PANEL MEMBER

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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

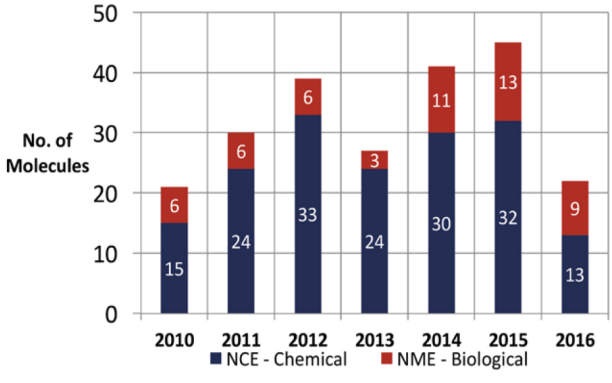
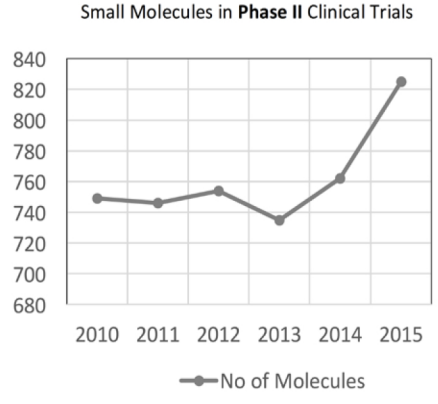
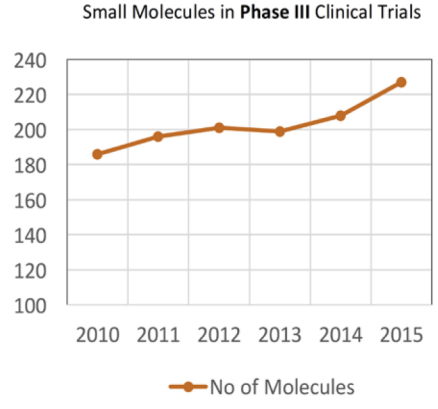


Figure 2: Small Molecules in Clinical Trials





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.

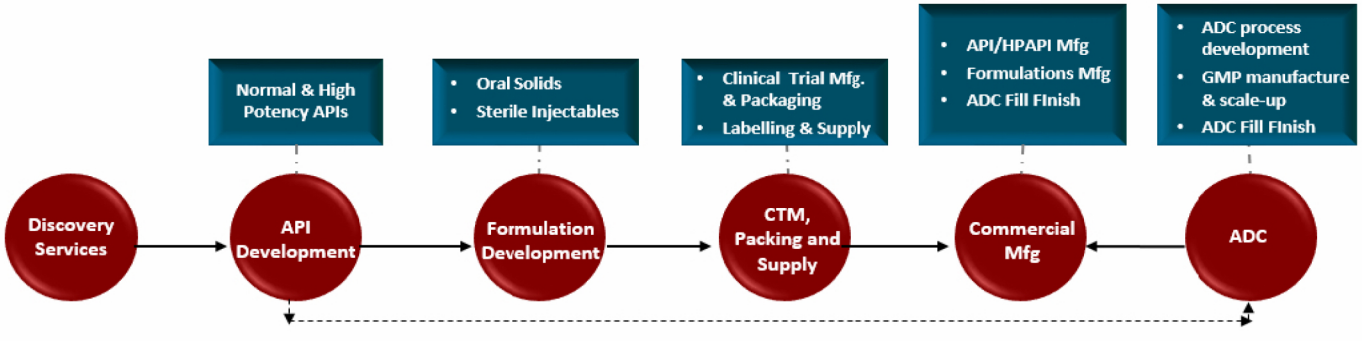
These drivers have all led to the interest from pharmaceutical firms, both big and small, for strategic, integrated partners, who can seamlessly deliver on multiple verticals – such as both drug substance and drug product. By forming strategic alliances with Contract Development and Manufacturing Organizations (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. CDMO's with integrated approaches improve 'customer stickiness', as customers doing multiple parts of the program at one partner are less liable to leave. In addition, CDMO's 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.

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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.

1. Palmer, E, 2017. Fierce Pharma (27th February, 2017) < http://www.fiercepharma.com/pharma/sanofi-and-lonza-partner-a-eu270-million-biologics-plant-will-employ-200>