentation allows life-saving drugs to be produced with economic scalability, large-scale GMP fermentation is a complex process. It requires high technical skills, large capital investments, specialized manufacturing facilities and a commitment to excellence at each stage of the manufacturing and supply process. Biotechnology companies need to make substantial investments in fermentation equipment, expertise, process, and quality control.
The manufacturing technology for biopharmaceuticals is divided into upstream and downstream processes. The upstream process is defined as the microbial growth required to produce biopharmaceuticals or other biomolecules and involves a series of events including the selection of cell line, culture media, growth parameters, and process optimization to achieve optimal conditions for cell growth and biopharmaceutical production. The main goal of the upstream process is the transformation of substrates into the desired metabolic products. This requires well-controlled conditions and involves the use of large-scale bioreactors. Downstream processing includes all steps required to purify a biological product from cell culture broth to final purified product. The purification process must be robust, reliable, easily scalable, and capable of removing both processes- and product-related impurities to ensure product safety.

The capital investment for a properly equipped current good manufacturing practices (CGMP) fermentation facility, including manufacturing equipment and utilities, is significant and often runs into the high tens of millions of dollars.

Advances in fermentation technology are making bioprocessing more efficient and leading to higher yields of biomolecules in the shortest period of time at the lowest cost.

At a time when other drug companies were using E. coli to make insulin, Biocon developed a proprietary yeast platform based on Pichia pastoris for the expression of the drug substance. Being a single-celled organism, Pichia is easy to grow and manipulate in the lab and provides the advantage of a high-yielding biological factory that combines the advantages of a bacterial and mammalian cell culture systems.

This fermentation technology enabled Biocon to introduce India’s first indigenously developed recombinant human insulin (rh-insulin) in 2004 at a third of the price of imported insulins, thus enabling access to this complex therapy for people with diabetes. Since then the company provides Insulins and analogs in multiple emerging markets and recently also introduced first biosimilar from India in Japan with the launch of Insulin Glargine. Today, Biocon is among the top 3 biosimilar players globally for insulins in terms of volume market share (measured in number of units sold; Source: IMS Year End 2016).

The current market size of fermentation-based drugs is between USD 75 billion and USD 100 billion, according to IMS data, and this is expected to grow at 15-20% over the next five years.

Fermentation to Be Mainstay in Producing Many Therapeutic Molecules

Fermentation technology will continue to play an important role in the coming years in the production of a wide range of pharma products such as antibiotics, vaccines as well as small and large molecule drugs.

The development of well growing cell substrates; high-yield recombinant expression systems; animal product-free media; and efficient bioreactors has led to the economically feasible manufacture of hundreds of kilograms of drug substances annually. Rapid, flexible and scalable biomanufacturing systems are leading to affordable, safe and consistent production of biologics.

Industry overall capacity utilization, now a healthy 74.7% for mammalian cell culture production, is capable of producing the increased gram quantities of drugs demanded without a commensurate scale-up of manufacturing equipment, staffing, or expenses. This has been accomplished by increasing overall productivity and reducing costs. For example, average commercial-scale mammalian cell culture titer is now 3.2 g/L, nearly doubling over the past 10 years and up magnitudes of order over the past couple decades.

Antibiotics: We are seeing heightened interest in efforts to develop new generation antibiotic drugs and fermentation will have a big role to play in this pursuit. In 2014 the US FDA approved two antibiotics, Oritavancin and Dalbavancin, which are semi-synthetic derivatives of naturally occurring compounds derived from bacterial
fermentation. New antibiotic scaffolds continue to be discovered from bacterial/fungal fermentation. Exploitation of these scaffolds by chemical means has been successful in the development of newer antibiotics. These antibiotics are increasingly becoming chemically more complex and preclude total chemical synthesis. Hence, microbial fermentation will remain the mainstay of development and manufacturing of newer scaffolds and new semi-synthetic antibiotics. The global market for antibacterial drugs is expected to grow to ~USD 36 billion in 2022 from ~USD 27 billion in 2015, according to a 2017 market study.

