Biopharmaceutical RD outsourcing: Short-term gain for long-term pain?

Billette de Villemeur, Etienne and Scannell, Jack and Versaevel, Bruno

Université de Lille LEM UMR 9221, Science, Technology, and Innovation Studies, University of Edinburgh, EM Lyon Business School GATE L-SE UMR 5824

2021

14 April 2021

Biopharmaceutical R&D outsourcing: Short-term gain for long-term pain?

Author names and affiliations : Etienne Billette de Villemeur[a], Jack Scannell[b,c], Bruno Versaevel[d]

a. Université de Lille & LEM UMR 9221, France. etienne.de-villemeur@univ-lille.fr

b. Science, Technology, and Innovation Studies, University of Edinburgh, Edinburgh, UK. EH1 1LZ, United Kingdom. jack.scannell@ed.ac.uk

c. JW Scannell Analytics LTD, 32 Queens Crescent, Edinburgh, EH9 2BA, United Kingdom. jack.scannell@btinternet.com

d. EM Lyon Business School & GATE L-SE UMR 5824, France. versaevel@em-lyon.com

Corresponding author: Etienne Billette de Villemeur

Abstract
From the perspective of pharmaceutical companies, R&D outsourcing offers a range of benefits. For example, costs that were otherwise fixed can become variable, and firms can gain rapid access to a large set of new technologies. Recent theoretical work has added to the list by connecting R&D activities characterized by economies of scope and knowledge spillovers -- those that are likely to have the biggest effect on industry economics and social welfare – to the ability of large drug companies to capture a disproportionate share of economic value from, and transfer a disproportionate share of financial risk to, small new technology providers. The low profitability and high risk associated with the provision of such outsourced R&D activities reduce incentives to invest in new for-profit ventures that specialize in the most promising early-stage projects. We hypothesize that the short- to medium-term efficiency gains from R&D outsourcing may, therefore, be offset by slower innovation in the long run.

Keywords research; development; biotechnology; pharmaceuticals; externalities

Classification Codes L13; L65; O31

Funding Sources

Competing interests
J.W. Scannell is a director and shareholder of JW Scannell Analytics Ltd., which sells consulting services to the biopharmaceutical and financial services sectors. He is a paid advisor to Evaluate and to Protodigm (a subsidiary of Idea Pharma) and an unpaid advisor to Molecule. B. Versaevel is a shareholder and unpaid advisor to ViroScan3D.

1. Introduction

Recently, long-awaited evidence of an increase in the productivity of research and development (R&D) has appeared in the biopharmaceutical industry. When measured by the number of new molecular entities (NMEs) approved each year in the US, divided by the effective number of researchers, productivity started increasing around 2007 (Bloom et al., 2020). When considering the ratio of the same number of NMEs to R&D spending, the upturn occurred in 2010 (Ringel et al., 2020). Until that change, the latter ratio had halved approximately every nine years since 1950, indicating an exponential rise in R&D costs per new drug approval for 60 years, a trend known as 'Eroom's Law' – from the familiar Moore's Law (Lundstrom, 2003), but in reverse – after a paper by Scannell et al. (2012). The extent to which financial productivity measures will follow these other measures is not yet clear (Ringel et al., 2020).

The productivity upturn occurred several decades after the start of major R&D outsourcing, which began in the early 1980s. Established pharmaceutical companies initiated contractual relationships with new biotechnology firms in complement to -- or as a substitute for -- internal discovery programs (Pisano, 1991, 2006), and also with contract research organizations (CRO) for a range of activities (e.g., animal toxicology testing, chemical synthesis, etc.), including clinical testing services (Azoulay, 2004; Shuchman, 2007). An acceleration was observed in the number of arrangements of all kinds -- e.g., minority holdings, joint R&D partnerships, arms-length R&D contracts, etc -- in the early 1990s (Lerner and Merges, 1998; Roijakkers and Hagedoorn, 2006; Mowery, 2009). The range of capabilities covered by these arrangements has evolved in waves, starting from screening systems, rational drug design and combinatorial chemistry in the late 1980s, followed by technologies related to gene expression, proteomics and bioinformatics by the early- and mid-1990s (Hopkins et al., 2007). Since then, leading R&D-investing companies have increasingly engaged in multi-year contracts with specialized technology and service providers for the co-discovery and development of new therapies. The majority of alliances involved early-stage projects, although the share of mid- and late-stage agreements increased in the early-2000s, contributing to a steady decline in the number of products originated in-house among the larger firms (Thiel, 2005). In the last decade, high growth in the outsourcing of both discovery functions and in CRO-conducted clinical trials has been observed (Schuhmacher et al., 2016), and is expected to continue (Buvailo, 2020).

