Editorial

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The need to consider market access for pharmaceutical investment decisions: a primer

Sreeram V Ramagopalan*,[1], Catherine Bacon[2], Mel Walker[3] & Michael L Ryan[4,5]

[1]Centre for Pharmaceutical Medicine Research, King's College London, London, SE1 9NH, UK

[2]Fingerpost Consulting, Pure Offices, Cheadle Royal Business Park, Brooks Drive, Cheadle, Manchester, SK8 3TD, UK

[3]Founder & CEO, Access InVivo, London, UK

[4]Founder & CEO, Koios Enterprises & Consulting, USA

[5]Executive Advisor, Numerof & Associates, USA

*Author for correspondence: sreeram@ramagopalan.net

Biotech/Pharma investors employ valuation methods to support capital deployment that consider the costs of drug development, projected sales and risks of failure. Often, the major focus for valuation is placed on the likely success rates of taking a compound from phase I to regulatory approval, with the notion being that just by obtaining regulatory approval sales will follow. However, as exemplified by recent cases with hemophilia gene therapies, achieving forecasted sales depends not only on regulatory success but crucially on market access outcomes. This primer examines how pharmaceutical investment decisions must consider market access factors, particularly in light of recent regulatory changes such as the US Inflation Reduction Act and European Union Joint Clinical Assessment. Effective market access strategies can enhance commercial success through better pricing, broader reimbursement, and/or faster uptake, and having a clear market access plan should encourage investment by providing a clearer path to commercial success. As health technology assessment processes become more sophisticated globally, treating market access as an essential strategic capability rather than a tactical exercise will be important for attracting investment and ultimately, successful drug development and commercialization.

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Drug discovery and early development represents a resource-intensive and high-risk endeavor, predominantly undertaken by startup companies that lack revenue streams from existing products. The process follows a rigorous sequence beginning with preclinical trials, encompassing both *in vitro* studies and animal testing, followed by up to three distinct phases of clinical trials, each requiring substantial research and development (R&D) expenditure. Companies can only market their drugs for approved indications after completing registrational trials and securing regulatory approval. Estimates have suggested that developing a new drug costs approximately $2.6 billion (in 2013 US dollars) [1,2], with an average duration of 81 months between clinical testing initiation and regulatory submission. Moreover, the probability of a drug candidate progressing from phase I clinical trials to regulatory approval stands at less than 12% [1]. However, while the main focus for drug developers has historically been on securing regulatory approval, market access is imperative to achieve sales revenues as evidenced recently by hemophilia gene therapies [3]. Companies often fail to realize that the evidentiary requirements needed for optimal market access are greater than that required for regulatory approval (Figure 1); and therefore, do not always plan accordingly to generate the evidence necessary, leading to suboptimal market access and thus sales. In this primer we discuss how important market access is to maximize commercial returns.

Investment decision making & net present value

Biotech startups fund their drug development through capital from government agencies, universities and most importantly, venture capitalists. Venture capitalists typically make a return on their investment when a larger

