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CURRENT OPINION

Powered by Open Innovation: Opportunities and Challenges in the Pharma Sector

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Abstract

The value of innovation in medicines is clear. Despite all of the progress in the twenty-first century, there are still many unmet medical needs and opportunities to improve healthcare. The challenges for pharmaceutical companies include ways in which to stay competitive and flexible in an environment of constant knowledge growth and increasingly sophisticated technologies, and ways to generate sufficient revenues to sustain their own growth. To that end, pharmaceutical companies are compelled to adapt different business models in the face of new challenges. The industry is plagued with long research and development (R&D) cycles and low success rates for innovative treatments; something has to change. The need to collaborate externally across the process of discovery, development, manufacturing and commercialization is a must. Furthermore, collaborations have increased in frequency and scope, expanding the opportunities to access global scientific talent in academia, research institutes and biotechnology companies. Despite the perception that pharma companies are 'closed' or tightly controlled industries, open innovation is already well established in the pharmaceutical sector and used to supplement R&D in the process of bringing new medicines for patients faster, and at a lower cost. Over the years, each pharma company has tailored the open-innovation concept to develop its own model based on particular needs and offerings. Independently of the model, the creation of successful partnerships in external innovation requires reaching out and connecting beyond the traditional organizational boundaries. Substantial internal cultural changes are required to implement open-innovation strategies that should co-exist without competing with the traditional ways of operating. Major changes bring challenges but create multiple opportunities for scientists and organizations. High-quality drug discovery requires continuous learning and an open way of thinking to adopt novel operational models and to implement efficient collaborations.

Key points

Pharmaceutical companies continue to face challenges to stay competitive and utilize external networks to identify solutions to scientific issues in research and development.

Pharmaceutical companies are open to collaborate with academia to foster a more creative environment and produce innovative results.

Cultural changes are instrumental in implementing successful open-innovation strategies.

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1 Introduction

The drug-discovery process is continuously evolving, and pharmaceutical companies have designed different strategies for effective collaborations in research [1]. In the twentieth century, globalization fostered acquisitions and strategic alliances in late-stage clinical trials. The scientific community perceived strategic changes with the turn of the twenty-first century, where the advance of personalized medicine deemphasized the traditional business model built on blockbusters. The open-innovation model gained momentum then and is currently a promising driver to advance and increase productivity in the pharmaceutical industry [2]. For the research-based pharmaceutical industry, the prescription for success is clear. To be competitive in today's economic, regulatory, and political environment, pharmaceutical companies must reduce product development time and cost, terminate unpromising candidates sooner, boost the design process, focus on areas of high therapeutic need, and dramatically increase productivity while maintaining quality standards [3]. Major pharmaceutical

companies have been attempting to address these performance issues over the last decade, unfortunately with limited success. What, then, makes the chance of success any greater now than in the past? The answer lies in the ability of the industry to transform an outdated research and development (R&D) paradigm. The closed model of research is inadequate to address the emerging challenges, increase productivity, and reduce drug-development costs from the billion dollar mark. To succeed in this new environment, big pharmaceutical companies must continue to invest in collaboration models where multiple partners create innovation. In order to foster industry-academia collaborations, it is especially attractive to share ideas and generate value that may amplify the research of novel medicines. Open innovation in drug discovery will continue to grow over the next decade. Seeking ideas and expertise from external sources is a well-established practice in the pharmaceutical industry, with about one-third of all drugs in the pipeline of the top ten companies being initially developed elsewhere.

In this article, we review the open-innovation concept and the most common models of open innovation, with a particular emphasis on Eli Lilly's innovation journey. The final purpose is to examine the challenges and opportunities associated with open innovation, with recommendations for efficient collaborations.

2 Evolution of Open Innovation

Henry Chesbrough introduced the open-innovation concept in 2003 [4], as "a paradigm that assumes that firms should use external ideas as well as internal ideas, and internal and external paths to market, as the firms look to advance their technology". He described then a small number of companies that shifted from a closed- to an open-innovation model, showing that no company could innovate effectively on its own. A few years later, he redefined the term as "a distributed innovation process based on purposively managed knowledge flows across organizational boundaries, using pecuniary and non-pecuniary mechanisms in line with the organization's business model" [5]. The open-innovation model triggered the creation of a new area of knowledge, where hundreds of articles disclosed its application in different industries.