Over the years that preceded the improvement in R&D productivity, the growth in external technology sourcing was seen by some as instrumental in improving cost efficiency in discovery and in clinical

development. Scholars and industry experts have recognized in these strategies "a new engine of growth" (Quinn, 2000), "a new, more effective way of conducting R&D" with biotechnology companies (Kettler, 2000), and "new models of working" with contract research organizations (Cavalla, 2003) for a more efficient allocation of resources. Specialized industry publications – often emanating from the management consulting profession – have also presented R&D outsourcing as part of the solution to the problem of declining R&D productivity. For example, the same year that the ratio of the number of approved NMEs to R&D spending finally started to increase, one could read that "[t]he majors – Big Pharma, often outsource parts of their R&D value chain to improve productivity of their R&D efforts. The overall idea is always to increase the pace of drug development, reduce cost and maintain standards" (Bhagwat, 2010).

In this note, however, we question the contribution of the increasing use of R&D outsourcing on the productivity of discovery and development operations at the industry level. We first briefly review the advantages and disadvantages, from the viewpoint of pharmaceutical companies, of sourcing R&D externally over the use of internal capabilities, together with the empirical evidence on the relative efficiency of the two approaches. We then discuss the characteristics of outsourced R&D operations that drive the distribution of profits and risks among industry participants, and thereby shape incentives to invest. We find that certain kinds of early-stage firms will systematically fail to appropriate the industry-level value their R&D services create. We conclude that policy measures may be needed to shift the distribution of value from the consumers of outsourced early-stage R&D, typically larger companies, to the providers of outsourced early-stage R&D, and to shield the latter from the transfer of risk that is a standard feature of many R&D contracts.

2. R&D outsourcing by pharmaceutical companies

The main advantages of R&D outsourcing, as identified by scholars and industry experts, and from the viewpoint of pharmaceutical companies, include: (1) more flexibility, with fixed costs transformed into variable cost, and an easier exit from unsuccessful programmes; (2) higher productive efficiency when a specialized external R&D provider has distinctive proprietary capabilities, or a platform technology allows for economies of scope across a range of projects conducted for several partners; (3) better management of uncertainty, as outcome-based transfers -- e.g., milestone payments -- allow for risk-sharing among contracting parties (Quinn, 2000; Cavalla, 2003; Mittra, 2007); (4) and perhaps, as some industry participants have argued to us, that outsourcing makes the cost of R&D more transparent, which encourages users to consume only the services that are genuinely important.

On the other hand, R&D outsourcing arrangements create problems. For example: (1) new biotechnological firms often lack the financial strength necessary to successfully run highly risky projects that address new disease targets of interest for established pharmaceutical companies (Arora et al., 2004); (2) at the development stage, performance in knowledge-intensive clinical projects, for the identification of new hypotheses and causal associations -- as opposed to more routine data-intensive projects -- is more difficult to measure when conducted by a CRO than internally (Azoulay, 2003); (3) at all stages of the R&D process, there may be loss of control, know-how leakages, and regulatory compliance failures by a contracting party (Cavalla, 2003; Jones, 2007); and (4), serendipitous observations, which play an important role in pharmaceutical R&D (Mittra, 2008; Yaqub, 2018), may be less likely to occur when a biotech or a CRO conducts contracted activities for its downstream partners.[1]

Given these pros and cons, did outsourcing discovery and development activity mitigate the long-lasting decline in R&D productivity?

The empirical evidence is mixed. Some studies that used US data prior to 2001 found better performance for R&D conducted in alliances rather than in-house (Nicholson et al., 2005). The alliances had a higher probability of success in late-stage clinical trials, even more so if the licensee was a large firm (Danzon et al., 2005). However, other studies reached different conclusions. They found that failure rates were higher when a biotechnology firm undertook a drug project with a collaborative partner rather than when a single pharmaceutical firm conducted the project (Pisano, 1997). Further, although alliance projects – where a drug is developed by a small firm and financed by a larger one – were more likely to move from phase-1 to phase-2 clinical trials than integrated projects, they were then less likely to move from phase 2 to phase 3 and to receive regulatory approval (Guedj, 2005). In another empirical study, biotech firms had lower innovative performance – measured by the probability of drug approval – compared to established pharmaceutical companies (Arora et al., 2009).

