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An Economic Assessment of the Relationship between Price Regulation and Incentives to Innovate in the Pharmaceutical Industry

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Foreword

In this paper, we explore the possible consequences that pricing and reimbursement regulation may have on pharmaceutical innovation. We first investigate qualitatively how a pharmaceutical firm is likely to strategically respond in its R&D activities to pricing and reimbursement regulation. We then quantitatively evaluate these effects in the context of a calibrated decision-theoretic model of drug development in which a pharmaceutical firm is forward-looking and takes future pricing regulation into account in making current development decisions. Our findings indicate that, in designing optimal pharmaceutical pricing and reimbursement regulation, the benefits of more affordable or cost-effective drugs must be traded against the costs of less pharmaceutical innovation, with fewer projects being developed in general and in particular in low-margin therapeutic areas and with little potential of being considered highly innovative at the time of market launch.

Executive summary

Motivation

In the context of healthcare cost-containment efforts, pharmaceutical products are increasingly subject to strict pricing and reimbursement conditions in many European countries and it is widely believed that the U.S. are following suit. However, little attention has been paid to the adverse consequences that pricing and reimbursement regulation may have on pharmaceutical innovation, by reducing the value of pharmaceutical projects and by curtailing the resources available to carry them out. Furthermore, because pharmaceutical discovery and development is a long-lasting process, the adverse consequences of the pricing and reimbursement regulation that are introduced today will be observed in the number and characteristics of the drugs that will be launched in the market only in the future.

Objectives

In this report we set out to analyze the effect of pricing and reimbursement regulation on innovation in the pharmaceutical industry by:

- first, qualitatively exploring how a pharmaceutical firm is likely to strategically respond in its R&D activities to pricing and reimbursement regulation;
- then, quantitatively evaluating this effect in the context of a calibrated decision-theoretic model of drug development in which a pharmaceutical firm is forward-looking and takes future pricing regulation into account in making current development decisions.

The point of view that we take throughout this report is that of a representative pharmaceutical firm which, when taking development decisions, optimally reacts to the incentives provided by the pricing and reimbursement regulatory environment. It is beyond the scope of this report to evaluate the net effect of pricing and reimbursement regulation on the welfare of patients and society at

large by comparing the potential welfare benefits of lower drug prices and the potential welfare costs of fewer drugs being developed and launched in the market.

The innovation process and how it interacts with the commercial environment

The pharmaceutical innovation process is a long, costly, and risky process that is paced by rigorous marketing authorization rules ensuring that marketed drugs are safe and effective.

From an economist's perspective the pharmaceutical innovation process is characterized by two key decision stages. First, a decision on the overall R&D budget is taken. Arguably because of the presence of asymmetric information between pharmaceutical firms and outside investors, R&D projects are primarily financed by current cash flows, resulting in a relatively stable ratio between R&D expenditures and sales over time. Second, once an R&D budget is allocated, a variety of decisions must be taken regarding which projects to accelerate, which projects to delay, and for what therapeutic indications to perform clinical trials.

The later part of the process can be characterized as a time-phased process during which go/no go decisions, as well as a variety of "softer" decisions, are taken. While in the past these decisions were based primarily on scientific and technological grounds, in the recent years—and arguably because of the stricter cost-containment policies implemented—there has been an increase in the importance assigned to commercial factors, including considerations about potential pricing and reimbursement regulation outcomes. This is reflected in the early stages of the development process in a careful, but not necessarily quantitative, meditation on the unmet medical need that a drug candidate would fill and its degree of differentiation relative to other drug (candidates). Then, especially later on in the development process, these reflections find their way into Expected Net Present Value calculations. These calculations—which explicitly take into account development costs, risks, and the life cycle of expected future sales—allow decision-makers to rank their projects and make better resource-allocation decisions.

Main categories of pricing and reimbursement regulation

There exist a large number of pricing and reimbursement regulation schemes that are applied to pharmaceutical products around the world. In addition, these frameworks are present in different countries to different degrees. This fact stands in sharp contrast with the global nature of the pharmaceutical discovery and development process.

For the purpose of this report and consistent with the existing literature, we classify national pricing and reimbursement regulatory schemes into three main

groups (in addition to simple across the board price cutting schemes or bilateral negotiation):

- External Price Benchmarking, according to which the price of a drug in a country is pinned to the price of the same drug in a basket of other countries;
- Internal Reference Pricing, according to which the price of a drug in a country is pinned to the price of similar, potentially already off-patent, drugs in the same country;
- schemes based on a pharmaco-economic assessment, according to which the price of a drug depends on its cost-effectiveness.

In terms of ongoing and future trends, it is observed that the health authorities are in general moving away from crude cost-cutting policies towards cost-effectiveness considerations, thereby moving in the direction of more rational, evidence-based, and predictable regulatory decision making. This trend thus seems to move in the direction of fostering innovation. The potential societal benefits of this trend must however be traded against the movement away from national policies and towards local responsibilities, entailing that pharmaceutical firms will have to devote more effort and resources to coping with a more complex regulatory environment.

Qualitative assessment - Strategic responses to changes in pricing and reimbursement regulation

In the analytic part of the report we then qualitatively analyze how pharmaceutical firms are likely to strategically respond in their R&D activities to the individual forms of pricing regulation, taking into account the specificities of supply and demand conditions in the pharmaceutical industry, notably:

- the person that makes the ultimate decision to purchase the product (typically a medical practitioner) is not usually the same person or organization that pays for those products (typically a public or private health insurer);
- a health insurer's willingness to pay depends in particular on incremental benefits of a treatment;
- the willingness to pay varies also across countries, depending inter alia on the country's ability to pay (which is determined by its income or wealth), the standard of health care that the government wishes to provide to its population, or cultural differences.

We argue that all forms of pricing regulation—compared to a counterfactual of market-based pricing—are likely to reduce the value of projects and the resources available for R&D activities. This is most obvious for the simplest forms of price regulation like bilateral negotiations or across the board price cutting, but holds also for the more elaborate forms under plausible assumptions.

For the three core regulatory schemes, we identify the following potential strategic responses of firms in addition to the already mentioned effect on the availability of development resources.

External price benchmarking

In principle, one could conceive an extreme form of External Price Benchmarking; in this case, the prices in a high-willingness-to-pay country are benchmarked against a low-willingness-to-pay country effectively rendering price discrimination impossible. A less extreme action that a government health insurer might take is to benchmark the price against a set of comparable countries with similar willingness to pay. Depending on which form of External Price Benchmarking is chosen, the following effects may arise to various degrees:

- a change, potentially even an increase, in the average price of a drug as a consequence of inducing price equalization across countries;
- strategic differentiation of products across countries in order to limit price comparisons;
- a delayed launch of the product in the countries with low willingness to pay or the focusing of R&D efforts of products that address the specific needs of high-willingness-to-pay countries.

As a side effect of External Price Benchmarking, it could also happen that in the context of a bargaining game between a national health insurer of a country that is referenced by other countries and a pharmaceutical firm, External Price Benchmarking might lead to more favourable reimbursement conditions and thus higher incentives to innovate. This would occur because a pharmaceutical firm stands to lose more from unfavourable pricing and reimbursement conditions in a country if that country is referenced by other countries. Thus, the pharmaceutical firm would be a tougher negotiator and will most likely be able to win better conditions.

Internal reference pricing

We distinguish between the effect of internal price referencing on prices before and after the patents on the first-in-class drug expire. Under the more lenient form of Internal Reference Pricing patented drugs were excluded from internal price referencing (whether they are first or later in class). Under the more stringent form of Internal Reference Pricing, later-in-class drugs—even those with different, patented characteristics than the first-in-class drug—are referenced against the first-in-class drug unless they can convince the regulator that the drug is “highly innovative.” This is a fact that is particularly relevant if the first-in-class drug is not protected by patents or data exclusivity any longer and is thus subject to generic entry.

In particular the later effect seems to be important: the price that the owner of a later-in-class but innovative drug can charge will be significantly more constrained by the price of the generic under a system with internal price referencing than under a market-based pricing counterfactual, assuming that the innovative character of the later-in-class drug is not appropriately recognized by the regulatory system.

In response to the more stringent form of Internal Reference Pricing, pharmaceutical firms are likely to direct their R&D investment toward indications where there is a lower probability that a drug will end up being "later in class" and therefore have its price referenced against a generic drug in the later years of its patent protection. The indications where there is likely to be a lower probability of being later in class are likely to be those with lower expected returns and therefore a lower probability that other firms will invest. These may be either products in therapeutic indications that affect a smaller number of patients (such as rare diseases) or projects with a lower expectation of success—for instance, because the mechanism of action still needs to be validated.

A related response to Internal Reference Pricing is that pharmaceutical firms investing in indications with high expected demand are also more likely to cancel projects at later stages of the development process when they discover that there is a higher-than-expected probability that another firm will launch a product to treat the same therapeutic indication before them. This is because the realization that the firm will be later in class significantly lowers the expected return to further investment. Moreover, because this realization typically does not happen until later in the R&D process (for instance, at the time of entering Phase III clinical trials), it means that otherwise-worthwhile projects are more likely to be abandoned and the sunk investment wasted under Internal Reference Pricing. This fact is consistent with the increase in attrition rates observed over the last decade, in particular between Phase II and Phase III clinical trials.

Value-based pricing (i.e., pharmaco-economic assessment)
In theory, a value-based pricing system will largely replicate the prices that would arise under market-based pricing. However, different outcomes may arise under the two systems due to the way each system is implemented. To start with, under a value-based pricing system delays may occur in obtaining reimbursement; this increases the pharmaceutical firm's uncertainty about the revenue profile for its product.

At the same time, market-based and value-based pricing may reward different types of drugs in different ways because of the process by which prices are set. Under market-based pricing, the prices are set to closely reflect the individual patient's varying willingness to pay across products. By contrast, under a value-based pricing system based on pharmaco-economic assessment, the benefits are measured against a relatively objective standard that reflects the economic considerations of the health system as a whole more than the willingness to pay of individual patients. This may lead to different drugs being reimbursed, or drugs being reimbursed at different levels under the two systems.

Finally, since a pharmaco-economic assessment attempts to capture the costs and benefits explicitly, it is likely to focus on costs and benefits that are easy to measure. It is relatively easy to measure the therapeutic benefits that accrue to the specific patients who are treated by a drug and the cost savings that are realized in the activities involved in treating the patients. It is more difficult to account for the benefits that a drug may generate to the health system (for instance, preventive medicine that avoids subsequent treatment) or to society at large. Therefore these benefits may be undervalued.

General considerations

All three major forms of price regulation involve some form of benchmarking or referencing to the prices of other products. However, the prices that result from reference pricing will only be as good as the price of the original (referenced) product and the mechanism by which the referencing occurs. If the prices of the referenced products are inefficient or the conditions under which they were set do not exist in the new environment, then the referenced prices will create, perpetuate, or enhance any distortions. Furthermore, whenever a pricing regulatory scheme requires a judgment whether a drug is highly innovative or not, the risk is incurred that a drug that is highly innovative from the point of view of the patients (in terms of higher safety and efficacy today and tomorrow) is not perceived as equally highly innovative by the pricing regulator.

Quantitative assessment - Optimal responses to changes in pricing and reimbursement regulation within a decision-theoretic model

The effect of pricing regulation on pharmaceutical innovation is further complicated by the fact that different pricing regulatory schemes in different countries are in place at the same time, and it is their combination that affects global pharmaceutical innovation. In this report, we provide a rigorous and comprehensive framework—in the form of a decision-theoretic model of drug development—that allows us to quantitatively evaluate the effect of the main existing schemes of pricing regulation and their interaction.

The model

In the model proposed, a pharmaceutical firm evaluates a portfolio of drug candidates, ranks them on the basis of their Expected Net Present Value (ENPV) and their Expected Profitability Index (EPI), and—because of a constraint on the development budget—selects the highest-ranking ones. Projects are in different therapeutic areas, are in different development phases, and have different potentials of being considered highly innovative by the pricing regulator at the time of market launch. Development is dynamic and risky, and the evaluation of a project takes into account the alternative possible realizations of future events and the future development and launch decisions contingent on such realizations. For example, a project in an early development phase that has the potential of being considered highly innovative by the pricing regulator if and when it will be launched in the market may lose its potential in later development

phases, at which point the decision maker may decide not to develop the project further. In another example, the decision maker may decide about the set of countries in which to launch its drug depending on whether the pricing regulator considers the drug highly innovative or not.

Indeed, in the model proposed there exist different regions, which are heterogeneous in their pricing regulation. Because of Internal Reference Pricing (IRP) in one region, it matters whether a drug is highly innovative or not; because of External Price Benchmarking (EPB), whether or not a drug is launched in one region has consequences in another region.

In addition to the risk of failing clinical trials or not receiving marketing authorization, in the model proposed highly innovative projects face the risk of not being considered highly innovative by the pricing regulator at the time of market launch. This may be due to external competition (competition from other pharmaceutical firms) or due to internal competition (competition from other projects in the portfolio of the pharmaceutical firm itself).

Policy experiments

On the basis of the model, which we calibrate to replicate several quantitative aspects of the real world (in particular, the pharmaceutical firm in our model resembles for the number and the characteristics of the projects a representative pharmaceutical firm in the real world), we perform a variety of policy experiments to evaluate the effect of pricing regulation on pharmaceutical innovation.

To begin with, we find that—relative to an environment of market-based pricing—in an environment in which approximately one fourth of the world adopts Internal Reference Pricing, the value of all projects—including highly innovative projects—is reduced. It is interesting to note that this result is arrived at under the conservative modeling assumption that Internal Reference Pricing does not affect the price of all drugs but only of those drugs that are not considered highly innovative by the regulator at the time of market launch, while in the real world also highly innovative drugs may not be able to fetch a market-based price. In particular, this result is arrived at because also projects that are highly innovative during development face the risk of not being considered highly innovative by the pricing regulator at the time they are launched in the market.

Because the decision maker is forward looking, she takes this event into account in evaluating projects and making optimal development decisions. The projects that are most heavily affected by Internal Reference Pricing are projects in earlier development phases—whose expected present value of net sales is smaller relative to expected present development costs—and projects in low-sales/low-margin therapeutic areas. Taking into consideration its composition in terms of therapeutic area, development phase, and degree of innovativeness, the whole portfolio of the pharmaceutical firm in our model loses 8.5% of its value under Internal Reference Pricing.

The ranking of projects on the basis of their Expected Profitability Index is only moderately affected by Internal Reference Pricing, with highly innovative projects gaining only few positions relative to market-based pricing. However, the fewer resources available for development under Internal Reference Pricing entail a reduction in the number of selected projects from 54 (out of which 32 are highly innovative) to 49 (30 highly innovative) and a reduction in the number of projects expected to be launched in the market from approximately 22 (14 highly innovative) to 20 (13 highly innovative). The combined effect of the lower value of individual projects, their different ranking, and the fewer resources available for development implies that under IRP the value of the selected portfolio declines by approximately 12%.

When we next compare to an environment of market-based pricing an environment in which approximately one fourth of the world adopts External Price Benchmarking, we find that the decline in the value of projects is less heterogeneous across therapeutic areas, development phase, and degree of innovativeness than under Internal Reference Pricing, implying that the ranking of projects is virtually unchanged. The value of the whole portfolio declines by approximately 3%.

In terms of the number of projects selected and expected to be launched in the market under External Price Benchmarking, 51 projects (out of which 29 are highly innovative) are selected and approximately 21 (13 highly innovative) are expected to be launched. Compounding the effect of External Price Benchmarking on the evaluation of projects with its effect on the resources available for development implies that the value of the selected portfolio declines by approximately 6%.

In the last policy experiment considered in the report, an environment of market-based pricing is compared to an environment in which at the same time one fourth of the world adopts Internal Reference Pricing and another fourth of the world adopts External Price Benchmarking—the environment that most closely resembles the world as it is today.

We find that the value of a project under jointly Internal Reference Pricing and External Price Benchmarking drops by an amount that is greater than the sum of the amounts by which it drops under Internal Reference Pricing and External Price Benchmarking separately: through External Price Benchmarking, the consequences of not being considered highly innovative in a country adopting Internal Referencing Pricing spill over to other countries. As a result, the value of the whole portfolio and the selected portfolio shrink by 13% and 20%, respectively. The number of projects selected and expected to be launched in the market is reduced to 45 (out of which 26 are highly innovative) and 19 (11 highly innovative), respectively.

Conclusions

We conclude that, in designing optimal pharmaceutical pricing and reimbursement regulation, the benefits of more affordable or cost-effective drugs must be traded against the costs of less pharmaceutical innovation, with fewer projects being developed in general and in particular in low-margin therapeutic areas and with little potential of being considered highly innovative at the time of market launch. Because through External Price Benchmarking pricing decisions in one country spill over to other countries, even the pricing regulatory changes introduced in an individual country may affect pharmaceutical firms' global incentives to innovate. Because pharmaceutical discovery and development is a long-lasting process, the adverse consequences of the pricing and reimbursement regulation that is introduced today will be observed in the number and characteristics of the drugs that will be launched in the market in the future.

At this point, we would like to remind the reader that the results that we arrive at depend on the model that we specify, the data that are available to us, and the calibration of the model parameters that we implement. However, one of the appealing features of our methodology is that we are explicit about the behavioral assumptions underlying the model. Furthermore, the data sources and the calibration strategy are clearly described, and sensitivity analysis is performed with respect to the value of several model parameters.

Road map

The remainder of this report is structured as follows: Section 1 presents some vocabulary and facts regarding pharmaceutical innovation, Section 2 provides an overview of the pharmaceutical innovation process. Section 3 describes the main forms of pricing and reimbursement regulation existing around the world, and identifies ongoing and future trends. The remaining two sections contain the core of our analysis. In particular, in Section 4 we qualitatively explore how pharmaceutical firms are likely to respond in their R&D activities to pricing and reimbursement regulation, and in Section 5 we quantitatively evaluate the effect of pricing and reimbursement regulation on pharmaceutical innovation in the context of a decision-theoretic model of drug development.

1. Pharmaceutical innovation

Innovation is a crucial priority of the pharmaceutical industry, as pharmaceutical firms' aim is to address unmet medical needs. Pharmaceutical innovation, however, has many dimensions, and different stakeholders emphasize different dimensions. In this section, we shed light on various notions of pharmaceutical innovation and document the level of innovative activity in the pharmaceutical industry. This section also identifies major trends in pharmaceutical innovation, including the rise of tailored drugs and the development of drugs preventing and treating diseases affecting an increasing portion of the world's population—the elderly.

1.1 Varieties of innovation

The aim of pharmaceutical firms is to address unmet medical needs, and there are several ways in which this goal can be attained. In particular, addressing an unmet medical need may take the shape of discovering and developing a drug that utilizes a novel mechanism of action to treat a disease (a so-called "breakthrough" drug), but it may also take the shape of discovering and developing a drug that—while utilizing the same mechanism of action as an existing drug—is safer, more effective, and more convenient. For this reason, the distinction between "breakthrough" and "me-too" drugs that is sometimes made is not very appropriate. A more appropriate distinction, made by Garnier (2008), separates "first-in-class" drugs from "best-in-class" drugs. As the case of cardiovascular drugs shows,[1] best-in-class drugs are typically the result of incremental modifications over time of first-in-class drugs.

[1] See Sheridan and Attridge (2006).

To encourage pharmaceutical innovation, to make sure that patients receive high-quality, safe, and effective treatment, and to keep healthcare affordable, drugs are the object of intense regulation. In particular, pharmaceutical products may benefit from patent protection, are subject to marketing approval, and their price may be de jure or de facto regulated. What makes things interesting is that the characteristics of a drug that are relevant for a dimension of regulation (say, marketing authorization) may or may not coincide with the characteristics that are relevant for another dimension of regulation (say, pricing and reimbursement). In turn, the characteristics of a drug looked at by regulation may or may not coincide with the characteristics physicians and patients care about.

While the details may vary across countries and regions,[2] the substantive requirements to receive a patent have to do with an invention being useful, novel, and nonobvious (requiring an inventive step). As far as the novelty requirement is concerned—the most demanding requirement—it is straightforward for a scientist to assess whether a pharmaceutical (that is, small-molecule) drug is innovative or not. In case of biological (also known as large-molecule) drugs a first-in-class status must be assessed. In the case of biological (also know as large-molecule) drugs, a first-in-class status must be assessed.

Marketing authorization[3] requires that drugs be of high-quality, safe and effective, and it is in the context of marketing application that the massive amount of information collected during a drug's discovery and development process (in particular but not exclusively in clinical trials) is first examined by regulators.

The FDA classifies all new drug applications (NDAs) along two dimensions:[4]

- chemical type;
- therapeutic potential.

Regarding chemical type, the FDA designates drugs that rely on compounds that have never been approved before for the U.S. market as new molecular entities (NMEs)[5] and those whose active compounds are already available in a marketed product as incrementally modified drugs (IMDs).[6]

Regarding therapeutic potential, the FDA assigns new drug applications to a standard or a swifter review track depending on their potential for clinical improvement. Often, the fast review track is adopted for breakthrough drugs—that is, drugs using a novel mechanism of action—but it may also happen that the fast review track is adopted for drugs with greater safety and effectiveness than existing drugs in the same therapeutic class.

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[2] In Europe, patents are granted by the European Patent Office (EPO) and by national patent offices, and in the US by the US Patent and Trademark Office.

[3] Marketing is authorized in Europe by national authorities or the European Medicines Agency (EMEA), and in the US by the Food and Drug Administration.

[4] See NIHCM Foundation (2002).

[5] The EMEA's counterpart of the FDA's notion of NMEs is that of New Active Substances (NASs). The definition of an NAS is broader than the definition of an NME, because new combinations of active ingredients and new salts or esters of existing drugs are NASs without being NMEs.

[6] The FDA also approves a few NDAs for drugs whose active ingredients are available in identical marketed products.