To truly implement open innovation, it is necessary to build a culture of innovation to establish an environment that fosters creative thinking and puts into practice original ideas to become innovations. It is important to use creativity and innovation together, because creative ideas may translate into innovative solutions.

In the pharmaceutical sector, there are considerably more biased collaborations, especially with academic institutions, because companies want to invest in research centers with expertise in a field, or in scientists doing research aligned with pharmaceutical areas of interest. However, as the industry moves towards an innovation business model, many new unbiased initiatives are emerging. Chesbrough argues that closed-innovation models, combining R&D departments to develop in-house technology for internal corporate use only, are archaic. In the past, pharmaceutical companies were more likely to broaden their knowledge by contracting professors and graduate students as summer consultants, sponsoring university research, investing in and collaborating with small biotechnology companies, allotting their own innovations through spin-off companies, etc. By contrast, open innovation is to challenge the *status quo* by joining internal and external ideas to create a new value that nurtures diversity of thought.

3 Open Innovation Models

Innovation in the life sciences presents many challenges. The sophisticated technology, strict regulation, intellectual property (IP) concerns and R&D profit pressures restrict the opportunities for significant collaborations. Today, a growing number of pharmaceutical companies are addressing these challenges with innovative models to overcome the difficulties in early drug discovery [6, 7]. Many companies have implemented open-innovation strategies to attract external talent, share knowledge and leverage synergies to create value. In this ecosystem, each pharmaceutical company has implemented its own open-innovation model with different degrees of openness [8], maturity, access and scope [9].

A very recent review article describes the different initiatives, centers and research alliances that pharmaceutical companies, government and non-profit organizations have put into practice to accelerate the drug-discovery process [10]. A more sophisticated classification establishes four models (knowledge creator, integrator, translator and leverager), based on the proportion of externally acquired R&D projects and the preference for innovation management [11]. This classification, however, only looks at the innovation that is a consequence of acquiring compounds in clinical development phases (Phase 1 to registration) from external sources.

Open-innovation collaborations simplistically could be categorized as either "biased" or "unbiased". Biased collaboration pre-selects institutions, groups, or scientists based on who the initiating party believes will provide the best result. On the other hand, in an unbiased collaboration any group or individual may participate regardless of their location or institutional origin. Adopting both biased and unbiased collaborations is a necessary part of business, which allows companies to take advantage of the benefits found in both types of models.

In the last decade, there has been significant growth in unbiased open-innovation initiatives. These are predominantly led by public initiatives and open-innovation platforms, such as web-based interfaces where people can collaborate virtually. This space is dynamic as initiatives come and go quickly. The second most prevalent are Funding Projects, which are proposal submission based, whereby the winners receive funding support from a public or government entity. Crowd Sourcing has been exploited in other industries for quite some time and is now gaining traction in the pharmaceutical sector [12], while Crowd Funding is used primarily in the non-profit space [13].

The following cases of open-innovation interaction models are known to be adopted by the pharmaceutical sector. This is not meant to be a comprehensive list, as new models continuously emerge in this space.

In Pre-Competitive Consortia, the goal is to share information and pre-competitive data with all consortium members (most big pharmaceutical companies) to promote shared learning and advancement of basic science [14].

The terms Public Private Partnership (PPP) and Consortium are often used interchangeably, even though consortium is funded by membership fees, whereas PPP is primarily funded by a public or government entity. PPPs aim to advance research in a particular therapeutic area, or to exchange knowledge for resources [15]. Many PPPs are biased and originate from emerging markets with the goal of advancing scientific capabilities within a region [16].

Challenge Models work by bringing companies with specific research needs together with solvers in a virtual space [17]. Eli Lilly's InnoCentive spin-off seems to be the leader of the challenge model and several companies have embraced it because of its success rate. This model attracts talent from all disciplines [18]. Diverse participant perspectives give valuable insight and can lead to better solutions than single industry views.