[1] Yaqub (2018) introduced a taxonomy of serendipitous discoveries: "Mertonian" serendipity when a work on a defined problem serendipitously finds a solution to that problem (e.g., the discovery of the drug Salvarsan after a long series of failures against the same bacterial pathogens); "Walpolian" when work on a defined problem serendipitously finds a solution to a different problem (e.g., the discovery of Penicillin, or the discovery of anti-angiogenic drugs in oncology); "Bushian" when the solution of a pre-existing problem is serendipitously applied to a new problem (e.g., the successful anti-cancer drug methotrexate as a treatment for rheumatoid arthritis); and "Stephanian" when an unexploited technology, that was hitherto waiting for a problem, serendipitously finds a new problem (e.g., pertuzumab added to trastuzumab in HER2 positive breast cancers).

In a large dataset on R&D projects between 1990 and 2017, various types of originator-developer relationships yielded higher attrition rates than cases in which a pharmaceutical company integrated the two roles (Pammolli et al., 2020).[2] Recent empirical results outside the biopharmaceutical context are no more favourable to R&D outsourcing. A study with firm-level data across all industries over the 1983-2000 period finds that a 10% rise in outsourced R&D does not increase revenues (a measure of firms' output), while the same rise in internal R&D increases revenues by 1.3% (Knott, 2020).

3. Economies of scope and knowledge spillovers

Has R&D outsourcing contributed to the recent reversal of the long term decline in R&D productivity?

New formal modelling helps answer that question by shedding light on the effect of R&D outsourcing on the financial performance of a producer (an independent for-profit unit) and on downstream users of R&D outputs, and on incentives to start uncertain projects (Billette de Villemeur and Versaevel, 2019). Our central argument is that outcomes of outsourcing R&D operations are not limited to enhanced flexibility or increased efficiency in the conduct of *existing* projects, as investigated in the empirical literature. The contractual arrangements between an external R&D provider and its pharmaceutical partners also have an effect on the distribution of profits and risks among participating parties, and thus on the anticipated rewards to entrepreneurs and capital providers for starting *new* ventures (a biotech start-up, a CRO, …). In some circumstances, that depend in particular on the nature of outsourced activities (discovery, pre-clinical studies, management of clinical development, …), the distribution of profits and risks can be so favourable to the downstream pharmaceutical partners as to undermine upstream incentives to invest. It follows that outsourcing has not only an effect on the performance of current R&D programs, but may depress the investment in the new technologies that, in the long run, make R&D more productive.

In economic terms, the distribution among participants of the profits generated by and risks inherent in alliances depends on structural characteristics of the market for R&D. Specialized technology and service providers are positioned on the supply side. We call these firms "R&D providers". A smaller number of large established pharmaceutical firms, on the demand side, earn revenues from a variety of franchises, and can adjust -- to some extent -- their sourcing of external inputs by modulating

[2] Pammolli et al. (2020) also find that the performance of biotech firms acting as developers – a case of forward integration -- improves over time, and thus contributes to the recent improvement of R&D productivity in pharmaceuticals.

investments in internal capabilities. We call these firms "big drug companies." They have bargaining power when the time comes to design an external contract with an R&D provider that faces a high rate of entry of new competitors, and needs financial resources (Cockburn, 2004). Another important, and countervailing, market feature is that several big drug companies might have interest in tapping the distinctive competences of the same R&D provider. It has been documented that, from 1994 to 2001, biotech companies started an average of six partnerships with large pharmaceutical firms (Higgins, 2007). Competition among the big drug companies can benefit the R&D provider whose management is in a position to respond positively to only some, and possibly none, of the contenders' contract proposals. The terms of these contract proposals (typically an upfront amount, possibly an equity stake, plus payments that are conditional on *ex post* contracting R&D outcomes and sales) provide financial incentives to engage in uncertain R&D tasks. They also determine the R&D provider's bottom line if the project fails, and its appropriable share of the economic value generated by a new medicine in the event of success. The R&D provider's expected financial performance, as considered before operations start, thus depends on the transfers received from each big drug company in return for defined R&D outcomes both in adverse and in favourable circumstances.[3]

