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Make, Buy Or Partner: Strategic Alliances Continue To Fuel Biopharma Growth

by Oded Ben-Joseph

The biopharma market has been highly active throughout the COVID-19 pandemic with a substantial focus on strategic alliances between 2020-H1 2021. Partnership deals present exciting liquidity and risk mitigation opportunities for early-stage companies. Small molecules still comprise the largest segment of partnered drugs, but alliances for other modalities are on the rise.

The challenges and obstacles to bringing novel drugs from the laboratory bench to the patient are immense, with inherent scientific risk and exorbitant capital expenditures. Recent reports from Pharma Intelligence suggest that the overall likelihood of achieving approval from Phase I for all developmental candidates over 2011-2020 was a mere 7.9%, and Phase II remains the largest hurdle in drug development, with just 28.9% of candidates proceeding to Phase III. Furthermore, development of a drug that will eventually reach the market often entails a decade or more of R&D expenditure at a cost ranging from $1bn to more than $2bn. These dynamics force pharmaceutical and biotechnology companies to seek inorganic growth in an effort to rein in cost and risk, as well as replenish their pipelines by gaining access to innovation.

Emerging drug companies (annual revenues of < $500m) now account for more than 70% of the nearly 3,000 drugs in Phase III clinical trials, according to *IQVIA Holdings Inc.* data. They are also responsible for a growing share of drugs already on the market; since 2009, about one third of the new drugs approved by the FDA have been developed by pharmaceutical firms with annual

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revenues of less than $100m, noted HBM partners in a 2019 report. Large companies (annual revenues of >$1bn) still account for more than half of new drugs approved since 2009 and an even greater share of revenues, but they have only initiated about 20% of drugs currently in Phase III clinical trials. For a large drug company, one option for pipeline enrichment is to acquire or partner with a smaller firm that is developing new drugs. Indeed, pharma companies are increasingly partnering with other stakeholders to address scientific and technological challenges, increase research and development efficiencies, and accelerate discovery, manufacturing and delivery of novel treatments to patients. Similarly, there are innumerable benefits of partnerships for the earlier stage biotech companies. Beyond providing an inflow of cash, they increase a development program's probability of success, and enable rapid discovery and scale-up of investigational drugs at a pace not achievable by either party alone. Some additional benefits for earlier stage biotech companies include access to knowledge, resources, and technical expertise, as well as the ability to drive commercialization and overall risk mitigation. Since early 2016 through 1H 2021, Outcome Capital notes that there have been more than 2,500 transactions ranging from M&A to licensing agreements and partnerships. While large acquisitions (such as *Bristol Myers Squibb Company*/*Celgene Corporation* and *AstraZeneca PLC*/*Alexion Pharmaceuticals Inc.*) often receive broad coverage, biopharmaceutical players are increasingly partnering with earlier stage biotech companies to address scientific and technological challenges, accelerate discovery and manufacturing, and deliver new treatments to patients. Given the benefits of strategic alliances for both large pharma and earlier stage biotech players, multinational strategics will continue to establish co-development partnerships, licensing agreements, joint ventures and co-marketing transactions.

Overview of Strategic Alliances

Despite the economic uncertainty resulting from the COVID-19 pandemic, the biopharmaceutical industry has seen an influx of capital, whether through new venture funds/investments, IPOs/follow-on offerings, or government grants. This has led multi-national biopharmaceutical companies with large cash positions to actively pursue strategic alliances across their disease focus areas. Over the course of the last year and a half (January 2020-June 2021), 384 strategic alliances with at least $5m in value have been established across all stages of drug development. Total deal value and transaction structures were noted to be highly dependent on disease indication and stage of drug development. However, from a high-level perspective on transaction activity, the number of strategic alliances per quarter remained steady across the last year and a half even as the pandemic rages on (*see Exhibit 1*).

Exhibit 1.

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Strategic alliance activity was driven by large pharma and biotech companies seeking to strengthen their pipeline by introducing novel therapeutic approaches and platform technologies. Depicted in Exhibit 2 are the most active strategic partners in the studied period. These 21 companies collectively accounted for ~40% of all partnering activity (149 deals). Among the 21 most active corporations, 15 were among the largest multi-national biopharmaceutical companies by market cap, five were Asia-based strategics, and one was a private corporation in *Boehringer Ingelheim Pharma KG*. Conversely, only five target companies completed more than two out-licensing deals within the last year and a half. Taken together, this indicates that the universe of potential acquirers is limited when compared to the number of biotech companies seeking partnerships. This observation suggests that emerging biotech companies should focus early efforts on identifying a highly synergistic partner to enable continued development of their technology toward the next value inflection milestone. *(Also see "Intense Transactional Activity Continues To Propel Biopharma Growth*" - In Vivo, 9 Nov, 2020.))

Exhibit 2.