Research collaborations with Non-Profit Organizations (NPO) are a fast-growing segment of R&D partnerships, and many are focused on the neglected tropical diseases field [19]. In the past decade, R&D collaborations in neglected tropical diseases have been established mainly with PPPs [20]. NPOs operate using various open-innovation business models, but it is interesting that most of their project funding comes from non-pharmaceutical sources such as patient groups, foundations (e.g. Bill and Melinda Gates Foundation [21], Michael J. Fox Foundation [22]) and crowd funding. It is common in these networks to look for the appropriate partners that facilitate the identification of opportunities in the early stage of the drug-discovery process, and to share the results with the scientific community.

4 Eli Lilly's Innovation Journey

The pharmaceutical sector has gone through various innovation paradigms over the years and these models will keep evolving to meet the demands of patients, payers, and shareholders. Each pharmaceutical company has its own open-innovation story. As an example, the innovation journey at Eli Lilly is summarized below [23].

Eli Lilly realized that the "one size fits all" is not an efficient approach for all R&D projects. Thus, it established the Chorus group in 2002, a small independent unit to run clinical studies focused on reaching proof of concept (POC) data packages faster and with lower cost [24]. Chorus operates under a virtual R&D model, working with fewer internal employees and managing external capacity with certain flexibility. Their strategy is to develop, de-risk and increase the value of early phase internal (Lilly) and external assets supporting Lilly's capital fund strategy; develop assets outside Lilly's core focus areas and provide an alternative development approach for Lilly's therapeutic focus areas. Eli Lilly's concept of virtual R&D proved successful. The average success rate in Phase 2 increased from 29% (Lilly) to 54% (Chorus), compared with Eli Lilly's traditional clinical development model. By 2017, Chorus managed 72 development programs (57 from Lilly and 15 external) throughout North America, Europe and Asia, some of which progressed to Phase 3 and were further commercialized.

In 2008, Eli Lilly moved from being a fully integrated pharmaceutical company (FIPCO) to a fully integrated pharmaceutical network (FIPNET). At that time, most of the big pharmaceutical companies had externalized certain operations, but Lilly was going a step ahead working with partners in all areas of business. The FIPNET model leveraged external competencies by establishing collaborations as a key driver in all scientific departments. Some other companies adopted this model as a business objective, and they all recognized that they were able to do more by working with outside organizations than alone. Nowadays all pharmaceutical companies have externalized certain research services to Contract Research Organizations (CROs) increasing the variable cost to adjust expenses depending on portfolio needs [25].

Lilly was one of the first pharmaceutical companies to establish an open-innovation strategy, offering an array of opportunities to collaborate with universities, research centers and biotechnology companies. In 2009, the Phenotypic Drug Discovery (PDD) was the first initiative whereby external research groups could submit compounds for testing in a panel of phenotypic assays [26]. A couple of years later, this platform was supplemented with the Target Drug Discovery (TDD) initiative that added a set of target-based assays [27]. In 2013, the final evolution of the platform reached the

current Open Innovation Drug Discovery (OIDD) program, an example of unbiased model that has demonstrated that lead generation is increasingly becoming a joint pursuit, without foregoing IP rights or commercial opportunities [28]. The OIDD program operates under the assumption that the company shares, with research institutions and academia, a common desire to advance innovative biomedical science. OIDD is a premier collaborative platform that connects external investigators with Lilly scientists to both uncover and create innovation in the early drug-discovery stage.

Inspired by Lilly's initiative, nowadays some other companies (Merck, Bayer, Astra Zeneca, Leo Pharma) offer the opportunity to evaluate external partners' compounds as part of their open-innovation strategy [29].