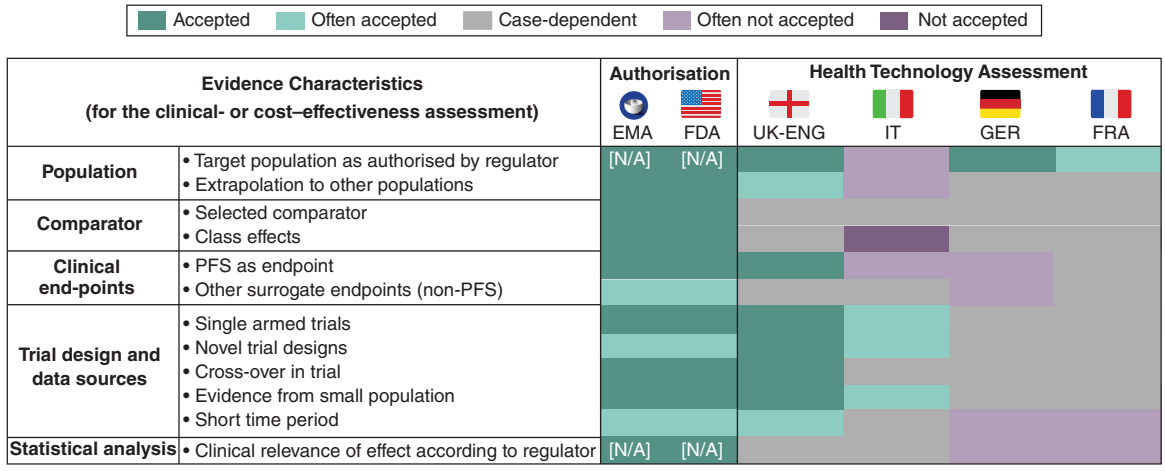

Figure 1. Comparison of acceptability of different elements of trial data by regulators and health technology assessment agencies. Compares the acceptability of various elements of trial data by the EMA, the US FDA, and by HTA agencies in the UK, Italy, Germany and France, adapted from the European Federation of Pharmaceutical Industries and Associations (EFPIA) [4]. As can be seen from the figure, while regulators are not often concerned with the comparator used, willing to accept surrogate end points, data from small trial populations, data from trials running for a relatively short time period and single-arm trials, this is not always the case for HTA agencies, and as such a drug can achieve regulatory approval but not be reimbursed. It is imperative to consider the needs of HTA agencies/payers and not just regulators in order to achieve commercial success.
EMA: European Medicines Agency; FRA: France; GER: Germany; HTA: Health technology assessment; ITA: Italy; PFS: Progression-free survival.

company acquires or licenses an asset so equity investments are based on valuation assessments that consider the drug candidate's projected sales, development costs and regulatory risks. Net present value (NPV) analysis serves as a potential decision-making tool in pharmaceutical investment evaluation, where investors discount future cash flows to present value to account for both the time value of money and risk. When calculating NPV, investors consider projected revenues from successful drug commercialization, weighted against development costs and the opportunity cost of capital. The analysis incorporates multiple factors, for example, revenue analysis includes anticipated market size, pricing strategies and competitive dynamics. Cost considerations encompass R&D expenses, clinical trial expenditures, manufacturing and marketing costs and regulatory compliance requirements. An overview of these financial flows is shown in Figure 2. Time considerations play a crucial role, as the analysis must account for the development timeline, expected approval date, commercial life cycle and potential generic entry timing. Investors must also carefully weigh various risk factors, including phase-specific success probabilities, regulatory approval likelihood and market acceptance uncertainty, which is achieved through risk adjusting the NPV [5]. Investment decisions typically proceed when the NPV is positive, indicating expected positive returns. This methodology enables systematic comparison of diverse investment opportunities while accounting for the unique challenges and uncertainties of pharmaceutical development.

A simple example to illustrate NPV is as follows. A friend asks to borrow $1000 today and promises to pay you back $1200 in 2 years. Is this a good deal? To decide, you might compare it to an alternative investment – for example, putting $1000 in a savings account earning 5% annual interest. With compounded interest, this would grow to $1103 after 2 years ($1000 x $[1 + 0.05]^2$). Your friend is offering you nearly $100 more than the bank, but lending is riskier than saving in the bank. As putting money in a bank is generally low risk, using the 5% interest rate as the discount rate (representing an investor's required rate of return or opportunity cost of investing) yields a NPV of 0 ($1000- ($1103/ $[1 + 0.05]^2$). Now, your friend's loan of $1200 looks more attractive, but lending money carries more risk (e.g., higher chance of no or delayed repayment from your friend). To account for this higher risk, a higher discount rate should be used, for example, 15%. With a 15% discount rate, the NPV of lending to your friend equals $-93 ($1000–$1200 / $[1 + 0.15]^2$). Loaning to a friend thus actually has a negative NPV and therefore purely from a financial perspective, putting your money in a bank offers a better projected return.

