**H**EALTH **I**NNOVATION NE**X**T GENERATION **P**AYMENT & PR**I**CING MODELS **(HI-PRIX)**:

Balancing Sustainability of Innovation with Sustainability of Health Care


# M9: Price discrimination with multi-indication products: underpinning economic theory and empirical evidence

WP4: Pricing dynamics throughout the lifecycle of pharmaceutical products

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## 1 Introduction

Indication-based pricing (IBP), also referred as multi-indication pricing, refers to a pricing strategy in which a pharmaceutical company sets different prices for a drug based on the specific indications or conditions it is approved to treat. This approach recognizes that a drug may have multiple approved uses, each with varying levels of effectiveness and clinical benefit, and assigns different prices accordingly.

The literature on indication-based pricing can be divided into two broad lines: an empirical literature, describing mechanisms that implement some version of differentiated pricing according to therapeutical indication, or at least have in consideration the existence of multiple indications that can be addressed by the same pharmaceutical product; and a theoretical literature, that puts forward principles and arguments in favour of differential pricing according to indications that generate different value to patients being treated. There is not, at present, clear rules for pricing that emerge from the theoretical literature, and the empirical literature reveals that IBP is often guided by an approach of trial-and-error rather principles-based rules.

We discuss here the main features of those two strands in the literature, avoiding repetition with existing surveys whenever adequate.

The focus is on the main points made in the existing literature. Also, the many examples and motivations for the interest on IBP will not be repeated here.

## 2 The economics of indication-based pricing

In the competitive market benchmark, prices are driven down to the level of (marginal, in the sense of incremental) cost of production by competition among existing companies in the market. Even if there are different groups of consumers with distinct valuations to the product, the wellbeing of society is highest when prices equal

(marginal) costs and one price holds for all consumers buying the product, even if they hold different valuations from the use of the product.

Thus, in this benchmark, a single price is efficient from a societal point-of-view and ensures a fair return on investment to firms as the relevant economic costs include the opportunity cost of investing in the firms.

The interest in indication-based pricing needs to result from deviations in market conditions to the competitive benchmark model. The main deviation is the role of innovation and the need of economic signals to invest and to develop new products, and new indications for the use of new pharmaceutical products.

This point of rewards to innovation being a deviation to the simple benchmark of a perfectly competitive economy is well known, and it should be present in the discussion of IBP.

Two distinct aspects co-exist: rewards should be enough to compensate the effort of innovation; and, rewards need to differentiate between alternative innovations of different value if not all, in particular the highest value innovations, would not be pursued otherwise.

The first aspect is about absolute rewards to innovation, making it worthwhile to make the investment and develop the new products. The second aspect is about relative rewards, to use price (rewards) signals to guide innovation efforts across different possibilities.

The discussion of IBP cannot be done in a complete way if incentives to innovation are not explicitly considered.

From a health systems perspective, besides the innovation incentives, there are goals of health systems to be considered: equity, access, and affordability (to payers and to patients) are three key goals that are of interest, as different prices may result in differential access to treatment for patients with different indications.

# 3 The use of indication-based pricing and evidence on its effects

## 3.1 The use of indication-based pricing

There are several recent literature reviews reporting on the use of IBP in pharmaceutical

markets (several countries and product markets). This literature proposes a classification of models used by payers that take into account the existence of multiple indications of use for a pharmaceutical product. We follow here the systematic review of Preckler and Espin (2022), with reference to other works when adequate, to complement their review.[1] The authors identify three different types of application of indication-based pricing: a) different brands per indication, b) a single weighted average list price across indications, and c) a single list price that corresponds to the highest-value indication and discounts leading to different net prices (discounts can be kept confidential, though not secret – their existence is known, but not the value of the discount). See Table 1 in Preckler and Espin (2022, p. 3).

The summary description to the weighted average list price is "This price reflects the weighted average price by either or both the volume and value of the different indications. The volume can be estimated ex ante or reconciled ex post through rebates, reflecting the actual number of patients in each indication. This approach is widely accepted as the simplest in practice, albeit an ex post reconciliation could add some administrative complexities", with a reference to Pearson et al. (2017).

These ways of setting IBP deserve several comments. The brand approach creates an artificial difference between indications, so as to apply distinct prices to different groups of patients (consumers). If no off-label use can be enforced, the brand approach can avoid arbitrage in use across indications. In case of the different brands corresponding to distinct dosages and presentations of the pharmaceutical product, the no arbitrage condition necessary for IBP to work is more likely to be satisfied.

The average price approach can only work as intended if there is strict control over quantities consumed per indication being independent of the price per indication (say, when patients are fully insured and clinicians decide without regard for the price, this will be satisfied). Otherwise, averaging the price over indications will provide signals to use that are different from the ones resulting from different price per indication.

Several countries have used a single price across indications (group of consumers). From

[1] Other relevant reviews on the issue are due to Towse et al (2019) and Campilo-Artrero et al (2020).

a public policy perspective, the uniform price should on the one hand be low enough to provide access, and high enough to cover production costs and (over the drug's lifetime) the initial investment in creating the drug and getting it ready for use. The trade-off may be fundamentally similar to that of the producer but will tilt towards a lower price and more access. Given that different indications may have widely different value for patients as well as for society, the above implies that when a single price is set, not all indications may not be covered. The reason is that low-value indications may not justify the R&D (and eventually production and commercial) expenditure at the given single price. Especially when a drug is first introduced in the market to attend to high-value indications, its price will be set high. If a single price must be kept over the lifetime of the product, then the producer may have no interest in lowering the price later to allow for lower-value indications. (These implications are also discussed below)

The third type of mechanism for IBP relies again on consumption decisions being independent of the prices, otherwise lower priced indications will have their consumption level decisions distorted (towards lower use, as the price observed is higher than the effective price). The use of average weighted prices or of discounted prices requires detailed information on use of pharmaceutical products, which may be easier to gather, register and manage for some products than for others.

