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Limits to the Development of Causal Treatments in Neurodegenerative Diseases – Indications for Market Failure?

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Final report

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Zusammenfassung

Arzneimittel spielen eine wichtige Rolle bei der Verbesserung der Gesundheit in modernen Gesellschaften. Dennoch hat die Pharmaindustrie bei einigen Krankheiten Schwierigkeiten, kausale oder krankheitsverändernde Behandlungen zu entwickeln. Einige neurodegenerative Erkrankungen (NDD) wie Parkinson (PD), Demenz oder Alzheimer (AD) sind prominente Beispiele hierfür. So steht zum Beispiel trotz der Entwicklung einer symptomatischen Behandlung von PD vor mehr als 50 Jahren bis heute keine kausale oder krankheitsverändernde Behandlung zur Verfügung.

Alternative, ökonomische Erklärungen für das Fehlen kausaler Behandlungen. Während diese Sachlage lediglich die wissenschaftlichen Herausforderungen bei der Entwicklung neuer Medikamente widerspiegeln könnte, untersucht dieser Bericht mögliche alternative, ökonomische Erklärungen, die für das Fehlen kausaler Behandlungen verantwortlich sein könnten. Diese alternativen und möglicherweise ergänzenden Erklärungen oder Hypothesen werden auf der Grundlage der ökonomischen Literatur, einschließlich der Gesundheitsökonomie, der Industrieökonomie, der Regulierung und der Finanztheorie, sowie auf der Grundlage qualitativer Interviews und bestehender empirischer und qualitativer Studien im Bereich von AD und insbesondere von PD entwickelt. Im Mittelpunkt dieser Hypothesen stehen die wirtschaftlichen oder finanziellen Anreize für Forschung und Entwicklung (F&E) aus der Perspektive der Pharmaindustrie. Anhand von einfachen Modellen, Mechanismen und Illustrationen werden die F&E-Anreize der Unternehmen, d. h. wie viel, wo und wann – wenn überhaupt – investiert werden soll, diskutiert.

Besondere Einflussfaktoren für F&E bei NDD, insbesondere PD. Die wirtschaftlichen Anreize werden vor dem Hintergrund des beobachteten Mangels an einer wirksamen Heilung bei PD und anderen NDD analysiert. Zu diesem Hintergrund gehören:

- relativ gut funktionierende bestehende Behandlungsmethoden für einen beträchtlichen Teil der betroffenen Bevölkerung;
- langwierige und kostspielige klinische Studien;
- eine Reihe gescheiterter Forschungsprojekte und das damit verbundene Risiko, ein neues Medikament nicht entwickeln zu können;
- Unsicherheit über die Größe des Patientenpools, die mit einem neuen Medikament behandelt werden könnte;
- und das Risiko, dass ein Entwickler für die Verringerung der sozialen Kosten, die ein kausales Medikament mit sich bringen könnte, nicht ausreichend entlohnt wird.

Mögliches Markt- oder Regulierungsversagen. Darüber hinaus wird mit Hilfe der normativen Ökonomie ermittelt, ob vorhandene Anreize zu sozial optimalen Marktergebnissen führen. Der in diesem Bericht entwickelte Analyserahmen veranschaulicht, wie die Anreize der Unternehmen zu potenziellem Marktversagen oder – wenn die Anreize der Unternehmen durch das regulatorische Umfeld beeinflusst werden – zu potenziellem Regulierungsversagen führen können.

Die wesentlichen Ergebnisse lassen sich wie folgt zusammenfassen:

- **Auf der Grundlage qualitativer Belege und theoretischer Grundlagen gibt es Hinweise darauf, dass einige der Mechanismen, die zu suboptimalen Ergebnissen – Markt- oder Regulierungsversagen – führen, auch im Zusammenhang mit F&E für Behandlungen für NDD wie PD und AD vorhanden sind.**
- **Neue finanzielle Anreizsysteme, eng begleitet durch empirische und fallspezifische Forschung, können dazu beitragen, die richtigen Anreize zur Überwindung von Markt- und/oder Regulierungsversagen zu setzen.**

Diese Studie bildet dabei die Grundlage für eine empirische Analyse, ob die hier beschriebenen Mechanismen durch ihre Wirkung auf die Anreize zur Durchführung von F&E tatsächlich für das Fehlen kausaler Behandlungen verantwortlich sind. Die Durchführung einer solchen empirischen Arbeit wird dringend empfohlen.

1. Introduction and key findings

(1) Pharmaceutical products play a major role in improving health in modern societies, yet for some diseases, the pharmaceutical industry has been struggling to develop a causal or disease-modifying treatment. Some neurodegenerative diseases (NDD) such as Parkinson's disease (PD), Dementia, or Alzheimer's disease (AD) are prominent examples of diseases that fall into this category. Despite the discovery of a symptomatic treatment more than 50 years ago for PD, for instance, no disease-modifying treatment is available to date.[1] Likewise, no disease-modifying therapies exist for AD as of now.[2]

(2) While this situation could merely be a reflection of scientific challenges in the development of new drugs,[3] this report explores and compiles possible alternative, economic explanations that may be responsible for the lack of causal treatments. These alternative and possibly complementary explanations, or hypotheses, are developed based on a review of the economic literature, including health economics, industrial economics, regulation, and finance theory, and based on qualitative interviews and existing empirical and qualitative studies in NDD and in particular PD. At the core of these hypotheses are the economic or financial incentives for research and development (R&D) from the perspective of the pharmaceutical industry. By way of simple models, mechanisms and illustrations, firms' R&D incentives, i.e. how much to invest, where to invest, and when to invest – if to invest at all – are discussed. The economic incentives are analysed against the background of the observed lack of an effective cure in PD and other NDD, and references to that background are made to provide some context for the analysis. This background includes relatively well-working existing treatments for a substantial share of the affected population; lengthy and costly clinical trials; a record of failed projects and the associated risk not to discover a new drug; uncertainty on the size of the population a new drug could treat; and the risk that an innovator may not be sufficiently rewarded for the reduction of the social burden a causal drug could bring.

(3) In addition, normative economics is used to determine if any incentives in place lead to socially optimal market outcomes. The framework developed in this report illustrates how firms' incentives may give rise to potential market failures, or, considering how firms' incentives are shaped by the regulatory environment, what could be considered regulatory failures.

(4) The focus of this study is to collect and combine economic mechanisms which may be at play and that may be responsible for the observed lack of causal treatments. This work provides the basis for an empirical analysis targeted at PD and on the question whether the mechanisms described here are in fact responsible for the absence of causal treatments through their effect on the incentives to conduct R&D in that area. We note, however, that absent the empirical dimension, the extent to which the conditions that lead to the described incentives are in place for the development of causal therapies for NDD, in particular PD, remains a question open to empirical analysis. While an empirical study will be needed, the hypotheses presented here may well have applicability for the development of pharmaceutical products beyond NDD, including for example early-

[1] See e.g. Oertel & Schulz (2016).

[2] See e.g. Lam *et al.* (2020).

[3] For a summary of failed attempts of disease modification for PD and AD, see e.g. Oertel & Schulz (2016) and Lam *et al.* (2020).

stage treatment of cancer.[4] Only empirical work, however, can bring more clarity if some or all of the particular elements described here actually explain the lack of incentives to develop causal therapies and are therefore responsible for the lack of causal therapies for NDD and in particular PD.

(5) The structure and key findings of this report are as follows:

- **Framework and market failure**: Section 2 provides the framework for analysing firm-level incentives to conduct R&D and contrasts these with collective (or public) incentives, the social optimum. It is then shown how the misalignment of private and collective incentives can lead to market or regulatory failures, including R&D underinvestment in certain health areas.
- **Firm-level incentives for R&D**: Section 3 draws on the framework developed in Section 2, discussing a range of models and examples taken from the economic literature in health economics, industrial economics, regulation, and finance theory. This selection of theories is used to explain under what circumstances firms may prefer to invest less, devote more resources to other areas, or simply postpone their R&D efforts.
  - Section 3.1 draws on competition or industrial organisation models to study the interaction between firms and when incentives to innovate are higher. In these models, new drugs are more likely to be developed in less concentrated markets or when those new drugs do not replace any profits on existing drugs being made. Spill-over effects may also reduce innovation incentives.
  - Section 3.2 considers regulatory constraints, including price controls, the drug development process, and the patent system, to make predictions which class of innovations are more profitable from a firm-level perspective. All else equal, pressure on prices through public policies or a relatively long drug development period can dampen the incentive to develop causal treatments.
  - Section 3.3 investigates which R&D projects are financeable, and, to the extent they are, at what moment it would be individually rational to pursue them. With imperfect capital markets, the required funding for valuable R&D may not be provided, and to the extent it is, a high uncertainty in the market can lead to delay of that valuable R&D.
- **Conclusions**: Section 4 concludes:
  - **Based on qualitative evidence and theoretical foundations reviewed in this report, there are indications that some of the mechanisms leading to suboptimal outcomes – market or regulatory failures – may also be present in the context of NDD such as PD and AD.** However, we strongly suggest further empirical and theoretical research to identify the relevance and magnitude of the specific market and regulatory failures and on this basis allow appropriate remedies and countermeasures to be devised and deployed.
  - **New financial incentive schemes, closely monitored by empirical and case-specific research, may help to set the right incentives to overcome any market and/or regulatory failures.**

[4] See e.g. Budish *et al.* (2015).

2. Framework and market failure

(6) The incentive to innovate is the expected difference between the profit a firm would earn if it successfully invests in R&D and the profit it would earn absent that investment. This incentive depends on many factors, such as the characteristic of the innovation, the protection of intellectual property, market risk (e.g. the degree of competition before and after innovation), technological risk (e.g. probability of success in making the innovation), barriers to entry in R&D, and so on. This section provides a framework for innovation incentives and discusses the potential risk of a diversion between individual firm-level incentives and what would be considered collectively optimal. Such a divergence between individual interest and what would be of interest for society overall is typically called market or regulatory failure.[5]

(7) Section 2.1 starts with a framework in which the incentives for R&D in the pharmaceutical industry are analysed. It begins with a brief set of stylised industry facts that are characteristic for the pharmaceutical industry (and potentially other industries). These characteristics are used to formalise the incentives to invest and to derive basic results where R&D effort is more likely to occur ("private optimum"). A more detailed analysis of some of the distinct incentives inherent in the framework is carried out in later sections (see Section 3).

(8) Section 2.2 then contrasts this framework against a possible benchmark of the public incentives ("social optimum"). It discusses whether there can be cases of underinvestment, i.e. situations in which firms do not have sufficiently strong incentives to innovate despite its appeal in the possible benchmark. Reverse situations, i.e. overinvestments, are also discussed. The section closes with an example that illustrates the conditions that might give rise to such market or regulatory failures.

2.1. Framework

(9) The analytical framework builds on some of the key industry characteristics (Section 2.1.1) to provide basic predictions of firms' incentives to innovate (Section 2.1.2).

2.1.1. Stylised industry facts

(10) The objective of the enumerated stylised industry facts below is to provide a useful framework in which to assess the incentives to innovate. These stylised facts, or assumptions, are neither intended to give a full picture of the conditions for R&D in the pharmaceutical industry nor do they reflect local conditions, which may vary from country to country. Arguably, for diseases prevalent across the globe,[6] the incentive to innovate will normally not strongly depend on the specificities of any particular country.[7] To keep the analysis tractable, not all of these assumptions are always used cumulatively, and some of the later sections (see Section 3 in particular) will focus more on certain assumptions than on others.

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5 Arguably this is one of the fundamental questions in economics dating back at least to Adam Smith.

6 NDD occur on a global scale. See e.g. WHO (2006), figure 2.4.

7 The US as the largest pharmaceutical market might constitute an exception. Section 3.2.2 draws on the US patent system, but comparable conditions are also present in other countries.

(11) The discussion focuses on the following four characteristics: (i) the cost structure, consisting of an investment cost and, in case of successful development, a production cost; (ii) the timing, i.e. distinguishing the investment or development period from the marketing or commercialisation period; (iii) any regulation or public policies that may be in place, including intellectual property rights (patent protection), price controls, health insurance, R&D subsidies, and the drug approval process; and (iv) uncertainty, in that tomorrow's returns or profits achievable from any investment undertaken today can be highly unsure. Because this section focuses on a single firm, a discussion on other factors such as degree of competition and any barriers to entry in R&D is reserved for Section 3.1.

(12) The cost structure is the first stylised fact in this framework. R&D is an irreversible investment, i.e. a sunk cost. R&D cost cannot be recovered.[8] Since a large proportion of the investment cost in R&D relates to salaries, irreversibility is a plausible assumption to make. Once a drug is launched and sold in the marketplace, it can be produced at a typically small and – for the sake of simplicity – constant unit cost. Unlike the investment cost that is at the core of a firm's R&D decision, production or manufacturing cost are put aside throughout most of this report.[9]

(13) The timing, or life cycle of a new drug, is the second main feature, and it is closely related to the cost structure just discussed. The investment cost is borne in a first stage, and if successful, the drug is marketed in a second stage. In this section, the dynamics are taken into account in an implicit manner: the firm's expectation of the second stage, i.e. the commercialisation or marketing period, can inform its decision in the first stage, i.e. the investment or development period. The dynamic relationship is more explicitly analysed in later sections (see Section 3.2.2 on the drug development process and Section 3.3.2 on uncertainty), for which a more detailed description of the drug's life cycle will follow.

(14) Regulation, including public policies, is the third building block of the analysis. The pharmaceutical industry is subject to multifield regulation, of which only few aspects will be discussed in this report. First, due to the industry's cost structure, with a high up-front investment cost and a relatively low production cost, patent protection is required to provide the firm with an incentive to innovate and to avoid free-riding on originators' R&D investments. The assumption of patent protection is made throughout this report. In this section, for example, patent protection gives the firm a monopoly right over its innovation over a limited period. Second, subsidies may be in place to encourage R&D. For brevity, subsidies are considered only in this section. And third, other public policy and regulatory aspects such as price controls[10] and insurance (see Section 3.2.1) as well as the drug development process and the length of the patent protection period (see Section 3.2.2) are discussed later.

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8 For a definition of sunk costs, see e.g. Belleflamme & Peitz (2015), p. 15. Estimates of the R&D costs of a new drug, including all R&D costs for failed projects, vary from about $500m to about $2,000m, according to Adams & Brantner (2006). More recent work puts the average cost above $2,000m. See e.g. DiMasi *et al.* (2016), who also provide an overview of related studies.

9 In practice such manufacturing costs cannot be put aside. A higher production cost typically leads to higher unit prices. The reason why this report largely abstracts from the manufacturing cost is that it would unnecessarily complicate the analysis.

10 Country-specific price controls can be another free-riding problem. On the one hand, the investment cost needs to be recouped on a global level, but on the other hand, each country could have a unilateral incentive to "free-ride" by covering only the marginal cost of production. See e.g. Danzon (2012), p. 2.

(15) Uncertainty constitutes the final key characteristic. Firms in the pharmaceutical sector are typically confronted with a high and multi-facetted degree of uncertainty. There is no guarantee that an R&D investment project will be successful from a scientific point of view, e.g. leading to the discovery of a new drug, and if so, that it will pay-off from a commercial perspective. In addition, the innovator may not be sure about the price it can charge when selling its drug in the marketplace or may only have a broad estimate of the demand for its new drug, which will also depend on alternative treatments possibly being developed at the same time. For presentational ease the assumption of uncertainty is sometimes relaxed (see e.g. Section 2.2 on market or regulatory failures).[11] In this context, a related assumption employed is that of risk-neutrality. For risk-neutral firms, an investment project with a sure return of €100m is as good as a project that would generate a return of either €200m or zero with a respective probability of 50%. By contrast, and all else equal, a risk-averse investor would prefer the project with the sure return of €100m. Risk-aversion is not considered in this report, and while it may explain why some projects are underfunded, it is not required to explain why some R&D projects may not obtain sufficient funding (see Section 3.3.1). Another related assumption is that the firm either decides to invest or not to invest. How allowing the firm to simply delay the investment decision influences the incentives in the presence of uncertainty is analysed later in this report (see Section 3.3.2).

2.1.2. Basic predictions of firms' incentives to innovate

(16) The assumptions presented above are now used to derive some basic predictions of firms' incentives to innovate. For an investment project or an R&D project to be optimal from a firm's perspective, it needs to be profitable in expectation. In other words, the Net Present Value (NPV), i.e. the expected future stream of discounted profits minus the investment cost, needs to be positive. In a simple two-period framework, consisting of an investment cost and the potential discovery of an innovation in the first stage and possible returns to the innovator in a second stage, Equation (2-1) formalises this simple theory of innovation investments:[12]

$$\underbrace{NPV}_{\substack{\text{Net}\\ \text{Present}\\ \text{Value}}} = \underbrace{p(I)}_{\substack{\text{Probability}\\ \text{of discovery}}} \cdot \underbrace{E(\pi|D=1)}_{\substack{\text{Expected profit}\\ \text{with discovery}}} - \underbrace{(1-s)\cdot c(I)}_{\substack{\text{Investment cost,}\\ \text{potentially subsidised}}} \geq 0. \qquad (2\text{-}1)$$

(17) Equation (2-1) describes the key components a firm will need to take into consideration when making investment decisions. The first term, $p(I)$, captures the probability of discovery associated with a given investment level or a certain investment project. The higher this probability, the higher the firm's chance of making profits in the second stage. This first term reflects both the uncertainty about the outcome of a given investment decision and the cost structure in that the R&D investment is a cost.

[11] In a situation that involves uncertainty possible outcomes are unknown and agents cannot (or will not) assign probabilities to each outcome. In contrast, risk describes a situation akin to the roll of a dice, i.e. a situation where all possible outcomes are known and probabilities can be assigned to each possible outcome.