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Strategic Alliances Span Across Molecule Type & Disease Indication

To understand transaction drivers of large biopharmaceutical companies, Outcome Capital studied the relationship between the number of strategic alliances and both molecule type and disease indication. Small molecules still comprise the largest segment of partnered drugs, representing 47% of deals (*see Exhibit 3*). Among small molecules deals, ~70% were for clinical stage or marketed assets. Further, 60% of all strategic alliances for clinical stage assets were for small molecules. The fact that small molecules account for most clinical stage partnerships is in line with the dynamics of current drug approvals. In 2019, >75% of all new molecular entity (NME) approvals by the FDA were for small molecules. However, recent advancement in drug development has resulted in a shift towards biologics, with numerous antibody, oligonucleotide, and cell therapy approvals. The growing interest in biologics has translated to strategic alliances across these platforms. Over the last year and a half, 17% of the deals have been for antibodies, 12% for cell and gene therapies, and 10% for proteins/peptides (see Exhibit 3). In contrast to small molecules, biologics represented ~70% of all discovery stage alliances and ~63% of all preclinical stage deals. These dynamics suggest that large molecule approaches will make a significant near-term clinical impact.

Exhibit 3.

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Another key factor that influences the strategic alliance activity and total deal values is disease indication. As we have previously reported, oncology remains the most active segment for strategic alliances in the biopharmaceutical industry (*see Exhibit 4*), representing 153 transactions. The alliances were spread proportionally across stage of development as oncology deals represented ~40% of discovery, preclinical, clinical and marketed therapeutic deals, respectively (*see Exhibit 5*), which demonstrates demand at each stage of development. In addition, and not surprisingly, oncology deals commanded significant value, with average total deal value of $718m. (Also see "*Immuno-Oncology: Unicorns, China And The Perfect Storm* " - In Vivo, 24 Oct, 2018.)

Exhibit 4.

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A more recent shift in the industry has been the re-emergence of interest in CNS diseases, which was the second most funded disease area in 2020, according to data from PitchBook. This trend carried over into the partnering ecosystem, with 39 deals completed in the studied period, the second most frequent of any indication. Surprisingly, after many high-profile failures in the space that led to many biopharmaceutical players jettisoning the segment, companies are eager to re-enter development, with deal values that were the highest of any indication at $757m (*again see Exhibit 4*). Some noteworthy deals highlighting the renewed interest in CNS research include Biogen/Sage Therapeutics for treatment of mood disorders (>$3bn),*Takeda Pharmaceuticals USA Inc.*/*BridGene Biosciences, Inc.* ($2.5bn), *Eli Lilly and Company*/*Evox Therapeutics Limited* ($1bn), and *Novartis AG*/*Sangamo Therapeutics, Inc.* for the treatment of neurodevelopmental disorders ($795m).

Platform transactions spanning across multiple indications were also consummated at a fast pace (39 deals in the last year and a half) and commanded a premium average deal of $660m. These deals include Bristol Myers Squibb's partnership with *Schrodinger, Inc.* to accelerate identification of small molecule compounds for oncology, CNS and immunology-based diseases using Schrodinger's computational biology platform, and *AbbVie Inc.*'s alliance with Frontier Medicines Corp for the use of a chemoproteomics platform to identify small molecules directed to novel E3 ligases for certain oncology and immunology targets. Beyond the fact that pharma is interested in exploring platforms with applicability across multiple indications, it is noteworthy that ~50% of these deals occurred at the discovery stage (*see Exhibit 5*). This suggests that biopharmaceutical players are eager to identify and implement innovation, whether for drug discovery or drug development. It also demonstrates an intent to leverage and incorporate new platforms into their pipeline, while offering risk management play as they can identify specific indications where the platform has highest probability of success during early stage, multi-year agreements.

Exhibit 5.

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Transaction Dynamics Influenced by Drug Development Stage

As expected, strategic alliance deal structure is heavily influenced by stage of asset development. For this reason, Outcome Capital examined the relationship between time to commercialization, total deal value and deal structure. Over the last year and a half, discovery and preclinical stage assets accounted for the majority of the strategic alliances with 112 and 66 deals, respectively (*see Exhibit 6*). The emphasis on the early-stage deals highlights the desire of larger biopharmaceutical companies to leverage innovative platform technologies within their areas of interest, whether oncology, immunology, cardiovascular or central nervous system. Once assets reached the clinic, transactions were primarily driven by the demonstration of clinical efficacy (Phase II and beyond).

Exhibit 6.