While marketing authorities consider therapeutic potential only to discriminate between standard and fast review track, therapeutic potential is usually an important concern for pricing and reimbursement authorities, in particular those that emphasize efficacy or cost-effectiveness rather than affordability. As an example, pricing and reimbursement regulation in Germany is such that, if a drug is considered the first-in-class or shows major therapeutic advantages, it is free to set prices as it wishes; otherwise, the amount that the statutory health insurance reimburses is determined by the price of similar, potentially off-patent, drugs (a form of pricing and reimbursement regulation that, as we will see in Section 4, is often referred to as Internal Reference Pricing).

1.2 Facts about innovation

Because innovation is so important for the pharmaceutical industry and because discovering and developing a drug—as we will see in Section 2—is so costly, pharmaceutical firms spend vast resources on R&D.[7] Table 1 shows that worldwide the Pharmaceuticals and Biotechnology industry is ranked highest in R&D expenditures, both in absolute terms and as a fraction of sales.

Table 1: Ranking of sectors by aggregate R&D from the world top 1,400 companies in the 2007 EU Scoreboard

ICB Sector	R&D Investment (Millions of Euros)	Sector Share	R&D Investment/ Sales Ratio
Pharmaceuticals and Biotechnology	70,524	19.3%	15.9%
Technology Hardware and Equipment	64,352	17.6%	8.6%
Automobile & Parts	60,807	16.6%	4.1%
Electronic & Electrical Equipment	27,139	7.4%	4.4%
Software & Computer Services	26,523	7.3%	9.8%
Chemicals	17,186	4.7%	3.1%
Aerospace & Defence	15,991	4.4%	4.8%
Leisure Goods	14,209	3.9%	6.5%
Industrial Engineering	9,319	2.5%	2.7%

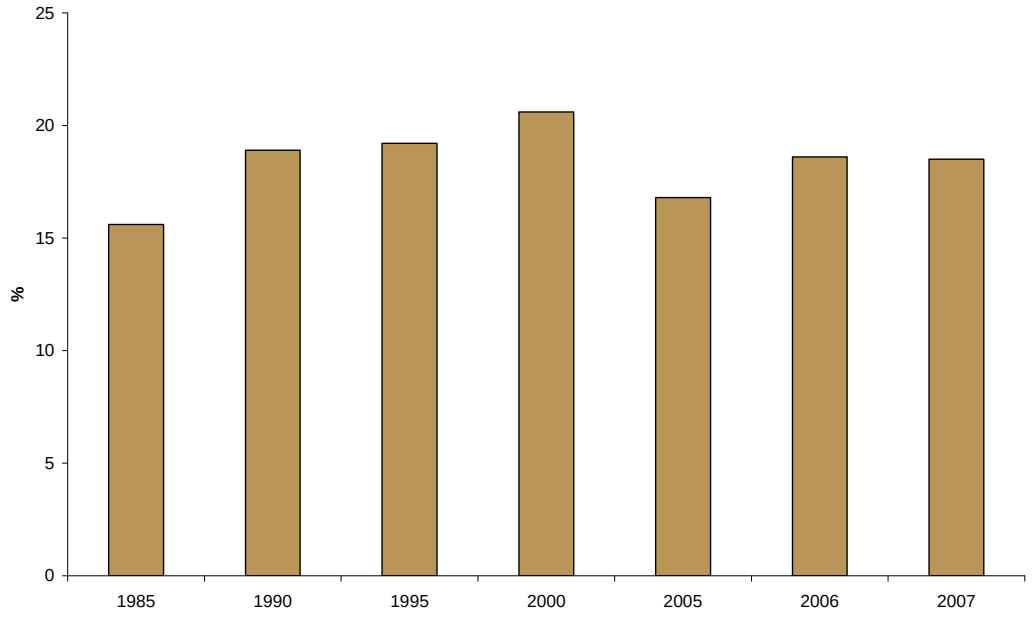
[7] In this report, we use the words innovation and R&D interchangeably.

ICB Sector	R&D Investment (Millions of Euros)	Sector Share	R&D Investment/ Sales Ratio
General Industrials	8,868	2.4%	2.1%
Fixed Line Telecommunications	7,283	2.0%	1.6%
Healthcare Equipment & Services	6,446	1.8%	6.8%
Oil & Gas Producers	4,924	1.3%	0.3%
Food Producers	3,919	1.1%	2.2%
Household Goods	3,912	1.1%	1.6%
Others	24,244	6.6%	0.9%
Total	365,646	100.0%	3.4%

Source: Directorate General Research, European Commission, as reported in efpia (2008)

Regarding the trend in pharmaceutical R&D expenditures over time, Figure 1 documents that—as a fraction of sales—they have been fairly stable over the last decades, hovering at around 18%.

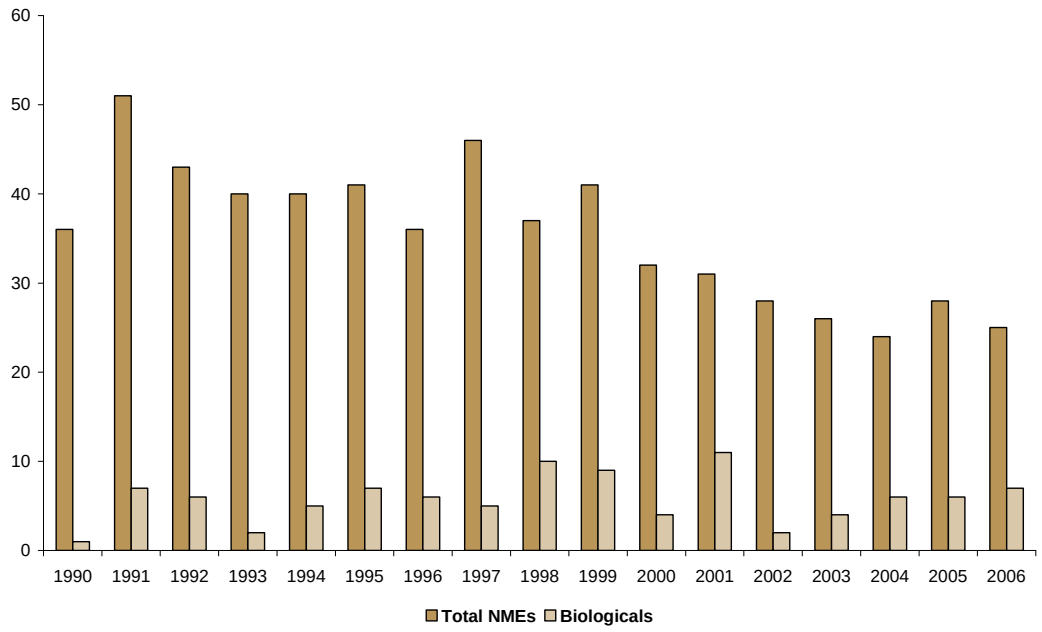
Figure 1: R&D as a percentage of sales in the pharmaceutical industry, 1985-2007



Source: efpia Member Associations as reported in efpia (2008)

The resources that a pharmaceutical firm spends on R&D finance the discovery and development of new drugs or the exploration of new applications for existing drugs. Figure 2 shows the number of NMEs that were launched worldwide in the period 1990–2006. While a drop in the number of NMEs launched can be observed starting in 2000, considerable uncertainty remains around the causes of this drop. Among the causes considered, there is the rise in pricing and reimbursement regulation around the world, which not only affects the expected value of developing and marketing a new drug, but also reduces current sales. Regarding the latter pathway, in an industry in which R&D projects are primarily financed by current cash flows,[8] this could have a negative impact on innovation. Regarding the former pathway, recent trends in pricing and reimbursement regulation—in particular in the form of Internal Reference Pricing—have the potential effect of discouraging the development of potentially less innovative drugs. However, the uncertainty about whether a drug candidate is innovative or not is resolved only gradually during the development process, as the results of the clinical trials performed by a pharmaceutical firm and its rivals become available. Once a firm realizes that its drug candidate will not be considered innovative enough to be exempted from unfavorable pricing and reimbursement conditions, it will be more likely—when faced with the decision whether to keep developing that drug or to discard it from its portfolio—to pursue the latter alternative.

Figure 2: Number of new molecular entities (NMEs) first launched worldwide, 1990-2006



Source: efpia Member Associations as reported in efpia (2008)

[8] See, for example, Scherer (2001).

1.3 Trends and conclusions

The pharmaceutical industry is shifting its innovation model from a more symptomatic large-population concept to a more causal "personalized" concept. Personalized drugs are drugs that either treat rarer diseases or treat only a part of the population that is afflicted by a disease. The subpopulation that is targeted can be identified with the aid of diagnostic tools on the basis of biomarkers or genetic markers.[9] Personalizing a drug for a smaller but homogeneous population offers potentially significant therapeutic advantages in terms of safety and efficacy.

Both scientific and regulatory factors are likely to be behind the rise in tailored drugs. Decreasing returns of the pharmaceutical discovery effort imply that it has become more and more difficult to identify new drug targets that can be safely and effectively "hit" in large and heterogeneous populations. Recent trends in pricing and reimbursement regulation—in particular when it is based on the efficacy or the cost-effectiveness of a drug—may also contribute to the phenomenon, potentially widening the gap in rewards between more or less effective drugs that would prevail under market-based pricing.

Pharmaceutical innovation is not only influenced by scientific and regulatory factors, but also by demographic trends—including the rise in the fraction of the world's population that is old. The elderly are disproportionately affected by chronic diseases such as certain forms of cancer and neurodegenerative diseases, and the pharmaceutical industry has taken on the challenge of addressing these unmet medical needs, despite pressures from governments worried about the financial sustainability of their old-age health-insurance programs, such as Medicare in the U.S. Effectively treating the elderly is also significantly benefiting from the rise in tailored medicines: indeed, it is often the case that in their old age individuals are affected by multiple diseases, requiring personalized care.

[9] See Garnier (2008) and Henderson and Reavis (2008).

2. The pharmaceutical innovation process

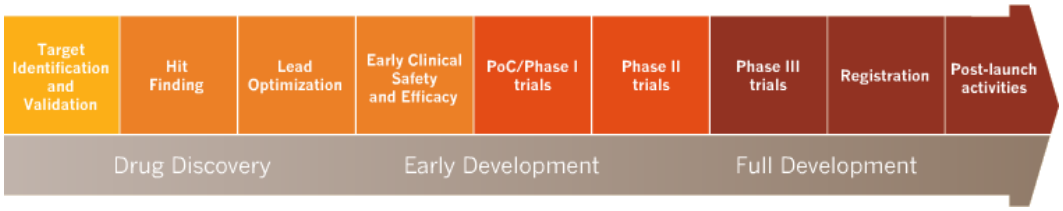
The pharmaceutical innovation process is a long, costly, and risky process that is paced by marketing authorization regulation ensuring that marketed drugs are safe and effective. In this section, we describe the phases of the pharmaceutical discovery and development process, looking in particular at how development decisions are made and what information they are based on. When looking at the pharmaceutical innovation process, it is useful to take two complementary points of view. According to the *life-cycle* (or time-series) point of view, the emphasis is placed on an individual drug candidate, which is followed over time as it goes through the different discovery and development stages. According to the *portfolio* (or cross-section) point of view, alternatively, the emphasis is placed on the full set of drug candidates that a pharmaceutical firm holds at a point in time, when different drug candidates may be at different discovery or development stages. Taken together, the life-cycle and portfolio points of view help clarify the decision-making process of pharmaceutical innovation. This section concludes with some observations on the increasing role that considerations about pricing and reimbursement regulation have played over time in this process.

2.1 Stages of the pharmaceutical innovation process

The pharmaceutical innovation process can be divided into a discovery phase and a development phase, even though it is somewhat arbitrary to define when discovery activities end and when development activities begin. While the production of large-molecule drugs differ considerably from that of small-molecule drugs, the discovery and development process of small- and large-molecule drugs follows the same phases.

Figure 3 shows that drug discovery and development starts with the identification of a drug target (that is, an individual protein or a pathway of proteins) and its validation (that is, the establishment and the definition of its relationship to the disease). Once a target is discovered and validated, so-called high-throughput screens of many chemical compounds are performed to find a "hit" compound, which may then be subsequently optimized.

Figure 3: Drug discovery and development



Source: Novartis

In the late stages of drug discovery (or early stages of drug development) initial safety and efficacy trials are run *in silico* (that is, by means of computer simulations), *in vitro*, and *in vivo* (typically in animals). Early trials are followed by Proof-of-Concept (PoC)/Phase I clinical trials, in which for the first time a drug candidate is administered to a small number (≤ 80) of patients to determine safety and dosage. In Phase-II clinical trials a number (100 to 300) of patients are enrolled to test safety, dosage, and efficacy. A larger number (1000 to 3000) of patients are enrolled in Phase-III clinical trials, during which the efficacy of the drug candidate is validated against a placebo (as it is typically the case in the U.S.) or the "gold standard" of treatment (in Europe). The evidence gathered during the entire drug discovery and development process is then submitted as part of a new drug application to a marketing authority (the European Medicines Agency, or EMEA, in Europe, and the Food and Drug Administration, or FDA, in the U.S.), which assesses whether the new drug meets high-quality, safety, and efficacy standards. Drug development activities, however, do not end with marketing approval: post-marketing surveillance activities (often including longer-term observational studies) are performed to further assess the safety and effectiveness of a drug, whose potential for new formulations and therapeutic indications in explored by life-cycle management activities.

Because of the time required to find a drug candidate, enroll the individuals participating in clinical trials, and receive marketing authorization, the drug discovery and development process is very long, lasting on average 10 years.[10] Furthermore, the drug discovery and development process is risky, because during clinical trials a drug candidate may prove unsafe or ineffective, or because the marketing authorization may consider the evidence gathered in support of a new drug application insufficient. It is estimated in the literature that only 1 in 5,000 to 10,000 drug candidates is successfully developed and authorized for marketing.[11]

On the basis of data on all clinical trials in the ADIS database, Girotra et al. (2007) computed indication/disease-specific probabilities of technical failure during clinical trials. These probabilities, reported for a selection of major indications/diseases in Table 2, indicate the probability that phase-n clinical trials (where n may be equal to I, II, or III) are successful and show a considerable amount of risk and heterogeneity in risk across indications/diseases and phases of clinical trials. Hepatitis B looks like a relatively safe indication, while Anxiety Disorders stand out as a particularly risky indication.

Table 2: Technical success probabilities for several indications/diseases

Indication/Disease	Prob. Phase-I Success	Prob. Phase-II Success	Prob. Phase-III Success
Alzheimer's disease	30.8%	65.9%	36.4%
Anxiety disorders	12.3%	38.9%	16.7%
Asthma	65.6%	37.6%	77.4%
Bacterial infections	62.4%	69.0%	89.1%
Cancer	61.9%	27.1%	82.4%
Cardiovascular disorders	58.2%	60.0%	75.0%
Chemoprotection	56.0%	60.0%	62.5%
Depression	35.2%	53.3%	47.5%
Diabetes mellitus	50.7%	57.2%	60.0%
Epilepsy	43.0%	58.9%	64.7%
Erectile dysfunction	80.0%	75.0%	80.0%

[10] See for example efpia (2008).

[11] See for example efpia (2008).

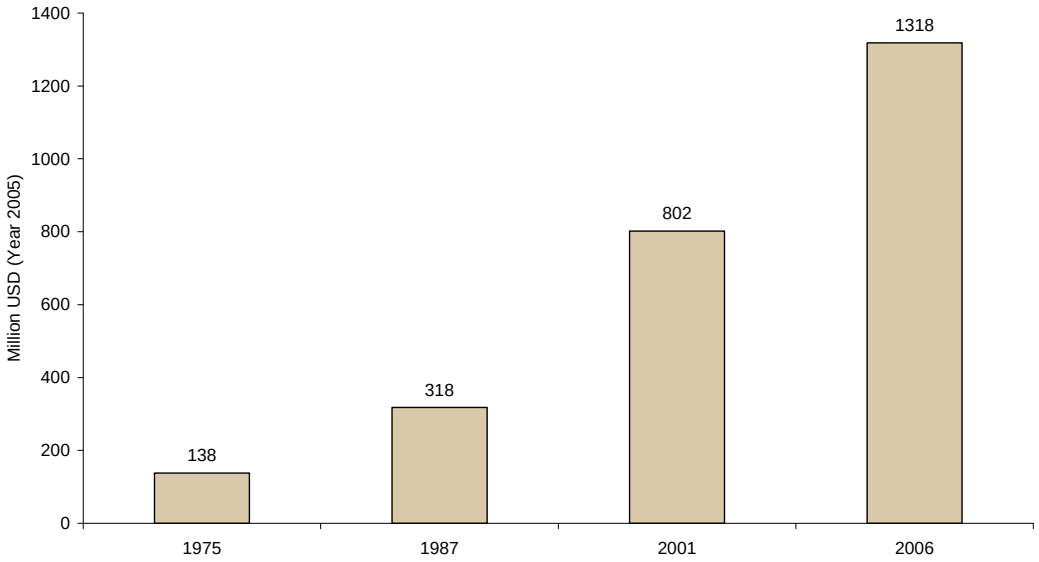
Indication/Disease	Prob. Phase-I Success	Prob. Phase-II Success	Prob. Phase-III Success
HIV-1 infections	53.5%	49.9%	62.5%
Hepatitis B	92.9%	79.1%	96.4%
Hypertension	59.9%	44.7%	81.0%
Malaria	81.7%	66.7%	100.0%
Migraine	59.5%	61.9%	71.4%
Parkinson's disease	61.1%	65.3%	70.0%
Psychotic disorders	39.6%	66.6%	50.0%
Thrombosis	45.5%	47.1%	64.3%
Transplant rejection	56.7%	56.9%	67.0%

Source: Electronic companion to Girotra et al. (2007)

A factor contributing to the observed increase over time in the failure of later-phase clinical trials has to do with the fact that pharmaceutical firms are increasingly focusing on surrogate endpoints during early-phase clinical trials, addressing clinical endpoints only later on; but as Jeffrey (2008) reports for the results of the important Phase-III FAST trial (testing a drug for the treatment of intracerebral hemorrhage), success on surrogate endpoints (in this case, reducing hematoma growth) does not always imply success on clinical endpoints (in this case, reducing death or severe disability).

Taking into account that for one drug candidate that succeeds many drug candidates fail, DiMasi et al. (2003) estimate that the costs of developing one drug are above $800 million (in U.S. dollars in year 2000). Figure 4, combining DiMasi et al. (2003) with DiMasi and Grabowski (2007), reports how such costs have increased in the last decades.

Figure 4: Estimated full cost of bringing a new chemical or biological entity to market



Source: efpia (2008)

Adams and Brantner (2006) report (see Table 3) similar results and show how the duration and costs of clinical trials (taking into account the technical failure of many drug candidates) vary across therapeutic areas: Cancer, Neurological, and Respiratory are among the therapeutic areas with the longest development duration and costs.

Table 3: Duration of clinical trials and full development cost per approved NME

Therapeutic Area	Duration Phase 1	Duration Phase 2	Duration Phase 3	Costs
Blood	18	32	33	906
Cardiovascular	14	35	30	887
Dermatological	13	29	24	677
Genitourinary	21	28	25	635
HIV/AIDS	19	23	19	540

Therapeutic Area	Duration Phase 1	Duration Phase 2	Duration Phase 3	Costs
Cancer	21	30	29	1,042
Musculoskeletal	19	39	30	946
Neurological	20	39	32	1,016
Antiparasitic	18	33	13	454
Respiratory	18	30	36	1,134
Sensory	11	44	30	648

Note: Duration of clinical trials is in month; costs are in Millions of U.S. dollars in year 2000).
Source: Adams and Brantner (2006).

2.2 Decision making

While the number of R&D projects that pharmaceutical firms could in principle undertake is unlimited, in practice pharmaceutical firms are constrained by their laboratory capacity, the number and skills of their researchers, and budget. With respect to budget, it is frequently noted in the literature that, arguably because of the presence of asymmetric information between pharmaceutical firms and outside investors, R&D projects are primarily financed by current cash flows.[12] As a consequence, as a survey of 45 leading pharmaceutical companies conducted by the Center of Medicines Research suggests,[13] the size of the R&D budget is frequently set based on the forecasted sales in the coming year, rather than being driven by a comparison between the cost of capital and the expected Return On Investment (ROI) of the individual R&D projects. This is consistent with the relative stability over time of the ratio between R&D expenditures and sales already documented in Figure 1.

Once an R&D budget is allocated, a variety of decisions must be made regarding which projects to accelerate, which projects to delay, for what therapeutic indications to perform clinical trials, how to best design a clinical trial, and what (clinical or surrogate) endpoints to observe.

While in the past these decisions were taken primarily on scientific and technological grounds (for example advancing drug candidates on the basis of their likelihood of technical success), recent survey evidence suggests that economic and/or commercial considerations are becoming an increasingly important factor in the development decision-making process and they are being made at earlier stages. For example, Skrepnek & Sarnowski (2006) report that pharmaco-economic models are being utilized

12 See, for example, Scherer (2001).

13 See Halliday, Drasdo, Lumley, & Walker (1997).

at every stage of the R&D process and applied to the management of R&D pipelines. In particular, it appears that commercial considerations (i.e., future prices/economic value) play a significant role already in determining whether to advance a product candidate into preclinical development.[14] Having said that, it is of little or no value for commercial considerations to play a role in earlier research stages. This is due to the fact that the commercial success of drug candidates that are still many years away from potential market launch, and whose therapeutic indications and effectiveness are still to be established, is subject to a huge degree of unpredictability. Furthermore, several R&D stories show that many times successful drugs are the result of serendipitous discoveries that would have not occurred had the discovery process been guided by commercial considerations.

Moving away from the life-cycle point of view and toward the portfolio point of view, what happens is that every year a board of individuals coming from a variety of functions meets and decides about which projects to accelerate and which projects to delay. Projects are at different development stages and come from different therapeutic areas. Project teams provide inputs in terms of a project's technical risk and its monetary and time costs.

The information about the commercial potential of a project is combined in a life cycle of expected revenues[15] that requires inputs in terms of:

- launch year, by region, based on first major launch in that region;
- forecast peak sales;
- profit margin;
- ramp-up in sales from market launch to peak;
- year of peak sales, coinciding with the start of the plateau, and taking into account competitors and patent expiries, among other factors;
- plateau duration;
- patent expiry, which identifies the start of sales decline;
- ramp-down in sales.