[12] Nordhaus (1969) is a seminal paper on incentives for innovation. For a more simplistic representation of his theory that resembles more closely Equation (2-1), see e.g. Lakdawalla (2018), pp. 404-405. Implicit in this representation is the assumption that the value of the outside option (with $I = 0$) is zero.

(18) The second term represents the expected returns conditional on a discovery being made, $E(\pi|D = 1)$, excluding the investment cost.[13] The components of the returns (or profits), π, include the price p[14] the firm can charge for its newly developed drug; the quantity of sales q the firm can make at that price; the production cost c, which reduces the firm's per-unit margin $m = p - c$ for a given price level;[15] and the timing of the returns, which through the interest rate r, the time operator t (reflecting that a certain return today is more valuable than the same return tomorrow), and other factors affect the value of the innovation at the moment the investment decision is to be made. This second term reflects uncertainty[16] and the cost structure, but also the regulatory context. For example, price regulation could have a dampening effect on innovation or bias the focus of R&D efforts (see also Section 3.2.1) by reducing the potential returns.[17] And while research has found a positive relationship between sales quantity and innovation,[18] R&D can also be stipulated for rare diseases where treatments are applicable for regulatory exclusivity and other policies under an orphan drug status.[19]

(19) The third term, $c(I)$, entails the investment cost associated with a given investment level or a certain investment project, corrected for any subsidies s that could reduce the private investment cost, i.e. $(1 - s) \cdot c(I)$.[20] A higher investment cost reduces the incentive to invest, all else equal. This last term reflects the cost structure – the investment cost – as well as any relevant public policies and the regulatory framework – in this case through possible subsidies.[21]

(20) Therefore, the derived incentives to innovate follow a simple mechanism. The first stage, i.e. any investment undertaken, influences the second stage, i.e. the returns when selling on the market. And a rational, forward-looking investor will, in making investment decisions, form expectations on the likely returns in the second stage.[22] All else equal, incentives to invest are higher, the higher the probability of discovery, the higher the expected return conditional on a discovery being made, i.e. the higher the price and the

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13 E stands for the expectation operator to reflect uncertainty of the profit. π is the profit, i.e. the return including any cost of production but not the investment cost. D describes the state of discovery, i.e. $D = 1$ if the R&D project is successful and leads to the discovery of a new drug, and $D = 0$ if it does not. For simplicity, the expected return in the non-discovery case is normalised to zero, i.e. $E(\pi|D = 0) = 0$. This means that if the project fails, e.g. does not lead to discovery, it has no value to the firm. For example, it does not change the probability of discovery of other drugs, or, in other words, any knowledge acquired through the failed innovation process is worthless. This assumption keeps the analysis more tractable.

14 Or the vector of prices if different prices are charged in different countries.

15 This report largely abstracts from any incentive to innovate coming from the cost of production.

16 Expressed through the expectation operator E.

17 The degree of competition may also affect prices, see Section 3.1.

18 Acemoglu & Linn (2004) estimate that an increase in the potential market size by 1%, i.e. an increase in the expected quantity of sales, is estimated to increase the number of new drugs in a given category by 4-6%.

19 See e.g. Yin (2008) for an empirical contribution on the effect of the US Orphan Drug Act (ODA) on R&D for rare diseases.

20 In this section, $c(I) = I$. For Section 3.1.1, it will be mathematically convenient to introduce a convex cost function, i.e. $c(I) = I^2$, and model the probability of discovery as a linear function of the investment level, i.e. $p(I) = I$.

21 The investment cost is taken as deterministic throughout this report but will realistically also be uncertain.

22 In this simple two-period framework the profit is made only once, namely in the second period. A multi-period analysis, however, will be a more realistic description of the world. In such a dynamic setting, the firm's return in the discovery state becomes a per-period profit that may change over time, e.g. due to competition or patent expiration, and that also needs to be discounted depending on the interest r and other factors (see Section 3.2.2 and 3.3.2).

quantity and the duration during which these prices and quantities can be sustained, and the lower the production and investment cost, among other factors.

(21) In sum, faced with a set of e.g. three potential investment projects $I \in \{A, B, C\}$,[23] a risk-neutral, profit-maximising firm will undertake investment projects that have an expected positive NPV. A simple illustration for these three investment projects without any uncertainty and absent any R&D subsidies is given later in the next section.

2.2. Market failure

(22) In the characteristic market environment described in the analytical framework above, the market equilibrium derived from firm-level incentives to innovate will generally not be (fully) aligned with optimal decisions from an overall welfare perspective. When the market equilibrium does not achieve the social optimum, a market failure may be said to arise.[24] Market failure can result from many factors, including externalities, market power, and asymmetric information.[25] A misalignment of private and collective incentives is considered a market failure. With the pharmaceutical industry being subject to regulation (see Section 3.2), any misalignment may also be (partially) due to regulatory failure. An illustration of such a market or regulatory failure is given next (Section 2.2.1). In the closing example of this section, it is asymmetric information that causes such a market failure (Section 2.2.2).

2.2.1. Illustration of a market or regulatory failure

(23) Whereas a firm will carry out an investment project if it is optimal from the perspective of the firm, i.e. if the expected NPV associated with that investment project is positive, in the social optimum all benefits of the innovation, even those that the firm cannot capture or monetise, i.e. the total surplus (or simply "surplus" to be short), is considered. As a result, it is easy to see that while a firm may not find it profitable to invest when confronted with a certain set of potential investment projects $I \in \{A, B, C\}$, the benefits of any particular investment may still be positive from an overall welfare perspective. It is in fact possible that scenarios arise where there is an important gap between the benefits to an individual firm and society overall. Formally, this can be written as follows:[26]

$$\underbrace{NPV}_{\substack{\text{Net}\\ \text{Present}\\ \text{Value}}} = \underbrace{p(I)}_{\substack{\text{Probability}\\ \text{of discovery}}} \cdot \underbrace{E(S|D=1)}_{\substack{\text{Expected surplus}\\ \text{with discovery}}} - \underbrace{c(I)}_{\substack{\text{Investment}\\ \text{cost}}} \geq 0. \qquad (2\text{-}2)$$

(24) Equation (2-2) differs from the private NPV in two dimensions: first, in that the decision-maker considers the overall surplus to society S instead of only looking at firm-level profits π. This necessarily increases the value of the investment. Correspondingly and secondly, however, also the full investment cost c(I) must be factored into the decision

[23] The investment I can be thought of as the level of expenditure on R&D, or, alternatively, the investment cost associated with specific projects targeted at certain diseases. In this section, the latter interpretation is adopted.

[24] More formally, if it is impossible to make some individuals better off without making some other individuals worse off, the outcome is said to be Pareto optimal. A market failure arises if the market outcome is not Pareto optimal. See e.g. Mas-Colell *et al.* (1995), p. 307, 350.

[25] See e.g. Mas-Colell *et al.* (1995), chapters 10-14.

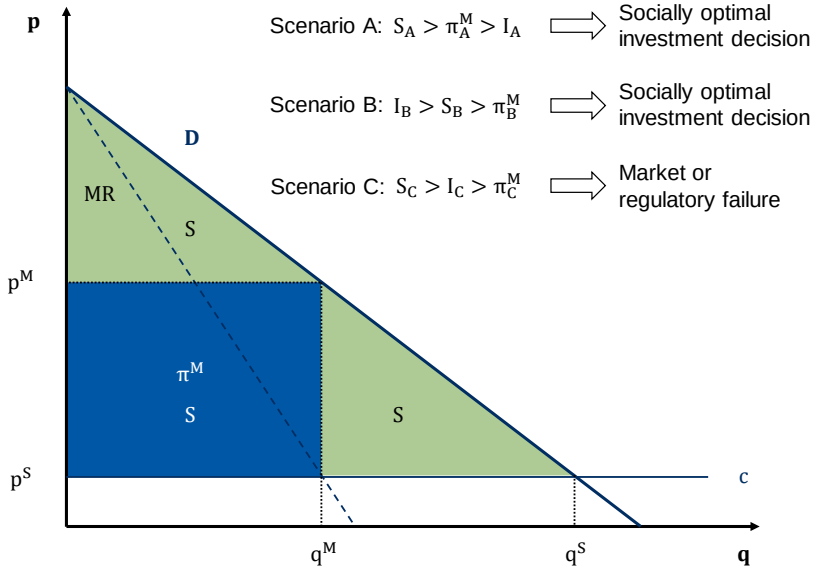
Section 3.1.3 discusses positive externalities (spill-overs), and Section 3.3.1 studies asymmetric information in the context of financing the investment.

[26] Again, this uses a similar representation as in Lakdawalla (2018), pp. 419-420.

because subsidies – if they are lump-sum payments – are a mere redistribution of wealth. These two conditions will typically lead to a different outcome compared to a firm-level perspective, giving rise to a market or regulatory failure. While the private return that a firm can expect to make from an innovation based on its investment and any subsidy it may receive may be such that the investment is made, the impossibility to fully appropriate the surplus an innovation could bring about can be a source of underinvestment even when investments take place. Equivalently, the failure to internalise the full investment cost can be a cause for overinvestment.

(25) Figure 2-1 illustrates an example for the misalignment between the market outcome, i.e. the private optimum, and the social optimum, based on the framework introduced in the previous section. For illustrational convenience, uncertainty is set aside, i.e. the firm can be sure that its investment will lead to discovery of a new drug that it can then sell to patients. To further simplify it is assumed that no subsidies are in place and that the regulatory framework, notably in the form of patent protection, allows the innovating firm to charge monopoly prices p^M, leading to monopoly profits π^M.[27]

Figure 2-1: Private and socially optimal investment decisions



Source: NERA illustration.
Note: *D* stands for the demand curve, c for the per-unit production cost, and *MR* for the marginal revenue curve to identify the profit-optimising price-quantity relationship. The market failure analysed is of dynamic nature, i.e. whether the right incentives are in place for an investment to be made or not. The additional market failure that is of static nature, i.e. the observation that at the monopoly price there is underutilisation of an already developed and marketed drug, a so-called "deadweight loss" (the right-hand green-shaded area), is not analysed here. If so, in this setting, Scenario A and B would also constitute a market failure. See e.g. Figure 3-5 for a co-payment that ensures efficient utilisation for a given drug.

(26) Figure 2-1 plots supply (cost) and demand, which in turn inform the private and social returns relating to the second stage pricing decisions. The private return is the smaller monopoly profit π^M (the blue-shaded box) and the social return is the larger surplus S (the triangle area between the demand curve and the production cost, i.e. the green-shaded triangles and the blue-shaded rectangle). Once a drug has been developed, it

[27] In this example, any risk of market failure would be amplified if the firm could only charge a regulated price, i.e. a price below the profit-maximising price for the firm.

would be socially optimal to set its price equal to the production cost, generating the described surplus under the demand curve. This, however, is not possible in practice[28] as the innovator would not be able to recoup at least its investment cost and would therefore never invest in the first place. One could think of the social optimum as a perfect competition benchmark in which no patent protection is granted. In that case, all the surplus would accrue to consumers, not producers (or innovators). In the market equilibrium, however, since the innovator could not recoup its R&D cost, it would not invest to begin with. This is a time-inconsistency or free-riding problem.[29] An alternative benchmark would be that of perfect price discrimination whereby the firm could charge individual prices to its patients. In that case, the firm can fully appropriate the entire surplus. The example given in Section 2.2.2 below and the analyses elsewhere in this report are more akin to this alternative benchmark due to the lack of incentives implied in the perfect competition benchmark.

(27) Potential allocative inefficiencies (static inefficiencies) arising from above-cost or even monopoly pricing decisions lead to suboptimal investment decisions (dynamic inefficiencies). Whether the firm's incentives to invest are aligned with the social optimum then depends on three scenarios:

- Scenario A: If the firm's profit for the investment project A, π_A^M, is larger than its investment cost, I_A, the firm will pursue A. Since the surplus, S_A, is larger than the profit and thereby also larger than the investment cost, the decision to pursue A coincides with the social optimum.
- Scenario B: If the firm's profit for the investment project B, π_B^M, is smaller than its investment cost, I_B, the firm will not pursue B. If I_B is also larger than the surplus, S_B, the decision not to pursue B coincides with the social optimum.
- Scenario C: If, similar to Scenario B, the firm's profit π_C^M is smaller than I_C, the firm does not pursue C. If I_C is smaller than S_C, then, however, the decision not to pursue C is no longer socially optimal. This is a market or regulatory failure.

(28) Scenario C represents a market or regulatory failure. On the one hand, the surplus from pursuing the investment project C exceeds its investment cost, making C socially desirable. On the other hand, the firm can only appropriate a fraction of this surplus smaller than the investment cost, rendering this investment unprofitable for the firm. The additional surplus that would be of value to society but that cannot be appropriated by the firm is not considered in the firm's investment decision. As a result, there is underinvestment.[30] In this specific and stylised scenario, the firm's incentive to invest

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[28] Theoretically, this outcome can be supported by granting a subsidy so that the marginal cost is reduced and the monopoly quantity is equal to the social optimal quantity (and the subsidies paid to the monopolist can be recovered by a lump-sum tax on the monopolist).

[29] See e.g. Kremer (2002), pp. 75-76.

Health insurance, and in particular co-payments, can be an instrument to replicate this benchmark without eliminating the incentive to innovate (see Section 3.2.1). An alternative, fundamentally different proposal is that of prizes rather than patents. See e.g. Stiglitz (2006) and Love & Hubbard (2007).

[30] A second market or regulatory failure, say Scenario D, is also possible. For example, if a subsidy s in a specific area of R&D is very large, firms are incentivised to invest in that area. But it may not be optimal to do so from a social perspective if e.g. the drug to be developed has a relatively low value, i.e. the private and public investment cost is not worth the money. In that case, there is overinvestment. Another cause of overinvestment could be patent races, whereby multiple firms compete to be the first to become a monopolist, resulting in duplication of the investment cost. See Section 3.1.1.

may be aligned with the social optimum if it could appropriate a higher share of the total surplus or obtain a targeted subsidy s on the investment cost when pursuing C.[31]

(29) In Figure 2-1 above, the appropriation share – the firm's profit (blue-shaded box) relative to the surplus that could be generated if drug pricing is efficiently set at the level of the production cost (the sum of the blue-shaded box and the green-shaded triangles) – is about 50%. Empirically, appropriation shares are estimated to be substantially lower, varying between approximately 2-20%.[32] Clearly, because these empirical contributions revolve around historical innovations, a low appropriation share (or the expectation thereof) cannot generally imply that an innovation will not be made. After all, the empirically analysed innovations have been made. And if little appropriation is adequate to set the right incentives, then anything on top of that would of course not be necessary to generate the right incentives. In any event, the empirical contributions highlight the risk of market failure due to insufficient appropriation as developed in Figure 2-1 above. The extent to which the economic or social burden of a disease is reduced by a new drug may then not be fully appropriated by the innovator.

(30) In the context of PD, various studies have found PD to impose a high economic burden on society, including direct medical costs (with only a small share relating to drugs), reduced employment and productivity, disability income, and non-medical costs.[33] If the development of a causal treatment cannot be expected to capture a sufficient share of the surplus it would generate through a reduction of the economic burden currently imposed, a market or regulatory failure may be present. As a result, such innovations may not be made.

2.2.2. Stylised example of a market or regulatory failure

(31) This section closes with a stylised example on where appropriation of the social surplus by the innovator, and therefore the incentive to innovate, may be higher. The higher the appropriation share, the larger the blue-shaded box relative to the green-shaded triangles in Figure 2-1, and thus, the lower the risk of a market or regulatory failure of underinvestment.

(32) The decision is between developing a preventive or a therapeutic treatment in the presence of asymmetric information (private information). The preventive drug is taken *ex ante*, i.e. before a disease status is realised, while the therapeutic drug is taken *ex post*. Preventive drugs can potentially be taken by any consumer, whereas a therapeutic drug will typically only be considered by consumers already being ill. In the latter case, the disease status is known, both to the affected consumer and the firm. This allows the firm to appropriate a high share of the surplus by pricing accordingly. In the former case, the disease status cannot be known because people are not (yet) ill. If consumers have private information on the likelihood of contracting the disease, for instance when risk factors

[31] Note that subsidies (or tax exemptions) may solve the underinvestment problem, and taxes may do so in the case of overinvestment (e.g. in the case of investment duplication by several firms). These instruments would generally not solve the deadweight loss associated with drug prices set at higher levels than the production cost. See e.g. Lakdawalla (2018), p. 420. Section 3.2.1 gives an example of insured patients who only incur a co-payment set at the production cost.

[32] Philipson & Jena (2006) estimate that innovators of HIV/AIDS therapies appropriated about 5% of the surplus. Lakdawalla *et al.* (2010) report an appropriation ratio of 5-19% for improvements in cancer survival. These findings are consistent with the more general estimate given by Nordhaus (2004) for the appropriability ratio of R&D innovations in the overall economy of about 2%.