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An interesting dynamic was apparent among deals of different asset stages. As assets became more advanced, the total deal value generally decreased; discovery assets commanded largest total deal at $873m, while commercial assets commanded only $361m (*again see Exhibit* 6). We have previously reported the uncoupling between asset value and asset stage in the immuno-oncology segment, a trend observed across other indications including central nervous system disorders, gastrointestinal diseases, immune and inflammatory disease and rare diseases. While counterintuitive, there were two main underpinning drivers: deal structure and deal focus. Regarding deal structure, earlier stage deals had lower upfront payments as percentage of total deal values when compared to more mature assets. Discovery stage deals had average upfront payments that on average accounted for 6% of the total deal value while Phase III assets on average received upfront payments equating to 29% of total deal value. Milestone-based structure for discovery stage transactions allows biopharmaceutical players to partner early while mitigating upfront risk and provides an option to opt out in the event scientific and/or clinical results are disappointing. The second element that affected the total deal value was the breadth of focus. Discovery stage deals were often focused on leveraging a platform technology to identify multiple potential targets or drug candidates across a variety of disease states, while clinical stage deals were typically single-asset deals that focused on a specific indication or geography. To illustrate these differing deal dynamics, we have selected a few examples of deals from each stage that highlight many of the elements that could be expected (*see Table 1*).

Among the four discovery-stage transactions highlighted in Table 1, which vary in total value

and indication of interest, each had very broad and heavily structured deal terms. First, they included multiple indications; AstraZeneca partnership with Silence Therapeutics was for the development of siRNA technology for 5 pre-determined therapeutic targets, while the others specified “multiple” targets. Second, they split the milestones (R&D, clinical, and commercial) across each of their multiple targets. This was specifically highlighted in both the AstraZeneca deal where it defined the potential for Silence Therapeutics to receive $400m per target, and the *[See Deal]* deal where *Merck KGaA* agreed to pay $860m in potential milestones per target. Lastly, each of these deals provided the partner with global commercialization rights for successful targets, with the developer receiving tiered royalties. This is in line with the fact that in the discovery stage partnerships, the target traditionally offers a technology that can be developed towards the partner’s interest/therapeutic focus. Since these assets were not under development prior to the partnerships and it was a joint venture, the acquirer typically took sole responsibility for development by exercising a predetermined option. It is also for this reason that there were high upfront values for discovery stage deals since the partner needed to fund the target to redirect resources to these efforts.

Table 1.

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Once drugs reach preclinical development, transactions are focused on a specific asset or set of assets, as seen in both the GSK/IDEAYA Biosciences and Eli Lilly/Fochon Pharma deals. While preclinical stage deals are targeted towards defined assets, they still share many of the same characteristics as discovery deals as the programs are early in development. Preclinical stage alliances are still heavily structured with multiple preclinical, clinical and commercial milestones in addition royalties on net sales. Additionally, the partner has the right to option the specific asset and take over development and commercial responsibility. One dynamic that begins to arise at the preclinical stage is the geographical focus of the deals. For example, in the deal between Eli Lilly and Fochon Pharma, Fochon retained the right to develop and commercialize the asset in Greater China while providing the option for Eli Lilly to develop and commercialize elsewhere.

Finally, once the molecules reach the clinic/market, deal structures often resemble traditional licenses, as opposed to partnerships with option agreements as seen in preclinical. In these deals, the partner (or licensee) will in-license an asset for a geography or indication of interest. These deals are structured with multiple sales milestones and fewer development milestones when compared to earlier deals. As with the Santen Pharma, Nuance Biotech and BeiGene deals, each company in-licensed assets for specific regions: Asia Pacific and EMEA, Greater China and Greater China, respectively. Lastly, while total deal value may be smaller as deal terms are typical narrower, the upfront values are on average a larger percentage of the total deal value, which makes sense as the assets are closer to or in market.

Key Takeaways

The biopharma market has been highly active throughout the COVID-19 pandemic with a substantial focus on strategic alliances between 2020-H1 2021. Partnership deals present exciting liquidity and risk mitigation opportunities for early-stage companies. CEOs and venture investors should thus seek partnerships as early as possible in the drug development process. As indicated by the data, many of the strategic alliances are formed in the discovery and preclinical stages, which reflects the desire of large biopharma strategics to innovate, expand and diversify their pipelines. These deals provide an opportunity for a company to receive non-dilutive capital to support development, as well as clinical know-how and risk mitigation. Further, while there is a competitive market in the preclinical stages, strategics continue to seek clinical stage assets. These transactions are typically asset specific and can often be focused on a specific indication or geography. Similar to earlier stage deals, there is an attractive financial component to clinical stage deals as they present larger proportions in upfront values and substantial royalties on commercialization, once again reducing risk by transitioning the sales efforts to organizations with an existing sales and marketing channel.

The biopharma industry will continue to rely heavily on strategic alliances to advance pipelines. With this in mind, Outcome Capital recommends CEOs of development stage biotech companies should pursue these alliances in parallel to their fundraising efforts and understand that these alliances provide a much-needed risk reduction measure and a higher probability of a liquidity event, whether M&A or an IPO. Moreover, a strong platform can serve as a crank to produce clinical assets toward multiple alliances and shots on goal.