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

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Research and development (R&D) outsourcing offers some obvious productivity benefits (e.g., access to new technology, variabilised costs, risk sharing, etc.). However, recent work in economics points to a productivity headwind at the level of the innovation ecosystem. The market for technologies with economies of scope and knowledge spillovers (those with the biggest impact on industry economics and social welfare) has structural features that allow customers to capture a disproportionate share of economic value and transfer a disproportionate share of economic risk to technology providers, even though the providers aim to maximise profit. This reduces the incentives to invest in new ventures that specialise in the most promising early-stage projects. Therefore, near-term gains from R&D outsourcing can be offset by slower innovation in the long run.

Keywords: Research; Development; Biotechnology; Pharmaceuticals; Externalities; Outsourcing



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Introduction

Recently, long-awaited evidence of an increase in the productivity of R&D has appeared in the biopharmaceutical industry. When measured by the number of new molecular entities (NMEs) approved each year in the USA, divided by the effective number of researchers, productivity started increasing around 2007.¹ When considering the ratio of the same number of NMEs to R&D spending, the upturn occurred in 2010.² Until that change, the latter ratio had halved approximately every 9 years since 1950, a trend known as 'Eroom's Law', from the familiar Moore's Law in computing,³ but in reverse, after a paper by Scannell *et al.*⁴ The extent to which financial returns will follow these other measures is not yet clear.²

The productivity upturn occurred several decades after the start of major changes in the market for technologies, compounds, and services within the biopharmaceutical industry. Ramping up from the early 1980s, established pharmaceutical companies initiated contractual relationships with new biotechnology firms in complement to, or as a substitute for, internal discovery programs.^{5,6} There was also growth in the use of contract research organisations (CRO) for a range of activities, including animal toxicology testing, chemical synthesis, and clinical trial services, among others.⁷ In this review, we refer to the full range of ways of acquiring R&D outputs from third parties as 'outsourcing', a broad definition of the term. Clearly, there are also many ways to pay for outsourced R&D, including capital investment for a minority holding, risk-based contracts for milestones and royalties, and fees for service arrangements, among others.

The quantity of outsourcing accelerated during the early 1990s.^{8,9} Since then, leading drug and biotech companies have increasingly entered multiyear contracts with technology and service providers for the co-discovery and development of new therapies. Most alliances involved early-stage projects, although the share of mid- and late-stage agreements increased during the early 2000s, contributing to a steady decline in the number of products originating in-house among the larger firms.¹⁰ Over the past decade, high growth in the outsourcing of both discovery functions and in CRO-conducted clinical trials has been observed,¹¹ and is expected to continue.¹²

Over the years that preceded the improvement in R&D productivity, the growth in outsourcing was seen by some as instrumental in improving efficiency. Experts variously described 'a new engine of growth',¹³ 'a new, more effective way of conducting R&D' with biotechnology companies,¹⁴ and 'new models of working' with CROs¹⁵ for a more efficient allocation of resources. Specialised 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'.¹⁶

However, we question the contribution of the increasing use of R&D outsourcing on the productivity of discovery and development operations in the broader innovation ecosystem. We

first review the advantages and disadvantages, from the viewpoint of pharmaceutical companies, of sourcing R&D externally over the use of internal capabilities, together with empirical evidence for the relative efficiency of the two approaches. We then discuss the characteristics of outsourced R&D that drive the distribution of profit and risk among industry participants, thereby shaping incentives to invest. Importantly, recent work from economics suggests that some types of outsourcing promise financial gain for the customers (hence their enthusiasm), but risk slower cumulative progress within the innovation ecosystem.¹⁷ This is because the customers capture so much of the economic value of the outsourced R&D that they undermine the incentives of the suppliers to invest; a hypothesis that finds empirical support in excellent long-term financial returns for investors in (downstream) pharmaceutical companies versus poor long-term financial returns for investors in (upstream) biotechnology companies¹⁸; returns that have occurred while the pharmaceutical companies have lost share of the pipeline and of end markets, and while biotechnology companies have gained shares.