The life cycle of net revenues for biological drugs is considerably different from the life cycle for pharmaceutical drugs. Indeed, in part because of the more complex structure of a biological molecule, the production costs for biologics are also higher—limiting the extent to which the price of biologics may fall at the time of generic (biosimilar) entry. Furthermore, the more complex structure of biological molecules has the consequence that while marketing authorization for generic pharmaceutical drugs is dramatically simplified,[16] that for biosimilar drugs is not—entailing large time and monetary marketing-authorization costs. The combination of these two facts implies that patent

[14] See Sharpe & Keelin (1998) and Stonebraker (2002).

[15] See Lehman Brothers (2008).

[16] Generic pharmaceutical companies seeking marketing authorization must only show the bioequivalence of their product with the corresponding innovator product whose patent has expired. This simplification was introduced in the U.S. with the Hatch-Waxman Act of 1984 and the FDA's Abbreviated New Drug Application (ANDA).

expiration and the loss of trial-data exclusivity do not have as drastic an impact on innovative biologics as they have for innovative pharmaceuticals.

Such life cycle profile of expected revenues, alongside with estimates about a drug's development costs and risks, are then used to compute a drug's Expected Net Present Value (ENPV), at times taking into consideration that the time-phased nature of the drug development process allows a project to be delayed or cancelled at any subsequent development stage if current development costs exceed future expected revenues. An alternative measure of the value of a project is the Expected Profitability Index (EPI), which accounts for the "size" of a project by dividing its ENPV by its current or its total expected development costs. Finally, the value of a project can be summarized by its Internal Rate of Return (IRR), which is defined as the discount rate that makes the ENPV of a project equal to zero.

In the following paragraphs we explicitly define these alternative project-evaluation methods and show how they are related to each other.[17] Ignoring the fact that at later development stages a project can be discontinued,[18] we suppose that there are T equally-spaced time periods: in periods 1 to 3 (corresponding to subsequent development phases) a drug is developed; in periods 4 to T the drug is marketed; Development in period t (t=1,2,3) costs ct and is successful with probability pt; (net) revenues in period t (t=1,…,T) are equal to Rt.

The ENPV of a project can then be expressed as

$$ENPV = -c_1 - p_1 \frac{c_2}{(1+r)} - p_1 p_2 \frac{c_3}{(1+r)^2} + p_1 p_2 p_3 \left[\frac{R_1}{(1+r)^3} + \ldots + \frac{R_T}{(1+r)^{T-1+3}} \right],$$

where cash flows ct and Rt are discounted back to period 1 using the discount rate r and are weighted by the probability of being realized. In particular, attention is drawn to the fact that the probability that a drug candidate is successfully launched is equal to $p_1 p_2 p_3$, that is the probability that all clinical trials are successful.

The EPI scales the ENPV of a project by its current or its total expected costs and can thus be formalized as

$$EPI = \frac{ENPV}{C},$$

where the quantity C in the denominator can be equal to either the current development costs (c_1) or the total expected development costs

$$(c_1 + p_1 \frac{c_2}{(1+r)} + p_1 p_2 \frac{c_3}{(1+r)^2}).$$

[17] For additional details, see Ross et al. (2002).

[18] This is a salient feature that we thoroughly address in our decision-theoretic model in Section 6 of the report.

Finally, the IRR is defined implicitly as the particular discount rate (call it r*) that makes the ENPV equal to zero:

$$r^* \text{ such that } ENPV(r^*) = 0.$$

Once ENPV (or, alternatively, the EPI or the IRR) are computed for all drugs in the portfolio, drugs are ranked and, starting from the highest-ranked drug, projects are selected until total current development costs exceed the budget allocation.

It can already be seen that there are at least two mechanisms whereby pricing and reimbursement regulation may have an effect on drug development:

- to the extent to which, as we documented above, the R&D budget is determined on the basis of current sales, and to the extent to which pricing and reimbursement regulation affects current sales, the resources available for drug development are also affected;
- because pricing and reimbursement regulation is likely to affect the profitability of one sort of drugs more than another, holding the budget constant, the set of drug candidates that are advanced is also affected.

2.3
Trends and conclusions

In this section, we described the pharmaceutical discovery and development process as a time-phased process during which go/no go decisions, as well as a variety of “softer” decisions, are taken. While in the past these decisions were based primarily on scientific and technological grounds, in the recent years there has been an increase in the importance assigned to commercial factors, including considerations about potential pricing and reimbursement regulation outcomes. This is reflected in the early stages of the development process in a careful, but not necessarily quantitative, meditation on the unmet medical need that a drug candidate would fill and its degree of differentiation relative to drugs already on the market and drugs that are currently in development by a pharmaceutical firm or its competitors. Especially in the later stages of development, these reflections find their way in Expected Net Present Value calculations for each of the drugs in the portfolio. These calculations—which explicitly take into account development costs, risks, and the life cycle of expected future sales—allow decision-makers to rank their projects and make better resource-allocation decisions.

3. Typical pricing and reimbursement regulatory schemes

Because of the high value that individuals and societies attach to health and because of the importance of drug innovation for effectively and safely treating diseases, the pharmaceutical industry is among the most heavily regulated ones. In addition to intellectual property (IP) protection and marketing authorization rules, the pharmaceutical industry is significantly affected by pricing and reimbursement regulatory schemes that governments have established to ensure that the goal of fostering pharmaceutical innovation does not conflict with the goal of having cost-effective or affordable drugs. In spite of the wide variety of existing national pricing and reimbursement schemes, they can be broadly categorized into three classes: (a) External Price Benchmarking, according to which the price of a drug in a country is pinned to the price of the same drug in a basket of other countries; (b) Internal Reference Pricing, according to which the price of a drug in a country is pinned to the price of similar drugs in the same country; and (c) schemes based on a pharmaco-economic assessment, according to which the price of a drug depends on its cost-effectiveness. In this section, these three typical pricing and reimbursement regulatory schemes are reviewed, and their implications for innovation are illustrated.

3.1
Across the board price cutting

Across-the-board price cutting is a very crude but effective measure of cost containment that is based on historic prices. What this pricing and reimbursement scheme does not however take into account is that in an environment, as the current one, in which pharmaceutical firms are rational and forward-looking in their decision making—this scheme curbs the incentives to innovate. Furthermore, as long as such scheme affects current sales and, as it is traditionally the case,[19] research and development is financed out of current profits, fewer resources will be available for innovation.

3.2
External price benchmarking

External price benchmarking is the most widely used price regulation scheme for pharmaceutical products in the OECD countries, according to a recent OECD report (2008). The extent to which different product groups are referenced, and the countries that are included in the reference basket, vary strongly amongst the followers of external price referencing schemes, but in essence the same principal notion underlies the process everywhere.

Upon the entrance of a new pharmaceutical product into the domestic market, the regulatory authority will determine the appropriateness of the price proposed by the pharmaceutical company based on two steps.

Firstly, a product's key characteristics and spectrum of applications will be identified and its price will be compared with the price of identical or similar products in the country(s) of reference. Secondly, if prices in the referenced countries are lower by a certain amount, then the price proposed by the pharmaceutical company will not be accepted and will have to be lowered.

If an identical product can be found on the reference markets in step one, then this is obviously the product whose price will be used in the second step. If, however, no such direct comparator product exists, then the authorities face the difficult task of assessing the degree of differentiation and the level of substitutability between products in the same area of therapeutic application.

While the process of external price benchmarking varies greatly amongst the different countries employing such a scheme, some generalizations can be made. In particular, countries tend to select reference countries on the basis of either economic or geographic proximity: countries within the European Union, for instance, tend to reference to each other. Nevertheless, in some cases also

[19] See for instance Scherer (2001).

political factors play a role in the decision about the countries to reference against: the Czech Republic, for example, references to Greece, Hungary, Poland and Portugal because of economic and/or geographic similarities, but does not reference to the Slovak Republic, in spite of great economic and geographic proximity.

In countries with a pluralistic healthcare payment systems—with the coexistence of public and private health insurance programs, or in federal system—external price referencing somewhat paradoxically even takes place within a country's boundaries. The Canadian province of Quebec, for example, references to other Canadian provinces, while the public Medicaid social assistance program in the United States requires by law that manufacturers of pharmaceuticals set their prices at the level of the lowest price offered to private customers.

3.3 Internal reference pricing

The process of Internal Reference Pricing is a common form of price regulation that is applicable in a situation where a similar (chemically, pharmaceutically, or therapeutically) pharmaceutical product already exists on the domestic market. This scheme is especially applicable to pharmaceutical products that, even though they might well be the best in their class because of their effectiveness—are not the first in class to exploit a particular mechanism of action (so-called "me-too" products) and generics. Furthermore, in some countries even highly innovative pharmaceuticals face the risk of falling into existing Internal Reference Pricing groups, if their area of therapeutic application is already populated by various somehow similar drugs.

According to ÖBIG (2008a), in the European Union, 17 member states employ (at least to some extent) an Internal Reference Pricing system, predominantly in countries which have a large number of generic pharmaceuticals on the market. [20] The OECD report (2008) states that Internal Reference Pricing is used in at least three non-European OECD countries, namely Canada, Japan and Switzerland. [21]

Similarly to the process of external price benchmarking, Internal Reference Pricing varies in extent and methodology across countries, leaving its fundamental aspects largely unaffected. Again, authorities identify the entrant product's key characteristics and determine identical (in the case of generics) or similar (in the case of me-too's or other entrants) pharmaceuticals, on the home market. The suggested price of the entrant drug is then compared to the reference drug's prices and adjusted accordingly.

While in the case of external price benchmarking the primary challenge is to determine the extent to which the price of a product in one country can and should reflect its price in another country, the case of Internal Reference Pricing entails the difficult

[20] Out of the 27 EU member states, the 17 states that adopt Internal Reference Pricing according to ÖBIG (2008a) are: Austria, Belgium, Bulgaria, Czech Republic, Estonia, Greece, Finland, France, Hungary, Italy, Lithuania, Latvia, Poland, Portugal, Slovenia, Slovakia, and the United Kingdom. This list does not include Denmark, Germany, and the Netherlands, where Internal Reference Pricing is used to set not prices but reimbursement levels.

[21] The OECD encompasses 30 member countries around the world. These are: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Japan, Korea, Luxembourg, Mexico, the Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Spain, Sweden, Switzerland, Turkey, United Kingdom, and the United States.

decision of the economic evaluation of one product relative to another. This evaluation, in particular if drastic improvements differentiate the entrant from the incumbent products, can be very hard as it ultimately relies on the evaluation of (improvements in the quality and quantity of) life.

In general it can be said that Internal Reference Pricing schemes categorize new pharmaceutical products into between three and six groups, depending on their degree of innovativeness and increased effectiveness over existing treatments. Attached to these categories are predetermined price modifiers which governs the relationship between the price of the entrant product and that of its comparators. In addition, most countries employ a separate internal benchmarking system for generics which are forced to be priced at a fraction of the original, off-patent, product.

A final important common factor amongst countries employing an Internal Reference Pricing scheme is that newly introduced products which closely follow the introduction of the therapeutic class creating drug will automatically be categorized in a similar manner. In this way losers of an innovation race, left with a me-too product, are not punished as severely by the price regulation scheme.

The case of Germany

In Germany, healthcare coverage is provided to a very large fraction of the population[22] by the Statutory Health Insurance. Under the statutory health insurance, Sickness Funds insure individuals against healthcare expenditures, including the purchase of drugs, and are paid by workers an insurance premium that is proportional to their earnings.

The ex-manufacturer pricing of drugs in Germany is free, while the ex-wholesaler and ex-pharmacy price of prescription drugs is regulated by the Pharmaceutical Price Ordinance by means of a flat-fee and a mark-up proportional to respectively the ex-manufacturer and the ex-wholesaler price. Furthermore, with the exception of drugs for the treatment of insignificant diseases, ineffective or potentially unsafe drugs, life-style drugs, and OTC drugs, all drugs are reimbursed by the statutory health insurance.

However, since the Fifth Book of the Social Code came into effect in 1989, the amount that the statutory health insurance reimburses a patient for a drug has been inspired by Internal Reference Pricing, and when physicians prescribe drugs whose price is above the amount reimbursed, they must inform their patients that they will have to pay for the difference out of their own pockets.

[22] According to ÖBIG (2008b), this fraction was 85.4% in 2005.

While patented drugs were exempt from this form of Internal Reference Pricing for several years, this exemption was lifted in 2004, when the Statutory Health Insurance Modernization Act came into effect. Nevertheless, if a drug is considered innovative,[23] it is still exempt from Internal Reference Pricing, and the amount reimbursed by the statutory health insurance is equal to its price.

If a drug is not considered innovative, the Federal Joint Committee, on the basis of the assessment by the Institute for Quality and Efficiency in Health Care (IQWiG), assigns it to up to three groups. In particular, Level-1 groups contain drugs that share the same active ingredient; Level-2 groups contain drugs with pharmacologically or therapeutically similar active ingredients, in particular if chemically related; and Level-3 groups contain drugs with therapeutically similar effects, in particular combinations.[24]

At least three drugs are required to form a group, and it is the Associations of Sickness Funds that set the reference price for a group, in the range between the bottom quintile and tercile of the price distribution in the group. Reference prices are updated annually because of drug entry, exit, and price changes. The amount that the Statutory Health Insurance reimburses a patient for a drug is the reference price for the lowest-level group in which the drug is contained.

On this point, Sheridan and Attridge (2006) carefully document the incremental nature of the innovation that occurred during the last fifty years in the drugs treating cardiovascular disease and argue that had a German-like Internal Reference Pricing scheme been in place, the treatment of cardiovascular diseases would not have developed as intensely. They also illustrate how in Germany effective patent duration was reduced, if not altogether eliminated, in the case of statins, a cholesterol-lowering class of drugs. The first drug in the statins class (lovastatin) was approved and marketed in 1987, and was followed by a sequence of new drugs that, while having the same mechanism of action, had in some cases better effectiveness and side-effects properties. (These drugs include simvastatin, pravastatin and atorvastatin, first marketed in respectively 1988, 1990 and 1997.) When the Statutory Health Insurance Modernization Act came into effect in 2004, all statins were lumped into the same Level-2 group, and because generics had by then entered the statins market they were assigned a low reference price, effectively shortening the patent life of younger-generation statins. It is not clear that, had the pharmaceutical firms foreseen such an unfavorable reimbursement environment for next-generation statins, they would have brought them to market. In fact rosuvastatin, which was first marketed in 2003, only in 2008 received marketing authorization in Germany.

[23] It is the Federal Joint Committee that decides whether a drug is innovative or not on the basis of an assessment by the Institute for Quality and Efficiency in Health Care (IQWiG). A drug is defined by §35 SGB V as innovative if (a) it is protected by patents; and (b) it has a new mechanism of action or therapeutic advantages.

[24] This classification resembles the 5-level Anatomical Therapeutical Chemical (ATC) classification which is endorsed by the WHO and which comprises (from top, or 1st level, to bottom, or 5th level) anatomical groups, and therapeutic, pharmacological, chemical-family, and chemical-individual subgroups.

3.4
Pharmaco-economic assessment

Price regulation systematically relying on pharmaco-economic assessment is a relatively novel form of determining the "correct" price of a newly developed drug. Since its introduction in Australia in 1993, it has to some extent been adopted in numerous countries to aid their pricing and reimbursement decisions.

The pharmaco-economic assessment of a new product generally takes the form of a cost-effectiveness analysis in which the (incremental) cost of the medicine is compared to the (incremental) effect it will have in terms of health outcomes. Provided that there are on the market comparable products for which pharmaco-economic assessments have been made, the entrant products's assessment will determine whether it is worth the suggested price. If no suitable comparators are available, then an implicit or explicit cost-effectiveness threshold is required.

While cost-effectiveness studies are by far the most common in pharmaco-economic assessment, other related studies like cost-benefit or cost-utility analyses are also used under certain circumstances. In essence, however, it is still the case that the value of a product is established and benchmarked. The main difference between a cost-benefit analyisis and a cost-effectiveness analysis is that while the former focuses only on the quantity of life that a drug would save, the latter is more comprehensive and takes into account the quality of life. In particular, a measure of quantity and quality of life that is frequently adopted in pharmaco-economic assessment is the Quality-Adjusted Life Years (QALYs): according to the QALY, while a year of life in full health is weighed with a factor of 1, a year of life without for example the capability of seeing or walking is weight with a factor that is lower than 1. Another important parameter of a pharmaco-economic assessment consists then in assigning a monetary value to a QALY. It is believed that in the U.K. a QALY is valued at around £30,000 and in the U.S. at $50,000.[25]

The determination of the value of a pharmaceutical product is, similarly to the internal benchmarking process, a very challenging, lengthy, and costly endeavor, involving experts from a range of fields and also ethical considerations. Due to the increased popularity of this form of price determination, many countries have set up government institutes which are focused exclusively on assessing new products with pharmaco-economic methods.[26] A thorough pharmaco-economic assessment is therefore especially challenging for smaller countries which lack the necessary resources and have to often resort to adopting the pharmaco-economic assessments of reference countries or the pharmaceutical firms' own assessments.

[25] See respectively Devlin and Parkin (2004) and Sullivan et al. (2007).

[26] These include the National Institute for Health and Clinical Excellence (NICE) in the U.K. and the aforementioned Institute for Quality and Efficiency in Health Care (IQWiG) in Germany.

Some key differences among the pharmaco-economic assessment schemes of the different countries that adopt it can be established. Some schemes include also affordability considerations into the assessment, while others take budget constraints into account only at a later stage. Further, while nearly all assessment schemes focus predominantly on the cost borne by the payer, i.e. the health insurance scheme of the final consumer, Sweden takes a broader societal perspective. This goes in the direction of reconciling the more static view of efficiency taken by the regulatory authorities, more concerned with lowering prices than with stimulating innovation, with the more dynamic view of efficiency that takes into consideration the welfare not only of the current but also of future generations.

3.5 Other schemes

There are various other schemes which do not fall into the previous three categories, but their occurrence is fairly limited. To give a full picture of the pricing and reimbursement regulatory environment, these schemes are briefly addressed in this subsection.

As already noted above, a form of non-regulation exists in Germany for innovative, on-patent medicines for which there are no comparable products on the market. For such a product the statutory health insurance acts as a price-taker and accepts the price proposed by the manufacturer, unconditional on any cost-effectiveness or budget considerations.

The United Kingdom has a special form of price regulation, the Pharmaceutical Price Regulation Scheme (PPRS), dating back over 50 years. This regulatory scheme limits the overall profits of a pharmaceutical company but allows it to independently set the prices of individual products, as long as the firms do not violate the profit ceiling. If a firm exceeds the assigned profit margin, it must decrease its prices; conversely, should the firm suffer from too low profits, then it is allowed to raise them.

Cost-plus price regulation is prevalent in the Slovak Republic, Spain, and Poland. Under this price regulation scheme ex-factory prices are limited by the production cost plus a certain margin. The cost-plus framework is, however, predominantly used for generics, where the assessment of costs is not complicated by R&D expenditures.

Other pricing schemes exist in the context of the procurement of medical products for public hospitals. These include price-volume agreements followed by rebates or procurement and tendering approaches.

Recent years have also witnessed the emergence of risk-sharing (or conditional pricing) mechanisms whereby national healthcare systems will be reimbursed for their drug expenditures if agreed-upon health outcomes goals are not met. These mechanisms, currently implemented in Belgium, the Netherlands, and the U.K., concern in particular drugs with a large potential for therapeutic benefits accompanied by substantial uncertainty regarding their cost-effectiveness. Risk-sharing agreements strike the balance between granting patients early access to new and potentially much better drugs, appropriately rewarding genuinely innovative drugs, and making sure that the money the national healthcare systems pay for drugs is spent on proven cost-effective therapies.

While pricing and reimbursement regulation it is primarily concerned with the regulation of prices and reimbursement levels of drugs that have been authorized for marketing, in several countries an additional layer of regulation is interposed between marketing authorization and pricing and reimbursement in the form of reimbursement lists (or formularies). Such lists indicate the drugs that the payer reimburses (positive lists) or the drugs that the payer does not reimburse (negative lists). As an example of negative lists, in Germany negative lists include drugs for the treatment of insignificant diseases, ineffective or potentially unsafe drugs, life-style drugs, and OTC drugs. As an example of positive lists, the Italian National Health Service keeps positive lists of the drugs it fully reimburses.

3.6
The regulation of orphan drugs

Before concluding this section, we briefly address rare diseases and the drugs used to prevent and treat them, known as orphan drugs. Rare diseases are diseases that affect a very small fraction of the individuals of a community,[27] and frequently have a genetic origin (and are thus chronic) and severe health consequences.

Because of their low prevalence, rare diseases require special attention by public health authorities, making sure that pharmaceutical firms are provided the appropriate incentives to discover, develop, and market drugs preventing and treating them. The Orphan Drug Act passed in the U.S. in 1983 encourages pharmaceutical R&D for rare diseases by means of time-limited market exclusivity and tax incentives on clinical trials. Analogous legislation was passed in subsequent years also in the EU.[28] To further reduce the costs for pharmaceutical firms to develop and market orphan drugs, the European Medicines Agency (or EMEA) and the Food and Drug Administration (or FDA) have agreed on a common application procedure, while maintaining separate approval procedures. In Europe, orphan drugs—along with biologicals and drugs treating cancer, diabetes, and auto-immune and viral diseases—are required to follow the Centralized authorization Procedure.[29]

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[27] Orphan diseases are defined as diseases with a prevalence of less than 5 per 10,000 individuals in a community. This prevalence rate translates in approximately 246,000 affected individuals in the 27-member European Union. See EC (2008).

[28] See in particular EU Regulation No. 141/2000. The EU includes among rare diseases also tropical diseases primarily encountered outside of Europe.

[29] There are three alternative procedures to receive marketing authorization in more than one country in the European Economic Area (EEA): these are the Centralized Procedure (CP), the Decentralized

3.7
Major trends and conclusions

As has become evident from this review, there exist a large number of pricing and reimbursement regulation schemes that are applied to pharmaceutical products. In addition, these frameworks are present in different countries to different degrees. This fact stands in sharp contrast with the global nature of the pharmaceutical discovery and development process.