Economic modelling (Billette de Villemeur and Versaevel, 2019) shows that the expected profit to R&D providers depends on economies of scope across R&D programs, and on knowledge spill-overs across big drug companies that intend to outsource new technology. The modelling assumes that both R&D providers and big drug companies seek to maximise their profit. There are economies of scope when competencies in the pursuit of one project can be leveraged to others, so that the cost to an R&D provider of engaging in a specific project with a big drug company is made lower by also contracting with other big drug companies. Science-based platform technologies are likely to generate economies of scope in early-stage R&D tasks (Mittra, 2008). There are knowledge spillovers when unsolicited technological inputs are received from other firms, as occurs for example by examining the information disclosed in patents filed by competitors, when a competitor's drug of known mechanism succeeds or fails in clinical trials, or because of labour mobility within the industry. The move of the drug industry towards more open models of R&D – involving the participation in precompetitive consortia, or the

[3] An historical discussion between a biotech and several potential partners, at a pre-innovation stage, occurred in early 1978. It involved the science-based start-up Genentech and two large producers of insulin from animal pancreas glands, Eli Lilly and Novo Industri (which merged with Nordisk Gentofte to become Novo Nordisk in 1989). A first arrangement was concluded whereby Eli Lilly agreed to finance Genentech's project on biosynthetic human insulin at $50,000 a month, "a modest research support" (Hughes, 2011, p. 86). It is only at a later stage, after Genentech had succeeded in producing human insulin with recombinant technology, that the two parties signed a twenty-year exclusive agreement with an upfront licensing fee of $500,000, plus royalties on product sales.

installation of research facilities in proximity of biotech clusters (Munos and Chin, 2009; Schuhmacher et al., 2018) – can enhance exposure to knowledge spillovers.

Empirical studies have shown that late-stage development activities are characterized by dis-economies of scope -- serving more than one firm implies congestion -- and reduced or non-existent knowledge spillovers (Danzon et al., 2005; Macher and Boerner, 2006). Such situations imply a high degree of rivalry among big drug companies, as each of them would strongly benefit from exclusive access to the technological assets. For example, a CRO may not be able to enrol a sufficiently large number of volunteers for several phase-3 trials that rival big drug companies contemplate starting to test their respective candidate vaccines against the same disease (diseconomies of scope). And if the technology platforms for these vaccines are different, there is little useful knowledge to be gained from the research milestones and subsequent clinical results of competitors (no technological spillover). Then our theoretical analysis predicts that an R&D provider can take advantage of competition between big drug companies to secure a significant margin, which indicates that incentives to supply late-stage development services are preserved.

The conclusion is different when the public good characteristics of early-stage research entail economies of scope and substantial knowledge spillovers, as empirically shown at the individual level of research projects by detailed data obtained from major pharmaceutical firms (Henderson and Cockburn, 1996; Cockburn and Henderson, 2001). Typically, a new platform technology that emerges from basic academic research, in connection to a university laboratory, is likely to offer a large set of different applications, possibly in relation to open science strategies, including publications co-authored by academic and industry scientists (Cockburn and Henderson, 1998; Fabrizio, 2009), resulting in an improved performance of discovery activities (Jong and Slavova, 2014). In that case, the conduct of operations by the R&D provider in contractual relation with big drug companies can result in lower costs and better targeted efforts – by cross fertilization and internalization of spillovers – toward the discovery and characterization of new active substances, and thereby improve research productivity. Such circumstances, however, do not entail the same degree of rivalry from the big drug companies as when technological conditions imply exclusive contracting and minimal knowledge spillovers from competitors. In a technological context characterized by significant spillovers, it can be rational for a big drug company to wait for a competitor to contract with an R&D provider and, only if a new therapeutic mechanism is discovered, to engage resources in order to develop a marginally safer

or more effective drug.[4] Should all big drug companies adopt the same reasoning, an equilibrium in contract offers is reached that precludes the R&D provider from appropriating a substantial share of the industry value generated by its research efforts.[5] For founders of an R&D provider, the consequences are a worse financial performance and higher vulnerability to adverse events, which lead to a reduced incentive to invest. This theoretical conclusion matches long-term measures of the financial returns across the pharmaceutical and biotech sectors; a dollar invested in diversified basket of pharmaceutical firms and a second dollar invested similarly in biotechnology firms in 1980 would, with dividends reinvested, have been worth $114 and $8, respectively, by the end of 2015 (Thakor et al., 2017). The biotech sector is also characterized by a much higher project-specific (idiosyncratic) level of risk (Thakor et al., 2017).