R&D outsourcing by pharmaceutical companies

The main advantages of R&D outsourcing, according to the academic and industrial literature, and from the viewpoint of pharmaceutical companies, include: (i) more flexibility, with fixed costs transformed into variable cost, and an easier exit from unsuccessful programmes; (ii) higher productivity when a specialised external R&D provider has distinctive capabilities, or a platform technology allows for economies of scope across a range of projects conducted for several partners. By 'economies of scope', we mean that unit costs decline (or unit quality improves) as the outsourced provider takes on more work from several customers (see [Glossary](#)); (iii) better management of uncertainty, because outcome-based transfers (e.g., milestone payments) allow for risk-sharing among contracting parties^{13,15,19}; and (iv) as some industry participants have argued to us, the fact that outsourcing makes the cost of R&D more transparent, which encourages users to consume only the services that are genuinely important, thus improving R&D capital efficiency. By contrast, R&D outsourcing arrangements have limitations. For example: (i) serendipitous observations, which have an important role in pharmaceutical R&D,^{20,21} might be less likely to occur when a biotech or a CRO conducts contracted activities for its downstream partners¹; (ii) 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 internally²²; and (iii) at all stages of the R&D process, firms might have limited 'absorptive capacity', in that

¹ Yaqub²¹ 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 to a pre-existing problem is serendipitously applied to a new problem (e.g., the successful anticancer drug methotrexate as a treatment for rheumatoid arthritis); and 'Stephanian', when a failed or underexploited technology, which was hitherto waiting for a problem, serendipitously finds a new problem (e.g., pertuzumab added to trastuzumab in HER2-positive breast cancers, or anti-TNFs in autoimmune disease).

they face difficulties in recognising the value of new external knowledge and in assimilating it.^{23,24} There might also be loss of control, know-how leakages, and regulatory compliance failures by a contracting party.^{15,25}

Glossary

The factors that drive profit creation and appropriation in our analyses do not feature in much of the conventional biopharmaceutical R&D productivity literature (see, for example the following references: 47–49, but draw on some concepts and terminology that are common in economics. We explain these here.

When two or more pharmaceutical firms compete in the final market for medicines, and also interact with a third party that provides outsourced R&D, there are **externalities** if the profitability of a firm is penalised (**negative externalities**) or enhanced (**positive externalities**) by the R&D of the other firm(s).

R&D externalities are **direct** if the knowledge from a R&D project from one pharmaceutical firm impacts the profitability of other pharmaceutical firms. This occurs when the new knowledge generated by a pharmaceutical firm or received from an external partner brings about informational **spillovers** that benefit other firms that have not paid for the knowledge. They occur via employee mobility, the know-how described in patent applications, academic publications, and so on. Effective knowledge spillovers are more likely between firms that are engaged in similar R&D projects. Spillovers are common and important. The rich generic pharmacopoeia (90% of US prescriptions) is the cumulative result of spillovers, as has been the widespread adoption of recombinant proteins as medicines. The patent system is designed to encourage spillovers while also incentivising innovation via a bounded monopoly for the inventor.

R&D externalities are **indirect** if they are transmitted between pharmaceutical firms via an outsourced R&D provider. For example, there might be **economies of scope** and, hence, the R&D provider operates at lower unit cost by serving more than one pharmaceutical client (e.g., new knowledge learnt in a project increases productivity in another project), because of technological complementarities that facilitate multitasking. Conversely, there may be **dis-economies of scope**, so that serving one customer makes it harder to serve others (e.g., recruiting patients with a rare disease into pivotal trials), when operations are characterised by anti-complementarities across projects.

Given these pros and cons, did outsourcing discovery and development activity either mitigate the long-lasting decline in R&D productivity or contribute to the post-2010 turnaround?