Pricing and reimbursement schemes must strike a balance between promoting innovation in the pharmaceutical industry and keeping the price of drugs low, and different societies seem to favor different compromises, running the gamut from schemes focusing only on affordability, to schemes considering cost-effectiveness, to schemes that do not constrain the rewards associated with the development of a highly innovative drug.

In terms of ongoing and future trends, it is observed that the health authorities are in general moving away from crude cost-cutting policies towards cost-effectiveness considerations, thereby moving in the direction of more rational, evidence-based, and predictable regulatory decision making. The potential societal benefits of this trend must however be traded against the movement away from national policies and towards local responsibilities, entailing that pharmaceutical firms will have to devote even more effort and resources to coping with an even more complex regulatory environment.

Procedure (DP), and the Mutual Recognition Procedure (MRP). See OECD (2008). A pharmaceutical firm's decision about which procedure to follow is also a function of IP considerations.

4. Strategic responses to pricing and reimbursement regulation

In the previous sections of this report we described the pharmaceutical R&D process and the various forms of price regulation that are or might be implemented by government health insurers in the European Union. In this section we analyze how pharmaceutical firms are likely to adjust their R&D activities in response to one or a combination of these various forms of price regulation, and how consequently price regulation is likely to affect pharmaceutical innovation. This analysis enables us to predict how the level and nature of pharmaceutical innovation is likely to change in response to price regulation.

4.1 Preliminaries

Before we describe our analysis, it is helpful to describe some of the assumptions that underpin it and the framework that we are using to make comparisons.

Demand for pharmaceutical products

The market for pharmaceutical products differs from other (more typical) products in that the person that makes the ultimate decision to purchase the product (typically a medical practitioner) is not usually the same person or organization that pays for those

products (typically a public or private health insurer). Unlike traditional consumer products, where price plays a significant role in the purchaser's decision whether to consume the product, medical practitioners decide whether to purchase a pharmaceutical product primarily on the basis of how effective it is in treating the specific disease or condition against which the product is targeted—that is, largely irrespective of price.

The quantity of a pharmaceutical product that practitioners prescribe depends on the therapeutic indication that the product targets (which determines the size of the potential patient population), the seriousness of the condition (which determines the benefits of treatment compared to non-treatment), and the qualities of the particular product relative to other treatments. We aggregate the various factors that affect the amount purchased and refer to them as the "demand" for a product. For instance, a product that treats a seriously debilitating condition that affects a large patient population and which provides a substantial improvement over the existing treatment will have a high demand. By contrast, a candidate that treats a minor condition that affects only a smaller number of patients and provides only a marginal improvement over existing treatments will have low demand.

That said, price is usually very important in the health insurer's decision whether to make a product available for prescription (i.e., to add the drug to its formulary). As for the medical practitioner, in deciding whether to make a drug available for prescription the health insurer takes into account the seriousness of the disease or condition and the relative benefits of the treatment that a particular product provides relative to other treatments. However, this decision also depends on its absolute and relative preferences for particular products.

A private health insurer's willingness to pay, especially in a competitive market, largely reflects the preferences of its insured patients, which in turn reflects the incremental therapeutic benefits of a treatment and their ability to pay for those benefits. A government health insurer's willingness to pay depends on incremental benefits of treatment, the country's ability to pay (which is determined by its income or wealth), and the standard of health care that the government wishes to provide to its population.[30]

However, a country's willingness to pay for different types of products may also vary because of cultural factors, even across countries that have similar levels of income and approaches to health care. For instance, countries such as France seem to put high value on—and therefore have a high willingness to pay for—products that treat serious, life-threatening conditions, even if those conditions are rare and the treatments have low probability of success (e.g., experimental treatments for rare forms of cancer). By contrast, countries such as the U.K. appear to place greater value on products that have greater chances of being effective in improving the life of a large number of people, even though those improvements may be only minor.[31]

[30] The difference in willingness to pay across countries has been extensively discussed in the literature on parallel trade.

[31] This paragraph is based on our conversation with Mr Miguel Bernabeu, Head of Market Access Region Europe, that took place in Basel on 10 February 2009.

A pharmaceutical firm's ROI depends on both the number of units sold and the profit margin that the firm earns on each unit. The optimum product is one that sells to a large population and earns a high margin. However, the remaining products in the portfolio will range from those that sell a large number of units at a relatively low margin (such as later-in-class drugs in a primary health care indication) and those that are targeted to a smaller population but earn a higher margin (such as highly innovative drugs for specialist indications). We characterize the products at these extremes as "low-margin/high-volume" and "high-margin/low-volume" products respectively.

The counterfactual

Any analysis of a policy change must compare the situation after the change to a situation that would exist but for the policy change. The 'but for' scenario is commonly known as the "counterfactual".

In the next section we consider the effect of price regulation relative to a situation where pharmaceutical firms set prices free of any form of price regulation, which we refer to as "market-based pricing". In the following section we analyze the effect of imposing new forms of price regulation on top of the regulated environment that already exists in European countries.

Under the situation which we call market-based pricing, the pharmaceutical firm is free to set prices as it chooses and the health insurer (be it public or private) then decides whether or not to add the drug to its formulary and for what indications. In economic terms, the health insurer is a "price taker". At a first glance, market-based pricing appears to give a pharmaceutical firm significant latitude in setting its prices. However, purchasers always have the option to continue purchasing the treatment that existed prior to the innovative product being launched. There may also be competitive products providing similar benefits that buyers can purchase instead. Moreover, no purchaser has an unlimited budget and as products get more expensive it may not be willing or able to pay for the full increase in value that a new product generates. Hence, the maximum increment that a firm can charge for an innovative new product is the marginal difference in purchaser's willingness to pay for the new product relative to the existing treatment or competitive alternatives. Moreover, it is further constrained by its bargaining position relative to the health insurer that pays for the product.

4.2
The effect of price regulation relative to market-based pricing

We now begin to analyze the effect of price regulation on pharmaceutical innovation, relative to a situation of market-based pricing.

Bilateral negotiation

The simplest form of price regulation that a government health insurer might implement is to refuse to accept the first price offered and instead to negotiate for a lower price. In some countries and in some circumstances, the government health insurer voluntarily chooses not to exercise any bargaining power and instead to take the price as given. For instance, the government health insurer in Germany allows market-based pricing if it considers a drug to be "highly innovative".[32] In another case (in the U.S. under the Part D of the Medicare Prescription Drug, Improvement, and Modernization Act, enacted in 2003), the government explicitly prohibited its health insurer (i.e., Medicare) from bargaining with pharmaceutical companies to secure lower drug prices. Nevertheless, the government has a range of devices by which it can extract a lower price than what would be optimal for the pharmaceutical firm.

It can threaten at the extreme not to reimburse the drug at all unless it is offered at a lower price. However, this may be a hollow threat if the resulting outcry from the population can force it to back down. Nevertheless, the government health insurer may be able to deploy other means to negotiate the price down. For instance, it may be able to link the price to its reimbursement of other drugs on which it can more realistically refuse to reimburse. Alternatively it may be able to use its influence to withhold any subsidies for R&D. Finally it can threaten to impose (or at least to lobby for) a more explicit form of price regulation (such as those discussed below).

That said, the pharmaceutical firm can also respond with threats of its own in the pricing negotiation. It can threaten to withdraw the product from the market altogether—a threat that is likely to be more realistic in smaller countries than in larger ones. It can also link funding of pharmaceutical products to the location of R&D labs or clinical-trial sites in those countries.

It is impossible to predict the outcome of bilateral negotiation with any certainty without understanding the specific details of the situation of the country. However, in general we can say that the prices that arise under a system of bilateral negotiation will be lower than under market-based pricing. Moreover, negotiating prices involves transaction costs, which will reduce the funds that can be spent on the products themselves. This lowers the pharmaceutical firm's ROI from drug development and means that some projects/potential products that would have exceeded the threshold ROI for financing under market-based pricing will maybe now fall below. Hence all else equal bilateral negotiation is likely to lead to a reduction in the number of projects that are financed and thereby the overall level of R&D investment.

[32] Nevertheless, there may be some negotiation over what is considered "highly innovative".

Nevertheless, because the government health insurer negotiates prices on a case-by-case basis it may be able to manage the effect on R&D investment and minimize its consequences. It may be able to allocate its funds in a way that achieves a preferred—or possibly even a more efficient—distribution of R&D investment than under market-based pricing.[33] If the government health insurer spends the same amount under both systems, the effects on the level of innovation are ambiguous.

Across the board price cutting

A step beyond bilateral negotiation is to impose an explicit form of price regulation. The most basic form of explicit price regulation that a government health insurer might implement is an across-the-board price cut.

The most direct effect of a price cut is to reduce the level of R&D investment. This effect may manifest itself through one or both of the following mechanisms. Firstly, to the extent that the pharmaceutical firm believes that the price cut will remain in place and/or reflects the government health insurer's willingness to pay for future products, the price cut lowers the expected revenues—and therefore the expected ROI—of future products. This means that some projects/potential products that would otherwise have exceeded the threshold ROI may now fall below. Hence the price cut is likely to lead to a reduction in the number of projects that are financed and thereby the overall level of R&D investment.

Meanwhile, if the R&D budget is financed out of cash flow (rather than on the capital markets) and is constrained to be a proportion of revenue from current sales, an across-the-board price cut also has a second effect. Because the price cut reduces the revenue from current sales, it reduces the R&D budget available for investment. Since the profitability of all projects is reduced by the first mechanism, whether the second mechanism has any effect depend on the specific facts of the situation. However, if there are more profitable products available to be financed than there is money available (i.e., the size of the R&D budget is a binding constraint) a price cut on current products will further reduce the level of R&D investment.

At the same time, an across-the-board reduction in prices may also affect the nature of the products that are financed. In particular, the ROI of a low-margin/high-volume project is much more vulnerable to a price cut than a high-margin/low-volume product. This means that, on top of reducing the overall level of R&D investment, a price cut will skew investment into high-margin/low-volume projects, which are likely to occur in niche areas.

To make this clear, suppose that a firm is developing two types of projects:

[33] A government health insurer will only achieve a more efficient allocation of R&D investment across different types of products under bilateral negotiation if it can account for costs or benefits that the pharmaceutical firm does not take into account when setting its prices alone.

- a "high-margin/low-volume" product that only sells 10,000 units per year but earns a 100% margin on top of costs of €1000 per unit; and
- a "low-margin/high-volume" product that sells 500M units per year but only earns a 2% margin on costs of €1 per unit.

A firm developing these products can expect to earn €10M per annum from either product, and—presuming that both projects have similar costs of R&D and launch—both will be equally viable. Now suppose there is a 2% across-the-board price cut. This will barely dent the earnings of the second product, reducing it to €9.6M. However, it will completely wipe out the profits of the first product and create a deficit of €0.2M that means the project will no longer be viable. This means that in anticipation of or following an across the board price cut, pharmaceutical firms are likely to avoid developing low-margin/high-volume products, such as those for primary health care indications, rather than high-margin/low-volume products for specialty indications.

External Price Benchmarking

Under market-based pricing, a pharmaceutical firm is free to set different prices in each country or even to different patients within each country. It is likely to set prices according to the country's—or the individual group of patients'—willingness to pay, meaning that it will charge higher prices to purchasers with a higher willingness to pay and lower prices where they have a lower willingness to pay.

A consequence is that some countries and/or patents will pay more for the same product. While this generates some inequity across different purchasers, it enables the pharmaceutical firm to recoup the maximum amount from sale of its product and therefore gives it the maximum incentive to invest in innovation. Moreover, under this system the pharmaceutical firm has an incentive to sell the drug to the maximum number of countries and/or maximum number of patients. The pharmaceutical firm has an incentive to set the price in any country or to any set of patients where the purchasers are willing to pay more than the marginal cost of supply. Since they can set different prices to different patients under a system that allows market-based pricing, it can lower price as low as it marginal costs for some purchasers while still recouping the fixed costs of development by charging a higher price to countries or patients with higher willingness to pay.

A government health insurer can undercut this system of price discrimination by benchmarking its price against the price at which the product is sold in other countries. At an extreme, it may set the amount it reimburses equal to the lowest price in all countries where the product is sold.[34] One argument it might use to motivate this arrangement is that the pharmaceutical firm has shown that it can profitably sell the product at the lower price so this action merely redistributes the profits from the pharmaceutical firm to the health insurer (and/or its patients).

[34] Under a less extreme form of external price benchmarking, prices in a specific country are set relative to the prices in another, but within a range that allows for some variation in prices across countries to account for different willingness to pay. This system may mitigate some of the disincentives caused by a single price. However, if the countries with the majority of demand require that their prices are set in the lower end of the range then this may come to approximate a single-price system.

A less extreme action that a government health insurer might take is to benchmark the price against a set of comparable countries with similar willingness to pay (e.g., France might benchmark against Germany and the U.K.). Since such benchmarking does not dramatically reduce the final price, it may be motivated less by redistribution than by short-cutting the price assessment and negotiation process, thereby allowing the health insurer to save on costs.

In response to the more extreme form of external price benchmarking, a pharmaceutical firm will be forced to harmonize the price it charges in different countries. This resulting price is likely to be higher than the price it would otherwise charge in those countries with low willingness to pay. As a consequence, the health insurers in those countries may decide not to purchase the drug at all or only to purchase it for a limited number of cases. (For instance, the provider may limit prescribing only for patients below 65 or only after all other forms of treatments have been exhausted). This means that less of the product may be sold, and the pharmaceutical firm will have to raise the price at which it sells the drug in remaining countries further to compensate for the loss in sales in the countries with lower willingness to pay. Nevertheless, the final price it sets across all countries is likely to be lower than the price it would have offered in countries with high willingness to pay under market-based pricing, benefiting the purchasers in those countries—at least in the short term.

Another response to external price benchmarking may be to delay the launch of the product in the countries with lower willingness to pay. Pharmaceutical firms can typically demand a premium for small-molecule drugs in the first few years after a product is launched. At this stage the product is most innovative, relative to the existing methods of treatment, and also is less likely to have direct competition. The firm may be able to maximize its revenues by selling the product at a premium price in those countries with high willingness to pay than selling a lower price across all countries. However, when the product's novelty wears off and especially when competitive products launch on the market, the price the firm can charge to the high-willingness-to-pay countries lowers and it may be better off selling at larger volumes across more countries.[35]

An alternative way in which pharmaceutical firms may respond to external price benchmarking is to differentiate the products they sell in different countries in terms of the product's characteristics so that the price cannot be directly compared. For instance, a firm could sell the product under a slightly different formulation (within the limits of the regulatory approval) so that the products cannot directly be compared. There are limits to which a firm can actively differentiate its product because it is limited to what nature allows. Nevertheless, to the extent that it has the option to commercialize more than one version of its product, it may choose to commercialize and launch different products in different countries.

[35] The firm's decision about the timing of launch in different countries may have a flow-on effect on the process by which it pursues regulatory approval in Europe. Typically firms use the EMEA's Centralized Procedure to obtain regulatory approval for patented drugs. However, if the firm may prefer to use the EMEA's Decentralized Procedure or the Mutual Recognition Procedure if it only seeks regulatory approval in a subset of the EU countries.

One effect of external price benchmarking (and the firms' responses) on innovation will be to lower the overall incentive to invest in developing new products. As a consequence of not being able to make sales at a lower price in low-willingness-to-pay countries and/or not bring able to recoup higher returns in high-willingness-to-pay countries over the full life of the product, the firm will earn lower overall returns relative to what it would have earned under market-based pricing. Meanwhile, if the firms spend additional resources on product differentiation, it will raise the costs of and lower the returns to innovation. Over the long run, the lower return on investment will reduce the firm's incentive to invest in R&D and is likely to result in less overall innovation.

As a side effect of external price benchmarking, however, it could also occur that in the context of a bargaining game between a national health insurer and a pharmaceutical firm, external reference pricing might lead to more favourable reimbursement conditions and thus higher incentives to innovate. Indeed, the willingness to pay for a drug in a country is largely unaffected by whether that country is referenced or not by other countries. On the contrary, a pharmaceutical firm stands to lose more from unfavourable pricing and reimbursement conditions in a country, if that country is referenced by other countries. Therefore, it will be a tougher negotiator and will likely win better conditions.

At the same time, external price benchmarking may affect the nature of products that are brought to market. If firms respond to external price benchmarking by launching first or only in high-willingness-to-pay countries, they will try to focus their R&D investments on products that address the specific needs of those countries. For instance, they may focus on treatments for diseases that are more prevalent in high-income countries or on rare diseases that are only profitable in countries with a higher willingness to pay. At the same time, because of the restriction that external price benchmarking places on the volumes they can achieve, they may choose not to develop and launch low-margin/high-volume products that require a large population to be profitable. This may push firms further towards niche products.

Finally, firms may introduce a different version of the drug, not because they are more appropriate for patients in the particular countries but simply because they are different. If a firm differentiates its product to avoid price benchmarking rather than therapeutic reasons, it is not likely to make patients any better off and may make them worse off. Finally, if a firm sells a differentiated product in each country, there will be less useful information on which to evaluate the performance and/or therapeutic benefits of a specific drug, and therefore may lead to less accurate prescribing of drugs by physicians.

Internal reference pricing

A second way in which a government health insurer may regulate prices is through Internal Reference Pricing—that is, setting the amount it will reimburse for a specific drug in reference to a set of comparable drugs that it deems to have the same or similar therapeutic effect. Under the more lenient form of Internal Reference Pricing that was in place in Germany prior to 2004, patented drugs were excluded from internal price referencing (whether they are first or later in class). However, under the more stringent form of Internal Reference Pricing introduced in 2004, later-in-class drugs—even those with different, patented characteristics than the first-in-class drug—are referenced against the first-in-class drug (a fact that is particularly controversial if the first-in-class drug is not protected by patents any longer and it thus subject to generic entry) unless they can convince the regulator that the drug is "highly innovative".[36]

We distinguish between the effect of internal price referencing on prices before and after the patents on the first-in-class drug expire. Since the first-in-class is exempt from internal price referencing until a group of drugs is formed, it will set the initial price of its drug at a level which captures the drug's incremental value relative to the existing treatments. Because market-based pricing will last only until later-in-class drugs enter the market, pharmaceutical firms have the incentive not only to develop drugs with the potential of becoming first-in-class, but also to find niches in which later-in-class drugs are least likely to emerge.

While the first-in-class is still under patent protection, the effect of internal price referencing on the price of later-in-class drugs depends on whether the owner of the later-in-class drug would have charged a premium above the price of first-in-class drug under market-based pricing. If it would have been able to charge such a premium because it could have convinced medical practitioners (and their patients) of the incremental benefits relative to the first-in-class drug (the so-called skimming pricing strategy), but it cannot convince the government health purchaser that its drug is highly innovative, then internal price referencing will dampen the price that it can earn relative to a market-based pricing scenario. However, if under market-based pricing the later-in-class drug would have been sold a price at or below the price of first-in-class drug, either because later-in-class does not generate any additional benefits relative to the first-in-class or because the owner is attempting to price lower in order to capture into market share (the so-called penetration pricing strategy), then internal price referencing will not reduce the price charged. In fact, internal price referencing may under certain conditions actually increase the price charged for the second-in-class drug before the first-in-class goes off patent because the owner anticipates that the amount it will be able to charge after the first-in-class goes off patent will depend on its relative price beforehand.

[36] In practice only rarely do later-in-class drugs escape internal price referencing.

After the first-in-class drug loses patent protection, generic manufacturers are free to enter the market. Since a generic manufacturer only has to cover the incremental cost of manufacture and sales, it is likely to charge a much lower price. Since the generic is (at least in chemical terms) a perfect substitute for the first-in-class drug, the price of a first-in-class drug is likely to be driven down close to the generic under either market-based pricing or internal price referencing. Under market-based pricing, the first-in-class drug may be able to maintain some premium above the generic due to the medical practitioner's inertia in prescribing, but this will decline as medical practitioners become convinced that the generic is equivalent. Under internal price referencing the price—or at least the amount reimbursed—for the first-in-class will be constrained to the price of the generic.

The price that the owner of a later-in-class drug can charge will be similarly constrained by the price of the generic under a system of market-based pricing or internal price referencing, but internal price referencing is likely to have a much greater impact on price. If the later-in-class drug provides no incremental benefits above the first-in-class drug then the firm will unable to charge any price premium relative to the generic under either system. However, if the owner of a later-in-class can convince doctors that the drug has significant benefits relative to the first-in-class drug—for instance, because it has fewer side effects or brings unique benefits to an identifiable set of patients—then under a market-based pricing system it will be able to maintain a premium over the price of the first-in-class drug or a generic version after the first-in-class loses patent protection. The absolute price will be lower after the generic enters because the price of the first-in-class drug is lower. But if the later-in-class generates significant benefits relative to the first-in-class drug its owners will nevertheless be able to maintain a price premium as long the drug is protected by patents and therefore does not have a direct substitute.

Under the more lenient form of internal price referencing a similar situation will occur because the later-in-class drug is able to set its price freely as long as it is protected by patents. However, under the more stringent version of Internal Reference Pricing, the price of the later-in-class drug will be constrained to the price of the generic as soon as the first-in-class drug goes off patent. This will substantially reduce the price that the owner of the later-in-class drug can charge, particularly in the case where it is able to convince medical practitioners that its drug has significant benefits relative to the first-in-class drug but it cannot convince the government health insurer that its drug is highly innovative. This means that under the more stringent form of Internal Reference Pricing, the producer of a later-in-class drug will earn a significantly lower ROI over the product's life span than under market-based pricing.