More specifically, a positive aggregate measure of economies of scope and inter-firm knowledge spillovers is found, in theory (Billette de Villemeur and Versaevel, 2019), to imply a share of expected profits to the R&D provider that is driven to zero despite the R&D provider's aim of profit maximisation. Moreover, some of the risks of the big drug companies – which appropriate the entirety of expected profits – are transferred through outcome-based contracts to the R&D provider. In that case, investing in an R&D provider is tantamount to buying a lottery ticket at a price equal to the expected value of the prize; something that few professional investors would consider doing. This formal result points to two important observations: the financial returns to an R&D provider can be disconnected from the economic (and medical) value – possibly very high – that outsourced research could generate; moreover, an R&D provider that exactly breaks even *ex ante*, together with the valuable projects to which it contributes, is highly vulnerable to unfavourable events that lead to a negative net return *ex post*. These two observations indicate weak incentives for financiers to invest in early-stage science-based projects which, in principle, are precisely the ones that have the potential to lead to critical advances toward new medicines.[6]

[4] This possible strategy is already clearly described in Rosenberg (1990, p. 167), with no reference to an external R&D provider though: "If there are significant spillovers of knowledge between firms, then a late-mover could gain the same knowledge at a lower cost while, at the same time, avoiding the major mistakes that the first-mover made en route."

[5] This conclusion is reminiscent of the "classic" analysis by Teece (1986) of an innovator's ability to appropriate the profits generated by its efforts: "when imitation is easy, markets don't work well, and the profits from innovation may accrue to the owners of certain complementary assets, rather than to the developers of the intellectual property" (p. 285).

[6] These two points echo a more general statement in a seminal paper by Nelson (1959, p. 302), according to whom "[i]t is clear that for significant advances in knowledge we must look primarily to basic research; the social gains we may expect from basic research are obvious. But basic research efforts are likely to generate substantial external economies. Private-profit opportunities alone are not likely to draw as large a quantity of resources into basic research as is socially desirable."

4. Conclusion: Towards a policy response

The entry rate of new R&D ventures is directly related to anticipations of financial returns by entrepreneurs and capital providers. These (expected) returns depend on the nature of tasks contracted-out by pharmaceutical firms. Formal economic analysis predicts positive returns to those who provide R&D services when economies of scope across projects and technological spillovers are limited, as in the provision of clinical development activities by a CRO, or in late-stage agreements (e.g., new compound licensing after proof-of-concept) with a biotech, which can benefit from competition between pharmaceutical firms. By contrast, early-stage research activities that are most likely to generate efficiencies toward critical discoveries and breakthroughs, and thus can greatly contribute to increase the productivity of efforts towards new therapies and preventives, are predicted to be at the lower bound of the range of expected profits to external R&D providers. The characteristics of these activities – akin to those of public goods – mean that they give up most of the value they generate to the large pharmaceutical partners, with outcome-based contracts that shield the latter firms from idiosyncratic risks. Financial returns to founders of independent science-based R&D providers thus fail to reflect the economic and medical value they can generate and the risks they bear. Weak investment incentives may therefore hinder the foundation of the start-ups with most potential at the industry and societal levels; those with large knowledge spillovers and economies of scope. The short- to medium-term benefits of R&D outsourcing are thus likely to be offset by slower cumulative progress than is socially desirable in the long run. This theoretical diagnosis also offers a powerful explanation for some otherwise puzzling past industry trends; most obviously, the markedly superior investment returns from the pharmaceutical sector versus the biotechnology sector (Pisano, 2006; Thakor et al., 2017) between 1980 and 2015; returns which accrued, paradoxically, while the biotechnology sector was *gaining* share of both the R&D pipeline and of global drug revenues. The theoretical results may also help explain some of the decline in biopharmaceutical R&D productivity between 1950 and 2010, a decline which occurred despite huge scientific progress and brute-force efficiency gains (Scannell et al., 2012).

Some strategies appear to have been adopted by industry participants to mitigate the problems that the theoretical analysis highlights. On the supply side of the intermediate market for new technology, entrepreneurs and the venture capital industry now invest large sums to build technologies with potential spillovers and economies of scope into integrated drug discovery firms rather than R&D service providers, and existing biotech platforms engage in downstream commercial operations (e.g.,

Galapagos NV).[7] As drug discovery firms, they can appropriate financial value by using their technology to develop drug candidates, apply on their own for regulatory approval, and enter the final market for medicines. However, biotechnology risk capital is expensive (Harrington, 2012) and investment can be very hard to secure. When compared with an R&D service business model, the approach is likely to forego economies of scope by addressing only a fraction of possible applications. Because of reduced interactions with downstream drug companies, the approach will also likely delay and reduce informational spillovers that might otherwise enhance collective knowledge, increase industry value, and benefit patients. Therefore, these approaches do not eliminate what is a structural problem.