The empirical evidence is mixed. Some studies that used US data from before 2001 found better performance for R&D conducted in alliances rather than in-house.²⁶ Between 1988 and 2000, in a sample of US biotech–pharmaceutical alliances, it was found that a compound had a higher probability of complet-

ing a development phase for a particular indication in late-stage clinical trials, even more so if the licensee was a large firm.²⁷ However, other studies reached different conclusions. For a sample of drug projects initiated before 1991, it was found that the likelihood of termination, as opposed to receiving marketing approval by the US Food and Drug Administration (FDA), was higher when a biotechnology firm undertook a project with a collaborative partner rather than when a single pharmaceutical firm was involved.²⁸ Furthermore, for a sample of drug projects over the period 1984–2001, although alliance projects (in which a drug is developed by a small firm and financed by a larger one) were more likely to move from Phase I to Phase II clinical trials than were integrated projects, they were then less likely to move from Phase II to Phase III and to receive FDA approval.²⁹ In another empirical study, between 1980 and 1994, a large sample of US biotech firms had lower innovative performance, as measured by the probability of drug approval by the FDA, compared with established pharmaceutical companies.³⁰ In a large data set on R&D projects started in the European Union, the USA or Japan between 1990 and 2017, various types of originator–developer relationship yielded higher attrition rates than cases in which a pharmaceutical company integrated the two roles.²³¹ 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 found that a 10% rise in outsourced R&D did not increase revenues (a measure of the output of a firm), whereas the same rise in internal R&D increases revenues by 1.3%.³²

Economies of scope, knowledge spillovers, and value capture

Has R&D outsourcing contributed to the recent reversal of the long-term decline in R&D productivity? New formal game-theoretic modelling helps answer this question by shedding light on the effect of R&D outsourcing on the financial performance of an R&D provider (an independent for-profit biotechnology company or CRO) and on downstream users of the R&D, and on incentives for R&D providers to invest in high-risk technologies that have broad application.¹⁷ The central argument is that outcomes of outsourcing R&D go well beyond the flexibility and efficiency of existing projects, as investigated in the literature. This is because the contractual arrangements between an R&D provider and its pharmaceutical partners 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

² Pammolli *et al.*³¹ also found 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.⁵ 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 US\$50 000 a month, 'a modest research support'.³⁵ It was only at a later stage, after Genentech had succeeded in producing human insulin with recombinant technology, that the two parties signed a 20-year exclusive agreement with an upfront licensing fee of US\$500 000, plus royalties on product sales.

CRO, etc.). In some circumstances, which depend on the nature of outsourced activities (see below), the distribution of profits and risks can be so favourable to the downstream pharmaceutical partners as to undermine upstream incentives to invest. Therefore, it follows that outsourcing has not only an effect on the performance of current R&D programs, but might also depress the investment in the new technologies that, in the long run, make R&D more productive.

Some R&D outputs have the characteristics of a public good, which, by definition, is both non-excludable and non-rival. Non-excludability means that one actor cannot exclude another actor from using the good. Non-rivalry means that the use of the good by one actor does not reduce its use by another actor. R&D outputs are non-excludable when knowledge spillovers mean that one firm can learn from projects of other firms' without financial compensation (e.g., via patents, FDA Advisory Committee materials, or academic publications). The services of a R&D provider are non-rival when contracting with several firms does not penalise, or even facilitates, its performance for any of its clients.

In economic terms, the distribution among participants of the profits generated by, and risks inherent in, R&D outsourcing depend on structural characteristics of the market for R&D. Specialised 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 investments in their own internal capabilities. We call these firms 'big drug companies'. They have bargaining power when the time comes to design a contract with the R&D provider. The R&D providers often face a high rate of entry of new competitors, and also need financial resources.³³

Another important market feature is that several big drug companies might have interest in tapping the distinctive skills of the same R&D provider. For example, in a study of the outsourcing of R&D through acquisitions in the pharmaceutical industry for the years 1994–2001, with the majority of the involved parties being based in the USA, it was found that, before the acquisition, target firms had more than six alliances on average with other firms.³⁴ Competition between the big drug companies can benefit an R&D provider the management of which is in a position to respond positively to only some, and possibly none, of the available 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 risky R&D tasks. They also determine the bottom line of the R&D provider if the project fails, and its appropriable share of the economic value generated by a new medicine in the event of success. The expected financial performance of the R&D provider, as considered before operations start, thus depends on the transfers received from each big drug company in return for defined R&D outcomes under both adverse and favourable circumstances⁸.