**Country examples of IBP**

In Australia, a weighted average price is calculated from utilisation data by indication.

In Austria, a weighted average price is calculated from utilisation data by indication.

In Belgium, a weighted average price is calculated from utilisation data by indication and different confidential risk-sharing arrangements at indication level create an IBP structure.

In Denmark, different brands approach is used.

In Estonia, there is public single price, and different confidential risk-sharing arrangements at indication level create an IBP structure.

In France, different prices for different brands and weighted average price.

In Germany, different prices for different brands and weighted average price.

In Italy, different prices for different brands and single listed price to highest valuation and discounts leading to different net prices.
In Spain, a national weighted average price coupled with (eventual) confidential discounts at regional level.
In Switzerland, different prices for different bundles (combinations), and use of discounts.
In the United Kingdom, different prices for different brands through the use of discounts.
In the United States, the Centers for Medicare and Medicaid Services (CMS) has explored the concept of indication-based pricing through its Oncology Care Model, which aims to test innovative payment and delivery models for oncology services. Otherwise, CMS defines a single price, with no IBP.

Overall, implementing multi-indication pricing is a complex process that requires careful consideration of factors such as clinical evidence, patient populations, disease prevalence, therapeutic alternatives, and the economic burden of the diseases being treated.
There are no specific countries or institutions that had officially announced the use of multi-indication pricing as a widespread policy, with published guidelines on its use by payers (even if determining only the guiding principles for negotiation and not necessarily automatic pricing rules).

## 3.2 What to learn from the practice of IBP

Indication-based pricing is based, in the cases in which it has been used, on a set if principles: a) use of clinical evidence and cost-effectiveness analysis: IBP considers the varying levels of clinical evidence and of cost-effectiveness of the pharmaceutical product across different indications. The pricing is intended to reflect the differences in efficacy, safety, and patient outcomes associated with each approved use; b) conditions with higher prevalence or those lacking effective treatment options may warrant different pricing approaches to encourage innovation and access, using IBP as way to induce innovation to address issues of unmet need; c) explicit use of value-based

health care considerations: improved patient reported outcomes, quality-adjusted life years (QALYs) as elements guiding different prices per indication.

A tension in definition prices is associated with transparency. It has gained ground the point that pricing decisions should be transparent, with clear justifications provided for setting different prices for each indication. This includes sharing information on the underlying factors considered, such as clinical evidence, cost drivers, and value assessments. Cost transparency is a difficult matter, as pharmaceutical companies refrain from disclosing publicly such costs (probably fearing prices defined with reference to such costs and not value generated), while from an economic point of view, prices defined as cost-plus would lead to further costs without necessarily bringing the discovery the most valued innovations. The dynamic efficiency of innovation can be hurt by pricing rules based on cost-plus, while over time also static efficiency will suffer (as increasing costs is the way to increase prices, and monitoring of costs will entail considerable costs, and may even be unfeasible in a widespread way).

### 3.3 Strategic introduction of indications

According to Michaeli et al. (2022) and Mills (2023), pharmaceutical companies have submitted for approval first indications that have a higher clinical benefit, usually with a smaller patient base, than it is the case with indication extensions. This suggests that timing of introduction of indications is strategically defined by pharmaceutical companies, at least to some extent. If discovery of indications was made at random (relative to value) and introduced immediately as they become available, it is unlikely that this regularity would emerge.

### 3.4 Gaps in the empirical literature

A critical missing point in the empirical literature is the assessment (measurement) of welfare effects from the existing IBP models.

None of the existing studies addresses, with measurement on the rate of innovation or another variable, the long-term issue of R&D incentives (how the IBP influences innovation patterns and choices).

The research pipeline of pharmaceutical companies includes situations in which

companies know, with a fair degree of certainty, what comes next, situations in which they are uncertain about the results of the research effort and situations in which they drop a particular research line as they found other companies are more advanced and/or have better products.

The development of multi-indication products often results from entering a therapeutic area, and then other indications are discovered after a first successful one.

Some works suggest that an effect is likely to be present. They argue on it by reference to lines of R&D that are discontinued by companies, as being unprofitable under current prices of indications using the same product. This indirectly suggests that the possibility of differential pricing according to indication would be able to induce R&D efforts that would not be present otherwise. Still, there is no causal analysis that establishes the link that presence of IBP leads to more R&D.[2] The observation that R&D lines are discontinued because firms consider them likely to be non-profitable at the current prices of other indications of the same product is not equivalent to say that with IBP (that is, a different price for a new indication) that line of research would be pursued and be profitable to do so. There is certainly a price that would make the firm continue the research line but there is no guarantee that such a price would below the value generated to patients and to society (or, in another way of describing the case, it is not possible to ensure that the highest price acceptable to society would be enough to make the development of the product profitable to society and to the company). The existence of IBP can be necessary but not a sufficient condition for all research lines to be pursued.

The three categories of IPB described above (section 3.1) raise different challenges to economic reasoning, to be met with both conceptual and empirical analysis, in the future.

## 4 Indication-based pricing and general economic principles

On the theoretical developments relative to indication-based pricing, there are two broad strands of discussion. The first one is built by accumulation of simple examples,

[2] Unlike in experimental setups, respecting completely the requirements for establishing a causality nexus is arguably quite difficult to set and to observe in the context of pharmaceutical innovation.

illustrating how access to new indications (therapies) may result from a more flexible pricing structure (differentiation across indications).

The second line in the literature explores the similarity with the problem of funding a pre-determined amount (a budget available) from several markets (with initial works having a focus on different geographical markets, different countries). The argument initially explored in a multi-country setting can be easily extended to a multi-indication setting.

