THE FAIR BET IN PHARMA PRICING – AN INVESTOR'S PERSPECTIVE

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Prices for medicines have been at the heart of the EU policy debate and centre stage of the global gap that is growing between pharma companies, payers and regulators[1]. Prices for expensive medicinal products, such as gene therapies and other orphan medicines, have especially been subject to criticism and sometimes even backlash.

In previous papers in this series, we have highlighted several ways that could help close this global gap and that can help avoid conflicts and disputes between payers and pharma companies and the consumption of regulatory resources: better procurement practices[2], innovative pricing agreements and replacing a zero-sum negotiation mentality through a partnership approach[3].

However, one additional element is required to avoid future conflicts: payers, companies and regulators must have a mutual understanding of how prices for pharmaceutical products come about, in other words, what constitutes a fair bet[4] in light of the investment costs and risks for bringing a medicinal product to market.

THE CASE FOR A BETTER UNDERSTANDING OF PHARMA PRICING IS A STRONG ONE

More and more today, price negotiations are at a standstill because payers consider pharma companies' price proposals 'simply too high'[5], not compared to the value of the medicine but compared to the development and manufacturing costs for the medicinal product which they suspect to be much below the proposed price level.

Therefore, payers and policy makers increasingly demand transparency on pharma companies' costs before engaging in negotiations. Pharma companies are hesitant or even outright refuse to reveal their costs out of fear that doing so will lock them into a

cost-plus logic where the 'plus' (i.e. the margin) would not appropriately remunerate them for the risk taken in medicine development.[6]

This indicates a lack of trust from both sides: payers and policy makers see large margins between the price and perceived costs as a sign of excessive profit, while companies perceive payers' interest in cost as a threat. Therefore, a common understanding of what constitutes a fair bet from a pharma company may be one of the missing links in price negotiations today.

The case for a better mutual understanding is a strong one because the price that a company can expect to charge for a medicinal product acts as a crucial investment incentive. Price levels that do not reward companies for their investment costs and risks will hamper investment incentives and innovation in the long run. Strong uncertainty about price negotiation principles and the consequent outcomes can also constitute an uncontrollable risk which may, at the margin, deter companies from pursuing riskier investments into innovative medicine development in the first place.

What constitutes a fair bet, then? What are the elements of the fair bet that payers, regulators and pharma companies should all agree on?

THE INVESTOR'S PERSPECTIVE

Since the development of medicinal products is both costly and risky, the fair bet is one that remunerates the company for the size of its investment and the risks taken in developing the medicinal product and bringing it to market.

We can see this when putting ourselves in the investor's shoes: an investor will only decide to invest in developing a specific medicine in the first place if the revenues generated will reward the costs and risks of the investment. What matters about the investor perspective is that it looks at the medicine development project *ex ante*, that is, at the time of the investment decision. Since medicine development is failure-ridden, a product that might seem very profitable when coming on the market might not have seemed so profitable from an ex-ante investor perspective. This is because an investor must factor in a certain probability that the product may fail at different stages of the medicine development path and might therefore never make it to market.[7] If the product does make it to market, the returns granted to the investor in this upside scenario should still compensate them for the downside risks from an ex-ante point of view.

When deciding whether to invest in the development of a particular medicine, an investor must answer three main questions:

1. **Costs:** how much will medicine development and market access for this medicinal product cost?

2. **Risks:** what are the probabilities that the medicinal product will make it to market, or conversely, what is the risk that the medicinal product may fail?

3. **Market size:** what levels of sales will the medicinal product generate once on the market?

On top of that, investors must have an idea of how long it takes for a medicine to go through the different development stages, or how much time goes by before they will see a return on their investment.

Investors typically combine all that information into a so-called **(risk-adjusted) Net Present Value model**, a standard valuation

model that allows them to assess whether the investment in a medicine development project is worthwhile[8], see Box 1. The price that would make the investment worthwhile given the investor's expectations of costs, risks and market size constitutes a fair bet. Let's look at each of these elements in turn.

Box 1 The risk-adjusted NPV model to evaluate a fair bet

Net Present Value (NPV) models are a class of valuation tools commonly used by investors across all industries to inform their decision-making. In the pharma industry, investors and valuation experts commonly use risk-adjusted NPV models (rNPV). Compared to standard NPV models, rNPV models allow for a more granular incorporation of the risk specific to the medicine development project. They capture the risk of the investment in (i) the discount rate, which reflects the market risk and company risk, and (ii) the probabilities of success, which reflect the project-specific risk of failure at different stages of the development path:

$$rNPV_0 = -I_0 + \sum_{t=1}^{T} Q_t * \frac{(p_t * q_t) - C_t}{(1+r)^t}$$

where I_0 is the initial investment, p_t is the expected price at time t, q_t is the expected volume sold at time t, C_t is the expected cost at time t, r is the discount rate and Q_t is the probability of success of the project at time t.