[33] See e.g. the studies by Huse *et al.* (2005), Mason & Dunnill (2008), the Lewin Group (2019), and Yang *et al.* (2020).

are well known in the general public or the disease is hereditary, consumers are better informed about their likely future disease status absent any prevention than the firm. For instance, the risk of developing AD is higher for those with a family history in AD and dementia diseases.[34] This information asymmetry makes it difficult for the firm to capture a comparably high share of the surplus. It does not know whether people interested in a preventive drug have a high willingness to pay because their probability of becoming ill is relatively high or not. Only the consumers themselves know that probability and are of course not willing to tell the firm. The firm may then not find itself in a comparably advantageous position as with a therapeutic drug in which case it knows that any consumer interested in the treatment is in fact affected by the disease. Therefore, the firm may be better off not investing in the development of preventive drugs.[35]

(33) Consider the following numerical example.[36] Let there be 100 consumers, each of whom have a 19% probability of contracting a certain disease, which would result in a harm of €100 per person. With a therapeutic drug, a firm could charge patients a price equal to the harm of the disease (€100), which is expected to affect 19 ($100 \cdot 19\%$) consumers. The expected return is then €1,900, assuming no production cost. With a preventive drug, the firm could charge a price equal to the expected harm per consumer, i.e. €19 (€100 · 19%), at which price it could serve all 100 consumers. The expected profit is the same as in the case of a therapeutic drug, i.e. €1,900. In this homogenous population in which all consumers have the same probability of falling ill, the firm is indifferent between developing a preventive or a therapeutic drug.[37]

(34) Consider now the case of a heterogenous population with different probabilities of becoming ill. 90 consumers become ill with a probability of 10%, and the remaining 10 consumers with a probability of 100%. Individual consumers have private information about which group they belong to whereas the firm only knows the aggregate probability of a disease emerging in the overall population. The harm per affected person is as before. With a therapeutic drug, the firm sets the same price as before (€100) and continues to expect to treat 19 ($90 \cdot 10\% + 10 \cdot 100\%$) consumers. The expected profit remains at €1,900. With a preventive drug, the firm can either choose to set a price equal to €10, at

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34 See e.g. Bird (2008) and Alzheimer's Association (2020).

35 The idea is based on Kremer & Snyder (2015), who consider a vaccine as the preventive medicine and a drug as the therapeutic medicine. This distinction between a vaccine and a drug needs not be the case, though. For example, therapeutic vaccines for the treatment of cancer have recently been approved in the US. See e.g. Gatti-Mays *et al.* (2017). Reversely, certain drugs such as Malaria pills (also) have preventive character. See e.g. Loutan (2003). Moreover, and as explained by Kremer & Snyder (2015), although vaccines are often characterised by strong external effects – a high immunity in a given population also reduces the risk of infection for the unvaccinated population – the idea solely rests on the concept of private information and not on any externalities.

A different argument is that the preventive is taken only once, and hence guarantees a one-time payment, whereas a treatment may guarantee permanent cash flows. This argument rests on the idea that the value that the preventive provides cannot be priced high enough. One reason for this may be reluctance to pay a large amount of money at once. Another reason could be a commitment problem, whereby the innovator cannot credibly commit to a price for its preventive, and consumers therefore wait for price reductions (Coase (1972)).

36 This example follows Kremer & Snyder (2015). A calibration exercise of the global demand for HIV pharmaceuticals further substantiates this view. See Kremer & Snyder (2018).

37 This assumes that the cost, time and probability of successful development is the same for both classes of drugs. The firm may also not be indifferent if considering that a preventive may serve consumers today rather than in the future (see also Section 3.3.2 on discounting). Consumers would also be indifferent if they had the choice between a preventive and a therapeutic drug. In this example, their risk is limited to the harm of €100, which is assumed to be avoidable in the case of prevention or reversible in the case of treatment.

which level it would serve all 100 consumers. At that price, it would attract the 90 consumers with a 10% chance of falling ill and who are hence willing to pay €10 for the preventive. At that price, it would also attract the 10 consumers with a willingness to pay €100. Or the firm could focus on the cohort of consumers with a guaranteed prevention or treatment need, demanding a price of €100 per person. Any price larger than €10 but smaller than €100 would not make sense from a business perspective because the firm would lose 90 consumers, in which case the firm is better off selling at a high price of €100. Both options – a price of €10 and a price of €100 – result in the same return of €1,000, which is substantially lower than in the *ex post* treatment scenario. From a demand side perspective, the firm prefers to develop a therapeutic drug.

Table 2-1: Preventive and therapeutic drugs under private information

Variable	Calculation	Homogeneity	Heterogeneity		
Number of consumers	[1]	100	90		10
Probability	[2]	19%	10%		100%
Harm per affected person	[3]	€ 100	€ 100		€ 100
Therapeutic drug (ex post)					
Price	[4] = [3]	€ 100	€ 100		€ 100
Expected number of consumers	[5] = [1] x [2]	19	9		10
Profit	[6] = [4] x [5]	€ 1,900	€ 900	**and**	€ 1,000
Preventive drug (ex ante)					
Price	[7] = [2] x [3]	€ 19	€ 10		€ 100
Expected number of consumers	[8] = [1]	100	100		10
Profit	[9] = [7] x [8]	€ 1,900	€ 1,000	**or**	€ 1,000

Source: NERA analysis based on Kremer & Snyder (2015).
Note: In this example, consumer heterogeneity no longer affects the firm's profits if the individual probabilities are public information and price-discrimination is possible. In that case, and *ex ante*, the firm could charge a price of €100 to the high-risk population of 10 consumers and a price of €10 to the remaining 90 consumers, yielding the same profit as a therapeutic drug (€1,900).

(35) In this example, the tendency to prefer the development of a therapeutic rather than a preventive drug does not constitute a market or regulatory failure per se. This can change when considering the supply side. Take an R&D cost of €1,700 for treatment and of €1,200 for prevention. The firm would still prefer treatment (€1,900 - €1,700 = €200) over prevention (€1,000 - €1,200 = -€200). Since both drugs are equally effective it would, however, be socially optimal to save €500 of the R&D cost and focus on prevention instead. Moreover, if the R&D cost rises by €300 for both treatment and prevention, neither drug is developed. In that case, the social value of a therapeutic drug of €1,900 would not, from a purely normative economics angle, justify its development cost of €2,000, and the market equilibrium would not pursue such an R&D project. This corresponds to Scenario B in Section 2.2.1 above, in which the firm's decision not to invest in the therapeutic drug is socially optimal. By contrast, the social value of the preventive drug of €1,900 (the same value as for the therapeutic drug) would justify its investment cost of €1,500, but the firm does not find it optimal to do so. This relates to Scenario C in Section 2.2.1, and is a market or regulatory failure. Another example of asymmetric information, this time with the firm being better informed than the other party, a funder, is given in Section 3.3.1.

3. Firm-level incentives for R&D

3.1. Competition

(36) The framework in the previous section has focused on a single firm, yet often, multiple firms will compete in the innovation space. This is the focus of this section. It analyses possible effects on the incentive to innovate – a competition or patent race effect, a replacement effect, and a spill-over effect – when there is an investment opportunity available to more than one firm. These effects are analysed in a simplistic setting. They are also considered in turn rather than cumulatively for ease of exposition. In practice, these effects may be intertwined and might shape incentives in a more complex fashion, potentially even in opposite directions. Which effect(s) predominate could be subject to empirical testing and/or analysis on a case-by-case basis.

(37) Section 3.1.1 starts by presenting a simple model with two interacting firms that choose to invest in an R&D lab. Here, firms are competing to become the first to obtain patent protection for an innovation. The setting can be considered a patent race, where firms strive to be the winner to incur monopoly profits. This analysis is then modified and extended to the case of more than two firms. Firms can now actively choose an effort level in R&D to reach a possible discovery of a new product. This extension exemplifies that the size of the industry measured by the number of firms can affect the overall likelihood of discovering a new treatment. In this case, if the number of firms increases, i.e. the market becomes less concentrated, chances are higher that new drugs are developed.[38]

(38) Section 3.1.2 compares firms' incentive to innovate under different pre-innovation competition scenarios: a monopoly and a contested market. It is analysed how the pre-innovation state informs firms' incentives to innovate, which in turn depends on how prices and sales quantities are affected by an innovation relative to existing sales. When the innovation of a firm largely replaces its profit on an existing drug, the incentive to innovate can be dampened.

(39) Section 3.1.3 analyses how an innovation rewards firms in the presence of spill-overs of R&D or knowledge on competitors that may be generated by an invention, and thereby, how this affects firms' incentives to innovate to begin with. Such spill-overs can lead firms to invest less, in which case larger firms, for instance following a merger, may have the higher incentives to innovate.

3.1.1. A simple patent race

(40) In the pharmaceutical industry, new drugs and treatments are eligible for patent protection. With patents at reach, an inventor that leaps ahead of its rivals and that is the first to obtain a patent on a valuable drug may, due to patent protection, also retain this competitive advantage for some time.[39] Therefore, competition in innovation can be

[38] This assumes that there are no critical thresholds of investment sizes required to have a positive probability of discovery. If this was not the case, the investment would need to be concentrated in order to successfully innovate.

[39] In the pharmaceutical industry multiple patents may be in place to protect one product. In fact, an overly fragmented patent rights structure and the potentially implied difficulty for innovating firms to access the necessary (existing) knowledge of other patent holders can be an impediment to innovation. See Heller & Eisenberg (1998) on this "tragedy of the anticommons" and Shapiro (2001), p. 119, for an explanation of a "patent thicket", i.e. "*an overlapping set of patent rights requiring that those seeking to commercialize new technology obtain licenses from multiple patentees*".

thought of as a race, where the loser of the race will have a high investment cost in R&D but no returns.

(41) To illustrate this, consider a market for a symptomatic treatment S with two competing firms, say firm 1 and firm 2.[40] At the start, the market provides no pre-innovation profit from selling the symptomatic treatment S[41] and the development of a superior, causal drug C requires investing in innovation, such as new research divisions and laboratories. Once the R&D division is established, each firm has a probability of discovery p, i.e. the likelihood of discovering drug C. If just one firm succeeds in innovating, the new product can be patented, guaranteeing the "winner" monopoly profits, i.e. the expected return of that firm given its own discovery, but no competitor's discovery is π^M. If both firms are successful, each of them can patent their new product with a 50% probability, i.e. the expected return of firm 1 and 2 is $\frac{\pi^M}{2}$ each. One can think of this case as both firms developing perfectly substitutable drugs, for which only one firm – the first to file the patent – obtains the profit. Alternatively, one can think of differentiated drugs, for which two separate patents can be obtained, and the (same) profit is split between the two firms. If neither firm sets up an R&D division or neither firm innovates, both earn zero profits (minus any investment cost).

(42) Determining each firm's profits after the investment in innovation requires an assessment of the expected NPV conditional on the discovery of drug C and the investment cost I. In a patent race with two competing firms, the NPV of firm 1 depends on its own, but also on its rival's decision. Firm 1's benefit from developing a new drug depends on whether firm 2 decides to invest or not, and vice versa.

(43) The following scenarios are possible. In the scenario in which only one firm establishes an R&D division by paying the investment cost I, there are two possible outcomes:

- The R&D division is successful, which occurs with probability p, leading to a monopoly, or patent profit of π^M.
- The R&D division is unsuccessful, which occurs with probability $(1 - p)$, leading to a profit of 0.

(44) Hence, if only one firm invests, its expected NPV is:

$$\underbrace{NPV}_{\substack{\text{Net}\\ \text{Present}\\ \text{Value}}} = \underbrace{p}_{\substack{\text{Probability}\\ \text{of disocvery}}} \cdot \underbrace{\pi^M}_{\substack{\text{Monopoly}\\ \text{profit}}} - \underbrace{I}_{\substack{\text{Investment}\\ \text{cost}}}$$

$$= \pi^M \cdot \left(p - \frac{I}{\pi^M}\right). \qquad (3\text{-}1)$$

(45) In the scenario in which both firms decide to set up their R&D divisions, the following outcomes are possible:

[40] This model is taken from Pepall *et al.* (2014), section 21.3.

[41] This assumption is made to abstract away from a potential replacement effect (see Section 3.1.2). One can think of this as a very competitive market for the symptomatic drug. Alternatively, one could assume that the new drug to be developed is sufficiently different from the drugs the firms 1 and 2 already sell.

- Only one R&D division is successful, which occurs with probability $p \cdot (1-p)$.[42] The profit of the innovator is π^M.
- Both R&D divisions are successful, which occurs with probability p^2. Each firm's expected, or contested profit is $\frac{\pi^M}{2}$.
- If neither is successful, their profits are zero.

(46) Hence, each firm's expected NPV is the sum of the profits from the previous scenarios minus the investment cost I:

$$\underbrace{NPV}_{\substack{\text{Net}\\\text{Present}\\\text{Value}}} = \underbrace{p \cdot (1-p)}_{\substack{\text{Probability of own}\\\text{but no rival discovery}}} \cdot \underbrace{\pi^M}_{\substack{\text{Monopoly}\\\text{profit}}} + \underbrace{p^2}_{\substack{\text{Probability of own}\\\text{and rival discovery}}} \cdot \underbrace{\frac{\pi^M}{2}}_{\substack{\text{Contested}\\\text{profit}}} - \underbrace{I}_{\substack{\text{Investment}\\\text{cost}}}$$

$$= \pi^M \cdot \left(\frac{p \cdot (2-p)}{2} - \frac{I}{\pi^M}\right).^{43} \qquad (3\text{-}2)$$

(47) The firms' optimal decision depends on the probability of discovery and on the relation of the investment cost to the monopoly profit that will be generated due to the patent. This cost-profit ratio is denoted by $\frac{I}{\pi^M}$. The cost-profit ratio is used in Table 3-1 to describe firms' NPV, or payoff, for any possible combination of firms' decisions, i.e. it summarises the outcome for every firm as a result of its own and its competitor's decision.

Table 3-1: Payoff matrix in a simple patent race

		Firm 2			
		No R&D		R&D	
Firm 1	No R&D	No profit 0	No profit 0	No profit 0	Expected monopoly profit minus R&D cost $\pi^M \cdot \left(p - \frac{I}{\pi^M}\right)$
	R&D	Expected monopoly profit minus R&D cost $\pi^M \cdot \left(p - \frac{I}{\pi^M}\right)$	No profit 0	Expected contested profit minus R&D cost $\pi^M \cdot \left(\frac{p \cdot (2-p)}{2} - \frac{I}{\pi^M}\right)$,	Expected contested profit minus R&D cost $\pi^M \cdot \left(\frac{p \cdot (2-p)}{2} - \frac{I}{\pi^M}\right)$

Source: NERA analysis based on Pepall *et al.* (2014), table 21.1.
Note: The first payoff of each cell is the payoff of firm 1, and the second payoff in each cell is the NPV of firm 2. For instance, if firm 1 invests in an R&D division and firm 2 does not, the expected NPV for firm 1 is the expected monopoly profit minus the R&D cost. The profit for firm 2 is zero.

(48) This matrix can be analysed for situations, or equilibria, in which a unilateral deviation is not profitable for any firm.[44] In such an equilibrium, no firm can generate a higher expected NPV by changing its decision given the decision by the other firm. For example,

[42] This is the probability of success from the perspective of the innovating firm. The overall probability that only one firm innovates is $p \cdot (1-p) + (1-p) \cdot p$.

[43] $NPV = p \cdot (1-p) \cdot \pi^M + p^2 \cdot \frac{\pi^M}{2} - I = p \cdot \pi^M - p^2 \cdot \pi^M + \frac{1}{2}p^2 \cdot \pi^M - I = p \cdot \pi^M - \frac{1}{2}p^2\pi^M - I = \frac{1}{2}\pi^M \cdot (2p - p^2) - I = \frac{1}{2}\pi^M \cdot \big(p \cdot (2-p)\big) - I = \pi^M \cdot \left(\frac{p \cdot (2-p)}{2} - \frac{I}{\pi^M}\right)$.

[44] In game theory, such a combination of strategies is called a Nash equilibrium.

it is an equilibrium for both firms to establish an R&D division (bottom right matrix field in Table 3-1) if neither firm 1 nor firm 2 can increase its expected NPV by not establishing an R&D division while the other firm sticks to its decision to invest.

(49) These strategically optimal situations between firm 1 and firm 2 depend on two factors, the probability of discovery and the cost-profit ratio. Suppose the probability of discovery for a new drug is relatively low, say 20%. Let the monopoly profit be €100m if the new drug is developed and the investment cost be €50m. There are four possible outcomes, corresponding to the four matrix fields in Table 3-1 above.

- No firm invests (upper left field): If no firm invests, the expected payoff is 0 for each firm, i.e. (€0m, €0m).
- Firm 1 invests but not firm 2 (bottom left field). If only one firm invests in R&D, say firm 1, its expected NPV will be $20\% \cdot €100\text{m} - €50\text{m} = -€30\text{m}$. Firm 2, which does not invest, makes zero profit. The expected payoff is then (-€30m, €0m).
- Firm 2 invests but not firm 1 (upper right field): This is just the reverse case, with an expected payoff of (€0m, -€30m).
- Both firms invest (bottom right field): If both firms invest, both firms will have an expected NPV of -€32m,[45] i.e. the expected payoffs are (-€32m, -€32m).

(50) In this example, taking the perspective of firm 1, investing is not an optimal decision irrespective of firm 2's decision. In other words, investing in R&D is not an optimal decision given any decision of the competitor and therefore, cannot lead to a strategically optimal situation. The strategically optimal decision in this setting is for neither firm to invest, i.e. the upper left matrix field with an expected payoff of (€0m, €0m).

(51) Suppose now that the probability of discovery increases from 20% to 60%. If only one firm invests, its expected payoff would be €10m.[46] If both firms invest, the expected payoff would become -€8m for each firm.[47] There would be two strategically optimal situations: firm 1 invests but not firm 2; and vice versa.[48]

(52) Finally, suppose further that the profit with discovery by just one firm rises to €200m. In that scenario, if only firm 1 invests, it would expect a payoff of €70m,[49] and if also firm 2 invests, either firm would have an expected return of €34m.[50] Therefore, the market conditions are sufficiently favourable to sustain innovation by two firms.

(53) Figure 3-1 summarises the results for general values of the cost-profit ratio and the probability of discovery.

[45] $0.5 \cdot €100\text{m} \cdot 20\% \cdot (2 - 20\%) - €50\text{m} = -€32\text{m}$.

[46] $60\% \cdot €100\text{m} - €50\text{m} = €10\text{m}$.