In response to the more stringent form of Internal Reference Pricing, pharmaceutical firms are likely to direct their R&D investment toward indications where there is a lower probability that a drug will end up being "later in class" and therefore have its price referenced against a generic drug in the later years of its patent protection. The

indications where there is likely to be a lower probability of being later in class are likely to be those with lower expected returns and therefore a lower probability that other firms will invest. These may be either products in therapeutic indications that affect a smaller number of patients (such as rare diseases) or projects with a lower expectation of success—for instance, because the mechanism of action still needs to be validated.[37]

The incentive to avoid indications with a high degree of competition and to invest in indications that are not well served also exists under market-based pricing. However the response to Internal Reference Pricing is likely to go beyond the level of product differentiation that would be usual with market-based pricing. It will instead lead firms to strategically avoid whole indications for which there is high aggregate demand but also high competition. This means that, rather than innovation leading to a range of differentiated products in a particular indication, each of which treats different patients with varying degrees of effectiveness, there is likely to be less innovation in drugs to treat indications with high expected demand and more innovation in drugs to treat areas with low expected demand.

A related response to Internal Reference Pricing is that pharmaceutical firms investing in indications with high expected demand are also more likely to cancel projects at later stages of the development process when they discover that there is a higher-than-expected probability that another firm will launch a product to treat the same therapeutic indication before them. This is because the realization that the firm will be later in class significantly lowers the expected return to further investment. Moreover, because this realization typically does not happen until later in the R&D process (for instance, at the time of entering Phase III trials) it means that otherwise-worthwhile projects are more likely to be abandoned and the sunk investment wasted under Internal Reference Pricing. This is an aspect of Internal Reference Pricing on which particular attention is drawn in our dynamic model of development and launch decisions—contained in Section 5 of this report.

The effect of Internal Reference Pricing on the overall level of innovation depends on how the government health insurer implements the scheme. If the provider simply keeps the money that it saves on later-in-class drugs under internal price referencing, and does not compensate first-in-class innovations anymore, then internal price referencing is likely to result in a lower level of innovation overall. Because pharmaceutical firms cannot predict whether they will be first or later-in-class in areas where there is likely to be competition, they will expect a lower return on investment in those areas. They will respond to this by redirecting their investment to areas with less likely competition, but unless they completely redirect their investments to areas where they are guaranteed being first-in-class they will still expect to earn less across all their projects. As a consequence, they are likely to reduce their investment in R&D and there is likely to be less innovation overall.

[37] In addition, because regulating prices involves significant transaction costs (including the costs of setting, monitoring, and the enforcing the regulated prices), which are similar regardless of the total demand for the product, regulators are more likely to ignore therapeutic areas with smaller aggregate demand and allow prices to be set freely.

However, if in implementing the Internal Reference Pricing the government health insurer at the same time increases the amount paid for first-in-class drugs (so the scheme is budget neutral) then the effect on innovation is not so clear. Although there will be less investment in indications with higher demand, there is likely to be a simultaneous increase in investment in indications with lower demand. Whether this increases the overall level of innovation depends on whether it results in a better distribution of drugs coming on the market from the perspective of overall welfare. If there is excessive investment in areas of high demand under market-based pricing then Internal Reference Pricing implemented in a fiscally neutral manner may actually increase on the overall level of innovation. One of the justifications provided for internal price referencing is that later-in-class drugs do not generate therapeutic benefits equivalent to their investment costs and instead merely capture some of the benefits generated by the first-in-class drug. If this is the case, and the dynamic incentives created by having competition in the market do offset the duplicate investment costs, then internal price referencing implemented in a budget neutral manner may achieve more than redistribution from the pharmaceutical firm and actually increase the rate of innovations coming on the market.

However, if internal price referencing does not lead to a more efficient allocation of R&D investment relative to the market-based pricing then introducing internal price referencing—even in a budget neutral manner—is likely to reduce the level of innovation. This is because the inefficient reallocation of R&D investment will result in drugs that produce fewer benefits for patients—and society as a whole.

Value-based pricing (i.e., pharmaco-economic assessment)

A more recent development in price regulation is to condition reimbursement on an assessment of the value the product generates for patients. The value is typically measured using some form of pharmaco-economic assessment.[38] In theory, a value-based pricing system will largely replicate the prices that would arise under market-based pricing. As discussed above, under a market-based pricing a pharmaceutical firm will set the price to reflect the incremental benefits—the difference between benefits and costs—that its product generates for patients (or by proxy their health insurers) relative to the next best alternative. In most cases, this assessment involves a comparison relative to the next best pharmaceutical product. Nevertheless, this calculation goes beyond the price and the therapeutic benefits, and will also take into account the benefits and/or costs in other parts of the health system. Meanwhile, under a value-based pricing system prices are set to reflect the incremental benefits that the new product generates for the health care system as a whole. This includes not only the benefits of the pharmaceutical product relative to the next treatment, but also other benefits such as savings in the hospital stay. Therefore in theory value-based pricing will lead to a similar result to a market-based pricing system.

[38] As documented in Section 3 of this report, common metric for assessing a product's value is Quality Adjusted Life Years (QALYs), and reimbursement may be based on a certain rate per QALY.

However, different outcomes may arise under the two systems due to the way each system is implemented. To start with, under a market-based pricing system the pharmaceutical firm is free to set the prices and adjust them as evidence comes to light about the incremental benefits that the drug generates and/or the insurer's willingness to pay. By contrast, under a value-based pricing system the pharmaceutical firm must usually wait until a pharmaco-economic assessment has been conducted before the firm knows whether and at what level the health insurer will reimburse the drug. This may cause some delay in obtaining reimbursement, and increases the pharmaceutical firm's uncertainty about the revenue profile for its product. Moreover, a pharmaco-economic assessment typically requires different evidence than is necessary to obtain regulatory approval or to set prices—for instance, evidence on the changes in patients' quality and length of life—and collecting this information may require additional costs than under a system of market-based pricing. This is the reason why pharmaco-economic assessments are frequently associated (as in the U.K.) with risk-sharing agreements whereby pharmaceutical firms are initially free to set the price of their drugs, but must later refund the health insurer in the case in which the drug does not attain the health-outcomes targets that were agreed upon.

The delay is especially relevant when medical practitioners wish to prescribe the drug for a different indication than the one for which it is approved. Medical practitioners often wish to prescribe a drug as treatment for a second indication as soon as they have scientific evidence that a drug is effective against the second indication. However, it typically takes several years before a drug actually gets regulatory approval for a new indication. It is not illegal to prescribe a drug for a different indication than for which it is approved, and under a market-based pricing system the pharmaceutical firm can sell and the medical practitioners can prescribe the drug for the new indication immediately as long as the health insurer does not explicitly refuse to reimburse it. By contrast, it may take years before a pharmaco-economic assessment is carried out and if an ex ante assessment is required then the drug will not be available for a new indication during this time. For instance, Genentech/Roche's drug Herceptin was initially approved as treatment for patients with a particular form of late-stage breast cancer. When it was discovered that it was also effective for preventing relapse after surgery in patients with early-stage breast cancer, doctors immediately wished to prescribe it for the new condition. However, while it could be reimbursed under market-based pricing systems such as the U.S., the U.K. regulatory body (NICE) refused to reimburse it for this new use until an assessment had been done and it required intervention from the U.K. Health Secretary to fast-track its reimbursement.

At the same time, free and value-based pricing may reward different types of drugs in different ways because of the process by which prices are set. Under market-based pricing, the prices are negotiated between the pharmaceutical firm and the patients (or by proxy the insurance insurer) and therefore are more closely reflect the individual patient or health insurer's varying willingness to pay across products. By contrast, under a value-based pricing system based on pharmaco-economic assessment, the

benefits are measured against a relatively objective standard that reflects the economic considerations of the health system as a whole more than the willingness to pay of individual patients. This may lead to different drugs being reimbursed, or drugs being reimbursed at different levels, under the two systems. For instance, if individual patients have a higher willingness to pay for treatments for serious conditions with a low probability of success than for reliable treatments to less serious conditions then this preference will be reflect under a system of market-based pricing. However, since a system based on pharmaco-economic assessment involves a more explicit cost-benefit analysis, and is taken from the perspective of the government health insurer (or the health care system as a whole), the latter is more likely to be preferred.

Finally, since a pharmaco-economic assessment attempts to capture the costs and benefits explicitly, it is likely to focus on costs and benefits that are easy to measure. It is relatively easy to measure the therapeutic benefits that accrue to the specific patients that are treated by a drug and the cost savings that are realized in the activities involved in treating the patients. It is more difficult to account for the benefits that a drug may generate to the health system as a whole (for instance, preventive medicine that avoids subsequent treatment) or society at large. Therefore these benefits may be under counted. It is however unclear whether a free-pricing environment would do a better job of accounting for such benefits than a reimbursement scheme based on a pharmaco-economic assessment.

General considerations

All three major forms of price regulation involve some form of benchmarking or referencing to the prices of other products.[39] However, the prices that result from reference pricing will only be as good as the price of the original (referenced) product and the mechanism by which the referencing occurs. If the prices of the referenced products are inefficient or the conditions under which they were set do not exist in the new environment then the referenced prices will create, perpetuate, or enhance any distortions. Furthermore, whenever a pricing regulatory scheme requires a judgment whether a drug is highly innovative or not, the risk is incurred that a drug that is highly innovative from the point of view of the patients (in terms of higher safety and efficacy today and tomorrow) is not perceived as equally highly innovative by the pricing regulator.

To illustrate, take an example where country 1 (say, France) benchmarks its price against the price of country 2 (say Germany). If the price in country 2 has been set freely according to that country 2's willingness to pay and country 1 has a similar willingness to pay to country 1, benchmarking against country 2 may simply save country 1 the costs of assessing the product's benefits and negotiating a price. However, if the conditions in country 2 are different—for instance, the drug is still protected by a patent in country 1 but not in country 2—then by benchmarking against country 2, country 1 effectively undercuts the effect of the patent protection in country 1. Alternatively the product may still be protected by a patent in country 2 but

[39] Value-based pricing involves referencing when the costs and benefits are assessed relative to an existing drug – typically using the Incremental Cost-Effectiveness Ratio (ICER).

be part of a "jumbo" group that includes a generic not available in country 1. Alternatively the prices in country 2 may have been set using a pharmaco-economic assessment, and set relative to an alternative treatment that is not available in country 1. In all cases, country 1 imports the prices of the product from country 2. But if the same conditions do not exist in country 1 then these prices may not be efficient for country 2.

These effects are most obvious in the case of external price benchmarking. However, they also apply in other case where the price for one product is referenced against another. Under Internal Reference Pricing, if the price of a patented product is referenced against a generic that has entered the market then the owner of the later-in-class drug is unduly penalized as its effective patent life is drastically reduced. Alternatively when pharmaco-economic assessment compares costs and benefits to a treatment that was recently made free or cheap because of government intervention then prices may be set inefficiently low.

The consequence of setting prices that are not efficient for their context is that a pharmaceutical firm may have insufficient incentive to launch its product in the country. If the prices do not allow the firm to recover its launch costs then it will not launch. Alternatively, for instance, under external price benchmarking it may launch the product only at a late stage in its life cycle. This reduces or eliminates the benefits that the government health insurer (and the patients it represents) would obtain from the product. It also reduces the incentives to the pharmaceutical firm to invest in future R&D, and thereby develop new products.

4.3
The effect of introducing new forms of price regulation in a regulated environment

The previous section analyzed the effect of the various forms of price regulation relative to a situation of market-based pricing. However, since prices are already subject to some form of regulation in all European countries, it might be more appropriate to make comparisons relative to the form of price regulation that already exists.

To completely analyze the incremental effect of new forms of price regulation relative to the system of price regulation that currently exists, we would need not only characterize the status quo in each country but also project the long-term effect of that system of price regulation on innovation (which is difficult since many of the changes are recent and some changes are still happening) and then analyze how introducing a new form of price regulation might change this long-term effect. These effects are difficult to analyze and depend on making many assumptions about how the current system would play out.

4.4 Aggregation of country-specific changes

Since the market for pharmaceutical products is worldwide and any individual country only comprises a small fraction of this market, one might argue that any country's actions might not have a noticeable effect on the overall level of innovation. However, if all countries benchmark their prices against each other then the result of one country lowering its price (even for reasons that are specific to the internal conditions within that country) would be a cascade in which prices in all countries are reduced. As a result of this 'race to the bottom' a pharmaceutical firm's overall ROI—and therefore the incentive for innovation—will be significantly reduced.

At the same time, even if the prices across countries are not so tightly interlinked, a country that uses price regulation to lower its spending on pharmaceutical products may be harmed because the pharmaceutical firms direct their investment toward products that suit the needs of countries that allow market-based pricing or are otherwise more supportive of innovation.

Because the population profile differs across countries, each country's needs for pharmaceutical products will be different. For instance, ethnic variation across countries will mean that genetic diseases are more likely to occur in some countries than others. Because of these differences, it is likely that a country's specific needs will not be completely addressed by drugs developed for other countries. The only way to have the drugs developed is to create incentives for pharmaceutical firms to invest in such products.

In this respect, the next years might experience a shift in pharmaceutical firms' attention from the U.S. to Europe and emerging-market countries as the current U.S. administration looks posed to implement a healthcare reform aimed at reigning in healthcare costs and ensure the fiscal sustainability of public entitlement programs such as Medicare and Medicaid. As an implication, the development of drugs aimed at treating conditions and diseases particularly prevalent in the U.S.—such as obesity—could lose ground relative to the development of drugs aimed at preventing and treating diseases more prevalent in other countries—like hepatitis in China and neurodegenerative diseases associated with the old age in Europe.

This political change of direction and the consequent shift in the attention of pharmaceutical firms is also likely to amplify the importance of the pricing and reimbursement schemes in place in Europe.

5. A quantitative decision-theoretic model of drug development

In this section of the report, a decision-theoretic framework is presented in which the effect of pricing regulation on pharmaceutical innovation can be quantitatively evaluated. The quantitative predictions arising in this framework complement the qualitative predictions described in the previous section of the report.

5.1 Introduction

Goals

A model of drug development decisions is specified and solved in which the decision-maker is forward-looking and takes into account future expected pricing regulation in making current development decisions. After the parameters of the model are calibrated such that the model replicates key characteristics of the real world, a battery of policy experiments is performed. In these policy experiments, features of the regulatory environment exhibited by the benchmark model are altered and the resulting consequences on innovation outcomes are analyzed.

Key questions the model can address

On the basis of the calibrated model, a set on interesting questions can be addressed regarding the effect of pricing regulation on pharmaceutical innovation. In particular:

- how is the expected value of a drug candidate affected by pricing regulation, depending on its therapeutic area, development phase, and degree of innovativeness?
- how many more or less drug candidates—and which ones—are expected to be developed and launched under pricing regulation?

While a detailed description of the model is given only in later subsections, we now describe its main aspects.

Main aspects of the model

In the model, a pharmaceutical firm evaluates a portfolio of drug candidates, ranks them, and selects the highest-ranking ones, until current development costs reach a development budget limit. Projects are in different therapeutic areas, are at different development phases, and have different potentials of being considered highly innovative by the pricing regulator at the time of market launch.

As the case studies by De Reyck et al. (London Business School, 2005) and Girotra et al. (Wharton, 2004) document, drug development is dynamic and risky. In particular, in order to prove their safety and efficacy and thus obtain marketing approval, drug candidates must go through a highly structured sequence of clinical trials, and the outcome of clinical trials is uncertain. The model reflects these key properties of the drug development process.

In the model, the decision-maker is forward-looking and in evaluating a project she takes into account the alternative possible realizations of future events and future development and launch decisions contingent on such realizations. For example, a project in an early development phase that has the potential of being considered highly innovative by the pricing regulator if and when it will be launched in the market may lose its potential in later development phases, at which point the decision-maker may decide not to develop the project further.[40] In another example, the decision-maker may decide about the set of countries in which to launch its drug depending on whether the pricing regulator considers that drug highly innovative or not.

As the OECD (2008) study documents, pricing regulation comes in a variety of flavors around the world, and this regulatory heterogeneity is captured by the model. In particular, because of Internal Reference Pricing (IRP) in one region, it matters whether a drug is highly innovative or not; and because of External Price Benchmarking (EPB), whether or not a drug is launched in one region has consequences in another region.

In addition to the risk of failing clinical trials or not receiving marketing authorization, highly innovative projects in the model face the risk of losing their high degree of innovativeness by the time they are launched in the market because of two reasons: external and internal competition. Under external competition, other pharmaceutical firms may launch competing highly innovative drugs before the development of the

[40] This event is typically referred to as attrition and it is frequently mentioned in the debate on the effect of pricing regulation on pharmaceutical innovation.

decision-maker's highly innovative project is completed. Under internal competition, the decision-maker may have in its portfolio a cluster of highly innovative projects that are competing with each other. This mechanism gives rise to interesting interactions among the projects in the decision-maker's portfolio, as the value and development decisions for a project in a cluster in an early development phase depend on the decisions for the projects in that cluster in later development phases.

The next subsection briefly surveys the existing literature and puts our contribution into context. The next two subsections describe in more detail the model: the former focuses on the pricing regulatory environment; the latter inspects the development and launch decision-making process. Subsection 4.5 shows how the model is solved and Subsection 4.6 describes how the model is brought to the data. Subsection 4.7 contains the main results and Subsection 4.8 explores how robust the results are with respect to the value of several of the model's parameters. Subsection 4.9 concludes.

5.2 Literature background

Our formulation of the innovation process as a portfolio management problem is well established in the R&D literature. Portfolio models typically consist in optimization problems where the decision maker needs to allocate resources to several projects under different constraints in order to optimize returns (Schmidt and Freeland, 1992). Early approaches have focused on static settings (that is with one development stage only) under full information (see Souder, 1978, for an overview of early developments in this stream of research).

More recent works have accounted for the multi-stage aspect of innovation processes, along with underlying sources of uncertainty (Loch and Terwiesch, 1999, Ding and Eliashberg, 2002). Several case studies have described the process of developing drugs in this framework (Pisano and Rossi, 1994, Ruback and Krieger, 2000, Girota et al., 2004, and De Reyck et al., 2005). In all of these studies, the different stages of the process correspond to the several development phases of a drug (in particular, Phases I, II, and III) and the underlying source of uncertainty are captured by the probabilities of technical success of each phase. Our model closely follows and further develops this approach.

In addition to this, different projects in an R&D portfolio may interact. For instance in a pharmaceutical context, a highly innovative drug may lose its innovativeness because in the meanwhile other highly innovative drugs are launched in the market by the same company (we refer to this type of interaction as internal competition). Loch and Kavadias (2002) propose extensions of the earlier dynamic models of R&D portfolios that account for different types of project interactions. Following this approach, Girota et al. (2007) run an event study to show that these interactions significantly impact the value of a drug portfolio. Our model follows Girota et al. (2007) and accounts for project interactions in the form of internal competition.

Some of the existing studies also consider risks related to regulation, albeit in a very simplified way. Typically the role of regulation is represented at an aggregated level by a single probability of marketing authorization failure (see for example De Reyck et al., 2005). Clearly, this does not allow studying the impact of different forms of pricing regulations. The main contribution of our study is then to propose a more explicit and complete representation of marketing authorization and price regulation and its interaction with the drug development process. To that end, we incorporate in our model a project's market launch phase following the innovation process, in which the potential payoffs in different markets under both Internal Reference Pricing and External Price Benchmarking are evaluated.

We solve our model using well established techniques of dynamic programming. We derive the corresponding Bellman equations (Bellman, 1957) that allow keeping track of how the decision process evolves over time. We then iterate on the value function to solve these equations (see Bertsekas, 2007, for a technical presentation of this procedure). This framework allows solving multi-stage decision problems where decisions are made under uncertainty. Bertsekas (2007) presents many examples of dynamic-programming applications in management, engineering and economics. Merton (1973) constitutes one of the first economic applications of dynamic programming. For further applications in economics, see Ljungqvist and Sargent (2004), and Stokey et al. (1989).

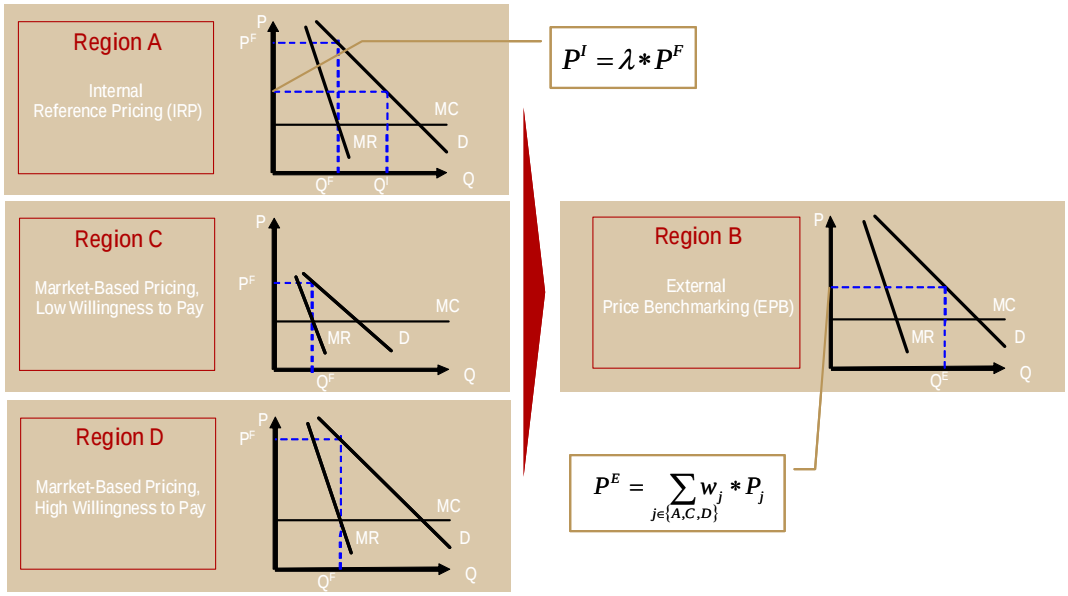
In order to be able to produce quantitative results, our theoretical model has to be "brought to the data." There are several different ways to bring a model to the data, depending on the richness of the model and the availability of data. Given in particular the paucity of data available for this project, the route of calibration is taken. Calibration consists in assigning values to the parameters of a model either by relying on values available in the existing economics literature or by setting them in such a way that some quantitative features of the model replicate the real world. The technique of calibration was introduced in the field of economics by Kydland and Prescott (1982) and has been recently developed by Castañeda et al. (2003).