The model has to be populated with the investor's best estimate of costs, risks and sales volumes generated by the project. These will often come from the relevant literature and data bases, the investors' experience and from studying the properties of the project in question. Since there is always uncertainty about the value for each input, it is best-practice to use Monte Carlo simulations to obtain a distribution, rather than a point estimate, of the rNPV that accounts for the uncertainty around the different inputs.

An investor decides to invest in a specific project if its rNPV is positive. In this case, the investment is profitable given the expected costs, risks, market size and timeline of the project.

rNPV models are also a useful tool to evaluate a fair bet. A price for which the rNPV is zero given the expected costs, risks (i.e. probabilities of success + discount rate), market size and timeline could be considered a 'fair bet', that is, a price that provides sufficient incentives to invest.

Source: Copenhagen Economics, Bogdan and Villiger (2010), Svennebring and Wikberg (2013); Dando, J. and M. Lebmeier (2020), Walker et al. (2015)[9]

1) Development costs

Development of medicinal products is indisputably costly. Estimates of the costs of bringing a medicinal product to market vary, and the costs of an individual medicine development project depend very much on its nature.[10] All else being equal, the higher the expected costs for bringing a medicine to the market, the higher the price needed to make the investment worthwhile.

An important aspect to recognise is that significant investments are required during the entire development path (see Figure 1), from preclinical and clinical trials, over regulatory approval to securing market access in several EU countries, manufacturing and securing a suitable distribution chain, conducting marketing and promotional activities and fulfilling regulatory obligations.

Figure 1

Development path of medicinal products

Source: Copenhagen Economics

Among those, payers and regulators tend to focus on investments in preclinical research and clinical development as well as manufacturing costs, as these two activities are tangible and clearly linked to the value of the product itself.

However, such a narrow view will create a mismatch of payers' and companies' perception of the investment the medicine price should remunerate. A more comprehensive view on the total investment needed to bring a medicinal product to the market is required. For example, navigating EU marketing authorisation can be a time-consuming and costly process. The same goes for gaining market access in various European countries, each of which with their own HTA (Health Technology Assessments), standards, requirements and procedures.

Taking a comprehensive approach on costs is not the only challenge. Even quantifying the size of the investment after the fact of bringing a medicinal product to market may be conflict-ridden as common or indirect costs are typically not attributed to individual development projects. One example is labour costs, which represent a significant share of costs for pharma companies. This means that identifying costs for an individual medicinal product's development project requires allocating common costs. This exercise entails a certain level of discretion on the choice and measurement of allocation keys. In fact, different methods for the allocation of common costs are available (e.g. based on input or output measures) and they can lead to widely differing total cost levels.

2) Development risks

It is common knowledge that bringing a medicinal product to market is risky and entails a significant risk of failure. Approximately only one in ten[11] candidate compounds that enter the clinical trial phase will succeed in obtaining regulatory approval and generate some level of revenue. In addition, not all medicinal products that reach the market are successful in generating enough revenue.

As a result, pharma companies cover the investments into failed and less successful medicinal products through the sales of 'more successful' ones. This is why accounting for the risk of failure, allowing companies to recover the costs of failed investments, is a key issue in any discussion on prices of pharmaceutical products. All else being equal, the higher the perceived risks in bringing a medicine to market, the higher the price needed to make the investment worthwhile.

Any pharma investment incurs different types of risk: general market-wide risk, company-specific risk (e.g. relating to company size) and project-specific risk. An rNPV model reflects the first two in the discount rate. An important characteristic of the rNPV model is that it helps capture project-specific risks through probabilities of success.

Similar to costs, it is crucial to look at risks and probabilities of success in a comprehensive way. Risks occur during the entire development path as the investment can fail at each step, see Figure 2.

Figure 2

Risks along the development path

Source: Copenhagen Economics

While the largest risk is typically associated with the R&D phase of medicine development, it is by no means limited to it. For instance, a product that has completed clinical trials can fail to obtain marketing approval because the level of evidence collected is not sufficient to prove a positive risk-benefit balance. Estimates of the average probability of success in this step are as low as 30 percent for specific types of medicinal products.[12]

Once a medicinal product has obtained marketing approval, obtaining market access through pricing and reimbursement negotiations is not automatically a done deal. This is because the characteristics that allow a medicine to be on the market are not the same ones that payers across Europe focus on when deciding whether and at which conditions to reimburse it.