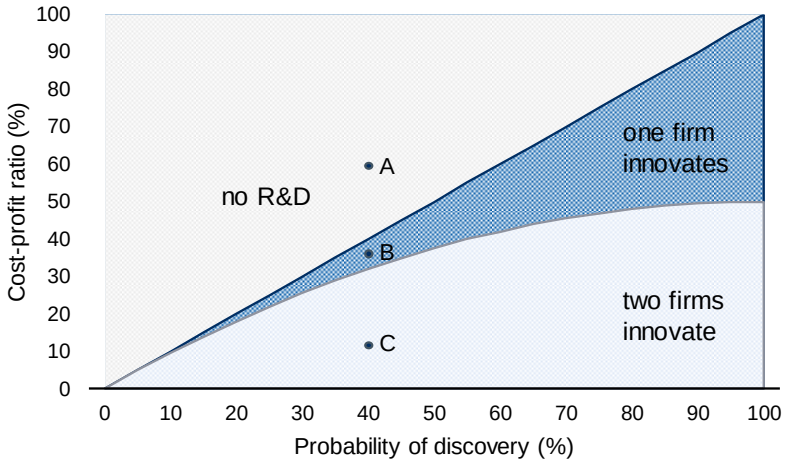
[47] $0.5 \cdot €100\text{m} \cdot 60\% \cdot (2 - 60\%) - €50\text{m} = -€8\text{m}$.

[48] The analysis abstracts from so-called mixed strategies.

[49] $60\% \cdot €200\text{m} - €50\text{m} = €70\text{m}$.

[50] $0.5 \cdot €200\text{m} \cdot 60\% \cdot (2 - 60\%) - €50\text{m} = €34\text{m}$.

Figure 3-1: Strategically optimal decisions in a simple patent race with two firms



Source: NERA illustration related to Pepall *et al.* (2014), figure 21.2.

(54) If the cost-profit ratio is higher than the probability of discovery, no firm would invest in R&D (light grey area). Hence, if the R&D cost is relatively high and the probability of discovery relatively low, any incentives for R&D are muted. If the probability of discovery is higher than the cost-profit ratio, at least one firm establishes an R&D lab (dark and light blue area).

(55) What is new compared to the framework in Section 2 is that the overall or industry probability of discovery not only depends on how attractive a certain R&D project is – which is informed by the cost-profit ratio and the individual probability of discovery – but also how this affects the number of firms pursing a given R&D opportunity. Take a high cost-profit ratio of 60% and a probability of discovery of 40% (point A in Figure 3-1). This is not attractive for any firm, and therefore, the R&D opportunity will not be pursued. If the cost-profit ratio decreases to 35% (point B), one firm will establish an R&D division, and the industry probability of discovery coincides with the individual probability of 40%. Finally, if the cost-profit ratio is only 10% (point C), two firms will seek to innovate. The individual probability of 40% has not changed, but the number of firms has, and therefore, the industry probability of discovery rises to $1 - (1 - 40\%)^2 = 64\%$. This competition or patent race effect is additional to the incentives analysed in the framework so far and has a positive impact on the overall success probability.[51]

(56) Consider now the following extension of the model with key modifications. First, firms can choose how much rather than only whether to invest or not. More R&D on an individual firm level means a higher investment cost but also a higher probability of discovery of a new drug. Second, there can be more than two firms interacting in the market. This model takes the number of firms as given and analyses how a change in the

[51] In analogy to the effect of a subsidy, the possibility of overinvestment cannot be ruled out if many firms are pursuing and thereby "duplicating" an R&D opportunity. Also note that this result hinges on the probability and investment cost functions, e.g. the absence of any critical investment size thresholds that would need to be met by firms to have a chance of discovery.

market structure or market concentration affects the firm's – or the firms' – incentive(s) to innovate.[52]

(57) Figure 3-2 shows the firms' optimal level of investment as the number of competing firms in the market increases. Here, the number of firms increases from one, a monopoly situation, to ten firms. In the model, a single firm exerts an R&D effort of 0.5, or 50%, when it does not face any competition. For simplicity, the maximum firm-specific R&D level is normalised to 1, or 100%. A firm's optimal effort level decreases with the number of competing firms. With two competitors in the market, i.e. in a duopoly, the individual investment level is reduced to 40%. With ten competitors in the market, a firm's optimal level of innovation falls to roughly 20%.

(58) As competitive pressure created by rival firms reduces the likelihood to become the winning firm, individual R&D levels fall. On aggregate, however, the investment level rises with the number of firms: with two firms, it is 0.8, and with ten firms, it is 2. A two-to-one merger would hence reduce the aggregate investment level from 0.8 to 0.5. Two investing firms impose a negative impact on each other in the sense that if one firm innovates, it reduces any profit the other firm could make. A merger internalises this effect, thereby reducing the overall investment level. This unilateral effect to reduce innovation effort is called a Downwards Innovation Pressure (DIP)[53] or crowding-out effect. It is similar in spirit to the unilateral effects to increase prices, as measured by the well-known Upwards Pricing Pressure (UPP) employed in merger analysis.[54]

(59) As a result, the overall probability of discovery increases from 50% in the monopoly case to around 64% in the duopoly case.[55] In a market with ten firms, the overall probability of discovery is at about 91%. With an increasing number of firms in the market the firm-level investment levels are reduced further, but the overall probability of discovery by at least one firm increases. With a higher number of firms, the industry R&D level is also increased, albeit to a lesser degree than in the previous model.[56] In sum, this model

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52 The model is related to Federico *et al.* (2017), who present a theory of innovation that played a major role in the European Commission's Dow-Dupont merger case. For a technical derivation, see Appendix A.

A related idea is that of "killer acquisitions", whereby the targeted firm's R&D projects are less likely to be developed if they overlap with the product portfolio of the acquiring firm. See e.g. Cunningham *et al.* (2019). For more empirical research on the effect of mergers on innovation in the pharmaceutical industry, see also Haucap *et al.* (2019).

53 See Federico *et al.* (2018).

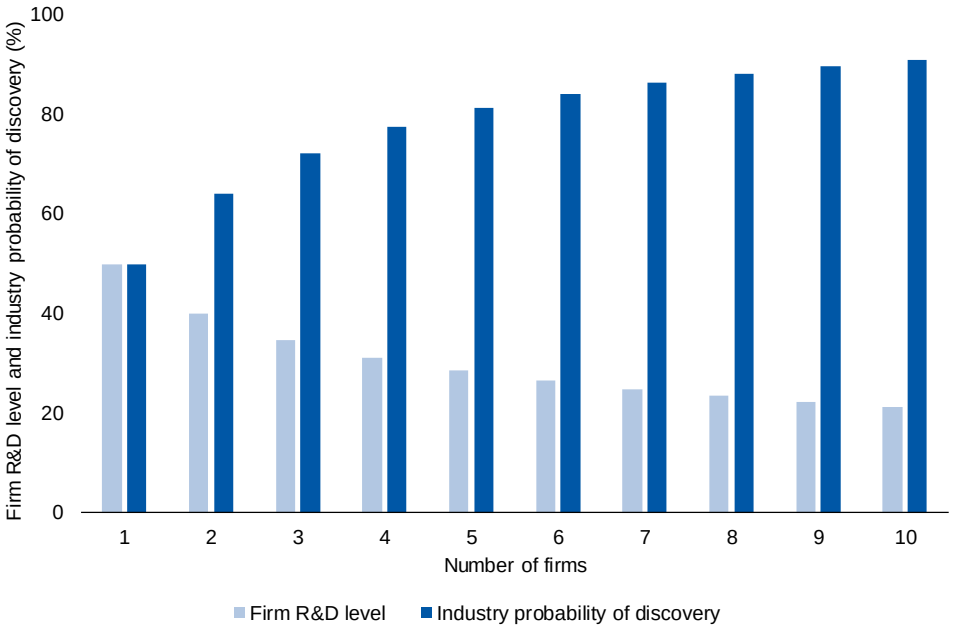
54 See Farrell & Shapiro (2010).

55 For simplicity, the probability of discovery is modelled as a linear function of the investment level, i.e. $p(I) = I$, with a maximum R&D level of 1 (or 100%). The probability is then given by the sum of (i) the probability that both firms discover, i.e. $40\% \cdot 40\%$; (ii) the probability that the first firm discovers but the second does not, i.e. $40\% \cdot 60\%$; and (iii) the probability that the first firm does not discover but the second does, i.e. $60\% \cdot 40\%$. The probability becomes then 64%. A general formula for N active firms in the market can be derived from this, i.e. $1 - (1 - I)^N$. See also Appendix A. As explained earlier this presupposes a specific relationship between investments and discovery. If for example a discovery can only be achieved if research efforts above a certain threshold lead to a positive probability of discovery, efforts need to be concentrated and results may be different.

56 Due to the specific assumptions employed – in particular, a linear probability function (see footnote 55 above), a convex cost function of $c(I) = I^2$, and that probabilities of discovery are i.i.d. (independent and identically distributed) across firms – the cost of achieving an industry probability of discovery of close e.g. 95% would be minimised by "forcing" just one firm to pursue the R&D investment rather than splitting any R&D effort levels across firms. To achieve a probability of discovery of 95% in a monopoly setting requires $I = 0.95$ and $c(I) = I^2 = 0.90$. To achieve the same industry probability of discovery in a symmetric duopoly setting, both firms need to set $I = 0.78$, resulting in the required industry probability of discovery of $1 - (1 - 0.78)^2 = 95\%$ but a higher industry cost of $2 \cdot c(I) = 2 \cdot I^2 = 1.20$. Nevertheless, in a free market where no firm can be "forced" into R&D, a higher success probability requires more firms to invest, as

predicts that a market structure with many firms is more likely to discover a new treatment than a concentrated market.

Figure 3-2: Firm-specific R&D level and industry probability of discovery as a function of competition



Source: NERA illustration.

3.1.2. Replacement effect

(60) This section investigates firms' incentive to develop a new drug depending on the level of pre-innovation profits made from other products. This type of innovation is typically labelled "product innovation". Product innovation corresponds to the type of innovation treated throughout this report, i.e. the analysis of the incentives to develop new (causal) treatments. By contrast, "process innovations", which reduce the cost of production, are not discussed in this report. This is an important difference and deserves highlighting for the purpose of this section. Within the framework of a product innovation, the analysis of incentives to innovate can become fairly complex, as a firm's profit before and after the innovation may depend on the mix of other products in the firm's portfolio and how the firm re-positions those existing products in the market. To keep the analysis tractable, the assumption of a "drastic" product innovation, namely, that a newly developed drug makes the existing drug obsolete, is considered.[57] This in turn renders it clear that any derived incentives cannot be interpreted to hold generally but that the specific circumstances have to be taken into account.

(61) Consider a monopolist producing a symptomatic drug S and generating a profit π_S^M or π_{ND} (ND denotes the non-discovery state) in this market. The monopolist can develop a new and better drug, i.e. a causal therapy C for the same disease also treated by drug S, generating a monopoly profit of π_C^M or π_D (D denotes the discovery state) that is larger than the profit currently made on the existing drug. Assume that a firm that is a

predicted by the model. For a short discussion on the relation between R&D cost functions and minimising industry-wide total R&D to achieve a given industry probability of discovery, see e.g. Gilbert (2019).

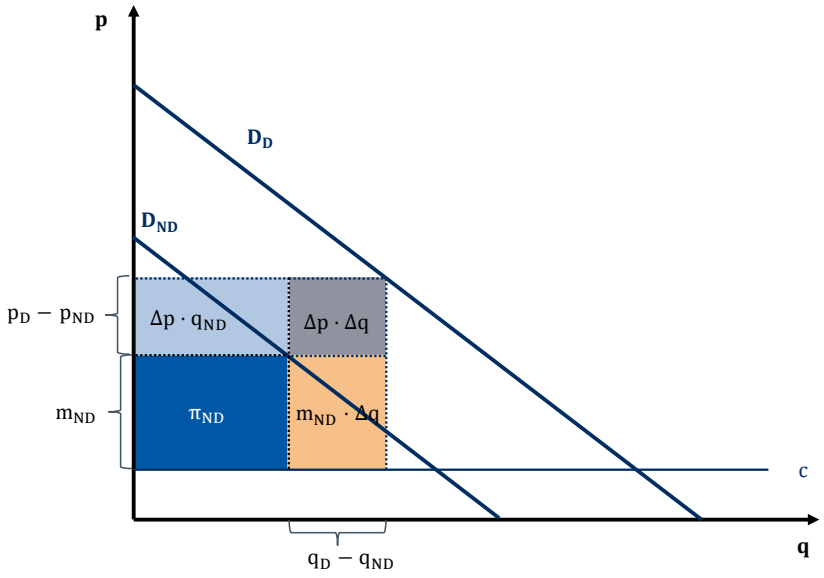
[57] The product innovation model by Federico *et al.* (2018) reverts to the same assumption.

monopolist for the existing symptomatic drug S is successful in its attempt to develop an improved drug C, and in doing so, makes S obsolete (drastic product innovation). This simplifies the analysis as it eliminates the possibility that the monopolist could continue selling the existing drug, possibly at a different price. In a regulatory context, for example, the assumption that a new drug makes an existing one obsolete may be justifiable through a reduction of reimbursement rates for the existing drug,[58] in which case the monopolist may simply de-list the drug. If the monopolist is not successful in innovating, it continues selling S. The profit margin on incremental units is given by the difference between the drug price p and the production cost c per unit, i.e. $m = p - c$. The firm's operating profit is hence the margin per unit times the number of units sold, i.e. $\pi = m \cdot q$. Abstracting from the upfront R&D investment cost, successful innovation increases the firm's profit by:

$$\Delta\pi = \underbrace{\pi_D - \pi_{ND}}_{\substack{\text{Difference in profits} \\ \text{with and without} \\ \text{discovery}}} = \underbrace{m_D \cdot q_D}_{\substack{\text{Profit with} \\ \text{discovery}}} - \underbrace{m_{ND} \cdot q_{ND}}_{\substack{\text{Profit} \\ \text{without discovery}}} . \qquad (3\text{-}3)$$

(62) Figure 3-3 depicts that due to a product innovation, the monopolist cannibalises its own existing profits on the symptomatic drug. With the existing symptomatic drug, the monopolist is making a profit of π_{ND}, i.e. the dark blue-shaded rectangle. With a new, causal treatment, the monopolist's profit increases by the orange-, the light blue- and the grey-shaded areas due to a demand expansion.

Figure 3-3: Quantity and price effect



Source: NERA illustration.

Note: Two demand functions are illustrated, D_{ND} corresponds to the demand in the situation of no discovery and D_D represents the demand under discovery. The constant marginal cost is depicted by c (and it is assumed to be the same for the new drug, i.e. no process innovation). The dark blue area illustrates the firm's profit with the existing drug, i.e. if it does not innovate. The orange, grey and light blue areas depict the difference in profits from a successful product innovation and no discovery. Note the assumption that post-discovery the monopolist can no longer sell the existing drug.

[58] See e.g. Parkinson *et al.* (2015).

(63) Suppose instead that the market for the symptomatic drug is competitive, such that the pre-innovation profit of any active firm is small. This could e.g. be the case if generics were already brought to the market. If only one of those firms had the ability to develop a new, better drug C, its incentive to do so would be larger than that of a monopolist, because that firm would replace a lower pre-innovation profit. In other words, that firm's optimal investment level is reduced to the extent a discovery would make the profit on the existing drug obsolete. This is a classic replacement effect, an idea going back to Arrow (1962).[59]

(64) Consider, for illustration, a profit of €120m accruing to the inventor of drug C. In Figure 3-3, this value corresponds to all four shaded areas. Consider a firm that, if it was a monopolist in the market for the existing drug S, generates a pre-innovation profit of €80m. In Figure 3-3, this profit relates to the dark blue area. The monopolist's incentive to innovate can be quantified by $€120\text{m} - €80\text{m} = €40\text{m}$ (taking into account any probability of discovery and any R&D cost). Assume now that the same firm was operating in a competitive market instead, thereby generating only a low pre-innovation profit of €10m. If only this firm had the ability to develop the causal drug C, and therefore, that firm would not be at risk of losing a patent race, its incentive to innovate can be expressed by $€120\text{m} - €10\text{m} = €110\text{m}$ (taking into account any probability of discovery and any R&D cost). This shows that incentives to innovate can increase if existing pre-innovation profits are low.[60]

(65) This increase in profit from a new drug, i.e. the incentive to innovate, can be re-formulated as:

$$\Delta\pi = \underbrace{\Delta p \cdot q_{ND}}_{\substack{\text{Price}\\ \text{effect}}} + \underbrace{m_{ND} \cdot \Delta q}_{\substack{\text{Quantity}\\ \text{effect}}} + \underbrace{\Delta p \cdot \Delta q}_{\substack{\text{Interaction}\\ \text{term}}} \qquad (3\text{-}4)$$

(66) Equation (3-4) shows how the development and market launch of a new product C might cannibalise the profit from sales of the old drug S by disentangling the different effects that influence a firm's innovation incentive, namely the quantity and the margin effect. Both these effects depend on the degree of contestability of sales in a market.[61] The first

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[59] Arrow made this point with regard to a "process innovation", which reduces the monopolist's production cost. The term "replacement effect" is used by Tirole (1988), p. 392.

Note that the result above is at least to some extent driven by the assumption that the existing drug becomes obsolete. In standard goods markets, this may not be the case if the monopolist can re-position its existing product, e.g. by setting a different price. On the competition-innovation relationship under product differentiation, see e.g. Gilbert & Newbery (1982), Reinganum (1983), Greenstein & Ramey (1998), Gilbert (2006), and Chen & Schwartz (2013). Due to the assumptions used in that literature, the incentives to innovate will generally differ to those presented in this section.