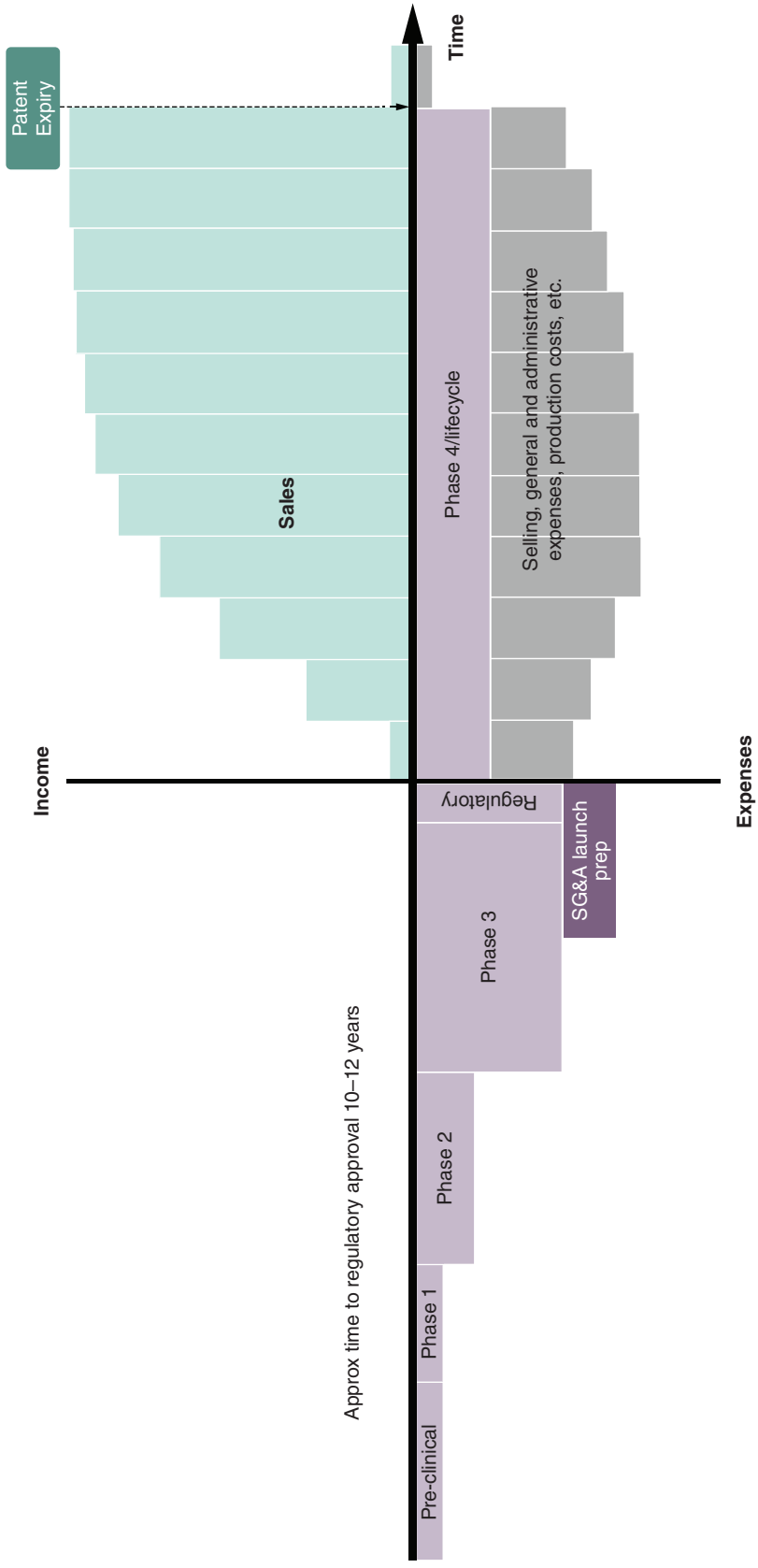

Figure 2. Overview of typical financial cash flows in drug development. The graph shows negative cash flows (investments) during preclinical research, the three phases of clinical trials and regulatory review, typically spanning 10–12 years. These investments include research costs, clinical trial expenses and regulatory submission fees. The commercial phase begins after regulatory approval, marked by positive cash flows (revenue) from drug sales (even during the commercial phase costs are incurred which include the costs of obtaining reimbursement, further evidence generation, manufacturing and marketing). Revenue typically starts low, increases to peak sales during the patent protection period, and then declines sharply when generic competitors enter the market (patent cliff). The area between the positive and negative cash flows represents the potential return on investment, which must be risk-adjusted in NPV calculations to account for the high failure rate in drug development. The timing and magnitude of these cash flows are critical inputs for NPV calculations and subsequent investment decisions.
NPV: Net present value; SG&A: Selling, general and administrative expense.