Game-theoretic modelling¹⁷ shows that the expected profit to R&D providers depends on economies of scope across R&D programs, and on knowledge spillovers across big drug companies

that intend to outsource R&D activity (see the [Glossary](#) for an explanation of these terms). 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 activities.²⁰ There are knowledge spillovers (see [Glossary](#)) when unsolicited, but useful, information is 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 toward more open models of R&D, involving the participation in precompetitive consortia, or the installation of research facilities in proximity of biotech clusters,^{36,37} can enhance exposure to knowledge spillovers.

We start with the situation in which there are dis-economies of scope (serving more than one firm implies congestion) and small or non-existent knowledge spillovers. This is often (but not always) the case in late-stage clinical development.^{27,38} Such situations imply a high degree of competition between big drug companies, because each of them would benefit from exclusive access to the services or technology. For example, a CRO might not be able to enrol a sufficiently large number of volunteers for parallel Phase III trials in which rival big drug companies want to start to test their candidate vaccines against the same disease (dis-economies of scope). In addition, if the technology platforms for these vaccines are different, or if the pandemic will be over before the product can be substantially modified, there is little useful knowledge to be gained from the Phase III results of the competitors (i.e., minimal technological spillover). In these cases, our game-theoretic analysis predicts that an R&D provider can exploit competition between big drug companies to secure much of the industry-level profit that its R&D helps to create. Therefore, incentives to supply such services are strong.

The numerical example presented in [Box 1](#) relates to circumstances in which the joint supply of R&D activities by an external provider is impractical, with outcomes that are highly specific to the respective projects of several large pharmaceutical firms. Therefore, these firms must compete aggressively for the exclusive benefit of these outputs.

Box 1 Numerical example 1. Minimal spillovers and low economies of scope.

Suppose that two large firms can choose to make (or not) contract offers to an R&D provider which can accept none of the contracts, or only one, or both. The contracts link payments to the completion of a project. Suppose that knowledge spillovers are limited and anti-complementarities impede the joint conduct of similar operations by the R&D provider.

For all possible contract strategy combinations, the payoff matrix ([Table 1](#)) represents profits to firm 1 (π_1), firm 2 (π_2), the R&D provider (π_0), and the industry as a whole ($\pi_0 + \pi_1 + \pi_2$):

Table 1. Payoff matrix.

Firm 1\Firm 2	No contract by firm 2	Contract by firm 2
No contract by firm 1	$\pi_1 = 100, \pi_2 = 100,$ $\pi_0 = 0$ (industry profit = 200)	$\pi_1 = 59, \pi_2 = 183,$ $\pi_0 = 0$ (industry profit = 242)
Contract by firm 1	$\pi_1 = 183, \pi_2 = 59,$ $\pi_0 = 0$ (industry profit = 242)	$\pi_1 = 67, \pi_2 = 67,$ $\pi_0 = 116$ (industry profit = 250)

In this example, each firm earns 100 as a net economic profit when neither partners with the R&D provider, for an industry value of 200.

Considering firm 1's viewpoint, profit increases from 100 to 183 when its project is conducted in exclusive partnership with the R&D provider for its value-added services. This gain in profit is explained by the partnership resulting in an innovation and by market interactions which harm firm 2 whose profit decreases from 100 to 59. If firm 1's payment to its exclusive R&D partner faces no competition from the other firm, it can be low-balled to merely cover the R&D provider's costs, so that the latter merely breaks even. In that case the R&D provider does not appropriate any of the extra industry value it helps to generate (an extra 42, from industry profits of 242 versus 200 in the no contract case).