[60] Given that PD can cause other conditions such as depression, one could hypothesise that by developing a causal therapy firms would cannibalise profits from other markets such as the market for anti-depressives.

[61] Shapiro (2012), p. 364, describes the relationship between contestability of sales and incentives to innovate as follows: *"The prospect of gaining or protecting profitable sales by providing greater value to customers spurs innovation."* The principle of contestability is also reflected by the European Commission as well as the US Federal Trade Commission (FTC). The Deputy Director General for Mergers of the European Commission, Esteva Mosso (2018), states that: *"Indeed, it is common, following a merger, for the merged firm to review its combined R&D activities and re-prioritise its R&D efforts. The existing overlapping lines of research or pipeline projects of one merged party may be abandoned, delayed or re-oriented post-merger, because those R&D efforts could cannibalise the profits from existing and future products of the other merged party."* FTC Horizontal Merger Guidelines, Section 6.4, p. 23, states*: "That curtailment of innovation could take the form of reduced incentive to continue with an existing product-development effort or reduced incentive to initiate development of new products. The first of these effects is most likely to occur if at least one of the merging firms is engaging in efforts to introduce new products that would capture substantial revenues from the other merging firm.*

term reflects the additional profit the firm generates due to a higher price – leading to a higher margin – for the new drug. The second term reflects additional profit due to the extra unit sales the firm makes. The last term is a positive interaction term between higher incremental sales volumes and a higher incremental price.

(67) Suppose that the new causal drug barely leads to an increase in unit sales. In this case the quantity effect for the inventor is largely muted and an increase in profits is mostly driven by a higher price of the improved drug C compared to the existing drug S. A firm's incentive to innovate is largely informed by its ability to generate a higher margin based on higher drug prices. Therefore, all else equal, an initially larger firm with larger sales on the existing symptomatic drug will have the larger incentive to innovate.

(68) Reversely, and again other things equal, suppose a firm cannot increase the price for the new drug substantially, but that the quantity effect primarily shapes a firm's incentive to innovate. A case in point could be a market for a drug with a price ceiling (see also Section 3.2.1). The change in profit due to innovation is then mainly driven by a change in quantity and not by a change in price. In that case, a firm's incentive to develop an improved drug is captured by the quantity effect, that is to say, the additional unit sales will provide a higher profit to the firm without changing its per-unit price and hence per unit margin. Then, a firm with substantial sales for the existing drug would have a smaller sales boost due to innovation and therefore has muted incentives to innovate.[62]

3.1.3. Spill-overs

(69) The previous theoretical discussions have focused on illustrating firm-level decisions to innovate in different competitive environments. In the case of a monopolist, the firm's profit from innovation depends exclusively on its own effort to develop a new drug whereas in a contested market, the effort to innovate is affected by the competitive pressure generated by rivals. This pressure creates two opposite effects on innovation. At the firm level, it reduces the optimal level of investment as the number of competitors increase. At the industry level, the overall likelihood to discover a new drug increases with the number of competing firms.

(70) The preceding analysis, however, ignores externalities associated with R&D that may flow across competitors. Activities that give rise to positive externalities among producers are called spill-over effects. The generation of spill-over effects may dampen a firm's incentive to innovate because firms tend to base their R&D investment decisions on private returns and do not to take into account any benefits they may create for third parties. This may in turn lead to underinvestment in R&D.

(71) R&D spill-overs among competing firms can arise due to a variety of reasons. The disclosure of information on an innovation through the patent system helps to reduce duplication of R&D and to enhance other firms' R&D. Another example of a positive spill-over, or externality, is the exchange of innovation knowledge when researchers migrate between firms or because researchers share their ideas or approaches at scientific

The second, longer-run effect is most likely to occur if at least one of the merging firms has capabilities that are likely to lead it to develop new products in the future that would capture substantial revenues from the other merging firm."

[62] For a discussion, see also Shapiro (2012).

conferences.[63] Typically, R&D externalities on competitors account for positive effects across firms, e.g. firm 1's effort to innovate can directly benefit firm 2's R&D division by reducing the latter's innovation cost. Spill-overs can also arise between suppliers of complements if, for example, the newly developed drug needs to be taken in combination with some other drug. Spill-overs can increase consumer surplus by promoting price competition among firms and facilitating follow-on improvements in the innovator's industry. Moreover, spill-overs are not necessarily limited to the same market and may also benefit other firms and consumers in other markets where a discovery adds value or advances innovation.[64] This seemingly positive and desirable effect generated by an inventor can, however, ultimately discourage the development of new products.

(72) To see how this can happen, and as explained in Section 2.2.1, how much of the social value of any innovation a firm can appropriate matters for its incentives to innovate. In a competitive setting, this continues to matter, and is further complicated by any externalities between rival firms. Larger firms, for instance through a merger, may then, in contrast to the analysis above, internalise those externalities, leading to an increased probability of discovery.[65] If the knowledge generated by an innovating firm spills over to rival firms, the innovator's ability to appropriate a sufficiently large share of the social value of its knowledge or innovation may be diminished and thereby also its innovation incentive.

(73) When the degree of spill-overs is relatively low, the investment level of each firm mainly affects its likelihood to discover a new drug and its private costs. Therefore, a firm could choose a significantly high level of R&D without creating positive externalities to its competitors. By contrast, with a high level of spill-overs, a firm's investment level affects its competitors' returns positively, but the inventor is not compensated for this positive effect. The formation of joint ventures could be a solution in such a setting since that joint venture could (partially) internalise those externalities.

(74) In an industry exhibiting important spill-over effects, rivals directly benefit from a firm's effort in the form of a positive externality. In this context it also needs to be considered how rivals respond to the inventor's product innovation. On the one hand, rivals can respond passively by reducing their own R&D effort or leaving the market. On the other hand, rivals can respond aggressively, by increasing their R&D effort. Aggressive rivals' responses then shift appropriability away from the inventor towards rivals or their customers.[66] In the pharmaceutical sector, there is empirical evidence that potential competitors do not abandon R&D programmes in the same field if a rival firm succeeds in innovating, which is suggestive of an aggressive response.[67] Taking this into

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63 See e.g. Cabral (2002), p. 306. The exchange of knowledge at conferences may be particularly relevant for research conducted at university level.

64 See e.g. Gilbert (2019), p. 477.

65 In merger analysis the appropriability of innovation is a key factor when examining if a merger decreases incentives to innovate. *"Conversely, a merger may stimulate innovation if it allows firms to better appropriate the social value of their innovation. For example, in the absence of a merger competitors may be able to free-ride on successful innovation carried out by their rivals."* See speech of Carles Esteva Mosso (2018), p. 4. "*The Agencies also consider the ability of the merged firm to appropriate a greater fraction of the benefits resulting from its innovations.*" See FTC Horizontal Merger Guidelines, Section 10, p. 31. See also the model by Gilbert (2019).

66 See e.g. Shapiro (2012), p. 388.

67 See e.g. Cockburn & Henderson (1994), who examine R&D expenditures by pharmaceuticals at the therapeutic programme level (drugs in the class of ACE inhibitors used to treat hypertension). They find that even in the search for

consideration a firm's incentive to innovate on the pharmaceutical market might be diminished.

3.2. Regulation

(75) This section explores the role of regulation and public policies as a possible source of hindrance to the development of new drugs. The analysis differs from the previous section in that only a single firm is considered, as previously in Section 2.

(76) Section 3.2.1 discusses the effects of any price controls and health insurance schemes that may exist. With respect to PD, for example, existing symptomatic drugs may provide a relatively good level of treatment for patients contracting the disease at an advanced age.[68] One may therefore hypothesise that existing treatments constrain any profit to be made with a new, causal treatment.[69]

(77) Section 3.2.2 then analyses the impact of the drug development process and the patent system on the incentives to innovate. A lengthy process can discourage innovation in specific areas and divert investments away from long-term projects.

3.2.1. Price controls and health insurance

(78) In the previous sections few regulatory restrictions on the price a firm can charge for a drug were considered.[70] Such regulatory price constraints have long been considered to have adverse effects on innovation.[71] The empirical relationship between price regulation and R&D investment is, however, arguably less well developed. The US as a largely unregulated market with respect to price relative to the rest of the world is reported to also have higher levels of pharmaceutical R&D,[72] a potential explanation consistent with the notion that price regulation dampens innovation. Alternative explanations, however, cannot be ruled out. For example, firms that focus on R&D may simply tend to operate from the US. After all, at least for global diseases,[73] the R&D decision should be a global one, informed by the worldwide sales a firm expects to make, and not how these sales are distributed due to country-specific regulation. In that case, a more stringent approach on price regulation in a larger market will arguably have a stronger adverse effect on global innovation than price regulation in a small country, but this alone does not imply any effect on where (in which country) R&D is undertaken.

(79) In this spirit, this section continues to take a global perspective, without considering any local conditions that may play a role. Thus, aggressive cost-containment policies can direct innovation away from certain research areas. Quite trivially, if treatments with a

ethical drugs, a field in which patent protection is a key feature, potential competitors do not abandon R&D programmes in the same field if a rival firm innovates.

68 See e.g. Ahlskog (2010).

69 The same logic applies to the previous section on competition.

70 Quite the opposite, that a firm could charge monopoly prices (see e.g. Section 2) was implicit in the assumption of patent protection. In Section 3.1.2, however, the assumption used for the replacement effect, i.e. that a new drug renders the old one obsolete, could be interpreted in the context of a regulatory constraint such as a reduction of the reimbursement rate.

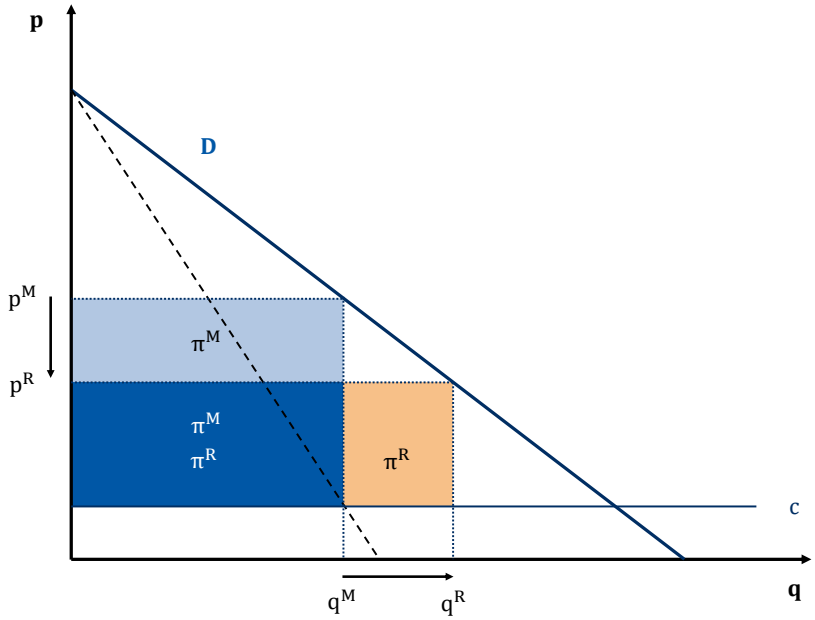
71 See e.g. Scherer (1993). This point has been made more generally, i.e. not just for the pharmaceutical industry. See e.g. Motta (2004), p. 69.

72 See e.g. Vernon (2005).

73 See footnote 6.

high incremental value ("large innovation") like the first causal treatment for a certain disease, which would be marketed at high prices, face more stringent price regulation than drugs with a lower additional benefit ("small innovation"), R&D efforts can be re-directed to the latter. In Figure 3-4, which illustrates this notion, a price control p^R reduces the firm's profit for a large innovation by the light blue-shaded box (price effect) and increases it by the orange-shaded box (quantity effect). Because the regulated price pushes the firm away from its optimal price-quantity relationship, the regulated profit π^R is smaller than the unconstrained monopoly profit π^M. Visually, the orange area is smaller than the light blue one. A potential shift away from a large to a small innovation could, as just explained, be caused by disproportional price reductions implied by regulation, e.g. a price cap of €90 for a small innovation that would otherwise be priced at €100, and a price cap of €200 for a large innovation that would otherwise be sold at €1,000.

Figure 3-4: Effect of price regulation on profits



Source: NERA illustration.
Note: As before, p^M is the unrestricted monopoly price. p^R is the regulated price.

(80) The incentives become more complex when health insurance schemes are included in the analysis. In the presence of insurance, patients may not bear the full price of a specific drug. Through fixed or proportional co-payments that are lower than the drug's price, patients' demand becomes less price elastic[74] compared to standard goods markets without insurance. A drug price increase for an insured patient does not affect the patient's demand for that drug if the full cost is borne by his or her health insurer. Similarly, insured patients who incur a fixed co-payment that is unaffected by a further price increase will behave alike, i.e. their demand for the drug remains unaffected. In either case, demand from the patient's perspective becomes perfectly inelastic. Insured patients with a proportional co-payment may react less strongly to a drug price increase than uninsured patients, depending on e.g. how critical or substitutable the drug in

[74] The price elasticity of demand measures the percentage change in the quantity demanded following a 1% increase in the price of the product in question. See e.g. Mas-Colell *et al.* (1995), p. 27.

question is. Insurance can therefore have a dampening effect on the patient's demand elasticity or, in other words, increase the patient's demand for drugs. Therefore, when insurance acts like a subsidy to consumers, firm's incentive to innovate is increased.[75] Reversely, if insurers can exert countervailing buyer power or even, in the case of centralised public insurance, monopsony power, this can put downward pressure on drugs' prices in a similar vein as regulation.[76]

(81) Figure 3-5 extends this idea to the case of price regulation, as before. Take a fixed co-payment set to the level of the per-unit product cost c.[77] The remainder of the drug price is paid by the insurer. From the consumer's perspective, the firm could set any price because with fixed co-payments patients are unaffected by any further price increase (as long as it does not feed back into their insurance rate). The drug price is therefore negotiated between the firm and the insurer, with the negotiated price denoted by p^N. Due to insurance the firm can, in this example, appropriate a share outside the surplus area beneath the demand curve (the sum of blue- and light blue-shaded box). This is so because the consumer – or rather his or her physician, see below – does not take into account, i.e. does not internalise, the full drug price payable, but merely the co-payment of c.

(82) The regulated price is as before in Figure 3-4. It is lower than the negotiated price, replacing that negotiated price. The negotiated price can then be interpreted as the price that would prevail had there been no price control. An alternative interpretation of the price reduction from the negotiated price, p^N, to the regulated price, p^R, is that of stronger negotiation power by insurers, effectively keeping the drug price low. This also means that insurance will not generally have an unambiguously positive effect on innovation through the increase in profits, as explained above. The difference in Figure 3-5 is that there is no longer a mitigating quantity effect that allows the firm to serve more patients at lower prices, and therefore, the regulated price affects profits – starting from a higher base level – more adversely than before.[78]

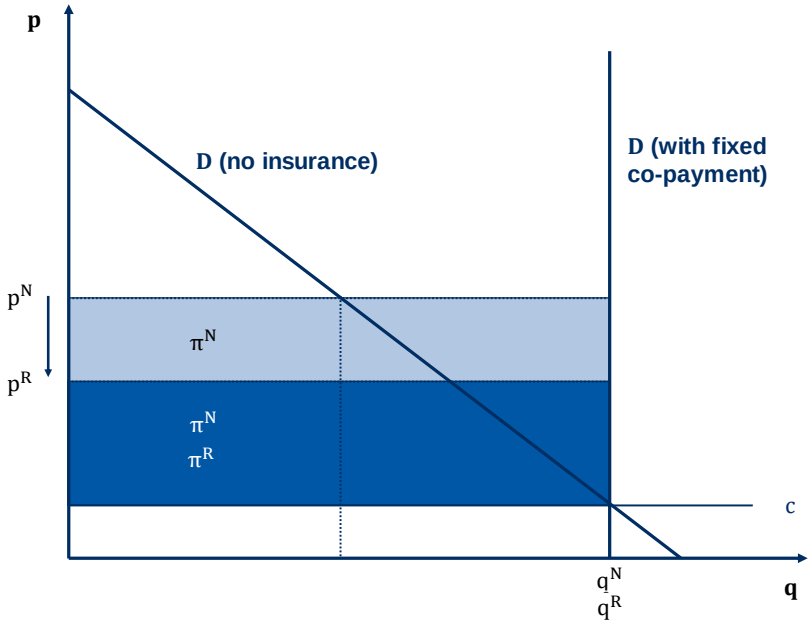
[75] See e.g. Garber *et al.* (2006) and Lakdawalla & Sood (2009).

[76] See e.g. Danzon & Keuffel (2007) and Lakdawalla (2018), p. 427. As in the case of country-specific price controls (see footnote 10), there can be a "free-rider" problem, which can cause underinvestment.

[77] This means that utilisation of an existing drug is efficient in the sense that all patients with a willingness to pay at least as high as the cost of production consume the drug (static efficiency).

[78] In practice, there can be quantity effects, e.g. if too stringent regulation leads a firm to delay or avoid entry in a specific market (country) or retreat from it, or if certain drugs are exempted from the insurance coverage. Also note the assumption of fixed co-payments used above. With proportional co-payments, changes in drug prices feed back directly into consumers' expenses, and may therefore well lead to quantity effects.

Figure 3-5: Effect of price regulation and insurance on profits



Source: NERA illustration.
Note: The negotiated price between the firm and the insurer is p^N. Patients pay a fixed co-payment at the level of the production cost c. At any price level, patients only pay the fixed price c, resulting in a vertical (perfectly inelastic) demand curve and thereby in a higher quantity of patients served (q^N). The firm can therefore reap a profit π^N outside the surplus triangle, i.e. the sum of the blue- and light blue-shaded box. A price reduction to p^R reduces the profit but not the number of patients. For a related illustration with profits outside the surplus triangle, see e.g. Garber *et al.* (2006), figure 1. For an illustration with proportional rather than fixed co-payments, see e.g. Berndt *et al.* (2011), figure 2.