5.3
Pricing regulation around the world

As Section 3 of this report documents in detail, pricing regulatory schemes around the world can be classified into Internal Reference Pricing (IRP) and External Price Benchmarking (EPB) schemes, and schemes based on a pharmaco-economic assessment. Briefly, under IRP the price of a drug that is not considered highly innovative by the pricing regulator is effectively forced to be equal to the price of comparable existing drugs (whose patent/data exclusivity may have already expired). Under EPB, the price of a drug in one country is set equal to the price of that drug in other countries—including countries that may have a low willingness to pay. Under a pharmaco-economic assessment, the price of a drug is determined on the basis of the effectiveness of that drug—as assessed by a government agency.

The model captures the richness of the real world by featuring four regions, each of which has different underlying (preferences) and pricing regulatory characteristics. Looking at the individual regions in turn, Figure 5 shows that Region C—whose analogue in the real world could be an Eastern European country—is a low willingness-to-pay free-pricing region, while Region D—whose analogue in the real world could be the United States—is a high willingness-to-pay free-pricing region.[41] The Demand (D) function traces how many packages of a drug would be bought at different prices. As standard microeconomic theory suggests, in Regions C and D price is thus determined by the intersection of the Marginal Revenue (MR) and the Marginal Cost (MC) curves, where marginal costs refer to the costs of manufacturing an extra package of a drug and do not include development costs.

Figure 5: Regions and pricing regulation



Source: ESMT CA

More interestingly, Region A—resembling several European countries and Germany in particular—is characterized by Internal Reference Pricing, which in the model works as follows. If Region A's pricing regulator does not consider a drug to be highly innovative, its price is set equal to a fraction λ of its price under market-based pricing. Pricing regulation in Region A could also be interpreted as being informed by a pharmaco-economic assessment, in which case the price of a drug would be set equal to a fraction λ of its price under market-based pricing in the event that the effectiveness of that drug was not considered by the pricing regulator high enough.

[41] The assumption that Regions C and D experience free pricing does not play an important role in our analysis.

We consider this modelling of Internal Reference Pricing regulation a conservative one, because it assumes that if the regulator considers a drug highly innovative, the pharmaceutical firm is free to set a market-based price. This modelling of Internal Reference Pricing, which is motivated in particular by reimbursement regulation in Germany (see Section 2 of this report), does not take into account that in some other applications Internal Reference Pricing may not permit market-based pricing also for what are considered to be highly innovative drugs. For example, in France and Switzerland (see OECD, 2008) highly innovative new drugs are indeed granted by the regulator a price premium over existing drugs, but this premium need not be equal to the premium that the market would be willing to accord. Furthermore, public health insurance providers are likely to deploy their large buying power in negotiating the pricing and reimbursement conditions of new drugs, making the event that even highly innovative drugs may fetch a market-based price unlikely.

Region B—resembling other European countries—is characterized by External Price Benchmarking. This implies that the price that a drug receives in Region B depends on the price that that drug receives in the other regions in which it is marketed. IRP and EPB interact in the sense that under EPB the price that a drug receives in Region B depends on whether that drug is considered highly innovative or not by the pricing regulator in Region A. As the next subsection illustrates, EPB in Region B may compromise market access in Region C (the low willingness-to-pay region), to the extent to which the sales that would be gained in Region C are dwarfed by the sales that would be lost in Region B due to a lower price.

5.4 Drug development

Overview

Against the pricing regulatory background described in the previous subsection, in the model a pharmaceutical firm evaluates a set of projects and makes optimal development and launch decisions. The current subsection illustrates how these evaluation and decision-making processes work.

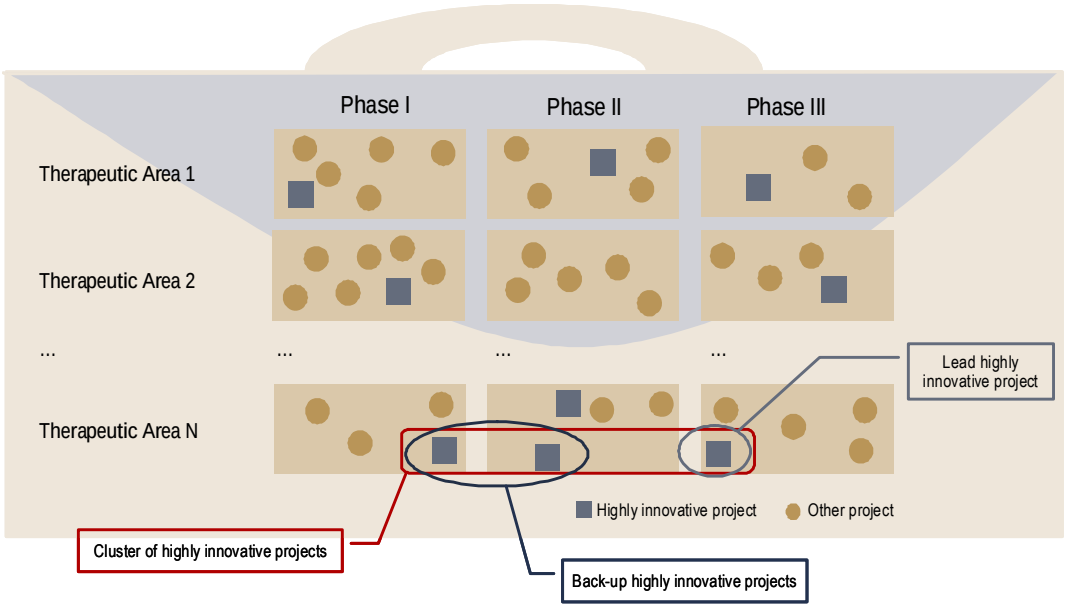
It is helpful at this point to recall from Section 2 that drug development can be looked at from two complementary points of view: the *portfolio* (cross-section) and the *life-cycle* (time-series) points of view on drug development. From the portfolio point of view, the emphasis is placed on the whole set of projects that a pharmaceutical firm holds at a point in time, when different projects are in different development phases. From the life cycle point of view, instead, the emphasis is placed on an individual project, which is followed over time as it goes through the different development phases.

The drug-development decision-making process can be broken down into two steps. In the first step, a project is evaluated on the basis of its profitability. In the second step, projects are ranked by their profitability and the highest-ranking projects are selected. To evaluate a project, the alternative possible realizations of future events and the future development and launch decisions contingent on such realizations are taken into account. In particular, at the end of the development process and once all the uncertainty about a project's technical success and its degree of innovativeness is resolved, the decision-maker decides on its optimal market launch strategy.

Project portfolio

As Figure 6 shows, in the initial decision period a pharmaceutical firm has a portfolio of drug candidates, and different candidates are in different therapeutic areas, in different development phases, and with different degrees of innovativeness. Regarding the degree of innovativeness, there are highly innovative and not highly innovative projects, and highly innovative projects are projects that—from the point of view of the initial decision period—have the potential to be considered highly innovative by the pricing regulator in Region A if and when they will be launched in the market. Having said that, both external and internal competitive forces may make a project lose its high degree of innovativeness by the time the development process is completed. In particular, highly innovative projects in different development phases and within the same therapeutic area may give rise to a cluster.

Figure 6: Project portfolio



Source: ESMT CA

Within a cluster, there is internal competition, and the value of a back-up project depends on the development decisions taken with respect to the back-up and lead projects that are in more advanced development phases: only the first drug in a cluster to reach the market will be considered highly innovative—provided that external competition will not reach the market first.

A project's life cycle

As it was already noted, drug development is a dynamic and risky process, and the evaluation of a project takes into account the alternative possible realizations of future events and the future development and launch decisions contingent on such realizations.

More specifically, in the model there are four decision periods: three development phases (Phases I, II, and III) and market launch. At each development phase, a go/no-go decision is taken as to whether or not to develop the project further. If a go decision is taken, current development costs are incurred and—depending on technical success—the project advances to the next development phase or (if the project is in Phase III) to market launch. Between consecutive periods, a highly innovative project may lose its high degree of innovativeness because in the meanwhile other highly innovative projects are launched in the market by the same (internal competition) or other (external competition) pharmaceutical firms. At market launch—once all uncertainty about technical success and degree of innovativeness is resolved—a decision is taken as to whether or not to launch in Region C.

A project's market launch

Once the development of a project is completed, the pharmaceutical firm decides its optimal market launch strategy. This decision is made interesting by the fact that under External Price Benchmarking the price received by a drug in one region (Region B) depends on the price received by that drug in other regions—including the low willingness-to-pay Region C—that are contained in the reference basket. In such case, the pharmaceutical firm faces in particular the dilemma of whether or not to launch in Region C, considering that the sales gained in Region C could be dwarfed by the sales lost (due to a lower price) in Region B. This is indeed the dilemma the model focuses on, as formalized in the following equation:

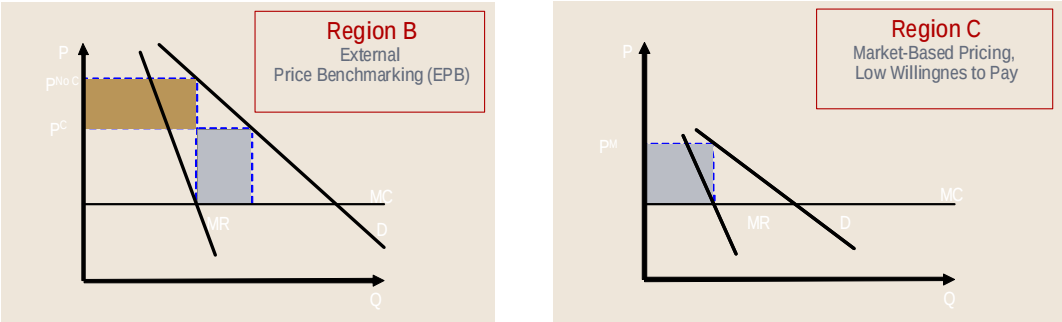
$$\text{Net Sales} = \max\left\{ \sum_{j\in\{A,B,C,D\}} \left(\mathrm{P}_j - c\right) * \mathrm{Q}_j\left(\mathrm{P}_j\right), \sum_{j\in\{A,B,D\}} \left(\hat{\mathrm{P}}_j - c\right) * \mathrm{Q}_j\left(\hat{\mathrm{P}}_j\right) \right\}.$$

This equation means that in deciding about launching in Region C the pharmaceutical firm compares the sum of region-specific net (of manufacturing costs, c) sales if it launched in Region C (the left-hand-side summation term) to the sum of region-specific net sales if it did not launch in Region C (the right-hand-side summation term). Because of EPB, the price in Region B in the former case (P_B) need not coincide with the price in Region B in the latter case ($\hat{\mathrm{P}}_B$).[42]

[42] To conclude the illustration of the equation, $\mathrm{Q}_j(\ )$ is the region-specific demand function.

Further light on this trade-off is shed by Figure 7, which shades in light blue the net sales that would be gained (in Region C, but also in Region B) by launching in Region C and in light brown the net sales that would be lost (in Region C). On the vertical axis of the graph for Region B, P^{C} denotes the price that would prevail in Region B if the drug were launched in Region C and $P^{No\ C}$ denotes the price that would prevail in Region B if the drug were not launched in Region C.

Figure 7: Trade-off in launching in Region C



Source: ESMT CA

Ranking and selection

Optimal development and launch decisions yield an Expected Net Present Value[43] (ENPV) for every project in the portfolio—an ENPV that rigorously takes future decision-making opportunities (that is, real options) into account. Furthermore, because of internal competition, optimal development decisions (and the resulting ENPV) for earlier-phase highly-innovative projects depend also on development decisions for later-phase highly-innovative projects in the same cluster.

In the absence of a development budget constraint, a pharmaceutical firm would select all projects with a positive ENPV. However, in the model the pharmaceutical firm is constrained in its development budget and can potentially select only a subset of them. For this reason, (clusters) of projects are ranked and the highest-ranking (clusters of) projects are selected until the cumulative sum of initial development costs reaches the development budget limit.

Projects are ranked on the basis of their Expected Profitability Index (EPI), which is constructed as the ratio of the ENPV to the initial development costs. Ranking projects on the basis of their EPI is more consistent with constrained portfolio optimization than ranking them on the basis of their ENPV. Indeed, the latter measure is biased in favor or large projects that—per dollar of initial development costs—may not be as profitable as smaller projects. A related motivation has to do with the fact that there is an obvious tendency for the ENPV of a project to grow over time, as early development costs become sunk: using the EPI instead of the ENPV narrows the evaluation gap between

[43] The next subsection makes this link explicit.

projects that are in early development phases and projects that are in later development phases. This is because later development phases (involving clinical trials with larger number of patients) are more expensive than earlier development phases.

Ranking at the level of clusters (when applicable) instead of at the level of individual projects makes sure that the following undesirable event does not occur: in the process of selecting projects (due to a binding development budget constraint), a project is excluded on whose inclusion the evaluation of another selected project is based.

Output statistics

The solution of the model allows us to produce a set of interesting results pertaining innovation effort and outcomes. In particular, the model allows us to produce the following results, across therapeutic areas, initial development phases, and initial degrees of innovativeness:

- average ENPV/EPI/expected net sales of a project;
- number of projects selected;
- expected number of projects launched;
- total ENPV/EPI/expected net sales.

To evaluate the effect of pricing regulation on pharmaceutical innovation, we compare these results (the benchmark results) with results (the counterfactual results) coming from versions of the model in which pricing regulation is altered or altogether eliminated.

5.5 Model solution

Solution algorithm

The first step of the solution algorithm consists in finding, for every project in the portfolio, optimal decisions and the resulting ENPV in every period and state of the world. This goal is accomplished using the tool of dynamic programming (Bertsekas, 2007), a tool which is very popular in the fields of economics, engineering, and operations research, and which serves the purpose of breaking down a complex problem (in this case, there are four decision periods, and in every period several alternative circumstances may arise, depending on the degree of innovativeness of a project and its lead or back-up status) into a set of simpler problems. Because the problem is a finite-horizon problem (there is a finite number of decision periods in the model), the dynamic-programming technique of backward recursion is adopted, starting to solve the model from the last decision period (the time of market launch) and moving backwards to the initial development phase.

The solution algorithm becomes slightly more involved when a project belongs to a cluster of highly innovative projects. In this case, as it was already noted, the solution for a project depends on the solution for the projects that are in later development phases in the same cluster. For this reason, for projects belonging to a cluster the solution algorithm can be labelled backward recursion squared:[44] a solution by backward recursion is first provided for the project in the cluster that is in the latest initial development phase; then—recursively—a solution is provided for the projects in earlier initial development phases, taking into account the solution for the projects in later initial development phases.

The second step of the model solution is then as follows. Once the value of all projects in the portfolio is calculated, (clusters of) projects are ranked on the basis of the EPI, and the highest-ranking (clusters of) projects are selected until the cumulative sum of initial development costs reaches the development budget limit.

Some cases

To briefly illustrate how backward recursion works, some examples are shown of Bellman equations (see Bellman, 1957)—the equations that are at the core of dynamic programming.

Consider first the case of a not (superscript N) highly innovative project—the simplest case. The following Bellman equation,

$$ENPV_k^N = \max\left\{0, -C_k + \frac{1}{1+r}\pi_k ENPV_{k+1}^N\right\},$$

means that the ENPV of such a project (in development phase k) is equal to the maximum between zero (if the decision not to pursue development further is taken) and the term on the right-hand side (if the decision to continue development is taken instead). In the latter case, the pharmaceutical firm must incur phase-specific development costs C_k but, with the probability of technical success π_k, development will be successful and the project will move to the next development phase, phase k+1. In the latest development phase—Phase III— $ENPV_{k+1}^N$ showing up on the right-hand-side of the equation should be replaced by Net Sales, a quantity that was already defined in the previous subsection. The factor $\frac{1}{1+r}$ allows for time discounting between consecutive decision periods.

A slightly more involved case is the case of a lead highly (superscript H) innovative project. In this case, the Bellman equation looks as follows:

$$ENPV_k^H = \max\left\{0, -C_k + \frac{1}{1+r}\pi_k\left[(1-\rho)ENPV_{k+1}^H + \rho ENPV_{k+1}^N\right]\right\}.$$

[44] For an analogous labeling, see Ljungqvist and Sargent (2004).

Indeed, in the case of a lead highly innovative project internal competition is not an issue but external competition (occurring with probability ρ) is: if other pharmaceutical firms launch a competing highly innovative drug on the market, the project loses its high degree of innovativeness, even though development is technically successful.

In the case of a back-up highly innovative project, its value depends on the decisions taken with respect to the other projects in later development phases in the same cluster. To be concrete, consider the case of a back-up highly innovative project in Phase II (call it project A). This project has, by definition, another project ahead of itself in Phase III (call it project B). In the case in which a no-go decision is taken for project B, then its Bellman equation looks very much as in the previous case:

$$ENPV_{II}^{A} = \max\left\{0, -C_{II} + \frac{1}{1+r}\pi_{II}\left[(1-\rho)ENPV_{III}^{H} + \rho ENPV_{III}^{N}\right]\right\}.$$

However, if a go decision is taken for project B, then its Bellman equation looks as follows:

$$ENPV_{II}^{A} = \max\left\{0, -C_{II} + \frac{1}{1+r}\pi_{II}\left[(1-\rho)(1-\pi_{III})ENPV_{III}^{H} + \{1-(1-\rho)(1-\pi_{III})\}ENPV_{III}^{N}\right]\right\},$$

taking into account the fact that project A is under these circumstances subject to both external and internal competitive forces. Project A will be able to preserve its high degree of innovativeness into the next decision period if both other pharmaceutical firms and project B fail. This event occurs with probability $(1-\rho)(1-\pi_{III})$.

More complex cases, which are not reported here, arise when a back-up highly innovative project has more than one project ahead of itself or when it has a lead project that is not close to market launch.

5.6 Calibration

Preliminaries

In order to be able to produce quantitative results and come up with quantitative predictions about the effect of pricing regulation of pharmaceutical innovation, the model that was presented in the previous subsections has to be "brought to the data." There are several different ways to bring a model to the data, depending on the richness of the model and the availability of data. Given in particular the paucity of data available for this project, the route of calibration is taken. Calibration—a technique introduced in the field of economics by Nobel-prize winners Kydland and Prescott in 1982 and recently developed by Castañeda et al. (2003)—consists in assigning values to the parameters of a model either by relying on values already

available in the existing economics literature or by setting them in such a way that some quantitative features of the model replicate the real world. As it is illustrated in detail below, this combination of approaches is the route we follow.

Parameters

In the model there are a variety of parameters to which values must be assigned. They are listed here:

- therapeutic areas and number of projects by therapeutic area and development phase;
- for every development phase, development costs and probability of technical success: C_k, π_k;
- development cost premium for highly innovative projects: φ;
- probability of external competition's success: ρ;
- discount rate: r;
- for every region and every therapeutic area, demand intercept and slope: a^i_j, b^i_j;
- average/marginal manufacturing cost: c;
- price discount for not highly innovative drugs in Region A (IRP): λ;
- development budget constraint: B.

Therapeutic areas and number of projects

In deciding about what therapeutic areas the modeled pharmaceutical firm is present in, a balance was struck between on the one hand recognizing the fact that even large pharmaceutical firms tend to specialize—especially in the recent years—on a subset of all existing therapeutic areas and on the other hand building a portfolio that reflected all the major therapeutic areas in which pharmaceutical firms are active. This balance was struck by including all the therapeutic areas in which four out of the thirteen firms listed by Lehman Brothers' PharmaPipelines (2008) as Large Pharmaceuticals are active.

Table 4 shows the sixteen selected therapeutic areas as well as the average (across the four firms) number of projects that according to the PharmaPipelines is present in each therapeutic area/development phase cell.

Table 4: Therapeutic areas and number of projects

Therapeutic Area	Phase I	Phase II	Phase III
Analgesia	1	1	0
Anti-Infective	4	2	2
Cancer	10	4	4
Cardiovascular	3	2	2
CNS	5	3	2
Diabetes	1	1	1
Gastro-Intestinal	1	0	0
Genito-Urinary	1	1	0
Hormone Control	0	1	1
Immune System	0	1	0
Inflammation	2	2	1
Metabolism/Endocrinology	0	1	0
Obesity	1	1	1
Ophthalmic	1	1	1
Respiratory	0	3	1
Vaccines	1	1	2
Total	31	25	18

Source: ESMT CA calculations based on Lehman Brothers' (2008) PharmaPipelines

It can be seen from Table 4 that the number of projects varies widely across therapeutic areas, with Cancer being the most populated therapeutic area. It can also be seen that the total number of projects declines over development phases, with 31 projects in total being in Phase I, 25 in Phase II, and 18 in Phase III.

Because of the lack of information regarding this issue, whether a project has the potential to be considered highly innovative or not is resolved as follows. The first project within a therapeutic area and a development phase is considered to be highly innovative and to potentially belong to a cluster. If within a therapeutic area and a development phase there are at least three projects, then the second project is also considered to be highly innovative but not to belong to a cluster. Following this procedure, there are 46 initially highly innovative projects in the portfolio, out of a total number of projects equal to 74.

Other empirical statistics

Also computed on the basis of the PharmaPipelines are the figures presented in Table 5. By therapeutic area, they represent the (expected) lifetime net sales and margins in the U.S. for a typical project. Consistent with the original data source, net sales are expressed in millions of U.S. Dollars in year 2008.

Table 5: Other empirical statistics

Therapeutic Area	Average Lifetime Net Sales in the U.S.	Median Lifetime Margin in the U.S.
Analgesia	281	30%
Anti-Infective	332	30%
Cancer	933	40%
Cardiovascular	570	26%
CNS	728	36%
Diabetes	1150	28%
Gastro-Intestinal	568	22%
Genito-Urinary	373	23%
Hormone Control	480	30%

Therapeutic Area	Average Lifetime Net Sales in the U.S.	Median Lifetime Margin in the U.S.
Immune System	409	38%
Inflammation	1326	30%
Metabolism/Endocrinology	473	35%
Obesity	664	35%
Ophthalmic	608	35%
Respiratory	1122	21%
Vaccines	1505	35%

Source: ESMT CA calculations based on Lehman Brothers' (2008) PharmaPipelines

According to this table, there is considerable heterogeneity in net sales and margins across therapeutic areas: Vaccines and Inflammation have large sales, while Analgesia and Anti-Infective have small sales; Cancer and Immune System have high margins, while Respiratory and Gastro-Intestinal have low margins.