It is in the interests of the R&D provider to solicit contracts from both firms to make them compete. This situation is less attractive to the firms than their own exclusive arrangement, so they pay the provider less than they would have done for exclusivity. However, it is still better than being left out. In this example, by accepting two contracts the R&D provider appropriates a profit of 116, that is 58 from each firm. It is the best outcome for the R&D provider, and the second worst outcome for each of the firms.

The outcome depends on each firm's relative valuation of the decisions it can make in response to the rival's possible moves. From firm 1's viewpoint, choosing to contract with the R&D provider results in more private profit regardless of the choice of firm 2. Indeed, if firm 2 does not contract with the R&D provider, firm 1 builds a competitive advantage by contracting exclusively with the R&D provider ($183 > 100$); and if firm 2 contracts with the R&D provider, firm 1 loses less by contracting than by standing alone ($67 > 59$). In game theoretic terms, contracting is "a dominant strategy". The same comparisons of alternatives apply from firm 2's viewpoint, so that both firms choose to contract with the R&D provider. However, each firm would have more benefited from an exclusive contract ($67 < 183$) and, had the two rivals been able to commit not to contract with the R&D provider, they would also have been better-off ($67 < 100$), despite lower total industry profits ($200 < 250$).

In the illustrative situation presented in [Box 1](#), interfirm competition in the R&D market is so strong as to imply a Prisoners'

Dilemma situation, in which the profit of each downstream firm is lower than in the status quo situation with no innovation from the R&D provider, and the net profit to the latter is higher than the net value generated by its R&D (in the example presented in [Box 1](#), numerically, $116 > 250 - 200$).

The conclusion is different when there are economies of scope and substantial knowledge spillovers, as is often (but not always) the case with early stage R&D.^{39,40} A new platform technology that emerges from basic research, from a university laboratory for example, typically offers a broad set of applications. Open-science strategies initiated by pharmaceutical companies specifically aim to explore these possible applications. The induced connection between science-based and more business-oriented research efforts is notably evidenced by publications co-authored by academic and industry scientists,²⁴ which have been observed to relate to an improved performance of discovery activities.⁴¹ Indeed, the conduct of operations by an R&D provider with strong basic science capabilities in contractual relation with big drug companies can result in lower costs and better targeted efforts (by cross-fertilisation and internalisation of spillovers) toward the discovery and characterisation of new compounds, thereby improving research productivity. However, such circumstances do not entail the same degree of rivalry between the big drug companies as when technological conditions imply exclusive contracting and minimal knowledge spillovers. When there are major 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 to develop a similar drug; perhaps marginally safer or more effective.³ Should all big drug companies adopt the same logic, their incentives to pay for being the first to acquire new knowledge in the R&D market would be weak, making it difficult for R&D providers to appropriate a large share of the industry value generated by their research efforts (see [Box 2](#) for a numerical example).⁴ For founders of such R&D providers, the consequences are poor absolute financial performance plus high financial risk, which both reduce the incentive to invest in the first place.

This game-theoretic conclusion matches long-term measures of the financial returns across the pharmaceutical and biotech sectors. Between 1980 and 2015, the biotech sector gained a share of the global pipeline and of the final market for medicines, but it appropriated much less economic value than did conventional pharmaceutical companies. A dollar invested in a diversified basket of pharmaceutical firms and a second dollar invested similarly in biotechnology firms in 1980 would, with dividends reinvested, have been worth US\$114 and US\$8, respectively, by the end of 2015.¹⁸ The biotech sector is also characterised by a much higher project-specific (idiosyncratic) level of risk.¹⁸

³ This possible strategy is already clearly described by Rosenberg,⁴² although with no reference to an external R&D provider: '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'

⁴ This conclusion is reminiscent of the analysis by Teece⁴³ of the ability of an innovator 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).