The simplest context is to frame the relevant problem as how to structure prices in order to cover the R&D expenditures incurred to obtain the innovation, the different indications for the new pharmaceutical product. This becomes a straightforward application of Ramsey prices from regulation theory.[3]

Two specific features of pharmaceutical innovation and prices can be introduced in this simple context. The first is the existence of health insurance and delegation of decisions to consume (use) the pharmaceutical product to another economic agent (the clinician, an expert). These two elements change profoundly the price elasticity of demand, the critical factor in price differentiation under Ramsey pricing.[4]

A second relevant difference is that under regulation, Ramsey prices are set by a regulatory agency while in pharmaceutical prices there is often a negotiation procedure. Moreover, companies may face therapeutic competition from other close innovative products and/or have the option of not introducing the product in the market. Another key change is that the total amount to be funded is not exogenously given. The R&D effort directed to each indication can be endogenously determined.

## 4.1 Indication-based pricing as price discrimination.

Indication-based pricing and price discrimination are related as both concepts involve setting different prices for the same product. They differ in the underlying rationale and methods used. IBP focuses on setting different prices for a pharmaceutical product based on the specific indications or conditions it is approved to treat. The aim (see previous section) is to reflect the varying value and benefit the product provides across

[3] Danzon and Towse (2003); Jack and Lanjouw (2005).

[4] Barros and Martinez-Giralt (2008)

different medical conditions (leading to different indications of use).

On the other hand, price discrimination refers to the practice of charging different prices to different customers or market segments for the same product or service. Price discrimination can be based on various factors, such as customer characteristics, geographical location, purchasing power, or willingness to pay. The objective of price discrimination is to capture the maximum value from different customer segments, taking advantage of their varying price sensitivities and abilities to pay.

In the context of pharmaceutical pricing, IBP can be seen as a form of price discrimination, as it involves charging different prices for the same drug based on the indications, where the criterion to discriminate prices is the medical condition of patients.

A relevant work on the similarities and differences of IBP and Ramsey pricing is due to Danzon et al. (2015), as characterizes conditions for dynamic efficiency and second-best static efficiency properties of pharmaceutical differential pricing based on value. They set the analysis in terms of countries, where each country is a different market that can be served with a different price given its underlying characteristics. Countries can be replaced by groups of patients, and as long as groups of patients are independent of each other (like they were residing in different countries, to keep closer to the paper terminology), the analysis goes through. The key insight from the paper is that payers should set their constraints on prices, through determination of an incremental cost-effectiveness ratio, and then let pharmaceutical companies set prices within those limits. Prices will adjust to the maximum threshold, meaning that higher benefits from a new product will be met with a higher price, thus providing the signals for innovation of higher value. Still, this mechanism will transfer all value generated to pharmaceutical companies, which can be disputed on distributional grounds and on efficiency grounds if a social cost of raising funds to make such payments is included.

## 4.2 Strategic interaction

To these settings, one needs to add the strategic considerations of sequential discover, investment and pricing structures resulting from the interaction of pharmaceutical companies and payers (regulatory bodies) that define regulated pharmaceutical prices, or that contract prices with pharmaceutical companies.

As mentioned above, companies seem to select high value – low patient base indications for first approval, as these will command a higher price. Differential pricing by indication may decouple time of introduction from prices of earlier indications approved. Still, there is not clear guidance, from theory, at this point, to design the optimal time path of prices per indication, taking into account both static and dynamic efficiency.

### 4.3 Economics of price differentiation and IBP

Setting prices of an indication equal to its value to consumers leads to IBP whenever the value varies across groups of patients targeted by each indication. However, this simple rule does not need to be socially optimal (as it may transfer too much value, make too large payments, to pharmaceutical companies, in the sense of transferring more than the amount required to have the innovation effort and allowing for an opportunity cost in raising the funds to make such payments).

At a broad level, we can have first-degree price discrimination in the future, resulting from discovery of new indications, if personalised medicine/health care becomes such that a pharma product and its price is tailored to each individual; we have third-degree price discrimination when clinical conditions are identified and used to stratify patients and their use of the products. But off-label use may introduce arbitrage between groups of consumers. Thus, the specific nature of each intervention area and products will influence the social outcomes from different pricing structures. Therefore, we can have a) personalized pricing, differential pricing based on individual characteristics; b) group pricing, differential pricing on clinical conditions; and, c) menu pricing, with eventual off label use as a constraint, differential pricing based on patient (clinician as patient's agent) choice.

### 4.4 IBP and social welfare

In a context with innovation given, from the general economics literature, the discrimination across groups of consumers can increase welfare if total output increases. The output effect is linked to the behavior of demand, and the welfare effects of allowing price discrimination versus uniform pricing are ambiguous in the sense that depend on the curvature of demand functions (Aguirre et al., 2010; Schmalensee, 2010; Vickers,

2020). Total welfare effect depends on each case. Generally, some stakeholders gain while others lose, so without looking into the specifics of each case the overall picture is ambiguous. But total welfare will only increase if there is more access to cover unmet needs on the patient side. In this sense, price discrimination can be a valuable instrument in the absence of other rules that guarantee access. This is the static point of view. The dynamics of price differentials as an incentive for R&D effort have not been thoroughly explored, and are a crucial element in the discussion of pharmaceutical pricing differentials per indication.

Indication-based pricing can incentivize pharmaceutical companies to invest in research and development for indications with higher unmet medical need or greater potential health benefits. This allocation of resources toward therapeutic areas with higher societal value can lead to improved health outcomes and overall welfare.

In a related way, it may encourage pharmaceutical innovation of more tailored indications by providing stronger financial incentives for developing drugs that can be used in multiple indications. That is, instead of a one pharmaceutical products used as "one size fits all" patients, IBP encourages to have "varieties" of the product within the therapeutic area.