A medicinal product could fail in securing market access because payers and national authorities do not recognise the added value compared to currently reimbursed alternatives or still have doubts about the efficacy of the medicine. The risk of failure at this stage can therefore be significant, and depends on the country and characteristics of the medicine.[13] Literature reports probabilities of success ranging from 50-85 percent for pricing and reimbursement negotiations.[14]

In some cases, investors also have to factor in the risk that a medicinal product may fail to comply with post-marketing obligations and have its authorisation withdrawn. For instance, this could be the case for conditional marketing authorisations or authorisations granted under exceptional circumstances.[15]

Given the many stages a medicinal product needs to pass to reach patients, it is intuitive that the overall probability of success is never 100 percent, that is, the risk of failure is never zero. From a practical point of view, determining the level of risk that an investment in the pharmaceutical sector entails can be challenging. While the literature provides useful insights on the average risk of failure, the assessment is ultimately conducted on a case-by-case basis. For instance, the risk can significantly vary depending on the type of molecule, therapeutic indication or whether the medicine is orphan or non-orphan.

3) Market size

What matters at the price negotiation stage is not only whether or not the medicinal product is reimbursed or at what price, but also the size of the market the pharma company will have access to. A lower (or higher) number of accessible patients who can take the medicine, the higher (or lower) the price for recouping the risky investment needs to be.

The ultimate size of the accessible market can also be a risk investors need to consider. Depending on the medicine development project, market size might be relatively well known or subject to different types of uncertainties. For medicinal products targeting new disease areas, the size of the actual patient population might be difficult to determine and will only be known once the medicinal product is on the market for a longer time. For example, this is the case when the disease is not well known and therefore underdiagnosed.

For treatments targeting well-known diseases, market size is affected by the presence of competitors and whether the medicinal product is considered a first-line treatment by relevant authorities.[16] Moreover, for expensive treatments authority might resort to conditional reimbursement approvals, meaning that the product is only accessible for part of the patient population.[17]

Any investor needs to factor in uncertainty about market size they will be able to serve when taking an investment decision. Early talks with payers and patient groups about patient needs may be a way of limiting part of that risk.

MUCH IS AT STAKE

A lack of mutual understanding of the elements discussed above can easily lead to different expectations and misalignment on the payer and company side of what a fair bet and a reasonable negotiation outcome should be. It may also lower the level of trust in the process that a price negotiation will result in a fair outcome in the eyes of both parties.

Therefore, mutually agreeing on what constitutes a fair bet, considering pricing under uncertainty and investment incentives in complex regulated markets, should be a goal for payers, pharma companies and regulators alike. The investor perspective can be a useful way of starting the discussion.

The investor perspective can also help point to opportunities when reviewing the overall policy framework for development and market access of medicinal products. In a nutshell, anything that policymakers can do to lower the costs, time needed and uncertainty linked to the regulatory process and pricing and reimbursement negotiations can improve investment incentives for companies at equal prices. We hope to cover this in a future paper.

FOOTNOTES

[1] See our article 'Why seemingly unrelated events are not and what it means for pharma and payers in Europe', 6 October 2020, available at: https://www.copenhageneconomics.com/dyn/resources/Filelibrary/file/0/320/1603881958/1.-the-show-down.pdf

[2] See our article 'Unfair pricing or unfit procurement? Avoiding disputes between payers and suppliers of pharmaceuticals', 20 October 2020, available at: https://www.copenhageneconomics.com/dyn/resources/Filelibrary/file/8/318/1603881705/3.-unfair-pricing-or-unfit-procurement.pdf

[3] See our article 'Expensive innovative treatments: How to increase patient access and avoid condition reimbursement approvals', 27 October 2020, available at: https://www.copenhageneconomics.com/dyn/resources/Filelibrary/file/9/319/1603881722/4.-expensive-innovative-treatments.pdf ; see also our article 'The way forward: value-based healthcare in partnerships', 13 October 2020, available at: https://www.copenhageneconomics.com/dyn/resources/Filelibrary/file/7/317/1603881692/2.-the-way-forward.pdf