Box 2 Numerical example 2. Large spillovers and high economies of scope.

Suppose that two large pharmaceutical firms can choose to offer a contract, or not, to a for-profit R&D provider, which can accept none, one, or both of the offers. In this example, there are high knowledge spillovers so each firm can learn from its rivals' R&D outcomes. There are also economies of scope so the R&D provider can take on extra clients at lower incremental cost. These conditions often apply to early stage "platform" technologies.

The payoff matrix (Table 2) describes the profits to firm 1 (π_1), firm 2 (π_2), the R&D provider (π_0), and the industry as a whole ($\pi_0 + \pi_1 + \pi_2$), for all contract strategy combinations:

Table 2. Payoff matrix.

Firm 1\Firm 2	No contract by firm 2	Contract by firm 2
No contract by firm 1	$\pi_1 = 100, \pi_2 = 100,$ $\pi_0 = 0$ (industry profit = 200)	$\pi_1 = 125, \pi_2 = 130,$ $\pi_0 = 0$ (industry profit = 255)
Contract by firm 1	$\pi_1 = 130, \pi_2 = 125,$ $\pi_0 = 0$ (industry profit = 255)	$\pi_1 = 220, \pi_2 = 220,$ $\pi_0 = 0$ (industry profit = 440)

In the status quo case, where no firm chooses to contract for R&D, the net profit to each of them is 100, and the R&D provider makes no profit.

If only one firm contracts with the R&D provider, the pair generate a value of 130, while the non-contracting firm – benefiting from substantial knowledge spillovers – earns 125. Both firms earn a higher profit than in the status quo, although an exclusive contract for tailored R&D is more profitable than spillovers ($130 > 125$). The R&D provider makes no profit because it cannot exert competitive pressure on its single customer, and the payments received from its exclusive partner only cover R&D costs.

If both firms contract with the R&D provider, each partnership generates a net value of 120 (in addition to the status quo value). However, the competition is so weak as to result in payments which, together, still only cover R&D costs, so that the R&D provider's net profit remains equal to zero, despite the large increase in industry profits (to 440).

The decision to contract or not for R&D depends on the comparison of alternatives. From firm 1's viewpoint, partnering with the R&D provider is profitable if firm 2 is not involved ($130 > 100$), and even more so if firm 2 is also a partner ($220 > 125$). The same comparisons apply from firm 2's viewpoint. It follows that total industry profitability improves substantially, by $2 \times (220 - 100) = 240$, a 220% increase relative to the status quo scenario (much more than in the situation described in Box 1). This outcome is a consequence of each firm learning from the R&D efforts of the other partnership (e.g., patent information on a new mechanism of action can be invented around for the

discovery of another molecular entity), and from technological complementarities that raise the efficiency of the R&D provider's efforts when it participates in two projects, as opposed to only one (e.g., a biological pathway identified by working on a project can be leveraged to address the medical challenges of the other project). Then each firm finds it even more beneficial to contract with the R&D provider if the competitor also chooses to do so.

There are real-world examples that illustrate the quantitative financial trends. For example, in the immuno-oncology area, the understanding of how immune responses are controlled by 'checkpoints' can be leveraged to a range of therapies, and firms can learn from the observed outcomes of competitors' projects. The shareholders of the most successful biotech firms in that domain, such as Medarex, involved in the development of anti-CTLA4 and anti-PD1 therapies since the late 1990s, acquired by Bristol Myers Squibb for US\$2.1 billion in 2009,⁴⁴ appropriated only a tiny fraction of the value they helped to generate. Annual sales by a few large pharmaceutical companies (Merck & Co, Bristol Myers Squibb, Roche, AstraZeneca, etc.) of immuno-oncology medicines, which pertain to the very same approach, amounted to ~US\$37 billion in 2021, and are expected to reach over US\$50 billion by 2025.⁴⁵

The numerical example commented in Box 2 illustrates circumstances in which competition by pharmaceutical companies for exclusive access to an R&D provider is weak, because activities can be applied at a low incremental cost to multiple applications and are characterised by significant knowledge spillovers. Then the R&D provider can appropriate little or none of the, possibly very high, economic value it generates. Consequently, the financial incentives to invest in the creation of the R&D provider are weak despite the substantial industry-level value it could create.