(83) Again, in this setting, an incentive to focus on small, incremental innovations rather than large innovations such as the first discovery of a causal treatment for a certain type of disease hinges on the regulatory approach, i.e. relatively stronger constraints on the price of an incrementally high-value than low-value drug. The use of quality-adjusted life years (QALYs), for example, can be a potential source of disproportionate constraints, a critique raised in the context of diseases that primarily affect the elderly.[79] Insurance could have a comparable effect as regulation through countervailing buyer power.

(84) This idea is well established in the economic literature. For example, the academic literature has analysed physicians' prescription decisions to derive consumer demand in the presence of health insurance.[80] Physicians who in deciding which drug to prescribe take into consideration the full price of that drug derive a demand akin to that of uninsured patients. These physicians fully internalise the price of the drug in their prescription decision (akin to the framework in Section 2).[81] By contrast, some physicians may base their prescription decisions only on the price paid by their insured

[79] For a discussion of possible biases in the measurement of the QALY, see e.g. Lipman *et al.* (2019), and for a brief reference on a possible bias in the use of QALYs in the elderly population, see e.g. Pettitt *et al.* (2016), p. 4.

[80] See e.g. Ganuza *et al.* (2009).

[81] Physicians are often budget-constrained, incentivising cost-conscious prescribing behaviour. For Germany, see e.g. framework agreement of the *Association of Statutory Health Insurance Physicians*, Kassenärztliche Vereinigung Berlin (2018).

patients (as used in this section) or disregard the cost of a drug altogether.[82] The derived demand function, together with a price control on drugs of different incremental value, can affect drug prices and thereby a firm's innovation decisions. For example, small innovations can be relatively attractive for the firm in the presence of lax price controls and physicians considering only their patients' co-payments. By contrast, with a relatively strict price cap on a large innovation, the presence of physicians who do not internalise the price of the drug in their prescription decision may not be sufficient to help to direct innovation to such a large innovation. Therefore, a firm may find it more profitable to focus on small innovations and target the price inelastic segment of demand rather than investing in large innovations. Section 3.2.2 identifies another regulatory feature that may provide firms with an economic rationale to focus on small innovations.

3.2.2. Drug development and patent system

(85) The hypotheses so far have looked at profits in a static setting, i.e. one-off profits. In this section, the role time – i.e. the life cycle of a drug – plays in explaining R&D efforts in the pharmaceutical industry is explored. To the extent that the life cycle of causal as opposed to symptomatic drugs differ, or if the life cycle varies by therapeutic category, the analysis presented below can help explain a firm's decision where to invest.[83] This section is motivated by the observations that "*[c]ertain types of medicine – for example, drugs for long-term use and prevention of disease, drugs to stop progressive or degenerative diseases, and drugs for early stage cancer – are more likely to require longer research and development programs*" [84] and that "*[t]here are significant differences in the length of the average clinical testing period by therapeutic category; for instance, central nervous system drugs, antipsychotics, antidepressants, anticonvulsants, and anti-Parkinson's agents take significantly longer in clinical testing than antibiotic and antiviral drugs. Drugs intended for acute use take less time to develop than drugs intended for chronic use, and there may be a correlation between the pharmacologic class of a drug and the length of the clinical timeline.*"[85] By streamlining the drug development process, among others, it is estimated that the cost of developing a disease-modifying treatment for AD can be substantially reduced.[86]

(86) The two key stages in this analytical framework are the development period and the commercialisation period. The former spans the time from drug discovery until the investment starts generating returns to the firm or innovator. The latter describes how these returns then evolve over time.

(87) Turning first to the development period, the typical stages prior to marketing or commercialisation of new medicines are drug discovery, pre-clinical testing (laboratory

[82] Hellerstein (1998) finds that some physicians are more likely to prescribe branded drugs than others, and vice versa, and that very little of the prescription decision can be explained by observable individual patient characteristics.

[83] The discussion of this section refers to the idea and model described in Budish *et al.* (2015), who find empirical evidence for research investments being distorted away from long-term projects in the case of cancer.

[84] See Lietzan (2018), p. 39.

[85] See Lietzan (2018), p. 46. See also figure 5 (p. 100) and table 3 (pp. 101-102). Similarly, so Lietzan & Lybecker (2019).

[86] See Scott *et al.* (2014).

and animal testing), clinical testing (human testing), review, and marketing approval.[87] These stages often take many years of research and development, and marketing approval is uncertain.[88] In the case of PD, for example, one challenge is that "*up to 15% of individuals taking part in clinical trials may not have Parkinson's. They are extremely unlikely to benefit from the new therapies being tested and their inclusion can affect both the trial results and ultimately the future of the potential treatment. Because Parkinson's is a progressive condition, caused by the gradual loss of cells in the brain, the best chance to intervene with treatments that can slow, stop or reverse the damage is during the earliest stages of the condition. However, during these early stages, symptoms tend to be mild, which makes selecting the right people to participate in trials very difficult.*"[89] To formalise the starting point (drug discovery) and end point (marketing approval) of this development period, assume that the innovation arises in $t_{invent} = 0$ and is commercialised $t_{comm} > 0$ years later. Therefore, t_{comm} gives the date from which onwards an innovator can generate returns on its discovery.[90]

(88) Turning now to the commercialisation period, conventional pharmaceutical products typically undergo two stages, monopolistic or oligopolistic competition during the patent protection period and generic competition thereafter.[91] While an innovator may be granted a patent, the patent does not warrant immunity from competing innovations, as substitutable drugs not covered by the patent may exist, be they launched before or after the patented drug in question. Thus, the innovator may yet face competition during the patent protection period.[92] With the entry of generics manufacturers after the end of the patent protection period, competition typically intensifies since generics can offer chemically identical products, i.e. products based on the same active pharmaceutical ingredient (API). All else equal, a longer patent duration pushes back the starting point of the generic competition phase and thereby provides larger incentives for R&D.[93]

(89) Since in many cases R&D decisions are taken from a global perspective, e.g. because a drug to be developed could treat a disease that is spread worldwide,[94] patent regulation is important in so far as it affects a firm's expected global returns. To facilitate the discussion, it is instructive to focus on patent regulation in the most important country

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87 See e.g. European Commission (2009) for an empirical investigation of the pharmaceutical sector from a competition perspective but also setting out the patent system in detail and Maier-Rigaud *et al.* (2019) discussing both the US and the patent system prevailing in Europe.

88 See e.g. Mossinghoff (1999). For instance, several thousands of medicinal candidates are tested on average for one drug to be approved. See e.g. Torjesen (2015).

89 See Port (2018a).

90 Discovery occurs with probability p(I) as introduced above. For notational convenience and mindful of its simplicity, no additional uncertainty is introduced between discovery in t_{invent} and commercialisation in t_{comm}.

91 See e.g. Lakdawalla (2018), p. 399.

92 See footnote 67. See also Lichtenberg and Philipson (2002) for empirical work on the degree of between-patent competition.

93 See e.g. Shy (1995), pp. 236-237.

The discussion abstracts from other forms of protection from competition, including: regulatory exclusivity through the granting of an orphan drug status, where during a certain period no new drugs can be approved for the same rare disease indication; regulatory exclusivity such as data exclusivity, which disallows others to rely on the safety and efficacy data generated by the first innovator; and natural barriers as in the case of large-molecule biologic products, which may be more difficult to imitate. See e.g. Lakdawalla (2018), pp. 399-400.

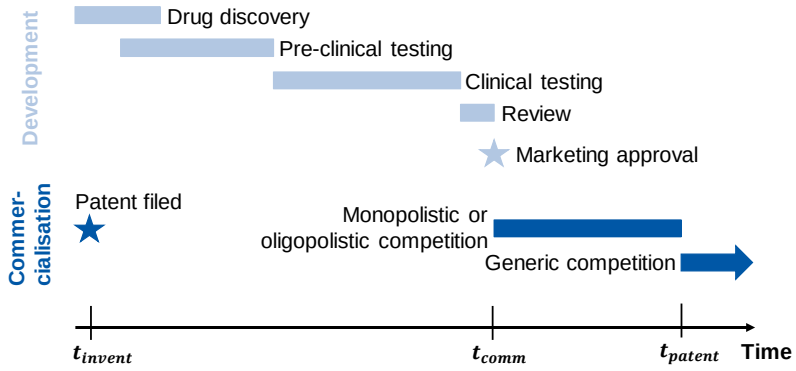
94 See footnote 6.

for pharmaceuticals, the US.[95] There, the Hatch-Waxman Act[96] provides a baseline period of patent protection of 20 years. It also grants innovators an extension of half of the time spent in clinical trials plus the full time spent in the review period. This extension can be up to 5 years but total market exclusivity from the point of marketing approval cannot be longer than 14 years. Time spent in pre-clinical trials cannot be recovered.[97]

(90) The effective patent protection period, which counts the years a drug is commercialised until patent expiry, depends on when a firm files a patent. Filing at the time of commercialisation, in t_{comm}, gives a longer patent duration but is highly risky. It is for this reason that patent filing in the pharmaceutical industry usually occurs much earlier in the development phase, typically before commencement of clinical trials.[98] In this setting, the firm files at the time of discovery, i.e. at $t_{invent} = 0$. Abstracting for now from possible extensions of the patent length, the patent protection period then ends in $t_{invent} + t_{patent} = t_{patent}$ rather than in $t_{comm} + t_{patent}$. Therefore, and again abstracting for now from patent extensions, the effective patent protection period is reduced by the number of years required to commercialise the drug. If half of the time spent in clinical testing is recovered through a patent extension, the number of years required for clinical testing stills reduces the effective patent protection period, albeit less so without the extension.

(91) Figure 3-6 depicts the life cycle of a new drug.

Figure 3-6: Life cycle of a new drug



Source: NERA illustration. For a more detailed representation, see e.g. Mossinghoff (1999).
Note: The patent may be filed some years into the drug discovery process. Setting the patent application to t_{invent} is for simplicity only. It does not affect the qualitative results of this section.

(92) Several additional factors have an impact on the time profile of the returns. First, the interest rate r. Second, the possibility of corporate short-termism or managerial impatience due to e.g. principal-agency problems, lowering the discount factor (which

[95] Patent protection may be stronger in some countries than in others but is generally established in virtually all countries. The TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement between member states of the WTO (World Trade Organization) sets a minimum patent protection period of 20 years. See WTO (1994), para. 33.

[96] Or, more formally, the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417).

[97] For an overview of the Hatch-Waxman Act, see e.g. Mossinghoff (1999). Similar provisions are in place in the European Economic Area (EEA) through supplementary protection certificates under Regulation (EC) No 469/2009. See European Union (2009).

[98] See e.g. Scherer (2004) and Mossinghoff (1999). Additional references on the timing of patent filing are contained in Budish *et al.* (2015).

reflects that a return is more valuable today than tomorrow) by a multiple of $\eta \leq 1$.[99] Third, the risk that the innovation becomes obsolete before the end of the patent protection period, e.g. because a competitor has developed a superior drug. This risk of obsolescence can be modelled as $1-\gamma$ in every year after t_{invent}.[100] Fourth, the growth rate g, which measures the annual increase in profits, e.g. due to an increase in the number of people affected by any given disease. Finally, for simplicity and despite the fact that this will not generally be an appropriate assumption, the drug in question is perfectly imitable (including the brand value), i.e. perfectly vulnerable to generic competition. Under these conditions, the entry of generics reduces the firm's profits to zero immediately after the end of the patent protection period.

(93) Equation (3-5) brings this all together by describing the firm's expected profit if successful in discovery:

$$\underbrace{E(\pi|D=1)}_{\substack{\text{Expected profit}\\ \text{with discovery}}} = \underbrace{\pi^M}_{\substack{\text{Annual}\\ \text{profit}}} \cdot \underbrace{\sum_{t_{comm}}^{t_{patent}-1} \left(\eta \cdot \frac{1}{1+r} \cdot \gamma \cdot (1+g)\right)^t}_{\substack{\text{Discounted}\\ \text{patent}\\ \text{duration}}}. \qquad (3\text{-}5)$$

(94) Equation (3-5) says that the firm's expected profit in the case of discovery depends on: the per-period profit (π^M);[101] the start and length of the effective patent protection period from t_{comm} to $t_{patent}-1$;[102] and the discount factor $\eta \cdot \frac{1}{1+r} \cdot \gamma \cdot (1+g)$, which in turn depends on corporate short-termism (if any), the interest rate, the risk of obsolescence, and the growth rate.

(95) Figure 3-7 represents two hypothetical scenarios for the expected profit at the time of discovery (i.e. at the time of patent filing): a small innovation with a commercialisation lag of 8 years, meaning a time span of 8 years between patent filing and the start of the marketing phase, including 4 years of clinical testing; and a large innovation with a commercialisation lag of 13 years, including 9 years spent in clinical trials, all else equal.[103]

[99] See e.g. Stein (2003) and footnote 105 for a short discussion. Note that short-termism does not affect the returns *per se*, but how a manager evaluates those returns.

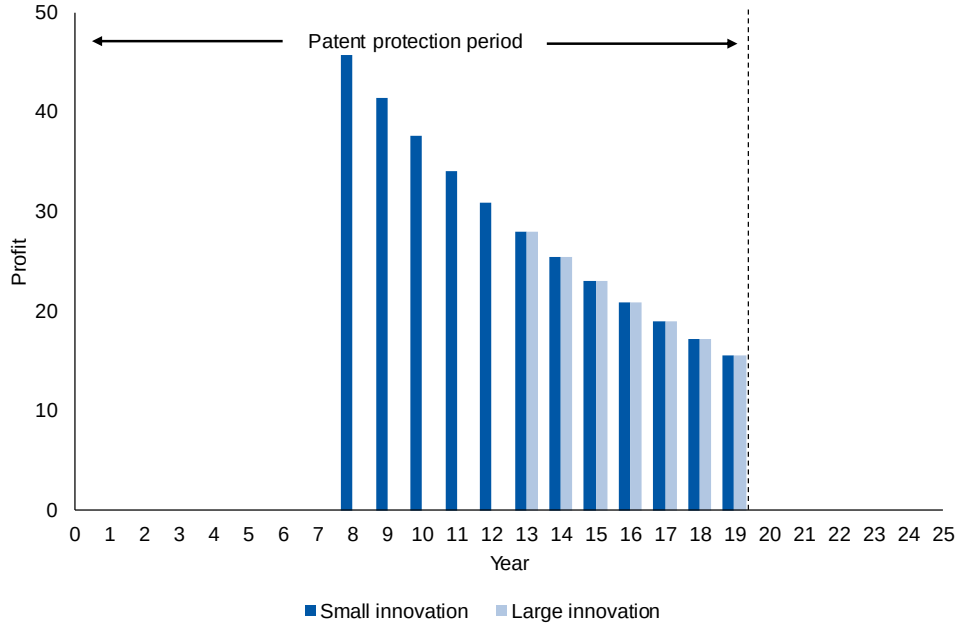
[100] The analysis abstracts from the possibility of oligopolistic competition. That is, if an alternative product is launched during the patent protection period it replaces the existing product and the first innovator obtains zero profits from that point onwards. The risk of obsolescence is taken as exogenous, i.e. firms cannot influence the probability of their drug becoming obsolete. This assumption differs from the patent race in Section 3.1.1, in which firms share the monopoly profit if successful in discovery.

[101] The per-period profit is taken as exogenous variable in this setting. More generally, one could hypothesise that a shorter commercialisation lag, i.e. a longer effective patent protection period, results in more competition and more entry, thereby lowering the per-period profits achievable with quick innovations. The analysis abstracts from this possibility.

[102] If the patent is filed in year zero, i.e. $t_{invent}=0$, and the patent duration is $t_{patent}=20$, i.e. 20 years, the patent protection period runs from years 0, 1, 2, …, 19, i.e. until $t_{patent}-1$.

[103] In this example and the following text, the underlying assumption is that a small (large) innovation has a small (large) commercialisation lag. This may or may not be the case.

Figure 3-7: Profits without patent duration extension



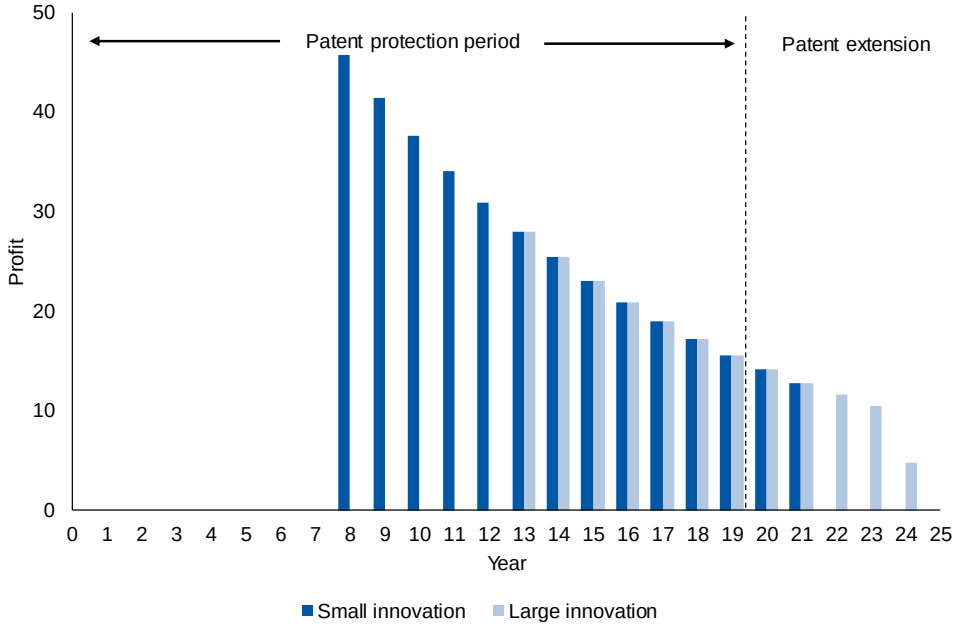
Source: NERA illustration.
Note: Analysis based on Equation (3-5) using the following calibration: $\pi^M = 100$, $\eta = 1$ (no short-termism), $r = 10\%$, $\gamma = 95\%$ (a 5% chance that the drug becomes obsolete in any year), $g = 5\%$, $t_{patent} = 20$. The short commercialisation lag uses $t_{comm} = 8$, the long commercialisation lag uses $t_{comm} = 13$.