In academia, many biology groups focus their research on target identification, with the final objective of exploring its therapeutic relevance. In the last decade, some academic institutions have built drug-discovery facilities where high throughput screening centers have been established to facilitate the discovery of chemical probes. These tools enable the pharmacological validation of novel targets and undergo medicinal chemistry optimization to produce a suitable clinical candidate. Screening facilities integrate automation and the most advanced biological technologies but sometimes have difficulties in acquiring high quality small molecule libraries. Eli Lilly was sensitive to this need and in 2016 designed the Emerging Biology offering as part of the OIDD program. Lilly provides access to the Biology Interrogation Compound (BIC) Cassette, a diversity-maximizing library of privileged compounds to be distributed to scientific institutions interested in testing novel biological hypotheses in therapeutic areas of common interest. The BIC cassette is a powerful tool for screening campaigns based on structural diversity with the appropriate drug-like properties. The company provides the compounds to help validate novel targets with potential therapeutic relevance, and the academic institutions share with Lilly the results generated with the BIC Cassette (Fig. 1). Based on the data obtained, Lilly discloses the structures of potentially interesting compounds to enable further investigation and publication. Findings may form the basis for subsequent collaboration and broader access to additional analogues from the Lilly collection.

Lilly is committed to external innovation as part of its core strategy and is constantly looking for ways to evolve and improve the efforts in this area. As result of this evolution, at the end of 2018 Lilly announced the retirement of the OIDD platform to allow for new approaches in external innovation to emerge. The OIDD learnings will be redirected to invest in new external innovation vehicles.

5 Challenges

In the last decade, pharmaceutical companies have established a number of collaborations with universities or public research centers under the open-innovation paradigm. Although some of these relationships have been very effective and productive, challenges and obstacles are common, some of which are easily solved, while others have increased the complexity of the collaborations [30]. The implementation of open-innovation strategies has forced big companies to change the corporate culture. Managers had to adjust their way of thinking to reorganize the drug-discovery process. Today we understand the shift to open models, something not easily done only a decade ago. In the internal dynamics of the traditional R&D model, pioneers of the transformation were often criticized, instead of being recognized for changing the

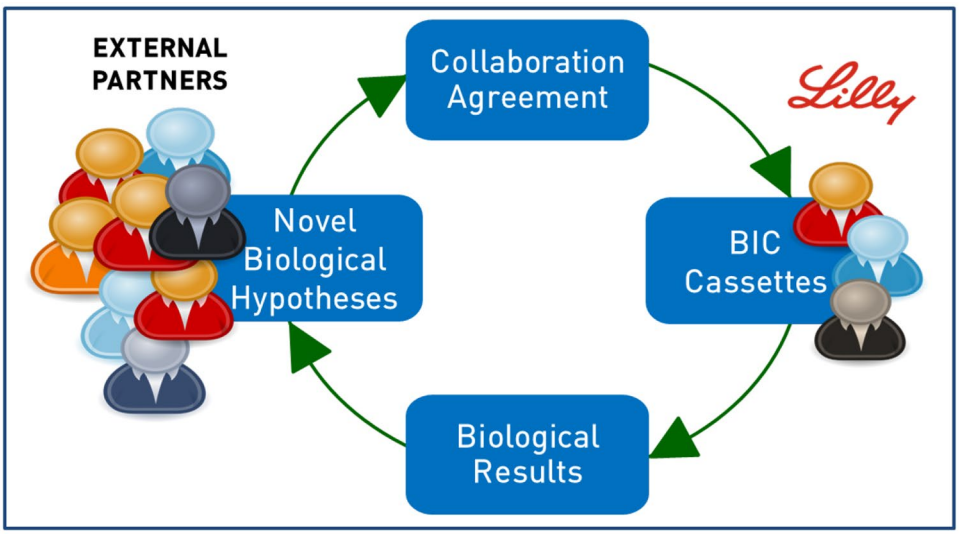

Fig. 1 OIDD Emerging Biology program

paradigm and implementing a novel approach. It took then a few years to educate organizations towards a more collaborative mindset.