A positive aggregate measure of interfirm knowledge spillovers and economies of scope is found, in theory, to imply a share of expected profits to the R&D provider that is driven to zero despite the aim of profit maximisation by the R&D provider (see Fig. 1 in Box 3, above the frontier). Moreover, some of the risks of the big drug companies, which appropriate all the expected profits, are transferred through outcome-based contracts to the R&D provider. In this trading arrangement, investors in the R&D provider are being offered an expected (i.e., average) return of zero percent with considerable risk to the capital they have deployed; not a prospect that should excite many professional investors.

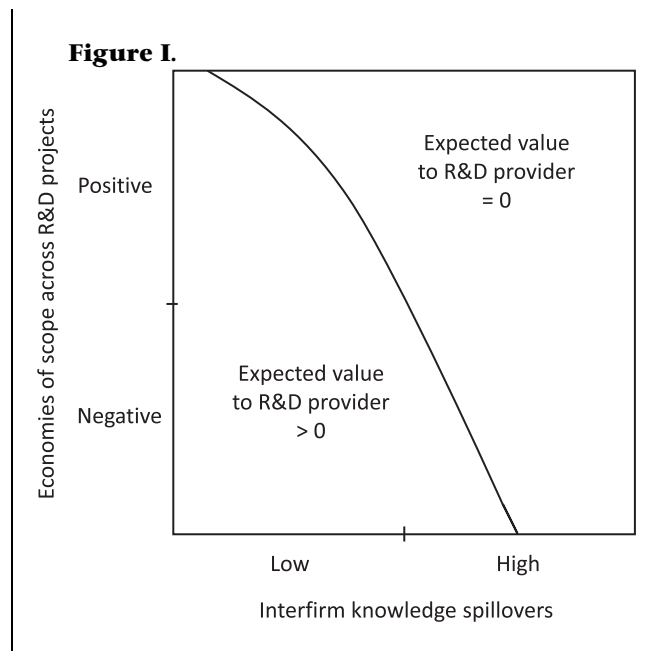
Box 3 Expected value capture by the R&D provider.

In Figure 1, the horizontal axis describes a continuous measure of interfirm knowledge spillovers. We refer to cases in which spillovers are either 'low' (little is learnt from the R&D projects of competitors) or 'high' (substantial knowledge is received). The vertical axis represents a measure of economies of scope, which can be 'negative' (working on a project raises the cost of working on another project to the R&D provider) or 'positive' (efforts engaged in a project reduce the cost of contributing to another one).

A firm that contemplates collaborating with an R&D provider will not encourage the latter to partner also with another company if no knowledge can be received from the rival project, and dis-economies of scope make multi-tasking costly. However, the firm might be in favour of seeing its R&D partner contract as well with another company if new knowledge is received from the latter, and economies of scope reduce the cost of outsourced activities. There are mixed situations in which the effects of spillovers and (dis)economies of scope on the profitability of competing R&D projects cancel out. This occurs when spillovers are substantial while dis-economies of scope penalise multi-contracting, or where spillovers are low and economies of scope are positive. It follows that, in Figure I, the space of points can be partitioned by a downward sloping frontier, depending on whether 'R&D externalities' that result from the combined effects of spillovers and (dis) economies of scope are negative (below the frontier) or positive (above).