(96) In Figure 3-7, a patent is filed in year 0. If the innovation can be marketed quickly, the per-period profits are positive from the 8th year onwards. If the innovation is commercialised late, the firm obtains its first returns only 13 years after discovery. From that point onwards and until the end of the patent protection period, the small and the large innovation generate the same per-period profits by assumption. Due to discounting, these profits decline over time. Finally, with entry of generics in the year 20, profits are assumed to be zero. This is not to say that innovations with a short commercialisation lag will generally be preferred over innovations that go through a long clinical trial period. For example, innovations of the latter kind may generate higher profits because they might be more valuable. A larger innovation may, however, also incur a higher investment cost or have a lower probability of discovery. On that basis, and to abstract from these opposing effects, Figure 3-7 is on an all-else-equal basis, highlighting the importance of the effective patent protection period on overall profitability.

(97) Suppose now that the innovator is granted an extension of half a year for every year spent in clinical testing.[104] Clinical testing accounts for 4 years for the small innovation and 9 years for the large innovation. Hence, patent extensions of 2 and 4.5 years are granted, respectively. Figure 3-8 expands on that example.

[104] This abstracts from any time spent during the review process.

Figure 3-8: Profits with patent duration extension



Source: NERA illustration.
Note: See note to Figure 3-7 above. Patent duration extensions of 2 years (small innovation) and 4.5 years (large innovation) are granted.

(98) In this example, an extension of the patent protection period has a relatively small impact on overall profitability for both the small and the large innovation. The incentive to invest in a small rather than a large innovation may, however, be mitigated by a patent extension, but the effect could be minor. This is for two key reasons: first, the patent extension may not fully offset the additional time spent in clinical trials but only a fraction of that time. Second, the additional profits from a patent extension are incurred further in the future, thereby being discounted more due to interest rate and the risk of obsolescence. Some years lost early on due to a longer commercialisation lag may have a comparable impact on profits as many years more of patent protection later on. Thus, differences in the development time for different types of drugs and/or diseases can incentivise a firm to shift its R&D efforts to innovations with small incremental value.[105]

3.3. Finance

(99) This section presents the sketch of two models from the finance literature. The first discusses investment decisions when firms face financial constraints and need to revert to external capital in the presence of capital market imperfections. Start-ups looking for early-stage funding are a case in point. Their projects may fall into the "valley of death", i.e. remain unfunded (Section 3.3.1).[106] The notion of such a "valley of death", or gap

[105] In addition, corporate short-termism can lead to excessive discounting, leading decision-makers to focus on R&D projects that amortise more quickly. The effect can be similar as the funding cost analysed in Section 3.2.2 but the mechanism – impatient managers – is rather simple. For a brief introduction on short-termism, see e.g. Stein (2003). For more recent empirical contributions, see e.g. Marginson & McAulay (2008) and Asker *et al.* (2015). In Figure 3-7 and Figure 3-8, no short-termism is assumed.

[106] See e.g. Kerr & Nanda (2011) and Kim *et al.* (2019). Howell's (2017) empirical analysis of early-stage grants for high-tech energy start-ups shows that even modest subsidies can have large impacts on patenting and revenue, especially when firms are financially constrained.

between basic science researchers in academia and applied science researchers in the pharmaceutical industry, is well documented for NDD, including PD and AD.[107]

(100) The second model is concerned with the question of finding the optimal time to invest. In that instance it may simply be uncertainty that can affect the firm's incentive to innovate. In other words, the firm wants to innovate but may be better off doing so "later rather than sooner" (Section 3.3.2). Policies aimed at reducing informational barriers and uncertainty in the market can stimulate innovation.[108]

3.3.1. Access to external funding under asymmetric information

(101) The framework presented in Section 2 is expectation-based. It predicts that investment decisions are based on expected returns, or, in other words, that a high level of R&D goes hand in hand with a high level of future profits. The picture given by the empirical literature of R&D in the pharmaceutical industry is, however, more complex. Other determinants such as today's returns, i.e. current cash flows, also tend to increase R&D levels. [109] While higher returns today may simply lead firms to reconsider their expectations, making it difficult to disentangle the two effects, an alternative explanation for the empirical findings rests on capital market imperfections. If external capital is more costly than internal capital, firms may increase their R&D when more of such cheaper internal capital is available, e.g. when current returns are high.[110] If this is the case, the framework needs to be extended to account for such market frictions.

(102) Various factors can drive a wedge between the return required by a firm using internal capital and that required by an investor providing external capital. One of these is asymmetric information between the firm and the investor, with the former being better informed about the project's prospects than the latter. In the presence of asymmetric information or other market imperfections, a "funding gap" or "missing market" problem for investment innovation can arise. Expectedly profitable R&D projects remain unfunded due to informational barriers that investors face.[111] For instance, one could hypothesise that informational barriers between innovator and investor be particularly high for novel R&D projects seeking to become the first to develop a causal drug for a specific disease.

(103) Figure 3-9 below illustrates this concept. The vertical axis depicts the cost of capital and the horizontal axis the level of R&D investment. For the cost of capital, the framework so far has taken the market interest rate r, adjusted for the risk of the corresponding R&D project. In that framework, internal funds do not affect investment decisions because firms could equally borrow at that market rate. The cost of capital becomes a flat line –

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[107] For medical researchers' views on the "valley of death" in NDD and the pharmaceutical industry, see e.g. Finkbeiner (2010), Beach (2017), and Seyhan (2019). For a suggested road map on bringing together various sources of funding for drug development for AD, see Cummings *et al.* (2018).

[108] Ongoing empirical work in the biopharmaceutical industry by Kim *et al.* (2019) suggests that a reduction in information asymmetry through public policy shifts investments towards early stages.

[109] See e.g. Grabowski & Vernon (2000).

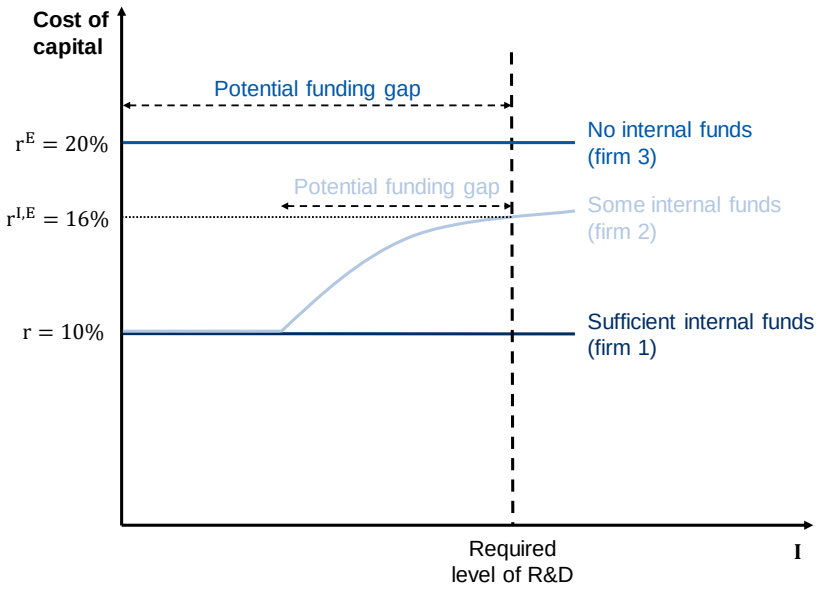
[110] Krieger *et al.* (2019) find that while large innovations ("novel drugs") indeed have higher value, they also tend to be the riskier investments with less certain market authorisation. Empirically, they observe that firms increase their focus on novel drug research when internal funds get expanded. A candidate reason for this is financing friction leading to higher costs of external funds. With a fund injection, reliance on external funds for large innovations decreases, thereby increasing *ex ante* value of large innovations compared to small innovations that can be internally funded anyway.

[111] See e.g. Hall & Lerner (2010).

here, at a market rate of 10% – that is independent of the size of the R&D project, i.e. independent of the required level of investment and therefore also funding.

(104) This picture changes when capital markets are no longer frictionless. With asymmetric information between the innovator and the investor, investors could require a higher return to compensate for the risk and cost of distinguishing good projects from bad projects (hidden information). A high degree of imperfect information and the resulting risk of adverse selection can lead to a "missing market" problem. No external funding may then be provided.[112] A higher premium may also be required for the monitoring cost to avoid the potential risk of moral hazard, i.e. the risk that the firm uses discretion in the allocation of the resources available in a way that is not in the interest of the investor (hidden action).[113] In these cases, internal funds can solve financing constraints. Because investor and innovator are the same, there is no information asymmetry between the two that could drive up the cost of capital. Internal funds are, of course, not wasted. If an R&D project is not worth the money, the firm will invest those internal funds instead in the marketplace at the prevailing rate r.

Figure 3-9: Cost of capital under information asymmetry



Source: NERA illustration.
Note: The risk-adjusted market interest rate r is 10% (black line), and the rate for external capital under information asymmetry is $r^E = 20\%$ (dark blue line). The light blue line depicts a firm endowed with some but ultimately insufficient internal funds to stem the investment cost for the envisaged R&D project. This firm's cost of capital is a mix of internal and external funds of on average $r^{I,E} = 16\%$. Up to the point of depletion of its internal fund, the cost of capital is 10% (flat part of the light blue line). Afterwards, the average cost of capital cost rises (curved part of the light blue line; it would converge to 20%). For a related but different presentation of the cost of capital with internal and external funds, see e.g. Grabowski & Vernon (2000), figure 3.

(105) In Figure 3-9 above, a firm with enough internal funds can avoid possible financing constraints due to imperfect capital markets and "pays" the market interest of 10%.

112 See e.g. Hall & Lerner (2010). Akerlof (1970) is the seminal paper on the "lemons" market.

113 See e.g. Hall & Lerner (2010).

Because the funds used are internal to the firm, it does not need to pay out to any lender, but the rate of 10% still constitutes a cost of capital that the firm could otherwise invest in the marketplace. A firm with no internal funds will have to revert to a premium rate, in this example of 20%. Finally, a firm with some internal funds available will first deplete these resources before seeking additional, more costly capital. In this example, if the project was profitable at a rate of 10% or slightly higher, firm 1 with sufficient internal funds could stem the investment cost and would find it profitable to do so, but not the other two firms.[114]

(106) In sum, this mechanism can render otherwise profitable R&D projects, for which much internal funding relative to the overall size of the investment is required, unfinanceable. This effect can be more pronounced for R&D projects with high information asymmetries between innovator and investor.

3.3.2. Uncertainty and the decision when to invest

(107) The previous sections have focussed on whether to invest, how much to invest, and where to invest. In this final analysis, the question is when to invest. Faced with the opportunity to take on a project that, while uncertain to be profitable, is profitable in expectation, the analysis so far suggested that the firm will invest. But is it still optimal to do so in a dynamic context? Or, in other words, if the investment opportunity remains available, should the firm wait for more information to arrive and take the investment decision when there is more certainty? This is the key question explored hereafter.

(108) As will be demonstrated, when there is uncertainty, a value of waiting may emerge. A firm may be better off postponing an investment decision even if carrying out the investment project in question today is expected to be profitable. This can be the case if for example the future brings more clarity on which direction the market is going. The concept of the value of waiting can explain a firm's incentive to delay investments in certain areas for which it is waiting for more information to arrive. Since this value can be very large, predictions made based on a standard investment rule that ignores the possibility of delay, including those made by the framework presented above, can be misleading.[115]

(109) The complex nature of a disease, as is the case for NDD,[116] can be a major source of such uncertainty, and it could arise in many dimensions. The probability of discovering a treatment, $p(I)$, could be uncertain. Components of the expected profit conditional on a discovery being made, $E(\pi|D = 1)$, including the price the firm could charge for its new drug, demand (market size), production cost, and patent length (see Section 3.2.2), could be uncertain. The investment cost itself, $c(I)$, which for simplicity is taken as deterministic throughout this report, could be uncertain. Moreover, the degree of uncertainty may change over time: it could increase, it could decrease, or it could evolve in some other, less systematic way.

[114] A firm without internal funds may still seek to obtain funding at a rate of 20% (or any other rate) because it will have no loss in case of no discovery and potentially have a profit in the other case. But the investor may not find it attractive to fund such a project.

[115] For an overview of those studies, see e.g. Pindyck (1991), footnote 1.

[116] See e.g. Lam *et al.* (2020), for the complexity of NDD.

(110) Against the background of PD, demand or market size is an interesting case. It is likely that PD is better conceptualised as an umbrella term for a number of diseases that become manifest in Parkinsonian symptoms. In connection to market size, it is not guaranteed whether a cure for one subtype would also be viable for all or many other subtypes of PD.[117] Reversely, innovation in PD could lead to much broader applications. For example, some non-pharmaceutical interventions such as transcranial magnetic stimulation and deep brain stimulation used for the treatment of PD can be applied more widely to NDD, despite constituting distinct diseases.[118] Finally, existing symptomatic drugs may provide a relatively good level of treatment for patients who contract PD at a late stage in life, i.e. after the age of 60. This age-cohort represents more than 80% of new PD cases.[119]

(111) Take the uncertainty of discovery, on which the example further below draws. As the scientific community learns more about a certain disease, that uncertainty may be reduced. If prior to extensive research the probability of discovery for an individual firm is estimated to lie somewhere in between 0-20%, after that research has been carried out it may be estimated with a higher degree of certainty, e.g. at either 0-10% or 10-20%. For example, it is conceivable that discovery of the first causal drug for a certain type of disease is more uncertain than subsequent modifications and improvements of causal drugs for the same type of disease once the first drug has been developed. The example below builds on this assumption. The probability of discovery for an individual firm may also generally increase through extensive research, say from 0-20% to 10-30%. In that case, waiting can be rational in the trivial sense that the probability of discovery will never be lower when investing at a later point in time. If R&D exerts a positive externality, with strategic behaviour, i.e. waiting for someone else to do the research, the necessary R&D may not be carried out in the first place (see also Section 3.1.3).

(112) Before exemplifying the value of waiting, it is worth re-emphasising some of the assumptions of the framework here. First, investment is irreversible and entails a sunk cost, i.e. the investment cost $c(I)$ cannot be recovered. Second, the firm's profits are uncertain, which is represented in the probability of discovery $p(I)$ as well as the expected profit conditional on a discovery being made $E(\pi|D=1)$ through the expectation operator E. And third, the decision is taken in a static context, i.e. the firm either invests today or it does not invest, in which case it cannot invest in the future either. The firm invests if the investment is expected to be profitable, i.e. if the expected NPV is positive:

$$\underbrace{NPV}_{\substack{\text{Net}\\ \text{Present}\\ \text{Value}}} = \underbrace{p(I)}_{\substack{\text{Probability}\\ \text{of discovery}}} \cdot \underbrace{E(\pi|D=1)}_{\substack{\text{Expected profit}\\ \text{with discovery}}} - \underbrace{c(I)}_{\substack{\text{Investment}\\ \text{cost}}} \geq 0. \qquad (3\text{-}6)$$

(113) This last assumption on the timing of the investment decision can, depending on the case, be a strong assumption and is therefore relaxed now. The second assumption on uncertainty is amended accordingly. Suppose that a firm is faced with a decision to invest today or to do so at some later point in time. This relaxes the third assumption. Suppose further that as time progresses, new information on the probability of discovery arrives,

[117] See e.g. EPDA (2020) and Port (2018b).

[118] See e.g. Lam et al. (2020).

[119] See e.g. Ahlskog (2010).

i.e. the probability of discovery not only varies with the investment project, but also over time t, i.e. $p(I, t)$. This amends the second assumption about uncertainty.[120]

(114) Notice that it is not necessary for a firm to be risk-averse for a value of waiting to exist. A risk-averse firm may be more inclined than a risk-neutral firm to wait for the uncertainty to be (partially) resolved. But risk-aversion is not required to demonstrate that waiting can be valuable even for a risk-neutral firm.[121] Therefore, and consistent with the analysis carried out so far, a risk-neutral firm is assumed. This means that the average profitability that the firm is expected to make continues to be the relevant investment criterion, as opposed to the distribution of this profitability.

(115) The following example demonstrates the principle that there can be a value of waiting even when investing today would already be profitable in expectation.[122] A firm can devote €80m of internal funds on an investment project that potentially provides a per-period return of €100m. The investment cost is born in the year in which the decision to invest is taken, and the profits are realised from the next year onwards until infinity.[123] The interest rate, i.e. the discount rate, is 10%. Rather than investing in the R&D project, the firm could use its funds to invest in some market portfolio. Discovery is uncertain, and therefore, there is uncertainty whether the firm can make those profits. The firm believes that a discovery will occur with a low probability of 0-20%, but that next year, this uncertainty will reduce to either 0-10% or increase to 10-20%. Figure 3-10 presents the cash flows the firm could obtain if discovery is successful.

[120] As discussed above, there is also uncertainty on the expected profit given discovery, which for simplicity is treated as deterministic in the example that follows. Likewise, the investment cost, which so far has been taken as certain, remains certain throughout this report.