Initiatives have also been observed on the demand side of the market for new technology, where major pharmaceutical companies investigate new modes of collaboration with external contributors. For example, pre-competitive consortia have been funded by drug industry coalitions that involve universities for the production of new science-based knowledge to be used by commercial and academic scientists alike (Williamson, 2000). Other moves include the relocation of research activities to regional innovation hubs close to universities (e.g., Cambridge),[8] the creation of innovation centers where company and external scientists are encouraged to discuss drug discovery challenges, and the setting up of crowdsourcing platforms where networks of experts are invited to help solving technological problems (Schuhmacher, 2016). Even though these open innovation strategies can generate medical value by facilitating the production of knowledge spillovers and the identification of economies of scope, they also reinforce the public good characteristics of R&D outcomes. [9] The likely consequence is an exacerbation of the profit appropriation and risk transfer issues that benefit downstream drug companies in relation to existing technology providers, at the cost of reduced private incentives to start new science-based ventures at the upstream level.

We believe that reflections on a policy response are needed, as efforts in that direction seem under-represented in the outsourcing and R&D productivity literature. One approach would be to mitigate

[7] Galapagos NV, which communicates on its ambition "to become a fully integrated biotechnology company" (van de Stolpe, 2019), is transforming itself into a commercial organization in order to launch a new treatment of rheumatoid arthritis after receiving approval for European markets in summer 2020.

[8] For example, AstraZeneca chose to relocate its global R&D centre and corporate headquarters in Cambridge Biomedical Campus, in the hope that "cross-fertilisation with other companies, institutes and researchers will create novel routes to discovery" (Buckland, 2018).

[9] Open innovation initiatives of this kind can be interpreted as attempts by big drug companies to "weaken the upstream appropriability regime" of upstream R&D providers, in the words of Pisano (2006, p. 1129).

the long-run incentive problem by requiring cross-equity transactions (e.g., the upstream partner receives some payment in the form of shares in the downstream partner and the downstream partner takes an equity stake in the upstream partner). It may also be desirable to cap outcome-based milestone payments in favour of higher upfront payments to limit the ability of downstream partners to transfer risk. A more profound approach would be to identify new redistribution mechanisms at the industry level for the financing of science-based new ventures, and for their protection from project-specific uncertainties. It may, of course, turn out that the optimum redistribution mechanism is general taxation and more public sector spending on technologies that offer economies of scope and large knowledge spillovers.

Acknowledgments

The authors are grateful to Andrew Elder, Bernard Munos, and Standish Fleming for insightful conversations, but their kind help should not be interpreted as support for the ideas we put forward.

References

Arora, A., Gambardella, A., Magazzini, L., Pammolli, F., and Riccaboni, M., 2004, "The nature and the extent of the market for technology in biopharmaceuticals," in: Cesaroni, F., Gambardella, A., and Garcia-Fontes, W. (eds), *R&D, Innovation and Competitiveness in the European Chemical Industry*, Springer, pp. 175-202.

Arora, A., Gambardella, A., Magazzini, L., and Pammolli, F., 2009, "Breath of fresh air? Firm type, scale, scope, and selection effects in drug development," *Management Science*, Vol. 55, N°10, pp. 1638-1653.

Azoulay, P., 2004. "Capturing knowledge within and across firm boundaries: Evidence from clinical development," *American Economic Review*, Vol. 94, N°5, pp. 1591-1612.

Bhagwat, A., 2010, "Trends in pharmaceutical R&D outsourcing". Available at: https://pharmaphorum.com/views-and-analysis/trends_in_pharmaceutical_rd_outsourcing/

Billette de Villemeur, E., and B. Versaevel, 2019, "One lab, two firms, many possibilities: on R&D outsourcing in the biopharmaceutical industry," *Journal of Health Economics*, Vol. 65, pp. 260-283.

Bloom, N., Jones, Ch. I., Van Reenen, J., and Webb, M., 2020, "Are ideas getting harder to find?," *American Economic Review*, Vol. 110, N°4, pp. 1104-1144.