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This example shows that money in the future is worth less than money today. First, inflation reduces purchasing power of money over time ($1000 will likely buy more today than it can in the future) and second, there is always some risk that you might not receive payments in the future at all. NPV helps compare investment opportunities to determine the best option. If the NPV is positive, it means the investment is worth making. Biotechnology investments follow the same principle but are far more complex. Developing a new drug typically requires:

- Much larger initial investments ($100 million or more).
- A much longer wait for any revenue (often 10–12 years).
- Multiple additional investments along the way.
- A high risk of complete failure (more than 88% of drugs fail during development).
- Uncertain future revenues due to market access and pricing challenges (more than a third of drug launches fail to meet forecasted revenues in their first year of launch with the main cause being market access challenges).

A $100 million investment in drug development might generate no returns at all if the drug fails in clinical trials (Figure 3), or it could generate billions in revenue if it successfully completes pivotal trials, secures regulatory approval and achieves optimal market access [6].

The importance of market access for revenue generation

Market access determines how quickly and how widely patients are able to receive a new therapy after regulatory approval. It has become fundamentally important as the payer has risen to become the dominant stakeholder in all major pharmaceutical markets over the last decade. It involves three key elements: pricing (what price payers will accept), reimbursement (whether and how much payers will pay) and patient access (which patients can receive the therapy). Good market access – achieved through strong evidence of clinical benefit and value to healthcare systems – can lead to higher revenues through favorable pricing, broad reimbursement and wide patient access. All three (favorable pricing, broad reimbursement and wide patient access) may not be possible but a comprehensive market access strategy will identify the optimal positioning scenario to deliver the best return. Poor market access can dramatically reduce revenues through multiple mechanisms: lack of evidence necessary to justify the holistic value of a therapy leading to lower prices than anticipated, restricted reimbursement to smaller patient populations, delayed launches in key markets or limited uptake by physicians due to administrative barriers. Indeed, as shown in Figure 1 market access and pricing evidentiary requirements are far more rigorous than regulatory standards for drug approval. In addition to clinical trial data, there are also additional requirements for health technology assessment (HTA) agencies/payers, for example, the development of health economic models. Unfortunately, too many companies focus solely on the evidentiary requirements for regulatory drug approval, and in so doing dramatically limit their ability to demonstrate the holistic value that their product deserves, and ultimately achieve the sales forecasted. For example, a cancer drug might be approved for all stages of disease but only reimbursed for late-stage patients, or a novel therapy might secure a lower price than expected due to insufficient evidence of superiority over existing treatments or loss of exclusivity of comparator products. An analysis has shown that more than a third of new product launches fail to meet forecasted revenue projections, and in more than half of the cases this is because of limited market access [7]. In order to develop a robust product net revenue forecast, insightful assumptions on the potential and extent of complex access restrictions, as well as the projected list and net price are required. As noted above, while some asset valuation methods look at potential price achievable and market share, a detailed consideration of market access outcomes is rarely performed. The failure to incorporate qualified market access expertise into valuations leads to overly optimistic or pessimistic forecasts, poor pipeline prioritization and product launches that fail to meet promised revenue objectives. Market access outcomes ultimately determine whether an approved drug becomes commercially successful and therefore can significantly impact NPV calculations (Figure 4). It is now observed that even drugs with strong efficacy data can fail commercially if their market access strategy is suboptimal [7]. As a result, the value of an effective market access strategy is being increasingly recognized by investors as well as drug developers and is a key point of leverage for smart biotech teams when raising capital in a more constrained funding environment. Companies with a comprehensive market access plan should be able to secure higher levels of investment more readily, and achieve higher exit values, as they can support how future revenues will be generated rather than focusing just on securing regulatory approval, which is not a guarantee of commercial success.