Setting different prices for different indications can potentially enhance patient access and affordability. Lower prices in indications with larger patient populations or higher disease burden may increase affordability and widen access to necessary treatments, when compared with imposition of a single price to all indications.[5]

On the working and processes used in resources allocation in health systems, there is another potential benefit from IBP: it encourages a value-based approach to decision making. The information requirements of IBP and the need to build the supporting processes will also help making more informed and efficient allocation decisions based on the relative value of treatments in general.

There are also some social welfare drawbacks associated with IBP. A clear one is that under less than full financial protection of patients (complete health insurance), IBP leads

[5] OHE documents.

to patients with some conditions paying more than patients with other conditions. Thus, IBP can lead to situations of inequity based on disease. The obvious implication is that financial protection of patients cannot be ignored in the design of IBP mechanisms, with complementary policies of financial protection (health insurance coverage) of patients being required to eventually keep equity in access to pharmaceutical products across patients that have medical conditions associated with different price-per-indication copayments of patients.

Indication-based pricing also creates a higher administrative burden. Implementing and administering IBP systems is complex, and requires extensive data collection, analysis, and coordination. The higher administrative burden falls in all economic agents. IBP creates complexities for payers, healthcare providers, and patients in navigating pricing structures and reimbursement systems, potentially increasing administrative costs for all of them.

## 4.5 Pharmaceutical firms' views on IBP

IBP allows pharmaceutical companies to capture the value of a drug in different indications, potentially maximizing revenue. The flexibility created by IBP can lead to increased revenue streams and better financial outcomes. IBP enables companies to expand their market reach by targeting multiple indications with a single product. This can increase the potential patient population and market size for the drug, opening up new revenue opportunities. It allows companies to address unmet medical needs across a broader range of conditions, potentially enhancing their market position and competitive advantage. IBP encourages companies to invest in research and development efforts that target indications (and products) with more advantageous prices.

## 4.6 IBP and market power

IBP for new pharmaceutical products has the potential to leverage the market power of pharmaceutical companies. Market power refers to the ability of a firm to influence market conditions, including prices and competition. Pharmaceutical companies often

possess significant market power due intellectual property rights (patents). By offering a drug with multiple indications and differentiated pricing, companies can create barriers to entry for potential competitors, particularly if they are unable to match the breadth of indications or pricing strategies. IBP can strengthen pharmaceutical companies' negotiating power with payers (including government agencies and health insurance companies). The ability to demonstrate the value of a drug across multiple indications gives companies leverage in price negotiations. Pharmaceutical companies can use the differentiated pricing as a bargaining tool to negotiate favorable reimbursement rates.

### 4.7 IBP and incentives for innovation revisited.

While most views argue that IBP favours innovation in the sense of promoting the discovery of more indications, an argument in the opposite direction as been presented by Straume (2023). The main argument, which was presented in the context of therapeutic reference pricing, may extend to development of further indications: whenever the marginal gain from introducing a new indication is negatively correlated with the price elasticity of demand, the incentive to introduce the innovation is lower. This suggests the need of a formal analysis of incentives for innovation on further indications of a product.

The role of innovation incentives can easily be shown by examples. In Cole et al (2021), a simple example of how IBP fosters innovation is presented. Of course, examples do not constitute a general theory, or even general presumption that innovations incentives are always higher under IBP, though suggest that this will be the case in many circumstances. The challenge for the theory is obtain results that establish conditions under which the presumption of positive (or negative) incentives for R&D generally result from IBP.

## 5 Adding elements to the discussion

### 5.1 What is an indication?

A different issue, not discussed in detail in the literature, is the definition of indication and what is included in it.

#### 5.1.1 Definition of indications and salami slicing

In the context of pricing strategies for multi-indication pharmaceutical products, a "salami strategy" refers to a pricing approach where companies incrementally increase prices for each additional approved indication of a pharmaceutical product. This strategy involves slicing the pricing "salami" into multiple parts, with each part representing a specific indication. The typical pricing strategy will have the following pattern: the initial price of a pharmaceutical product is set based on the first approved indication, typically at a level that reflects the perceived value and market dynamics for that indication. As additional indications, higher value indications, are approved, the company incrementally increases the price for each new indication while maintaining the pricing for the existing indications.

### 5.1.2 Definition of indications and bundling

A different problem is when two products are set as a bundle and present itself as a new indication. Thus, based on already existing use of products, new indications can be produced by combinations of products and demand a different price due to complementarities in effects produced.

## 5.2 The political economy of IBP

The "political economy" of IBP has not been addressed so far in the literature, requiring both theory and empirical contributions.

When pharmaceutical companies submit, at the same time, many proposals of indications for pricing and reimbursement decisions by payer entities, there is a risk of overloading resources-constrained entities. Does this overload of work results in faster or in slower approvals? Does it result in higher or in lower prices on average? Congestion in payer entities' services under public opinion pressure for approval of new pharmaceutical products results in any systematic bias in decisions?

Patient advocacy groups and organizations can mobilize public opinion to advocate for affordable access to IBP-possible products. Stories of patients struggling with high drug costs or limited access can draw attention to pricing practices, stimulating public

discourse and potentially leading to increased pressure on stakeholders to address affordability issues.[6]

There is no theoretical analysis pointing out which elements will bring results to one direction or to another direction. Empirical analysis faces the obvious "obstacle" of defining and measuring overload in services of payer entities.

Information on the submission of proposals of multiple indications for pricing and reimbursement, date of decision and associated prices by indication would make feasible an initial analysis (the obvious weakness being the potential endogeneity of the submission of proposal by pharmaceutical companies).

Indication-based pricing creates challenges to health care payers. For (public) payers that set contracts with specification of expected volume of patients treated and/or overall limit of disbursements, multi-indication pricing requires monitoring and comparisons across therapeutical areas that have costs. The evolution of monitoring costs of use per indication is a major issue in the definition of new pricing structures.