These are the figures on which the calibration of the model's demand parameters is based, which is the topic to which we now turn.

Calibration of demand parameters

Calibration of the demand parameters starts with the observation that under market-based pricing, constant marginal manufacturing costs, and a linear demand function, net sales can be expressed as

$$\text{Net Sales}_j^i = \frac{\left(a_j^i - c\right)^2}{4b_j^i}$$

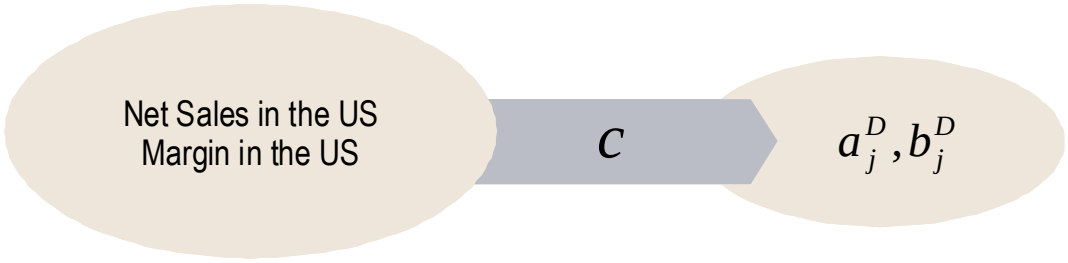
and the margin as

$$\text{Margin}_j^i = \frac{a_j^i - c}{a_j^i + c},$$

where a_j^i is the intercept of the (inverse) demand function, b_j^i is its slope, and the indices i and j denote respectively the therapeutic area and the region.

It is then straightforward, as illustrated in Figure 8, to use therapeutic-area-specific net sales and margins in the U.S., under the assumption that market-based pricing holds there, to recover the demand parameters for what in the model is Region D. This requires making an assumption about manufacturing costs, which are assumed to be equal to $10 per package of drugs—irrespective of therapeutic area.

Figure 8: Calibration of demand parameters



Source: ESMT CA

Regarding net sales in the other regions in the model, it is assumed that under market-based pricing Regions A and B would have net sales equal to each other and equal to 1/2 of net sales in Region D, while Region C has net sales equal to 1/20 of net sales in Region D:

$$\text{Net Sales}_j^A = \text{Net Sales}_j^B = \frac{1}{2}\text{Net Sales}_j^D, \text{Net Sales}_j^C = \frac{1}{20}\text{Net Sales}_j^D.$$

Regarding margins in the other regions, it is assumed that under market-based pricing Regions A and B would have the same margins as Region D, while Region C has margins equal to 5%:

$$\text{Margin}_j^A = \text{Margin}_j^B = \text{Margin}_j^D, \text{Margin}_j^C = 5\%.$$

Other parameters values

After the demand parameters are calibrated as described above, the value of several other parameters—concerning in particular the development process—remains to be set. A development phase is calibrated to last for two years and, as shown in Table 6, phase-specific development costs are calibrated on the basis of the values reported in DiMasi et al. (2003), while phase-specific success probabilities are calibrated on the basis of the values reported in the electronic companion to Girotra et al. (2007). If enough data were available, then it would be possible to have development costs and success probabilities to depend not only on development phase but also on therapeutic area. Consistent with Lehman Brothers' PharmaPipelines (2008), the annual discount rate is set equal to 10%.

Table 6: Other parameter values

Parameter	Value	Source/Target
C_1	30	DiMasi et al. (2003)
C_2	36	DiMasi et al. (2003)
C_3	127	DiMasi et al. (2003)
φ	0.1	
π_1	0.6	Girotra et al. (2007)
π_2	0.625	Girotra et al. (2007)
π_3	0.65	Girotra et al. (2007)
r	0.10	Lehman Brothers (2008)
λ	0.75	
ρ	0.025	
B	3,500	Approx. 90% of the value of the portfolio is selected

Source: ESMT CA calculations based on cited sources.

The value of the remaining parameters is harder to pin down on the basis of the available data and literature, and it is assumed that λ—the discount factor applied under Internal Reference Pricing in Region A to not highly innovative drugs—is equal to 75%. In other words, if a drug is not considered by the pricing regulator to be highly innovative, its price is set equal to 75% of the free-pricing price.[45] The budget constraint parameter is set equal to \$3,500m, implying that the budget constraint is loose enough that the pharmaceutical firm can afford to select approximately 90% of the value of the whole portfolio.

The parameter governing external competition (ρ, the probability that between consecutive periods other pharmaceutical firms launch competing highly innovative projects) is set equal to 2.5%. The parameter governing how more costly it is to develop highly innovative projects is set equal to 1.1. In other words, highly innovative projects are 10% more expensive than not highly innovative projects. Because the value of these last two parameters is particularly unclear, sensitivity analysis with respect to these parameters is performed and its results are reported later in this section of the report.

[45] Because in certain therapeutic areas the margin is below 25% already under free pricing, it is made sure that the margin under IRP never falls below 5%.

5.7 Policy experiments

In this subsection of the report we quantitatively analyze the consequences of pricing regulation on pharmaceutical innovation by comparing several interesting measures of innovative activity and output in an environment characterized by some form of pricing regulation and in a hypothetical environment characterized by no pricing regulation. With reference to the model's regional distribution of pricing regulation described above, we will be comparing to the hypothetical market-based pricing environment in turn:

- an environment in which in Region A there is Internal Reference Pricing but in Region B there is no External Price Benchmarking;
- an environment in which in Region B there is External Price Benchmarking but in Region A there is no Internal Reference Pricing;
- an environment in which in Region A there is Internal Reference Pricing and in Region B there is External Price Benchmarking, allowing for the two forms of pricing regulation to interact.

Before showing the results of the policy experiments, Table 7 and Table 8 report a set of results pertaining to two important model environments: the market-based pricing environment (the hypothetical environment against which we compare the other environments) and the environment which is closest to the real world. This is the environment—already listed in the third bullet point above—that features the coexistence and interaction of Internal Reference Pricing and External Price Benchmarking. We call the latter environment the status quo.

Table 7 shows in columns 4 to 9 the value—as captured by the ENPV coming out of the calibrated model—of a project depending on its therapeutic area, development phase, and perceived degree of innovativeness. To more easily associate a therapeutic area (in column 1) with its market characteristics, in this table the net sales and margins actually observed in the U.S. are also reported (respectively in columns 2 and 3). The monetary figures in this and the following tables are expressed in millions of U.S. Dollars in year 2008. Table 7 reveals that the value of a project naturally rises over development phases (as development costs drop out of the calculations and market launch approaches) and does not significantly depend on its degree of innovativeness. The latter result has to do with the fact that under market-based pricing whether a drug is perceived as highly innovative or not does not play a role. The discrepancy between the value of highly innovative projects and other projects (noticeable in particular for very small-sales therapeutic areas) is caused by the fact that highly innovative projects are (slightly) more costly to develop than other projects.

Table 7: ENPV of a project under market-based pricing, by therapeutic area, development phase, and degree of innovativeness

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Thera-peutic Area	Empiri-cal Net Sales	Empiri-cal Margin	Phase I		Phase II		Phase III	
			Highly Innova-tive	Other	Highly Innova-tive	Other	Highly Innova-tive	Other
Analgesia	281	30%	0	0	48	58	170	183
Anti-Infecti-ve	332	30%	5	13	77	87	226	239
Cancer	932	40%	175	182	418	428	887	900
Cardio-vascular	570	26%	72	80	212	222	488	501
CNS	728	36%	117	125	302	312	662	675
Diabetes	1150	28%	236	244	542	552	1127	1139
Gastro-Intestinal	568	22%	72	80	211	221	486	499
Genito-Urinary	373	23%	17	24	100	110	271	283
Hormone Control	480	30%	47	55	161	171	388	401
Immune System	409	38%	27	35	121	131	311	324
Inflam-mation	1326	30%	285	293	642	652	1320	1333
Metabo-lism/Endocri ino-logy	473	35%	45	53	157	167	381	394

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Obesity	664	35%	99	107	265	275	591	604
Ophthal-mic	608	35%	83	91	234	244	530	543
Respira-tory	1122	21%	228	236	526	536	1095	1108
Vac-cines	1505	35%	336	334	744	754	1517	1530

Source: ESMT CA calculations.

Table 8 is the analogue of Table 7 in the status quo pricing regulatory environment. It can be seen from Table 8 that, as expected, the value of a project crucially depends on its therapeutic area, sharply rises over development phases, and—because of Internal Reference Pricing—is affected by its degree of innovativeness. In particular, projects that have the potential of being considered highly innovative if and when they will be launched are substantially more valuable that if they are not. It is interesting to note that in the low-sales low-margin area of Anti-Infective, a project in Phase I is valuable if it has the potential of being considered highly innovative but it is not worth developing—not even absent development budget constraints—and thus have a value of zero if it does not have this potential. This fact is interesting because it speaks to the often cited problem of the attrition of projects under pricing regulation: a high-potential project that has been developed up until a certain phase (in this case, Phase I) ceases to be developed further at the time when it is realized that the pricing regulator will not acknowledge its high degree of innovativeness.

Table 8: ENPV of a project under the status quo, by therapeutic area, development phase, and degree of innovativeness

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Thera-peutic Area	Empiri-cal Net Sales	Empiri-cal Margin	Phase I		Phase II		Phase III	
			Highly Innova-tive	Other	Highly Innova-tive	Other	Highly Innova-tive	Other
Analgesia	281	30%	0	0	43	20	162	110
Anti-Infecti-ve	332	30%	2	0	71	42	216	152
Cancer	932	40%	166	145	403	352	860	752
Cardio-vascular	570	26%	67	45	203	151	473	362
CNS	728	36%	110	90	290	241	641	537
Diabetes	1150	28%	224	170	522	403	1094	850
Gastro-Intestinal	568	22%	67	47	202	155	472	371
Genito-Urinary	373	23%	13	3	94	66	261	198
Hormone Control	480	30%	42	23	152	106	374	276
Immune System	409	38%	23	16	114	93	299	251
Inflam-mation	1326	30%	272	205	618	474	1282	988
Metabo-lism/Endoc-rinology	473	35%	40	29	149	119	368	300

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Obesity	664	35%	92	73	254	208	572	472
Ophthal-mic	608	35%	77	60	224	182	513	422
Respira-tory	1122	21%	218	173	509	409	1069	863
Vac-cines	1505	35%	322	267	718	600	1474	1232

Source: ESMT CA calculations

The dependence of the value of a project on its degree of innovativeness is further clarified in Table 9, which reports the percentage difference between the value of a not highly innovative and a highly innovative project, depending on their therapeutic area and development phase.

Table 9: Percentage loss in the ENPV of a project under the status quo for not having the potential to be considered highly innovative

(1)	(2)	(3)	(4)	(5)	(6)
Therapeutic Area	Empirical Net Sales	Empirical Margin	Phase I	Phase II	Phase III
Analgesia	281	30%		-53%	-32%
Anti-Infective	332	30%	-100%	-40%	-30%
Cancer	932	40%	-13%	-13%	-13%
Cardiov-ascular	570	26%	-33%	-26%	-23%
CNS	728	36%	-19%	-17%	-16%
Diabetes	1150	28%	-24%	-23%	-22%
Gastro-Intestinal	568	22%	-30%	-23%	-21%
Genito-Urinary	373	23%	-81%	-30%	-24%

(1)	(2)	(3)	(4)	(5)	(6)
Hormone Control	480	30%	-46%	-30%	-26%
Immune System	409	38%	-29%	-18%	-16%
Inflammation	1326	30%	-25%	-23%	-23%
Metabolism/ Endocrinology	473	35%	-29%	-20%	-18%
Obesity	664	35%	-21%	-18%	-17%
Ophthalmic	608	35%	-22%	-19%	-18%
Respiratory	1122	21%	-21%	-20%	-19%
Vaccines	1505	35%	-17%	-16%	-16%

Source: ESMT CA calculations

What this table shows is that while not having the potential of being considered highly innovative uniformly lowers the value of a project, it does so differentially depending on the characteristics of the therapeutic areas. The value of high-sales and/or high-margins areas such as Cancer are not as significantly affected by the degree of innovativeness as low-sales and/or low-margins areas such Anti-Infective are. This occurs because, on the one hand, low-margin therapeutic areas are the areas that are most heavily affected by a price cut (this is the immediate effect of Internal Reference Pricing on not highly innovative drugs). On the other hand, the same percentage loss in the value of net sales across low- and high-sales therapeutic areas entails a larger percentage loss in the Expected Net Present Value of low-sales therapeutic areas, because the Expected Net Present Value takes into account not only expected net revenues but also expected development costs, which are assumed (primarily due to data limitations) to be constant across therapeutic areas.

Market-based pricing vs internal reference pricing

We can now turn to the policy experiments proper and we do that starting with the policy experiment in which an environment with Internal Reference Pricing but no External Price Benchmarking is compared to the hypothetical environment of market-based pricing. More specifically, in this policy experiment a world in which Region A follows IRP and Regions B, C, and D follow market-based pricing is compared to a world in which all regions follow market-based pricing.

To begin with, Table 10 shows how the value of a project is reduced by IRP, depending on its therapeutic area, development phase, and degree of innovativeness. One can notice that especially in early development phases not only not highly innovative but also highly innovative projects have their value reduced under IRP. It is interesting to note that this result is arrived at under the conservative modeling assumption that Internal Reference Pricing does not affect the price of highly innovative drugs but only of not highly innovative drugs, while in the real world also highly innovative drugs may not be able to fetch a market-based price. In particular, this result is arrived at because also projects that are highly innovative during development face the risk of not being considered highly innovative by the pricing regulator at the time they are launched in the market.

Another clear pattern that emerges from this table is that the therapeutic areas most heavily affected by IRP are the areas with low sales and/or low margins. Areas with low margins—as noted already in the strategic section of this report—are strongly affected by IRP, because for them a drop in price (this is the immediate effect of IRP) is particularly harmful. Areas with low sales also stand to lose considerably in terms of ENPV, which is a measure that includes both net revenues and development costs, and the latter are independent of market size.

Table 10: Percentage change in ENPV under IRP relative to market-based pricing, by therapeutic area, development phase, and degree of innovativeness

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Thera-peutic Area	Empiri-cal Net Sales	Empiri-cal Margin	Phase I		Phase II		Phase III	
			Highly Innova-tive	Other	Highly Innova-tive	Other	Highly Innova-tive	Other
Analgesia	281	30%			-3%	-47%	-1%	-29%
Anti-Infecti-ve	332	30%	-22%	-100%	-2%	-37%	-1%	-26%
Cancer	932	40%	-1%	-14%	-1%	-12%	0%	-11%

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Cardio-vascular	570	26%	-3%	-32%	-1%	-23%	-1%	-20%
CNS	728	36%	-2%	-19%	-1%	-16%	0%	-14%
Diabetes	1150	28%	-2%	-22%	-1%	-19%	0%	-18%
Gastro-Intestinal	568	22%	-2%	-29%	-1%	-21%	0%	-18%
Genito-Urinary	373	23%	-7%	-63%	-2%	-28%	-1%	-21%
Hormone Control	480	30%	-4%	-42%	-1%	-27%	-1%	-22%
Immune System	409	38%	-3%	-36%	-1%	-19%	0%	-15%
Inflam-mation	1326	30%	-2%	-22%	-1%	-20%	0%	-19%
Metabo-lism/Endocr ino-logy	473	35%	-3%	-31%	-1%	-20%	0%	-16%
Obesity	664	35%	-2%	-22%	-1%	-17%	0%	-15%
Ophthalmic	608	35%	-2%	-23%	-1%	-18%	0%	-15%
Respiratory	1122	21%	-1%	-19%	-1%	-17%	0%	-16%
Vaccines	1505	35%	-1%	-15%	-1%	-14%	0%	-13%

Source: ESMT CA calculations

While Table 10 focused only on lead highly innovative projects, thereby focusing only on the consequences of external competition under IRP, the framework proposed in this report also allows for internal competition. It is the consequences of internal competition under IRP that Table 11 focuses on. More precisely, this table demonstrates how the value of a highly innovative project in a therapeutic area in Phase I varies, depending on whether the project is a lead or a back-up project and on the number and spacing of competing projects ahead

of itself in the cluster. Looking in particular at the last four columns of the table, it can be seen that while a lead highly innovative project suffers only moderately under IRP (due only to external competition), back-up highly innovative projects are severely damaged—especially if they have several projects ahead of themselves in the cluster and if the lead projects are close to being launched (they are in Phase III rather than in Phase II).

Table 11: Value and percentage change in ENPV under IRP relative to market-based pricing, by therapeutic area, development phase, and lead or back-up status

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Thera-peutic Area	ENPV under IRP				Percentage Change in ENPV under IRP			
	Lead	Back-Up (Lead in PII)	Back-Up (Lead in PIII)	Back-Up (Lead in Pill and Another Back-Up in PII)	Lead	Back-Up (Lead in PII)	Back-Up (Lead in PIII)	Back-Up (Lead in PIII and Another Back-Up in PII)
Analgesia	0.0	0.0	0.0	0.0				
Anti-Infective	4.1	3.5	0.7	0.0	-22%	-67%	-94%	-100%
Cancer	172.7	168.6	163.8	161.3	-1%	-6%	-9%	-11%
Cardio-vascular	70.5	66.4	61.4	58.9	-3%	-15%	-22%	-26%
CNS	115.1	111.4	106.7	104.3	-2%	-9%	-13%	-16%
Diabetes	232.0	217.4	206.2	200.1	-2%	-10%	-15%	-18%
Gastro-Intestinal	70.1	66.8	62.4	60.2	-2%	-13%	-20%	-24%
Genito-Urinary	15.5	15.0	12.3	11.1	-7%	-32%	-46%	-53%
Hormone Control	45.1	41.9	37.5	35.3	-4%	-20%	-29%	-34%
Immune System	26.0	26.7	24.6	23.8	-3%	-17%	-26%	-30%

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Inflam-mation	280.9	262.4	248.9	241.3	-2%	-10%	-15%	-17%
Metabo-lism/Endocr ino-logy	43.8	42.9	39.9	38.6	-3%	-15%	-22%	-26%
Obesity	97.0	93.6	89.1	86.9	-2%	-10%	-15%	-18%
Ophthalmic	81.6	78.9	74.9	72.9	-2%	-11%	-16%	-19%
Respiratory	224.7	213.4	204.3	199.3	-1%	-9%	-13%	-15%
Vaccines	332.1	317.6	306.4	300.3	-1%	-7%	-10%	-12%

Source: ESMT CA calculations

When all the factors illustrated above and all the projects that in the model the pharmaceutical firm has in its portfolio are taken into consideration, the total value of the portfolio under IRP and under market-based pricing can be calculated. This operation leads to the following result: the value of the whole portfolio (before selecting projects because of the development budget constraint) under market-based pricing is equal to $27,177m and it is equal to $24,869m under IRP. That is, IRP reduces the value of the whole portfolio by 8.49%.

Because, however, the budget a pharmaceutical firm has at its disposal for pharmaceutical development is limited, not all projects in the portfolio can be developed further, and in the model it is assumed that projects are ranked on the basis of their Expected Profitability Index, and the highest-ranking (clusters of) projects are selected until the cumulative sum of initial development costs reaches the development budget limit. We implicitly assume that the development budget constraint is a fraction of contemporaneous sales, and that IRP affects drugs currently on the market in the same way it affects drugs still under development. This implies that under IRP the development budget is also curtailed by 8.5%, declining from $3,500m to $3,203m.

Table 12 shows the list of projects comprising the whole portfolio (columns 1 to 7), how they would be ranked under IRP and under market-based pricing (columns 8 and 9), and whether they are selected for further development or not (columns 10 and 11). The projects in the table are sorted by their rank under IRP. Highlighted in pink are the projects that would have been selected under market-based pricing but that are not selected under IRP; highlighted in blue is conversely the project that is selected under IRP but that would have not been selected under market-based pricing.