[4] The concept of 'fair bet' is also used by the UK Office of Communications (Ofcom), which it defines as "In practice, applying the fair bet framework requires giving investors at project inception the opportunity to earn the project-specific cost of capital, on an expected basis. This means allowing them to earn returns in excess of the cost of capital in the upside scenarios in order to balance downside risks", see, for instance, https://www.ofcom.org.uk/__data/assets/pdf_file/0016/105019/Openreach-vol-1-annex-3-Oxera-report.pdf

[5] For instance, we have discussed a number of examples in our first article in this series, 'Why seemingly unrelated events are not and what it means for pharma and payers in Europe', 6 October 2020, available at: https://www.copenhageneconomics.com/dyn/resources/Filelibrary/file/0/320/1603881958/1.-the-show-down.pdf

[6] See 'WHO guideline on country pharmaceutical pricing policies', Section 3.9, 2020, available at: https://apps.who.int/iris/bitstream/handle/10665/335692/9789240011878-eng.pdf

[7] Alacrita Consulting (2019), Pharmaceutical Probability of Success.

[8] Svennebring and Wikberg (2013) Net present value approaches for drug discovery, SpringerPlus, vol. 2(1), article id 140; Dando, J. and M. Leb-meier (2020), 'A novel valuation model for medical intervention development based on progressive dynamic changes that integrates Health Technology Assessment outcomes with early-stage innovation and indica-tion-specific clinical success rate'. Journal of Innovation and Entrepre-neurship, vol. 9(1), p.1-28.

[9] Bogdan, B. and R. Villiger (2010), 'Valuation in Life Sciences 3rd Edition', Springer Verlag, 2010; Svennebring and Wikberg (2013) Net present value approaches for drug discovery, SpringerPlus, vol. 2(1), article id 140; Dando, J. and M. Lebmeier (2020), 'A novel valuation model for medical intervention development based on progressive dynamic changes that integrates Health Technology Assessment outcomes with early-stage innovation and indication-specific clinical success rate' Journal of Innovation and

Entrepreneurship, vol. 9(1), p.1-28; Walker et al. (2015), Pharma and Biotech Valuations: Divergent Perspectives, Business Development and Licensing Journal, issue 22, July 2015.

[10] The Tufts Center for the Study of Drug Development (2019) estimated the investment up until regulatory approval at USD 2.6billion. Di Masi et al. (2016) find that the overall investment has also increased over time from USD 1.04billion in the 1990s to USD 2.56billion in the mid-2010s.

[11] Alacrita Consulting (2018) finds a probability of success from Phase I clinical trials to regulatory approval of 13 percent, based on a review of eight publications encompassing data from 1993-2015.

[12] This is the average probability of success of obtaining regulatory ap-proval for orphan medicinal products that submitted an application to the EMA across the following three articles Hofer et al. (2018), Regnstrom et al. (2010), Giannuzzi et al. (2017).

[13] Criteria for obtaining and pricing and reimbursement agreement very significantly across countries. In addition, the risk of failure is linked to the characteristics of medicine and the level of evidence that the company was able to collect on its effectiveness.

[14] For instance, these are the country-specific probabilities of success found by Malinowski et al. (2018) by analysing the reimbursement status for 95 authorised orphan drugs for 12 selected countries (Belgium, Denmark, England, Scotland, Wales, France, Germany, Italy, Poland, Spain, Sweden, The Netherlands). See Malinowski, K.P., Kawalec, P., Trabka, W., Sowada, C. and Pilc, A. (2018) 'Reimbursement of Orphan Drugs in Europe in Relation to the Type of Authorization by the European Medicines Agency and the Decision Making Based on Health Technology Assessment'. Front Pharmacol. 9:1263. DOI: 10.3389/fphar.2018.01263

[15] The EMA usually imposes post-approval obligations on Marketing Authorization Holders when granting an authorization under exceptional circumstance. The obligations are usually focused on collecting further evidence in support of the safety and efficacy of the medicinal product. This appears to be a less prominent risk. However, the case of the medici-nal product Xigris (drotrecogin alfa (activated)) confirms that it is not simply a theoretic risk, see EMA webpage at: https://www.ema.europa.eu/en/news/xigris-drotrecogin-alfa-activated-be-withdrawn-due-lack-efficacy.

[16] Other considerations might be required on a case-by-case basis. For instance, certain diseases and medications require continuity of treat-ment, meaning that patients that are already being treated with one medicine might not be able to switch to any new medicine, which further reduces market size.

[17] See our article 'Expensive innovative treatments: How to increase patient access and avoid conditional reimbursement approvals', 27 October 2020, available at: https://www.copenhageneconomics.com/dyn/resources/Filelibrary/file/9/319/1603881722/4.-expensive-innovative-treatments.pdf