## 5.3 Obfuscation

A related issue is the potential use of IBP for obfuscation. Obfuscation in pricing strategies refers to the intentional use of complex or convoluted pricing structures by companies. Obfuscation involves adding layers of complexity to pricing mechanisms to make it difficult for stakeholders, such as payers or consumers, to understand the true underlying costs, pricing rationale, or value proposition of the product. This ultimately can help firms set higher prices than under simpler and more transparent price setting procedures. The existence of list prices that are public information, coupled with confidential discounts to prices agreed on one-to-one price negotiations between healthcare payers and pharmaceutical companies make it hard to compare prices across different indications and countries (or regions inside a country, when health systems are regional in nature). Discounts and rebates are part of a competitive environment, though they can also

[6] This was the case of the first new-generation Hepatitis C in Portugal, with public opinion pressure expressed in a live broadcast from a Parliamentary hearing in 2014.

serve to obfuscate.

## 5.4 Strategic interactions

### 5.4.1 Companies competing in multiple dimensions

IBP can have complex effects on competition in the market between pharmaceutical companies. The impact is likely to vary depending on various factors and the specific market dynamics. As discussed elsewhere in this document, pharmaceutical companies may be motivated to invest in research and development to pursue multiple approved uses for their products, creating a competitive environment to capture value across different indications, with some being eventually more successful in some indications, while others are more successful in others. This positive effect on competition between firms may be countervailed by strategies of entry deterrence of competitors by indication proliferation.

### 5.4.2 Sequential negotiations with payers

Under sequential negotiations of prices for different indications of the same pharmaceutical product, the fallback values of one stage (later indication) are influenced by the previous negotiated prices (earlier indication) whenever the initial negotiation reveals information about the product (effectiveness and/or costs) or merely allows, at least, some patients to be treated anyway under the initial indication (partial therapeutic substitution across indications, as empirically it has been the case that off-label use from an initial indication of a innovative product took place)[7].

## 5.5 Indication-based pricing and data requirements

A major issue with IBP is the availability of data regarding consumption, value by consumers and costs by indication. Obtaining comprehensive and reliable data on multiple indications can be challenging. Data on clinical outcomes, disease prevalence, patient characteristics, and treatment patterns need to be collected and analyzed to

[7] To add examples.

inform pricing decisions. Access to high-quality data across various indications may be limited, making it difficult to accurately assess the value and clinical benefits of a pharmaceutical product in each indication.

Confidentiality and Proprietary Data: Pharmaceutical companies may possess proprietary data on the performance and value of their drugs in different indications. Access to such data for external stakeholders, including payers, regulators, and researchers, can be restricted due to confidentiality concerns. This limitation hampers the ability to conduct independent evaluations and hinders transparent decision-making in multi-indication pricing. Confidentiality and proprietary data bring additional problems. Pharmaceutical companies may possess proprietary data on the performance and value of their drugs in different indications. Access to such data for external stakeholders, including payers, regulators, and researchers, can be restricted due to confidentiality concerns. This limitation hampers the ability to conduct independent evaluations and hinders transparent decision-making in IBP.

Real data access for IBP necessitates standardization and harmonization of data across different sources and indications. Consistent methodologies for data collection, analysis, and reporting are essential to ensure comparability and accuracy. Efforts to establish common data standards and promote interoperability are critical to addressing this challenge.

# 6 A more general model of analysis

## 6.1 Under fixed demands (number of patients) per indication

Consider a decision context by a payer characterized by a set $I$ of indications of a new drug, with each indication $i \in I$ having a value $v_i$ of treating each of the $n_i$ patients eligible for treatment under that indication. The number of patients to be treated is taken as totally independent of the price $p_i$ that the payer sets for each indication $i$.

Let $c$ be the cost, to the pharmaceutical company, of producing the quantity of product to treat a patient, irrespective of the indication, and let $F$ be the total R&D costs incurred by the pharmaceutical company in obtaining the new pharmaceutical product that

can be used in all indications $i \in I$. The pharmaceutical company may choose to only introduce a subset of the available indications.

The first remark to be made, in this decision context, is that a uniform price, equal across all indications, is sufficient to characterize the payer's problem. The profit of the company, when introducing all indications, at some price $p_i$ is given by

$$\Pi = \sum_{i \in I} (p_i - c)n_i - F$$

This profit definition holds for the case of price of each indication being equal to value $(p_i = v_i)$ and to any other rule that is used by the payer to set $p_i$.

Since $n_i$ is independent of $p_i$ (by assumption), then it is possible to define an equivalent uniform price $\bar{p}$:

$\sum_{i \in I}(\bar{p} - c)n_i - F = \sum_{i \in I}(p_i - c)n_i - F$

Or

$$\bar{p} = \sum_{i \in I} s_i p_i,\ s_i = \frac{n_i}{\sum_{i \in I} n_i}$$

This uniform price is a weighted average of each indication price, with weights given by the number of patients of each indication. Since access to treatment is not dependent on prices and since introduction into the market of the set $I$ of indications is guided by the overall profits to the pharmaceutical company, using $\bar{p}$ or the set of prices $p_i$ leads to the same outcome.

The value of $\bar{p}$ obviously depends on the exact way each price $p_i$ is determined. This assumes that set $I$ is known to everyone and that prices are such that all indications are introduced into the market.

The existing literature on indication-based pricing has highlighted, mainly through examples, the trade-off between prices and access to care (treatment) for patients. These examples have used price-insensitive demand functions (that is, examples assume a fixed number of patients to be treated under each indication).

A natural concern is whether, or not, an average (uniform) price structure is able to accommodate voluntary introduction of all indications by the pharmaceutical company holding the rights to a new pharmaceutical product. To address this concern, let's start with a simple version of the problem.

To simplify exposition, indications are ordered by decreasing value of treating a patient ($v_1 > v_2 > \cdots > v_I$). Assume the highest-value indication can be introduced into the market at a price $p_1$. This yields profit $(p_1 - c)n_1$ to the pharmaceutical company. To keep in line with (part of the) previous literature, assume $p_1 = v_1$. Thus, profit is $(v_1 - c)n_1$ in this case. Since R&D costs are sunk costs at this stage of decision, those costs will be ignored, unless otherwise specified.