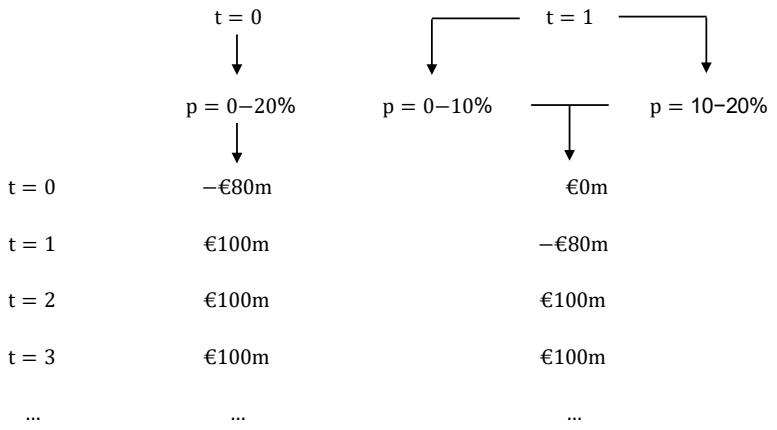
[121] See e.g. Dixit (1992).

[122] A similar example is made in Pindyck (1991).

This argument is more general. If in the present day, in $t = 0$, the investment is just worthwhile, i.e. $NPV(0) = p(I, 0) \cdot E(\pi|D = 1) - c(I) = 0$, the firm could invest now. But it could also consider the following strategy. It could wait for a fixed time period T, observe the expected profitability at the end of that period, and only if at that time $NPV(T) = p(I, T) \cdot E(\pi|D = 1) - c(I) > 0$, it would invest. This is not to say that this strategy is optimal, i.e. that the firm should wait the said amount of time and only then take a decision. The firm could also take a decision at any point in the meantime. And it is not to say that at the end of the period the expected NPV is necessarily positive. It could be negative instead, in which case the firm would not invest. But this alternative strategy to investing today illustrates that waiting can have a value if the current NPV is zero or very low, given that profitability is uncertain and the chance that it may become much higher in the future. Therefore, the standard rule to invest when the expected NPV is positive no longer applies in this setting in which the investment is irreversible, there is uncertainty, and decisions can be postponed. For a similar argument, see e.g. Dixit (1992).

[123] The assumption that profits run indefinitely is for simplicity only. See Section 3.2.2 for implications from the patent system. Simplistic is also the assumption that the firm can make profits a year after initialising the investment project. See also Section 3.2.2 on longer, more realistic lead times of development.

Figure 3-10: Cash flows when investing this year or next year



Source: NERA analysis.
Note: For a related example, see e.g. Pindyck (1991).

(116) If the firm invests today, in $t = 0$, it will trade a sure investment cost of €80m in return for an unsure stream of annual profits of €100m from the next year onwards. The probability that the firm's investment bears fruit is 0-20%, or simply 10%. By postponing its investment decision until the next year, in $t = 1$, the firm can make use of the information available by then, according to which the probability of discovery will either be low, at 0-10%, or simply 5%, or high, at 10-20%, or simply 15%. The investment cost and the associated possible profits remain as before but are shifted by one year, implying that waiting is not without any downsides.

(117) The NPV of investing today, in year 0, is:

$$\underbrace{NPV(0)}_{\substack{\text{Net Present Value}\\ \text{in year zero}}} = -\underbrace{I}_{\substack{\text{Investment}\\ \text{cost}}} + \underbrace{p(I)}_{\substack{\text{Probability}\\ \text{of discovery}}} \cdot \underbrace{\sum_{t=1}^{\infty} \pi \cdot \left(\frac{1}{1+r}\right)^t}_{\substack{\text{Future stream of}\\ \text{discounted profits}\\ \text{with discovery}}} = -I + p(I) \cdot \frac{\pi}{r}$$

(3-7)

$$= -€80m + 10\% \cdot \frac{€100m}{10\%} = €20m.$$

(118) The investment gives an expected NPV of €20m and is therefore profitable. Of course, in this example, the firm will never precisely obtain this NPV. Chances are high that discovery does not occur, in which case the realised NPV will be negative, at -€80m. If discovery does occur, the realised NPV will be positive, i.e. €920m.[124] The expected NPV is therefore $10\% \cdot €920m - 90\% \cdot €80m$, which is €20m, as above. From a risk-neutral, static perspective, the firm should invest.

(119) In this dynamic setting, however, the firm understands that the next year, the year 1, will bring more information on the probability of discovery. It will become clear whether the probability of discovery is at the low-end spectrum of 0-10% or at the high-end interval

[124] $-€80m + \frac{€100m}{10\%} = €920m.$

of 10-20%. If the firm waits for one year, and the probability of discovery turns out to be 0-10%, or simply 5%, the NPV (again assessed in the year 0) of investing in that year is:

$$\underbrace{\mathrm{NPV}(1)}_{\substack{\text{Net Present Value}\\ \text{in year 0}\\ \text{when investing in year 1}}} = -\underbrace{\frac{I}{1+r}}_{\substack{\text{Investment}\\ \text{cost}\\ \text{(disounted)}}} + \underbrace{p(I)}_{\substack{\text{Probability}\\ \text{of discovery}}} \cdot \underbrace{\sum_{t=2}^{\infty} \pi \cdot \left(\frac{1}{1+r}\right)^{t}}_{\substack{\text{Future stream of}\\ \text{discounted profits}\\ \text{with discovery}}}$$

$$= -\frac{I}{1+r} + p(I) \cdot \frac{\pi}{r \cdot (1+r)} \tag{3-8}$$

$$= -\frac{€80\mathrm{m}}{1+10\%} + 5\% \cdot \frac{€100\mathrm{m}}{10\% \cdot (1+10\%)} = -€27\mathrm{m}.$$

(120) This is the same formula as used in $t = 0$, except for the change in probability and the shift in the time period by one year. The NPV from investing becomes negative, at -€27m, and the firm would not invest.[125]

(121) If instead the probability of discovery is updated to 10-20%, or simply 15%, the NPV from investing in that year is:

$$\mathrm{NPV}(1) = -\frac{€80\mathrm{m}}{1+10\%} + 15\% \cdot \frac{€100\mathrm{m}}{10\% \cdot (1+10\%)} = €64\mathrm{m}. \tag{3-9}$$

(122) In that case, the NPV is €64m, and the firm would invest.[126]

(123) The question is then whether the firm should invest immediately or wait one year before deciding? If the firm invests directly, its NPV is expected to be €20m (see above). If it waits one year, it will only invest in the case the probability of discovery turns out to be round 15%, in which case the NPV is €64m. If the probability of discovery turns out to be round 5%, the firm will not invest as the NPV would be negative. Since the firm knows in year 0 that there is a 50% chance that the probability in year 1 averages 15%, the NPV from waiting one year is exactly half of the NPV in year 1, i.e. $50\% \cdot €64\mathrm{m} = €32\mathrm{m}$. Therefore, comparing the expected NPV from year 1 (€32m) with the expected NPV in year 0 (€20m) implies that the firm is better off to wait one year and decide then.

(124) This does not mean that the investment will turn out to be profitable later. The firm is still likely to incur losses on that project, which is a very frequent outcome in the research-intensive pharmaceutical industry.[127] Hence what matters in this setting for the decision-making is the expected return, which is higher when waiting one year. Of course, if discovery was certain, the firm would have been better off investing today because it would not forgo the profit from period 1. This is a trade-off the firm faces when contemplating an investment delay. Another trade-off is that the investment opportunity

[125] This is where the assumption of internal funds is relevant. If the firm could use external funds to finance that project in the bad state of a 5% discovery probability, it would find it profitable to do so. If there is no discovery, the money lost is the investor's. If there is discovery, the 10% interest rate payable still leaves the firm with a large profit. But under these conditions, the market would not finance such a project at 10%.

[126] In this example, there is no point in waiting any longer since no more information will flow in.

[127] See footnote 88.

may be open to more than just one firm, e.g. in a patent race (see Section 3.1.1), in which case the firm may not be incentivised to postpone its decision for long, if at all.[128]

(125) In sum, under irreversibility of investments, uncertainty means that waiting can have a positive value. This can lead to delayed investments despite them being expected to be profitable today.[129]

[128] See e.g. Dixit (1992).

[129] Under certain conditions, uncertainty can increase rather than decrease investment. See e.g. Caballero (1991) for an overview of the literature on the investment-uncertainty relationship. See also Czarnitzki & Toole (2013) for more recent research.

4. Conclusions

(126) This report has studied the firm-level incentives to innovate by investing in R&D projects, against the background of a lack of causal treatments for NDD such as PD and AD, including existing symptomatic treatments; a long drug development process; a record of failed projects; a high uncertainty on the market size of a new, to be developed drug; and the risk of an insufficiently small reward for new innovations in that area.

(127) The report identified a range of mechanisms that may be present and that may be able to explain the perceived lack of innovation in the treatment of these and possibly other diseases.

- There are indications that some of the mechanisms leading to suboptimal outcomes set out in this report – market and/or regulatory failures – may also be present in the context of NDD such as PD and AD.
- The findings of this report therefore provide a solid theoretical foundation for justifying specific empirical research in order to pinpoint specific innovation effects in NDD.
- Such an empirical analysis would allow identifying the pertinence of the market and regulatory failures described here in the context of NDD.
- Besides identifying the empirical relevance of the mechanisms set out in this report, such an analysis would then also be able to identify the magnitude of the specific market and regulatory failures and on this basis allow appropriate remedies and countermeasures to be devised and deployed.

(128) By reviewing a large number of mechanisms capable of explaining the perceived lack of innovation in the development of causal treatments in NDD, this report has laid the foundation for further empirical work. Such empirical work, based on the theoretical foundations provided in this report, could pave the way to devising solutions increasing innovation in NDD and other diseases.

Appendix A. Technical formulation of the patent race

(129) This section provides a technical derivation of the multiple-firm patent race in Section 3.1.1. Consider N symmetric firms, each of which has a single research lab.[130] In their search for a new product, firms exert costly effort in their labs. Extending the standard firm maximisation problem introduced in Section 2.1.2, firm i's optimisation problem can be described by:

$$\max_{I_i} \underbrace{p(I_i)}_{\substack{\text{Probability of} \\ \text{discovery}}} \cdot \underbrace{E(\pi_i|\mathbf{D})}_{\substack{\text{Expected profit with discovery,} \\ \text{given that rivals discovered or not}}} - \underbrace{c(I_i)}_{\text{Investment cost}}.$$

(130) Firm i's profit depends not only on its own potential discovery but also on the potential discovery of its rival firms, denoted by $\mathbf{D} = (D_1, D_2, \dots, D_i, \dots, D_N)$.[131] I_i is the research effort exerted by firm i, which directly determines said probability of discovery. For simplicity, assume that $p(I_i) = I_i$ for all $i \in \{1, \dots, N\}$, i.e. the investment level increases the probability of discovery on a proportional basis.[132] As innovating is costly, it is assumed that firms' R&D cost increases with an increasing level of effort, e.g. $c(I_i) = I_i^2$ for all $i \in \{1, \dots, N\}$.

(131) If only firm i innovates successfully, the new product can be patented, guaranteeing the "winner" monopoly profits, i.e. the expected profit is:

$$\underbrace{E(\pi_i|\mathbf{D} = (D_i, ND_{-i})}_{\substack{\text{Expected profit} \\ \text{if firm i innovates} \\ \text{and no rival does}}} = \pi^M.$$

(132) For simplicity, the monopoly profit is normalised to one, i.e. $\pi^M = 1$. If N firms are successful simultaneously, each of them can patent their new product with equal probability $\frac{1}{N}$. If firm i is not successful in making the discovery, its profit is 0.

(133) To gradually build up the analysis, the monopolist, duopolist, and the general case with N firms is now taken in turn.

(134) A monopolist's optimisation problem is as follows:

$$\max_{I_i} \underbrace{I_i}_{\substack{\text{Probability} \\ \text{of discovery}}} \cdot \underbrace{1}_{\substack{\text{Monopoly} \\ \text{profit}}} - \underbrace{I_i^2}_{\substack{\text{Investment} \\ \text{cost}}}.$$

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130 The analysis is related to Federico *et al.* (2017), where the investment level affects the probability of discovery, but not the value of innovation, which is π^M. There are at least two key differences to the setting presented above. First, Federico *et al.* (2017) analyse changes in the market structure following a merger through a reduction of firms while keeping the number of research labs constant. By contrast, the setting presented above assumes that the number of firms and research labs are the same. Second, their payoff as a function of the number of successful innovators differs in that if two firms innovate they make a fixed positive profit of δ each, and if more than three firms innovate, the profit is zero due to intensive competition. In the setting presented above, the winning profit of π^M is proportionally split among the successful innovators (or the probability that an innovating firm can obtain the winning profit is proportional to the number of all innovating firms).

131 If the firm is a monopolist, it does not take into consideration any rivals' effort level by definition.

132 For this reason, $I_i \in [0, 1]$.

(135) As the monopolist is the only firm in the market, it does not have to take into consideration any rivals' decisions. The monopolist's optimal effort level is given by the first order condition:

$$1 - 2I_i = 0.$$

(136) Hence, the optimal level of individual effort is $I_i^* = \frac{1}{2}$. The probability of discovery by the monopolist, which equals the industry probability of discovery, is $p(I_i^*) = I_i^* = \frac{1}{2}$, i.e. 50%.

(137) With two competing firms, i and j, the duopolist firm i's optimisation problem is:

$$\max_{I_i} \left[\underbrace{I_i \cdot (1 - I_j)}_{\substack{\text{Probability that} \\ \text{only firm i} \\ \text{innovates}}} + \underbrace{\frac{1}{2} \cdot I_i \cdot I_j}_{\substack{\text{Probability of winning} \\ \text{if both firms} \\ \text{innovate}}} \right] \cdot \underbrace{1}_{\substack{\text{Monopoly} \\ \text{profit}}} - \underbrace{I_i^2}_{\substack{\text{Investment} \\ \text{cost}}}.$$

(138) The first term, $I_i \cdot (1 - I_j)$, captures the probability that firm i succeeds in innovating and firm j does not. The second term, $\frac{1}{2} \cdot I_i \cdot I_j$, is the probability that both firms innovate, and firm i receives the patent with probability $\frac{1}{2}$. The 1 following the squared brackets represents the monopoly profit, and the last term, I_i^2, the investment cost.

(139) Firm i's optimal level of effort is given by the first order condition with respect to I_i:

$$(1 - I_j) + \frac{1}{2} I_j - 2 \cdot I_i = 0.$$

(140) Take a symmetric equilibrium in which all firms behave alike, i.e. all firms set $I_i = I_j = I^*$. The first order condition then becomes:

$$(1 - I^*) + \frac{1}{2} \cdot I^* - 2 \cdot I^* = 0 \quad \Leftrightarrow \quad I^* = 0.4.$$

(141) This condition illustrates the optimal individual effort level in R&D in a market with two competitors. The solution of the above equation specifies the optimal R&D level for each firm, i.e. in equilibrium $I^* = 0.4$. The aggregate R&D level is therefore $I_A^* = 2 \cdot I^* = 0.8$. The aggregate probability of discovery is not equal to the aggregate investment level. It is 100% minus the probability that neither firm is successful in discovery, i.e. $1 - (1 - 0.4)^2 = 0.64$, i.e. 64%.

(142) For the general case of $N \geq 3$, the following profit function can be derived:

$$I_i \cdot (1 - I_j)^{N-1} + \sum_{k=1}^{N-2} \frac{(N-1)!}{k!(N-k-1)!} \cdot \frac{1}{k+1} I_i \cdot I_j^k \cdot (1 - I_j)^{N-k-1} + \frac{1}{N} \cdot I_i \cdot I_j^{N-1}.$$[133]

(143) Firm i's optimisation problem is then as follows:

[133] For ease of simplicity, it is assumed that all other firms except the considered one behave alike and hence choose the same effort level I_i. This approach is reasonable if symmetric equilibria are examined. See also Federico *et al.* (2017) on this assumption.

$$\max_{I_i}\left[\underbrace{I_i\cdot\left(1-I_j\right)^{N-1}}_{\substack{\text{Probability}\\ \text{that only firm i}\\ \text{innovates}}}+\underbrace{\sum_{k=1}^{N-2}\frac{(N-1)!}{k!(N-k-1)!}\cdot\frac{1}{k+1}I_i\cdot I_j^k\cdot\left(1-I_j\right)^{N-k-1}}_{\substack{\text{Probability of winning if firm i}\\ \text{innovates and any possible combination}\\ \text{of rivals innovate}}}+\underbrace{\frac{1}{N}\cdot I_i\cdot I_j^{N-1}}_{\substack{\text{Probability of}\\ \text{winning}\\ \text{if all firms}\\ \text{innovates}}}\right]\cdot 1-I_i^2.$$

(144) Firm i's optimal level of effort is given by the first order condition with respect to I_i:

$$\left(1-I_j\right)^{N-1}+\sum_{k=1}^{N-2}\frac{(N-1)!}{k!(N-k-1)!}\cdot\frac{1}{k+1}\cdot I_j^k\cdot\left(1-I_j\right)^{N-k-1}+\frac{1}{N}\cdot I_j^{N-1}-2\cdot I_i=0.$$

(145) In a symmetric equilibrium the first order condition becomes:

$$(1-I^*)^{N-1}+\sum_{k=1}^{N-2}\frac{(N-1)!}{k!(N-k-1)!}\cdot\frac{1}{k+1}\cdot {I^*}^k\cdot(1-I^*)^{N-k-1}+\frac{1}{N}\cdot {I^*}^{N-1}-2\cdot I^*=0.$$

(146) This equation can be solved for different number of firms, deriving the results depicted in Figure 3-2.

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