Table 12: Ranking of projects under IRP and under market-based pricing

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
Project Identity	Therapeutic Area	Initial Dev. Phase	Initial Degree of Innov.	Initial Back-Up Status	ENPV (IRP)	ENPV (Market-Based Pricing)	Rank (IRP)	Rank (Market-Based Pricing)	Selection (IRP)	Selection (Market-Based Pricing)
58	Inflammation	2	0	0	524	652	1	1	1	1
68	Respiratory	2	1	0	522	526	2	3	1	1
73	Vaccines	3	1	0	1,512	1,517	3	4	1	1
72	Vaccines	2	1	1	681	752	3	4	1	1
71	Vaccines	1	1	1	300	343	3	4	1	1
69	Respiratory	2	0	0	447	536	6	2	1	1
22	Cancer	2	1	0	416	418	7	13	1	1
59	Inflammation	3	1	0	1,314	1,320	8	10	1	1
57	Inflammation	2	1	1	565	650	8	10	1	1
55	Inflammation	1	1	1	241	292	8	10	1	1

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
74	Vaccines	3	0	0	1,324	1,530	11	7	1	1
23	Cancer	2	0	0	378	428	12	8	1	1
24	Cancer	2	0	0	378	428	12	8	1	1
70	Respi-ratory	3	1	0	1,091	1,095	14	14	1	1
67	Respi-ratory	2	1	1	474	534	14	14	1	1
48	Diabe-tes	3	1	0	1,121	1,127	16	16	1	1
47	Diabe-tes	2	1	1	479	550	16	16	1	1
46	Diabe-tes	1	1	1	200	243	16	16	1	1
42	CNS	2	1	0	300	302	19	21	1	1
56	Inflamm ation	1	0	0	230	293	20	19	1	1
25	Cancer	3	1	0	885	887	21	22	1	1
21	Cancer	2	1	1	392	426	21	22	1	1
11	Cancer	1	1	1	161	182	21	22	1	1
43	CNS	2	0	0	263	312	24	20	1	1
26	Cancer	3	1	0	885	887	25	27	1	1
27	Cancer	3	0	0	802	900	26	25	1	1
28	Cancer	3	0	0	802	900	26	25	1	1
12	Cancer	1	1	0	173	175	28	37	1	1
44	CNS	3	1	0	659	662	29	38	1	1
41	CNS	2	1	1	277	310	29	38	1	1
36	CNS	1	1	1	104	124	29	38	1	1

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
13	Cancer	1	0	0	157	182	32	29	1	1
14	Cancer	1	0	0	157	182	32	29	1	1
15	Cancer	1	0	0	157	182	32	29	1	1
16	Cancer	1	0	0	157	182	32	29	1	1
17	Cancer	1	0	0	157	182	32	29	1	1
18	Cancer	1	0	0	157	182	32	29	1	1
19	Cancer	1	0	0	157	182	32	29	1	1
20	Cancer	1	0	0	157	182	32	29	1	1
63	Obesity	3	1	0	589	591	40	42	1	1
62	Obesity	2	1	1	242	273	40	42	1	1
61	Obesity	1	1	1	87	106	40	42	1	1
33	Cardio-vascular	2	0	0	171	222	43	28	1	1
45	CNS	3	0	0	580	675	44	41	1	1
60	Metabo-lism/ Endocri nology	2	1	0	155	157	45	48	1	1
66	Opht-halmic	3	1	0	528	530	46	45	1	1
65	Opht-halmic	2	1	1	213	242	46	45	1	1
64	Opht-halmic	1	1	1	73	90	46	45	1	1
37	CNS	1	1	0	115	117	49	56	1	0
34	Cardio-vascular	3	1	0	486	488	50	52	0	1
38	CNS	1	0	0	101	125	51	49	0	1
39	CNS	1	0	0	101	125	51	49	0	1
40	CNS	1	0	0	101	125	51	49	0	1

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
54	Immune System	2	1	0	119	121	54	58	0	0
53	Hormone Control	3	1	0	386	388	55	57	0	0
35	Cardiovascular	3	0	0	402	501	56	55	0	0
30	Cardiovascular	1	1	0	71	72	57	60	0	0
49	Gastro-Intestinal	1	1	0	70	72	58	61	0	0
31	Cardiovascular	1	0	0	55	80	59	59	0	0
9	Anti-Infective	3	1	0	225	226	60	65	0	0
51	Genito-Urinary	2	1	0	98	100	61	64	0	0
8	Anti-Infective	2	0	0	55	87	62	62	0	0
10	Anti-Infective	3	0	0	177	239	63	63	0	0
2	Analgesia	2	1	0	47	48	64	66	0	0
4	Anti-Infective	1	1	0	4	5	65	69	0	0
32	Cardiovascular	2	1	1	186	220	66	52	0	1
52	Hormone Control	2	1	1	138	168	66	70	0	0
7	Anti-Infective	2	1	1	63	85	66	70	0	0
29	Cardiovascular	1	1	1	59	79	66	52	0	1

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)
5	Anti-Infective	1	0	0	0	13	66	67	0	0
6	Anti-Infective	1	0	0	0	13	66	67	0	0
50	Genito-Urinary	1	1	1	15	22	66	70	0	0
1	Analgesia	1	1	1	0	0	66	70	0	0
3	Anti-Infective	1	1	1	0	12	66	70	0	0

Source: ESMT CA calculations

What Table 12 implies is that the number of projects that are developed declines from 54 under market-based pricing (of which 32 projects are highly innovative) to 49 (of which 30 projects are highly innovative). As a consequence of this, while under market-based pricing 21.94 projects are expected to be launched in the market (13.98 of which highly innovative), only 20.15 (of which 12.92 highly innovative) are expected to be launched under IRP.

The combined effect of the lower value of individual projects and the lower budget available for development implies that relative to market-based pricing under IRP the value of the selected portfolio declines from $24,808m to $21,912m, a drop of 11.67%. This result may be interpreted as a conservative one, considering that in our model IRP does not alter the price of all drugs but only of those drugs that are not considered highly innovative at the time of market launch by the regulator.

Market-based pricing vs external price benchmarking

In this subsection we consider a specular policy experiment: an environment with External Price Benchmarking but no Internal Reference Pricing is compared to the hypothetical environment of market-based pricing. More specifically, in this policy experiment a world in which Region B follows EPB and Regions A, C, and D follow market-based pricing is compared to a world in which all regions follow market-based pricing.

As Table 13 indicates, EPB has a more homogeneous effect across project types than IRP does. In particular, the effect of EPB appears to be independent of the free-pricing margin of a therapeutic area and to be only mildly declining over development phases.

Because of this, it is not expected that the ranking of projects under ERP be significantly different from the ranking under market-based pricing, entailing that the major effect of ERP on pharmaceutical innovation is driven by lower available development budget resources. In terms of access of drugs to Region C—the low willingness-to-pay region—it is found that under ERP only (but the results change once ERP is combined IRP in the next subsection) the pharmaceutical firm always launches also in Region C. Having said that, the difference in global net sales between launching and not launching in Region C is not big. It would be interesting to see how these results about regional launch, which are homogeneous across therapeutic areas, changed if richer data allowed us to have therapeutic-area-specific demand parameters for Region C.

Table 13: Percentage change in ENPV under EPB relative to market-based pricing, by therapeutic area, development phase, and degree of innovativeness

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Therapeutic Area	Empirical Net Sales	Empirical Margin	Phase I		Phase II		Phase III	
			Highly Innovative	Other	Highly Innovative	Other	Highly Innovative	Other
Analgesia	281	30%			-7%	-6%	-4%	-4%
Anti-Infective	332	30%	-37%	-15%	-5%	-5%	-3%	-3%
Cancer	932	40%	-3%	-3%	-3%	-3%	-3%	-3%
Cardiovascular	570	26%	-4%	-4%	-3%	-3%	-2%	-2%
CNS	728	36%	-4%	-4%	-3%	-3%	-3%	-3%
Diabetes	1150	28%	-3%	-3%	-2%	-2%	-2%	-2%
Gastro-Intestinal	568	22%	-4%	-4%	-3%	-3%	-2%	-2%
Genito-Urinary	373	23%	-11%	-8%	-4%	-4%	-3%	-3%

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Hormone Control	480	30%	-6%	-5%	-4%	-3%	-3%	-3%
Immune System	409	38%	-10%	-7%	-4%	-4%	-3%	-3%
Inflammation	1326	30%	-3%	-3%	-2%	-2%	-2%	-2%
Metabolism/Endocrinology	473	35%	-7%	-6%	-4%	-4%	-3%	-3%
Obesity	664	35%	-4%	-4%	-3%	-3%	-3%	-3%
Ophthalmic	608	35%	-5%	-4%	-3%	-3%	-3%	-3%
Respiratory	1122	21%	-2%	-2%	-2%	-2%	-2%	-2%
Vaccines	1505	35%	-3%	-3%	-3%	-3%	-2%	-2%

Source: ESMT CA calculations

When summing over all projects in the portfolio, the value of the whole portfolio declines from $27,177m under market-based pricing to $26,437m under ERP—a drop of 2.72%. The budget available for development activities declines correspondingly and goes from $3,500m to $3,406m.

In terms of the number of projects selected, instead of the 54 projects selected under market-based pricing (of which 32 highly innovative), there are 51 projects selected under EPB (of which 29 highly innovative. Of these projects, 20.64 (and 12.68 highly innovative) are expected to be launched. Compounding the effect of the evaluation of projects with the effect on the development budget implies that the value of the selected portfolio goes down to $23,389m—a 5.72% drop relative to market-based pricing.

Market-based pricing vs the status quo

In this subsection we consider a policy experiment that combines the two preceding policy experiments and analyzes how Internal Reference Pricing and External Price Benchmarking interact: in this policy experiment a world in which Region A follows IRP, Region B follows EPB, and Regions C and D follow market-based pricing—the status quo world—is compared to a world in which all regions follow market-based pricing.

Table 14 reports the percentage change in the value of different project types under this policy experiment. A comparison between this table with Table 10 and Table 13 shows the value loss under a combination of IRP and EPB is greater than the sum of the value losses under IRP and EPB separately. Taking for example a not highly innovative Cancer project in Phase I, one can see that such project stands to lose 14% of its value under IRP and 3% under EPB, but under the combination of IRP and EPB is predicted to lose 21% of its value. This occurs because EPB serves as an amplification mechanism for IRP, whereby not being considered highly innovative in Region A (the region under IRP) has unfavourable consequences also in Region B (the region under EPB).

Table 14: Percentage changes in NPV under the status quo relative to market-based pricing, by therapeutic area, development phase, and degree of innovativeness

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Therapeutic Area	Empirical Net Sales	Empirical Margin	Phase I		Phase II		Phase III	
			Highly Innovative	Other	Highly Innovative	Other	Highly Innovative	Other
Analgesia	281	30%			-11%	-65%	-5%	-40%
Anti-Infective	332	30%	-65%	-100%	-8%	-51%	-4%	-36%
Cancer	932	40%	-5%	-21%	-4%	-18%	-3%	-16%
Cardiovascular	570	26%	-8%	-44%	-4%	-32%	-3%	-28%
CNS	728	36%	-6%	-28%	-4%	-23%	-3%	-20%
Diabetes	1150	28%	-5%	-30%	-4%	-27%	-3%	-25%
Gastro-Intestinal	568	22%	-7%	-41%	-4%	-30%	-3%	-26%
Genito-Urinary	373	23%	-20%	-90%	-6%	-40%	-3%	-30%
Hormone Control	480	30%	-11%	-58%	-5%	-38%	-4%	-31%

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Immune System	409	38%	-14%	-53%	-6%	-28%	-4%	-22%
Inflam-mation	1326	30%	-5%	-30%	-4%	-27%	-3%	-26%
Metabo-lism/End ocrino-logy	473	35%	-10%	-45%	-5%	-29%	-4%	-24%
Obesity	664	35%	-6%	-32%	-4%	-25%	-3%	-22%
Ophthal-mic	608	35%	-7%	-34%	-4%	-26%	-3%	-22%
Respira-tory	1122	21%	-4%	-27%	-3%	-24%	-2%	-22%
Vac-cines	1505	35%	-4%	-22%	-3%	-20%	-3%	-19%

Source: ESMT CA calculations

As a result, the value of the whole portfolio reduces to $23,517, or 13.47% less than under market-based pricing. This brings the available development budget resources down to $3,028m and the value of the selected portfolio down to $19,904m, or 19.77% less than under market-based pricing.

The number of projects selected reduces sharply to 45, including 26 highly innovative projects, and the number of projects expected to be launched also reduces to 18.61, including 11.38 highly innovative projects. As far as the optimal regional market launch strategy in this policy scenario is concerned, it is worth pointing out that the pharmaceutical firm in the model is less reluctant to launch highly innovative projects than it is to launch not highly innovative projects.

5.8 Sensitivity analysis

In order to explore how dependent the results presented above are to the value that was assigned to several parameters, we performed a variety of sensitivity analyses. These analyses are especially important with respect to those parameters whose value was assigned on the basis of only scant information. In the following, we focus in particular on two parameters: the cost premium that highly innovative projects are subject to and the probability of external competition's success.

Different values of the development cost premium of highly innovative projects

It was assumed that the costs of developing projects that have the potential of being considered highly innovative was higher than the costs of developing other projects. This assumption was motivated by the observation that it could take more expensive clinical trials to entertain the hypothesis of being considered highly innovative by the pricing regulator. Namely, we assumed that the costs of developing highly innovative projects were 10% higher than the costs of developing other projects.

In this sensitivity analysis we compare some results achieved under this assumption to comparable results achieved under the assumption that highly innovative projects are no more and no less costly to develop than other projects—in the status quo environment in which Region A is affected by Internal Reference Pricing, Region B is affected by External Price Benchmarking, and Regions C and D exhibit market-based pricing.

We find essentially no change in the ranking of projects. We also find that the average ENPV of a highly innovative project in the portfolio—under IRP subject to the consequences of increased external competition—increases from $348.52m to $354.96m, or 1.90%; the average EPI of a project in the portfolio increases from 5.23 to 5.87, or 12.24%. It is interesting to observe that the quantitative difference in the outcome according to the two value measures is due to the way in which these measures are constructed. Indeed, the EPI is equal to the ENPV divided by initial development costs. When development costs are reduced, this not only increases the numerator of the EPI (that is, the ENPV), but it also decreases the denominator, yielding a larger overall effect. If we look at the value of the whole portfolio—including both highly innovative and other projects—its value increases to $23,813m, or 1.26%.

Different values of the probability of external competition's success

The other sensitivity analysis exercise that we perform pertains the model's parameter measuring the intensity of what we called external competition. In the model, highly innovative projects are subject to the risk that other pharmaceutical firms launch in the market competing highly innovative projects, making the proprietary projects lose their high degree of innovativeness. We set the probability that between consecutive development phases other firms would do precisely that equal to 2.5%.

In this sensitivity analysis we increase this value to 10%, sharpening external competition. What we find is that, as Table 15 shows, the value of highly innovative projects drops considerably. This is especially true for projects that are in earlier development phases, as they are the projects that are most distant from market launch and are thus most susceptible of being preceded at some point down the development road by external competition.

Table 15: Percentage loss in the ENPV of a highly innovative project under the status quo if the probability of external competition's success increases from 2.5% to 10%

	Phase I	Phase II	Phase III
Analgesia		-10.15%	-3.09%
Anti-Infective	-100.00%	-7.37%	-2.73%
Cancer	-3.42%	-2.11%	-1.08%
Cardiovascular	-8.72%	-4.30%	-2.01%
CNS	-4.97%	-2.83%	-1.40%
Diabetes	-5.69%	-3.58%	-1.81%
Gastro-Intestinal	-7.95%	-3.94%	-1.85%
Genito-Urinary	-25.45%	-5.52%	-2.25%
Hormone Control	-12.35%	-5.11%	-2.28%
Immune System	-10.97%	-3.52%	-1.55%
Inflammation	-5.64%	-3.61%	-1.84%

	Phase I	Phase II	Phase III
Metabolism/Endocrinology	-8.83%	-3.68%	-1.68%
Obesity	-5.68%	-3.10%	-1.51%
Ophthalmic	-6.16%	-3.22%	-1.55%
Respiratory	-4.93%	-3.10%	-1.57%
Vaccines	-3.94%	-2.58%	-1.33%

Source: ESMT CA calculations

Despite these changes in the evaluation of projects, the value of the whole portfolio declines only to $23,232, or by 1.21%, and the ranking of projects remain essentially unmodified.

5.9 Conclusions

In this section of the report we presented a decision-theoretic model of pharmaceutical innovation that allowed us to quantitatively evaluate the effect of the main existing schemes of pricing regulation and their interaction.

In the model proposed, a pharmaceutical firm evaluates a portfolio of drug candidates, ranks them on the basis of their Expected Net Present Value (ENPV) and their Expected Profitability Index (EPI), and selects the highest-ranking ones until current development costs reach a development budget limit. Projects are in different therapeutic areas, are in different development phases, and have different potentials of being considered highly innovative by the pricing regulator at the time of market launch. Development is dynamic and risky, and the evaluation of a project takes into account the alternative possible realizations of future events and the future development and launch decisions contingent on such realizations. For example, a project in an early development phase that has the potential of being considered highly innovative by the pricing regulator if and when it will be launched in the market may lose its potential in later development phases, at which point the decision-maker may decide not to develop the project further. In another example, the decision-maker may decide about the set of countries in which to launch its drug depending on whether the pricing regulator considers that drug highly innovative or not.

Indeed, in the model proposed there exist different regions, which are heterogeneous in their pricing regulation. Because of Internal Reference Pricing (IRP) in one region, it matters whether a drug is highly innovative or not; because of External Price Benchmarking (EPB), whether or not a drug is launched in one region has consequences in another region.

In addition to the risk of failing clinical trials or not receiving marketing authorization, in the model proposed highly innovative projects face the risk of losing their high degree of innovativeness by the time they are launched in the market. This may be due to external competition (competition from other pharmaceutical firms, not modeled explicitly) or to internal competition (competition from other projects in the portfolio of the pharmaceutical firm itself).

On the basis of the model, which we calibrate to replicate several quantitative aspects of the real world, we perform several policy experiments to evaluate the effect of pricing regulation on pharmaceutical innovation. A summary of the results of the policy experiments is reproduced in Table 16.

Table 16: Summary of results of policy experiments

Statistic				Policy scenario			
				Market-based pricing	IRP	EBP	Status quo
ENPV of a project	Highly innovative	High margin (Cancer)	Phase I	175	173	169	166
			Phase II	418	416	406	403
			Phase III	887	885	864	860
		Low margin (Respiratory)	Phase I	228	225	222	218
			Phase II	526	522	515	509
			Phase III	1,095	1,091	1,074	1,069
	Other	High margin (Cancer)	Phase I	182	157	176	145
			Phase II	428	378	416	352
			Phase III	900	802	876	752
		Low margin (Respiratory)	Phase I	236	192	230	173
			Phase II	536	447	525	409
			Phase III	1,108	936	1,087	863
ENPV of the whole portfolio				27,177	24,869	26,437	23,517
Number of projects developed		Highly innovative		32	30	29	26
		Other		22	19	22	19
Expected number of projects launched		Highly innovative		14	13	13	11
		Other		8	7	8	7
ENPV of the selected portfolio				24,808	21,912	23,389	19,904

Source: ESMT CA calculations

To begin with, we find that relative to an environment of market-based pricing, in an environment in which approximately one fourth of the world adopts Internal Reference Pricing the value of all projects—including highly innovative projects—is reduced. This occurs because also projects that are highly innovative during development face the risk of not being considered highly innovative by the pricing regulator at the time they are launched in the market. Because the decision-maker is forward-looking, it takes this event into account in evaluating projects and making optimal development

decisions. The projects that are most heavily affected by Internal Reference pricing are projects in earlier development phases—whose expected present value of net sales is smaller relative to expected present development costs—and projects in low-sales/low-margin therapeutic areas. Taking into consideration its composition in terms of therapeutic area, development phase, and degree of innovativeness, the whole portfolio of the pharmaceutical firm in our model loses 8.5% of its value under Internal Reference Pricing.

The ranking of projects on the basis of their Expected Profitability Index is only moderately affected by Internal Reference Pricing, with highly innovative projects gaining only few positions relative to market-based pricing. However, the fewer resources available for development under Internal Reference Pricing entail a reduction in the number of selected projects from 54 (out of which 32 are highly innovative) to 49 (30 highly innovative) and a reduction in the number of projects expected to be launched in the market between approximately 22 (14 highly innovative) to 20 (13 highly innovative). The combined effect of the lower value of individual projects, their different ranking, and the fewer resources available for development implies that under IRP the value of the selected portfolio declines by approximately 12%.

When we next compare to an environment of market-based pricing an environment in which approximately one fourth of the world adopts External Price Benchmarking, we find that the decline in the value of projects is by and large independent of therapeutic area, development phase, and degree of innovativeness, implying that the raking of projects is virtually unchanged. The value of the whole portfolio declines by approximately 3%.

In terms of the number of projects selected and expected to be launched in the market under External Price Benchmarking, 51 projects (out of which 29 are highly innovative) are selected and approximately 21 (13 highly innovative) are expected to be launched. Compounding the effect of External Price Benchmarking on the evaluation of projects with its effect on the resources available for development implies that the value of the selected portfolio declines by approximately 6%.

In the last policy experiment considered in the report, an environment of market-based pricing is compared to an environment in which at the same time one fourth of the world adopts Internal Reference Pricing and another fourth of the world adopts External Price Benchmarking—the environment that most closely resembles the world as it is today.

We find that the value of a project under jointly Internal Reference Pricing and External Price Benchmarking drops by an amount that is greater than the sum of the amounts by which it drops under Internal Reference Pricing and External Price Benchmarking separately: through External Price Benchmarking, the consequences of not being considered highly innovative in a country adopting Internal Referencing

Pricing spill over to other countries. As a result, the value of the whole portfolio and the selected portfolio shrink by 13% and 20% respectively. The number of projects selected and expected to be launched in the market is reduced to 45 (out of which 26 are highly innovative) and 19 (11 highly innovative), respectively.

We conclude that, in designing optimal pharmaceutical pricing and reimbursement regulation, the benefits of more affordable or cost-effective drugs must be traded against the costs of less pharmaceutical innovation, with fewer projects being developed in general and in particular in low-margin therapeutic areas and with little potential of being considered highly innovative at the time of market launch. Because through External Price Benchmarking pricing decisions in one country spill over to other countries, even the pricing regulatory changes introduced in an individual country may affect pharmaceutical firms' global incentives to innovate. Because pharmaceutical discovery and development is a long-lasting process, the adverse consequences of the pricing and reimbursement regulation that is introduced today will be observed in the number and characteristics of the drugs that will be launched in the market in the future.

Appendix. List of interview partners

Parts of this report draw on the interviews we had with Novartis representatives in Basel and during phone conferences. Apart from Meni Styliadou, Head of European Public Affairs, and Stephan Mumenthaler, Head of Economic Affairs—who guided us throughout the project—the list of our Novartis interview partners comprises:

- Miguel Bernabeu, Head of Market Access Region Europe;
- Kenneth Goldman, Director of IP Strategy;
- Jens Grüger, Head of Global Pricing & Reimbursement;
- Petra Keil, Head of Global Public Policy;
- Detlef Niese, Head of External Affairs;
- Romeo Paioni, Head of Scientific & External Affairs, Pharma Development;
- Gesa Pellier, Head of Drug Regulatory Affairs (DRA) Europe;
- Kristin Yarema, Head of Strategic Marketing Pharmaceuticals.

We also benefitted from conversations with Jack Calfee of the American Enterprise Institute, Trevor B. Jones of Allergan, W. Brian Healy and Monika Dorda of Merck & Co., and Ben Yeoh.

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