Once the collaboration has started, both parties should accept the uncertainty and risk associated with a research collaboration based on innovation and be ready to discuss results and offer solutions to the scientific issues. However, the main issues to be solved should be exclusively scientific, avoiding personality problems that may arise because of conflicting styles or poor communication. Choosing the right people with the appropriate attitude and communication skills is therefore essential to establishing a solid relationship and precluding potential obstacles. Open and honest communication helps to build trust and credibility, both critical ingredients in efficient collaborations. Along the same line, best practices prescribe establishing clear expectations, roles, responsibilities and timelines to work together with minimal conflict. It is also very important to have frequent meetings and open direct communication channels to avoid any confusion or misunderstanding during the course of the collaboration.

Big companies are usually bureaucratic organizations. It takes time to identify the appropriate partner, and to set up the collaboration agreement. Universal agreements are easy to handle, but tailored contracts need more discussions. The negotiations are usually focused on IP ownership or financial compensation, although other topics such as confidentiality, data sharing and publishing opportunities also need to be discussed. In order to build a successful partnership with external investigators, pharmaceutical companies should negotiate terms of mutual benefit and adopt an approach that takes the interests of both parties into account.

Most of the big pharmaceutical companies are developing open-innovation programs at the early stage of the drug-discovery process. At the time of negotiating agreements with the private sector, the tech transfer offices typically understand the open-innovation concept based on sharing and accessing information, materials, expertise and research results among all parties involved. However, some of them are used to licensing technologies and aspire to work with industry in commercialization of research, without appreciating that the outcome of an early stage collaboration is not going to be a medicine ready to market or even a clinical candidate. Some research centers, fortunately very few, approach industry as if they possess the monopoly of knowledge in a particular field, not considering the value that the industry may offer, and undermining the negotiation process. On the other hand, in effective collaborations all partners are considered equals, promoting collaborative work and teaming up to generate value and positive results.

It is not difficult to build efficient collaborations between pharmaceutical companies and academia and the benefits are great. Scientists are exposed to new ideas and viewpoints, and they may expand their network and professional opportunities. Open innovation is here to stay, and pharmaceutical companies will continue engaging in collaborations with academia as they look for new opportunities to innovate. Both parties will have to face scientific and non-scientific challenges, but they are worth overcoming to complete the collaboration successfully.

6 Opportunities and Future Perspective

Open innovation is a very valuable paradigm and many pharmaceutical companies and academic institutions have already established effective collaborations. However, the open-innovation concept does not guarantee automatic success and all parts should contemplate changes that make alliances more successful. Collaborative models have multiple advantages, but companies need to evaluate their models, and adapt them to operate more productively. Each company should develop metrics to track the progress, outcome and impact, and consider adjustments to optimize the process [31]. Academic institutions should be more open to collaborate and increase their flexibility to open up opportunities to work with industry. At the same time, funding agencies should implement financial help to support open innovation, as a way to reinforce the value of applied research.

In pharmaceutical companies, management should motivate scientists continuously to look for external innovation and establish strategies to combine it with internal development, even in areas outside their expertise. Innovation needs to be recognized more often, and scientists should devote more time to identify external opportunities. At the same time, companies should decrease the layers of authority and have in place clear decision-making processes to establish collaborations.

Choosing the right leader with the appropriate skills is key for every collaboration because managing an alliance is always a challenge. Each partner has different characteristics and it is essential to build a solid and trustable relationship to bridge the cultural gaps. In collaborations that work well, both partners recognize they learn from each other. Scientists with the relevant expertise add a lot of value to a collaboration; however, networking and team building skills are even more important. The human component of a team is critical, and individuals with big egos and narrow vision are a recipe for failure.

Industry and academy will continue to optimize their synergies and establish collaborations in common areas of interest. Scientists in both institutions may have different languages, goals, drivers, expectations, incentives and career

paths, but all recognize the benefits of working together. Industry needs to foster innovative research and gain expertise to translate these ideas into new treatments. On the other hand, scientists at public institutions are interested in testing and validating their hypotheses using company-specific technologies and obtaining additional funding. While operational differences between both partners exist, complementary expertise and the establishment of a trusting relationship are some of the key factors that increase the likelihood of success.

Compliance with Ethical Standards

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