The key question is under which conditions does the pharmaceutical company voluntarily introduces the second indication into the market. Under indication-based pricing, it suffices to have $p_2 = c$ (or slightly above $c$). With $v_2 > c$, making $p_2 = v_2$ will lead to the introduction of the second indication. The indication-based pricing approach makes the determination of $p_2$ independent of what was the decision regarding $p_1$.

Under a uniform pricing rule, the introduction of the second indication will take place if

$$(\bar{p} - c)(n_1 + n_2) > (p_1 - c)n_1$$

Or

$$\bar{p} > \left(\frac{n_1}{n_1 + n_2} p_1 + \frac{n_2}{n_1 + n_2} c\right)$$

This condition can be set in more general terms. Under a fixed number of patients by indication, $n_i$, to be treated, consider the profit under a uniform price for $j$ indications already present in the market, $\bar{p}_j$. Introduction of indication $j+1$ (with $v_j > v_{j+1}$) by the pharmaceutical company requires, under uniform pricing,

$$(\bar{p}_j - \mathrm{c}) \sum_{i=1}^{j} n_i \leq (\bar{p}_{j+1} - \mathrm{c}) \sum_{i=1}^{j+1} n_i$$

Let $\bar{n}_j = \sum_{i=1}^{j} n_i$. The new $\bar{p}_{j+1}$is given by

$$\bar{p}_{j+1} \geq p^*_{j+1} = \bar{p}_j \frac{\bar{n}_j}{\bar{n}_{j+1}} + c \frac{n_{j+1}}{\bar{n}_{j+1}} = \bar{p}_j - (\bar{p}_j - c) \frac{n_{j+1}}{\bar{n}_{j+1}}$$

This provides some flexibility in the use of the uniform price structure to induce introduction of indications by a profit maximizing pharmaceutical company.

The profit comparison details the critical trade-off from introducing one more indication from adding profits resulting of more patients with a positive margin versus having a lower margin on the previously treated number of patients.

A case of interest, given its presence in the literature, is when under indication-based

pricing, price is equal to value for each indication, $p_i = v_i$. In this case,

$$\bar{p}_1 = v_1$$

$$\bar{p}_2 = v_1 \frac{n_1}{n_1 + n_2} + v_2 \frac{n_2}{n_1 + n_2}$$

$$\bar{p}_j = \sum_{i=1}^{j} \frac{n_i}{\bar{n}_j} v_i$$

The uniform price that leads to the introduction of $j$ indications is, in this particular pricing rule, equal to the weighted average of price (equal to value) for each indication. Note that by adjustment of the uniform price to the number and value of existing indications in the market, there is no interest in removing indications by the pharmaceutical company. Removing one indication of low value increases the average uniform price but loses the demand associated with that indication. As long as the price of an indication is above the unit (marginal) cost of production, the weighted uniform price balances the price and the quantity effects of introducing/removing indications from the market.

On the incentives to do R&D, in case a pricing structure with $p_i = v_i$ is sufficient to pay for the R&D cost for some indications (if not all) introduced by the pharmaceutical company, then adjustment of a uniform price to the number and value of indications introduced that gives the same profit to the pharmaceutical company is also a sufficient instrument.

The discovery of a new indication may require additional R&D spending, $F_{j+1} > 0$. It is straightforward to see that

$$p_{j+1}^{*} = \bar{p}_j - (\bar{p}_j - c)\frac{n_{j+1}}{\bar{n}_{j+1}} + \frac{F_{j+1}}{\bar{n}_{j+1}}$$

The recomputation of the average weighted price can be expressed as the previous price with a discount given by the previous margin under uniform pricing weighted by the share of patients associated with the new indication. And adding a surcharge for extra R&D costs, if present.

Under the context of a fixed number of patients per indication, the only "efficiency" decision is about the the optimal number of indications introduced into the market. Both indication-based pricing and (adequately defined) uniform pricing are able to achieve

the desired number of indications. Only adjustments in the extensive margin are relevant. It makes the discussion of this decision context simple.

## 6.2 Under price-sensitive demands per indication

Under price-sensitive demands – the number of patients included for treatment in each indication is larger for lower price set by payer and pharmaceutical company interaction), $n_i(p_i)$ being a continuous function and $\frac{\partial n_i}{\partial p_i} < 0$, there is always a uniform single price that leads to the same profit to the pharmaceutical company where both indications are introduced under indication-based pricing.

Starting with introduction into the market of a second indication of lower value ($v_2 < v_1$), the pharmaceutical company will introduce the second indication at a uniform price $\bar{p}$ if

$$(\bar{p} - c)(n_1(\bar{p}) + n_2(\bar{p})) > (p_1 - c)n_1(p_1)$$

It is straightforward to check that for $\bar{p} = c$ this condition does not hold, while for $\bar{p} = p_1$ this condition holds with strict inequality as long has $n_2(\bar{p}) > 0$, which is assumed to hold. Then, by the Intermediate Value Theorem, there is a $p^*$(critical threshold for $\bar{p}$) such that for $\bar{p} > p^*$ the pharmaceutical company introduces the second indication.