Vaccines: There is renewed interest within the global pharma industry around novel DNA vaccines, which are produced by bacterial fermentation. Unlike traditional vaccines that contain dead or weakened virus, DNA vaccines have modified circular DNA sequences, or plasmids, which encode specific antigens for immunization against a particular infection. As these vaccines are safer, faster to develop, have greater temperature stability, are easier to store and transport and can be inexpensively manufactured by fermentation, they are ideal for combating global pandemics.

Several DNA vaccines are currently under development, including those that protect against infectious diseases as well as cancer vaccines that prime the patient’s immune system to fight against tumour cells.

Small Molecule Drugs: The role of fermentation in producing newer small molecules drugs will increase in the coming years as more genomic data becomes available for generating novel scaffolds, or proteins whose main function is to bring other proteins together for them to interact. As scaffolds for other small molecule therapies like immunosuppressants and anti-cancer drug are discovered, the role of fermentation in their development and manufacturing will increase too.

How Fermentation Will Help Bring Newer Advanced Therapies to Market

Biologics: Over the past several years, biologics have made many new, ground breaking treatments possible and gained significant traction in the pharmaceutical industry as novel biologic blockbusters have continued to enter the market.

Antibody-drug conjugates (ADCs), a promising new class of drugs, hold great promise as next-generation cancer therapies that can target and selectively kill cancerous cells while sparing healthy ones. ADCs combine the specificity of monoclonal antibodies with the anticancer potential of cytotoxic drugs to create a targeted class of anti-cancer drugs that are specific with lesser side effects. ADCs are manufactured through the process of fermentation. While the antibodies are produced through mammalian cell culture fermentation, the small molecules are of semi-synthetic or natural origin. To date, three ADCs have been approved for sale by the US FDA and all of them are antibodies conjugated with semi-synthetic natural products. Currently, only Brentuximab-Vedotin and Trastuzumab-Emtansine are commercially available globally.

Antibody-drug conjugates (ADCs), a promising new class of drugs, hold great promise as next-generation cancer therapies that can target and selectively kill cancerous cells while sparing healthy ones.

Medical advances are leading to the development of more specialized, personalized and targeted ADCs. Currently, an estimated 50 ADCs are in the clinical trial pipeline.

The global market for ADCs is projected to reach USD4.2 billion by 2021, growing at a CAGR of 25.5% from USD1.3 billion in 2016.
Conclusion

Today, fermentation technology is a multi-disciplinary melting pot of organic chemistry, biochemistry, microbiology and molecular biology, which has a potential impact on virtually all domains of human welfare, ranging from food, energy and environmental protection, to human health.

While fermentation has enabled us to use science to make immense societal impact in recent years, the challenge now is to take this science to another level. Going forward, it will be a common practice to see companies developing alternative microbial strains for efficient fermentation. The focus is moving towards improving strains optimized for rapid cycle times, high cell densities, and low-cost media. The application of Big Data is already allowing the tracking of the fermentation process to the minutest detail. The application of this technology is only predicted to increase in the future on the back of such advancements in the scientific and safety aspects of fermentation science.

Several emerging technologies, including the production of therapeutic stem cells, gene therapy vectors, and new vaccines, will require wider applications of fermentation technology in the future. Thus, fermentation technology holds huge promise in leveraging the advances in recombinant DNA technology to produce a variety of cutting edge therapeutics and technologies of the future that can have a profound impact on the quality of human life.
About CPhI
CPhI drives growth and innovation at every step of the global pharmaceutical supply chain from drug discovery to finished dosage. Through exhibitions, conferences and online communities, CPhI brings together more than 100,000 pharmaceutical professionals each year to network, identify business opportunities and expand the global market. CPhI hosts events in Europe, China, India, Japan, Southeast Asia, Russia, Istanbul and Korea co-located with ICSE for contract services, P-MEC for machinery, equipment & technology, InnoPack for pharmaceutical packaging and BioPh for biopharma. CPhI provides an online buyer & supplier directory at CPhI-Online.com.

For more information visit: www.cphi.com