Buckland, D., 2018, “AstraZeneca: building a new ‘open innovation’ pharma company,” *PMLiVE*, available at:
http://www.pmlive.com/pharma_intelligence/AstraZeneca_building_a_new_open_innovation_pharma_company_1255460

Buvailo, A., 2020, “The evolving pharma R&D outsourcing industry: A bird’s-eye view”. Available at: https://www.biopharmatrend.com/post/146-the-evolving-pharma-rd-outsourcing-industry-a-birds-eye-view/

Cavalla, D., 2003, “The extended pharmaceutical enterprise,” *Drug Discovery Today*, Vol. 8, N°6, pp. 267-274.

Cockburn, I. M., 2004, “The Changing Structure of the Pharmaceutical Industry,” Health Affairs, VoL. 23, N°1, pp. 10-22.

Cockburn, I. M., and Henderson, R. M., 1998, “Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery,” *Journal* of *Industrial Economics*, Vol. 46, N°2, pp. 157-182.

Cockburn, I. M., and Henderson, R. M., 2001, “Scale and scope in drug development: Unpacking the advantages of size in pharmaceutical research,” *Journal of Health Economics*, Vol. 20, N°6, pp. 1033-57.

Danzon, P., Nicholson, S., and Sousa Pereira, N., 2005, “Productivity in pharmaceutical-biotechnology R&D: the role of experience and alliances,” *Journal of Health Economics*, Vol. 24, N°2, pp. 317-339.

Fabrizio, K. R., 2009, “Absorptive capacity and the search for innovation,” *Research Policy*, Vol. 38, N°2, pp. 255-267.

Guedj, I., 2005, “Ownership vs. contract: how vertical integration affects investment decisions in pharmaceutical R&D,” McCombs Research Paper Series, No. FIN-01-06.

Harrington, S. E. (2012) “Cost of Capital for Pharmaceutical, Biotechnology, and Medical Device Firms”, in *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*. doi: 10.1093/oxfordhb/9780199742998.013.0004

Henderson, R. M., and Cockburn, I. M., 1996, “Scale, scope and spill-overs: the determinants of research productivity in drug discovery,” *RAND Journal of Economics*, Vol. 27, N°1, pp. 32-59.

Higgins, M. J., 2007, “The allocation of control rights in pharmaceutical alliances,” *Journal of Corporate Finance*, Vol. 13, N°1, pp. 58-75.

Hopkins, M. M., Martin, P. A., Nightingale, P., Kraft, A., and Hinder, S., 2007, “The myth of the biotech revolution: An assessment of technological, clinical and organisational change,” *Research Policy*, Vol. 36, N°4, pp. 566-589

Hughes, S. S., 2011, *Genentech: The Beginnings of Biotech*, The University of Chicago Press.

Jones, A., 2007, “Minimizing leakage of value from R&D alliances,” *Nature Reviews: Drug Discovery*, Vol. 6, N°9, pp. 711-719.

Jong, S., and Slavova, K., 2014, “When publications lead to products: The open science conundrum in new product development,” *Research Policy*, Vol. 43, N°4, pp. 645-654.

Kettler, H. E., 2001, “The role of the external network in the pharmaceutical R&D process: alliances and licensing strategies”, in: Kettler, H. E. (ed.), *Consolidation and Competition in the Pharmaceutical Industry*, Office of Health Economics, pp. 29-47.

Knott, A. M., 2020, “R&D Outsourcing and the Decline in R&D Productivity,” US Census Bureau Center for Economic Studies Paper No. CES-WP- 16-19. Available at SSRN: https://ssrn.com/abstract=2756220

Lerner, J., and Merges, R.P., 1998, “The control of technology alliances: An empirical analysis of the biotechnology industry,” *Journal of Industrial Economics*, Vol. 46, N°2, pp. 125-156.

Lundstrom, M., 2003, “Moore's Law Forever?,” *Science*, Vol. 299, N°5604, pp. 210-211.

Macher, J. T., and Boerner, Ch. S., 2006, “Experience and scale and scope economies: Trade-offs and performance in development,” *Strategic Management Journal*, Vol. 27, N°9, pp. 845-865.

Mittra, J., 2007, “Life science innovation and the restructuring of the pharmaceutical industry: Merger, acquisition and strategic alliance behaviour of large firms,” *Technology Analysis & Strategic Management*, Vol. 19, N°3, pp. 279-301.

Mittra, J., 2008, “Impact of the life sciences on organisation and management of R&D in large pharmaceutical firms,“ *International Journal of Biotechnology*, Vol. 10, N°5, pp. 416-440.

Mowery, D. C., 2009, “Plus ça change: Industrial R&D in the ‘third industrial revolution’,” *Industrial and Corporate Change*, Vol. 18, N°1, pp. 1-50.