The argument can be made mode general, using the same framework. Let $\bar{p}_j$ be the uniform price when indications $1$ to $j$ are in the market (and ordered by decreasing valua). Let $\bar{p}_{j+1}$ be the new uniform price when indication $j+1$ is added to the market. The pharmaceutical company is willing to introduce the new indication under a uniform price $\bar{p}_{j+1}$ if

$$\sum_{i=1}^{j} (\bar{p}_j - \mathrm{c}) n_i(\bar{p}_j) \leq \sum_{i=1}^{j+1} (\bar{p}_{j+1} - \mathrm{c}) n_i(\bar{p}_{j+1})$$

For $\bar{p}_{j+1} = \bar{p}_j$, the condition holds with strict inequality under the assumption of $n_{j+1}(\bar{p}_{j+1}) > 0$. For $\bar{p}_{j+1} = c$, the condition does not hold. Again by application of the Intermediate Value Theorem, there exists $p^*_{j+1}$ such that for any $\bar{p}_{j+1} > p^*_{j+1}$ the pharmaceutical company introduces the $j+1$ indication. Thus, if a payer (health authority or health regulatory agency) wants to ensure that $I$ indications are introduced into the market, a uniform price is able to achieve that result. There is no claim this is the optimal way to

reach the result for the payer. It just shows that uniform prices are a sufficient instrument to achieve whatever level of introduction of indications of a new product is desired by the payer (or health regulatory agency).

The discussion above established that a uniform price exists such that it originates the same profit to a pharmaceutical company from adding one more indication, given a previous uniform price. A critical issue is how to define that uniform price. An approximation to its value can be given under some conditions.

Define the contribution of each indication $i$ to the profit of the pharmaceutical company when introducing $j$ indications, at the price $\bar{p}_j$ equal to all indications:

$$f_i(\bar{p}_j) = (\bar{p}_j - \mathrm{c})n_i(\bar{p}_j)$$

Using a first-order Taylor approximation, it is possible to write

$$f_i(\bar{p}_j) \approx (p_i - \mathrm{c})n_i(p_i) + (\bar{p}_j - p_i)[(p_i - \mathrm{c})\frac{\partial n_i}{\partial p_i} + n_i(p_i)]$$

Equality of profits under a set of prices $p_i$ under indication-based pricing and under a uniform price $\bar{p}_j$ amounts to require

$$\sum_{i=1}^{j}(\bar{p}_j - p_i)\left[(p_i - \mathrm{c})\frac{\partial n_i}{\partial p_i} + n_i(p_i)\right] = 0$$

From which, one retrieves

$$\bar{p}_j = \frac{\sum_{i=1}^{j}(p_i)\left[(p_i - \mathrm{c})\frac{\partial n_i}{\partial p_i} + n_i(p_i)\right]}{\sum_{i=1}^{j}\left[(p_i - \mathrm{c})\frac{\partial n_i}{\partial p_i} + n_i(p_i)\right]}$$

Or,

$$\bar{p}_j = \sum_{i=1}^{j} p_i\,\omega_i, \omega_i = \frac{n_i(1 - \frac{(p_i - \mathrm{c})}{p_i}\varepsilon_i)}{\sum_{i=1}^{j}\left[n_i(1 - \frac{(p_i - \mathrm{c})}{p_i}\varepsilon_i)\right]}$$

Where $\varepsilon_i = -\frac{\partial n_i}{\partial p_i}\frac{p_i}{n_i}$. For prices below monopoly price in each indication, $\frac{(p_i - \mathrm{c})}{p_i}\varepsilon_i < 1$. This condition indicates that lower weight, in the uniform average price, should be given to indications with a lower number of patients, with a higher elasticity of demand and with a higher margin under indication-based pricing.

Under totally inelastic demand ($\varepsilon_i = 0$), the analysis recovers the previous section result

of a weighted average price, with weights provided by the number of patients in each indication.

## 6.3 An illustrative example

To make an easy comparison of the discussion above with other discussions in the literature, take the following example, with 3 possible indications, with valuation per indication and (fixed) number of patients per indication.

| Indication | $v_i$ | $n_i$ |
|---|---|---|
| 1 | 4,5 | 50 |
| 2 | 1,5 | 1000 |
| 3 | 1 | 2000 |

Ignoring production (unit) costs per person treated, under indication based pricing with price equal to value, the pharmaceutical company obtains the highest profit possible and a uniform price 1,22 applied to all patients all (3050) originates the same profit.

A more interesting issue arises if the pharmaceutical company has to choose a single price, applied to all indications (Chandra and Garthwaite, 2017). In this example, the number of patients under the low value indication make it worthwhile to have a low price and treat all patients (setting a price of 4,5 brings 225 of profit, setting a price of 1,5 brings 1575 of profit and setting a price of 1 brings 3050 of profit). In this case, the uniform price, as decided by firms, will bring lower prices and all indications are introduced. The point, however, it is not sufficiently general in the sense that by changing the volume of patients at each indication, the profit maximizing price defined by the pharmaceutical company can easily leave out of the market (lack of access) groups of patients. In such a situation, the use of indication based pricing would expand access to patients.

Consider the following alternative example:

| Indication | $v_i$ | $n_i$ | $R_i$ |
|---|---|---|---|
| 1 | 4,5 | 2000 | 9000 |
| 2 | 1,5 | 1000 | 1500 |

| | | | |
|---|---|---|---|
| 3 | 1 | 50 | 50 |

Under the above values, the best uniform price decided by the pharmaceutical company (highest profit) is 4,5, leading to a profit of 9000. Only patients in the first indication would have access to the drug.

These two examples assumed that the pharmaceutical company has full ability to set its prices, with the constraint of uniform pricing across groups of patients creating a trade-off that may, or may not, lead to access issues.

The way prices are set also has influence on the comparison of uniform price versus indication-based pricing. If there is a negotiation process between a payer and the pharmaceutical company such that prices and demand by indication are jointly determined, the trade-off faced by the pharmaceutical company changes. In the above example, a uniform price greater than 3 and all indications included would lead to higher profit to the pharmaceutical company, as long as the payer commits to treat patients within the second indication at a unit price that is above the valuation $v_i$ of that indication. Thus, the way demand is defined (which patients are treated) also matters for the comparison. In the discussion of regulated prices for new products, it is reasonable to consider that payers decouple the payment made to the pharmaceutical company from the decision to treat a patient and that only indication-based access is at stake (including, or not, indications in payment agreement defines whether, or not, patients under each indication are treated). The other polar situation occurs when, for each patient, the treatment decision is based on the expected benefit to the patient versus the price of the treatment.