Below the frontier, pharmaceutical firms cannot benefit substantially from the new technology that competitors outsource, and an R&D provider finds it difficult to contribute to several projects, so is likely to focus on only a selection of them. Late-stage, and often labour-intensive, clinical development tasks, which cannot be leveraged across projects and the outcomes of which are highly specific to a firm, are emblematic of that situation. This is a case of negative R&D externalities, implying a high degree of competition among potential downstream partners interested in accessing distinctive R&D capabilities. Thus, a for-profit provider (e.g., a CRO) finds itself in a position to benefit from the rivalry of sponsors of various projects and can expect a positive net profit as a result (see [Box 1](#) in the main text for a numerical example). The lower the spillovers, and the more negative the economies of scope, the higher the level of appropriated profit to the R&D provider (bottom left of Figure I).

Circumstances are different when spillovers are sufficiently high and/or economies of scope are strongly positive, as represented by all points above the frontier, where R&D externalities are positive. Such circumstances relate, typically, to a biotech engaging in early-stage activities the outcomes of which are transferable across projects, and where pharmaceutical firms draw new knowledge from the project of a rival. Then, competition between the outsourcing firms, the objectives of which are somewhat congruent, can be so mild as to prevent the R&D provider capturing a positive share of the economic value to which it contributes. Instead, this value exclusively benefits the pharmaceutical firms (as in [Box 2](#) in the main text).



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 suggest weak incentives to invest in early-stage science-based projects, which, in principle, are precisely those that have the potential to lead to critical advances toward new medicines.⁵

[Box 3](#) and Figure I show the general framework from which [Boxes 1 and 2](#) draw.

Concluding remarks

We conclude with three main ideas. First, there appear to be important differences in the economic appropriability of and, hence, the markets for, different types of R&D. As [Box 3](#) shows, there are at least two types of market; those to the lower left of the line in Figure I, where the R&D service provider can appropriate value, sometimes more value than its goods or services create ([Box 1](#)), and those to the upper right of the line, where the customers capture the overwhelming share ([Box 2](#)). This might not surprise readers working in the drug and biotechnology industries, but it is not reflected in the R&D outsourcing literature. Therefore, we suspect that future analyses of the pros and cons of R&D outsourcing, for both suppliers and customers, would provide clearer answers if they were to make this distinction, rather than treating R&D outsourcing as a single homogenous entity.

⁵ These two points echo a more general statement in a seminal paper by Nelson,⁴⁶ 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'.

Second, the entry rate of new R&D ventures is directly related to the expected financial returns for entrepreneurs and capital providers. Formal economic analysis predicts positive returns to those that provide R&D services when economies of scope across projects and technological spillovers are limited, as in the provision of certain 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, the research activities with large economies of scope and knowledge spillovers, those that resemble public goods, give up the profits they create to downstream customers while concentrating risk on their entrepreneurs and investors. Ironically, these are precisely the technologies that, if widely adopted by downstream customers, would create the most economic value at an industry level and, in all likelihood, the most therapeutic value for society. Thus, weak investment incentives might hinder the foundation of the start-ups with most potential at the industry and societal levels and the short- to medium-term benefits of R&D outsourcing to downstream customers might be offset by slower cumulative progress in the long run. Third, the weak incentives for private sector involvement in such public goods might deserve more policy attention, particularly when the public goods in question fall between conventional publicly funded academic research and the point in the commercial R&D pro-

cess at which strong competitive pressure can be exerted on downstream customers. Innovation with respect to better screening and disease models could be an example of something that often falls in this gap.⁴⁷ The problem could be mitigated through a variety of mechanisms, ranging from funding from general taxation at one end of the spectrum, through to market-based incentives that reward those who make the initial commercial investments in biopharmaceutical technologies with high spillover potential and economies of scope.

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Declaration of interests

J.W.S. is CEO of Unify Pharmaceuticals Corp, a director and shareholder of JW Scannell Analytics Ltd, a paid advisor to Evaluate and to Protodigm, and an unpaid advisor to Molecule. He holds stock options in Ochre Bio. B.V. is a shareholder and unpaid advisor to ViroScan3D, and an independent consultant.

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