Munos, B. H., and Chin, W. W., 2009, “A Call for Sharing: Adapting Pharmaceutical Research to New Realities,” *Science Translational Medicine*, Vol. 1, N°9, pp. 1-4.

Nicholson, S., Danzon, P. M., and McCullough, J., 2005, “Biotech-pharmaceutical alliances as a signal of asset and firm quality,” *Journal of Business*, Vol. 78, N°4, pp. 1433-1464.

Nelson, R. R., 1959, “The Simple Economics of Basic Scientific Research,” *Journal of Political Economy*, Vol. 67, N°3, pp. 297-306.

Pammolli, F., Righetto, L., Abrignani, S., Pani, L., Pelicci, P. G., and Rabioso, E., 2020, “The endless frontier? The recent increase of R&D productivity in pharmaceuticals,” *Journal of Translational Medicine*, Vol. 18, N°1, pp. 162-176.

Pisano, G. P., 1991, “The governance of innovation: vertical integration and collaborative arrangements in the biotechnology industry,” *Research Policy*, Vol. 20, N°3, pp. 237-249.

Pisano, G. P., 1997, “R&D performance, collaborative arrangements, and the market for know-how: A test of the 'lemons' hypothesis in biotechnology,” mimeo, Cambridge, MA: Harvard Business School. Available at SSRN: https://ssrn.com/abstract=41980

Pisano, G.P., 2006, *Science Business: The Promise, the Reality and the Future of Biotech*, Harvard Business School Press.

Pisano, G.P., 2006, “Profiting from innovation and the intellectual property revolution,” *Research Policy*, Vol. 35, N°8, pp. 1122-1130.

Quinn, J. B., 2000, “Outsourcing innovation: The new engine of growth," *Sloan* Management Review, Vol. 41, N°4, pp. 13-28.

Ringel, M. S., Scannell, J. W., Baedeker, M., and Schulze, U., 2020, “Breaking Eroom’s Law,” *Nature Reviews: Drug Discovery*, Vol. 19, N°12, pp. 833-834.

Roijakkers, N., and Hagedoorn, J., 2006, “Inter-firm R&D partnering in pharmaceutical biotechnology since 1975: Trends, patterns, and networks,” *Research Policy*, Vol. 35, N°3, pp 431-446.

Rosenberg, N., 1990, “Why do firms do basic research (with their own money)?,” *Research Policy*, Vol. 19, N°2, pp. 165-174.

Scannell, J. W., Blanckley, A., Boldon, H., and Warrington, B., 2012, “Diagnosing the decline in Pharmaceutical R&D Efficiency,” *Nature Reviews: Drug Discovery*, Vol. 11, N°3, pp. 191-200.

Shuchman, M., 2007, “Commercializing clinical trials: Risks and benefits of the CRO boom,” *New England Journal of Medicine*, Vol. 357, N°14, pp. 1365-8.

Schuhmacher, A., Gassmann, O., and Hinder, M., 2016, “Changing R&D models in research-based pharmaceutical companies,” *Journal of Translational Medicine*, Vol. 14, N°1, pp. 105-115.

Schuhmacher, A., Gassmann, O., McCracken, N., and Hinder, M., 2018, “Open innovation and external sources of innovation. An opportunity to fuel the R&D pipeline and enhance decision making?,” *Journal of Translational Medicine*, Vol. 16, N°1, pp. 119-133.

Teece, D. J., 1986, “Profiting from technological innovation: implications for integration, collaboration, licensing and public policy,” *Research Policy*, 15, Vol. 15, N°6, pp. 285-305.

Thakor, R. T., Anaya, N., Zhang, Y., Vilanilam, C., Siah, K. W., Wong, C. H., and Lo, A. W., 2017, “Just how good an investment is the biopharmaceutical sector?,” *Nature Biotechnology*, Vol. 35, N°12, pp. 1149-1157.

Thiel, K. A., 2005, “A very firm handshake: biotech’s growing negotiating Power,” *Nature Biotechnology*, Vol. 23, N°10, pp. 1221-1226.

van de Stolpe, O., 2019, “Letter from the management,” *H1 Report 2019*, available at: https://www.glpg.com/docs/view/5d39f7f0c03eb-en

Williamson, A. R., 2000, “Creating a structural genomics consortium,” *Nature Structural Biology*, 7, page 953.

Yaqub, O., 2018, “Serendipity: Towards a taxonomy and a theory?,” *Research Policy*, Vol. 47, N°1, pp. 169-179.