The analysis presented earlier takes as background the former process of defining demand associated with each indication, solving that way the concerns of payers regarding access to new products of patients under different indications. Under the latter way of demand definition, it will not be possible to rule out situations of lack of access to treatment of lower value indications (depending on the number of patients).

Another assumption in the discussion above was that offering access to patients of all indications was a key concern to the payer, in the sense of lexicographic preferences regarding access and costs. That is, the first objective of the payer is to have access to

all patients in all indications, and given that access is provided, how to achieve the lowest cost possible. This takes the pricing problem of defining a uniform equivalent price to be one of expanding access to treatment while giving pharmaceutical companies the same profits they would receive in the absence of the negotiation of the uniform price. This leaves out concerns about excessive prices (in the sense of abuse of market power) by pharmaceutical companies, which may also be a driver for negotiations between payers and pharmaceutical companies and for the existence of uniform price across all indications.

The performance of uniform prices versus indication-based prices is, therefore, conditional on several contextual elements regarding demand formation, value per indication, number of patients per indication and the value assigned by the payer to access to treatment by patients of different indications.

Under certain conditions, a negotiated uniform (equivalent) price can achieve the same market allocation as indication-based prices. Otherwise, the flexibility offered by indication-based pricing will make it able to achieve a higher total social surplus.

## 6.4 New pharmaceutical products and multi-indication pricing – summary

A key point associated with multi-indication pricing is related to the introduction of new indications of use, at the prevailing pricing rules. By prevailing pricing rules, we understand rules that define the price of existing indications of use.

The discussion has to accommodate the possibility of different contexts. Two situations have to be considered: a) the total number of patients to be treated under each indication is fixed. That is, the number of patients treated in each indication is independent of the price agreed between payer and the pharmaceutical company; b) the number of patients included for treatment under each indication is negatively related to the price of that indication. In economic terms, it means that demand is sensitive to price (this may result when effectiveness varies across patients and only patients with a value of expected effectiveness above a threshold related to price are considered for treatment).

The first context is the more common one in the literature. In this context, it is possible to

define all relevant decisions in terms of an equivalent uniform price across indications. This equivalent uniform price is computed as the (patient) weighted average price over all indications, whatever the rule used to define the price per indication.

The equivalent uniform price can reproduce the decisions of pharmaceutical companies regarding the introduction of new indications in the market that result from indication-based pricing.

This is a general result that covers the existing examples in the literature.

The analysis becomes considerably more complex when the number of patients treated on each indication is a function of the price paid in each indication. In this second contexts, changing prices also changes access of patients to care in the intensive margin, while under the context of a fixed number of patients to be treated per indication, only the effects associated with the extensive margin are present.

The general result that under a fixed-demand context a single, uniform, price can be used is of practical relevance as it will avoid concerns with arbitrage in use across indications. On the other hand, it imposes an additional cost: each time a new indication is introduced, the price in all indications must be changed. This is also true if a price per indication is used by payers, unless price is always set equal to the value of the new indication (in which case, it makes a full transfer of social value to pharmaceutical companies).

## 7 Concluding remarks

Indication-based pricing (IBP) presents a promising approach to pharmaceutical pricing, recognizing the differential value and clinical benefits that a single drug can offer across various indications. Both the theoretical underpinnings and empirical evidence surrounding IBP, revealing its potential to enhance social welfare, spur innovation, and optimize resource allocation in healthcare systems, were reviewed, with emphasis on setting a general framework of analysis whenever possible.

The theoretical framework highlights IBP's alignment with price discrimination principles, where prices reflect the varying efficacy and benefits across medical conditions.

Empirically, the adoption of IBP models across different countries demonstrates a range of strategies, from weighted average prices to confidential discounts, each addressing specific market and regulatory contexts. The strategic introduction of indications by pharmaceutical companies, often prioritizing high-value, low-patient base indications, illustrates the dynamic nature of this pricing approach.

Despite its advantages, IBP poses significant challenges. Administrative complexities, data requirements, and the potential for obfuscation in pricing structures necessitate robust regulatory frameworks and transparent practices. Additionally, the impact of IBP on equity and access remains a critical consideration, with the need for complementary policies to ensure that differential pricing does not exacerbate disparities among patient groups.

The analysis indicates several policy implications for the implementation of indication-based pricing. On regulatory transparency and data requirements, policies must mandate transparent pricing mechanisms and comprehensive data collection to monitor the efficacy and equity of IBP models. Standardized data protocols can facilitate the evaluation of IBP's impact on patient outcomes and healthcare costs.

On incentives for R&D, IBP can be structured to maximize incentives for pharmaceutical innovation, particularly for indications with high unmet medical needs. This involves balancing the reward mechanisms to ensure sustainable investment in R&D.

On equity in access to treatment, ensuring equitable access to treatments across different indications is a key policy goal. This can be more easily achieved with indication-based pricing, although under some technical conditions, an equivalent uniform price can provide the same incentives to firms, without risking arbitrage across indications with different prices per indication.

There also several important aspects requiring further knowledge. Conducting long-term empirical studies to assess how IBP influences the pharmaceutical industry's innovation patterns and R&D investment is central to understand the full implications of this pricing approach. This will provide insights into the sustainability and effectiveness of IBP in fostering innovation.

Performing comparative studies across countries and healthcare systems to evaluate the

relative success and challenges of different IBP implementations is also important. Small details may lead to different results. Such analysis can identify best practices and inform policy adaptations.

Investigating the direct impact of IBP on health outcomes and equity among patient populations is a need. This involves analyzing patient access, treatment affordability, and clinical outcomes to ensure that IBP aligns with broader health system goals.

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