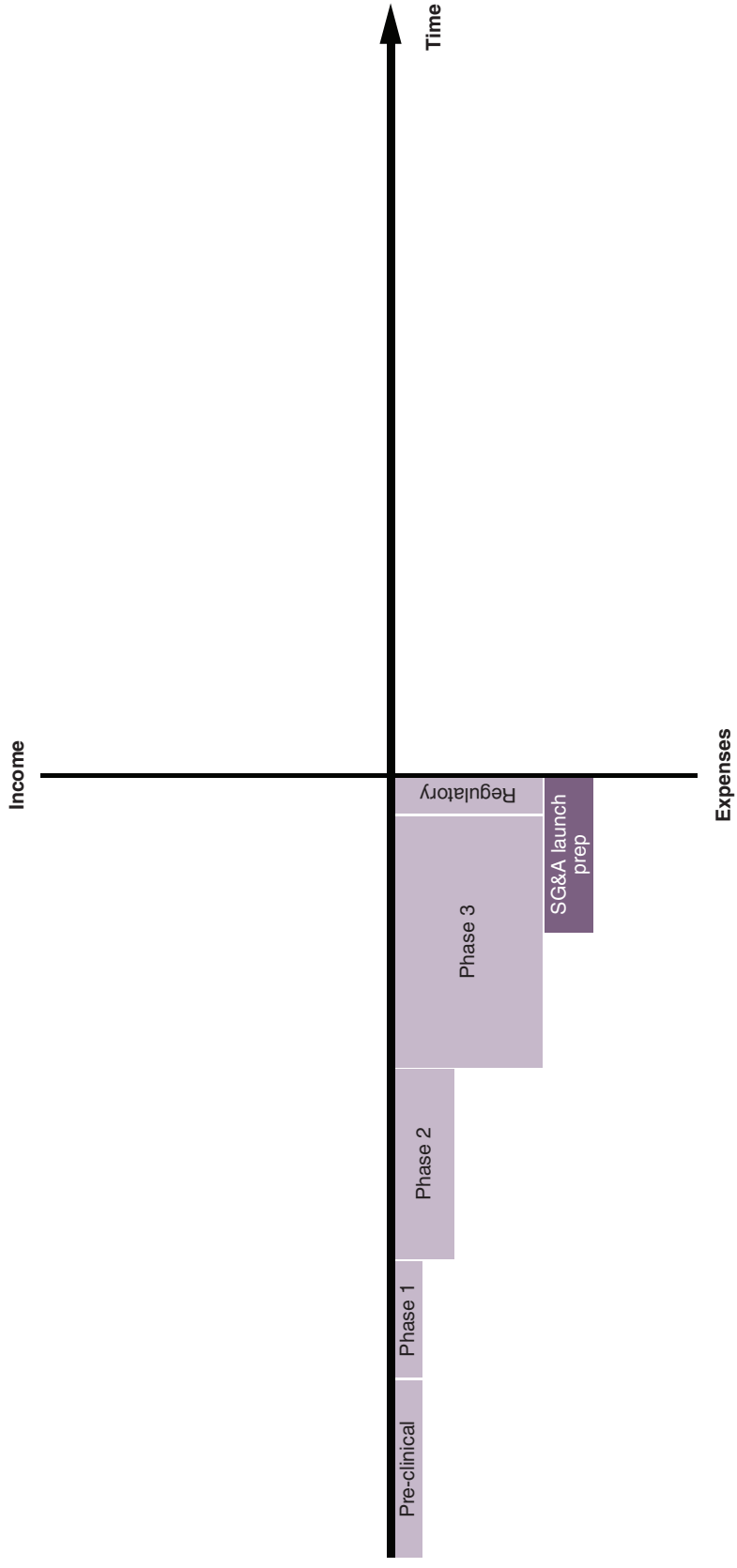

Figure 3. Financial cash flows in drug development when a drug fails clinical trials/does not secure regulatory approval. The financial outcome when drug development fails, which occurs in more than 88% of cases is illustrated. The graph shows only negative cash flows (investments) during development phases, with no revenue-generating commercial phase. These losses occur across preclinical research, clinical trials and regulatory review until the point of failure, which can happen at any stage of development. Once failure occurs (whether due to safety concerns, lack of efficacy or regulatory rejection), all investments made up to that point are lost with no opportunity for recovery. Selling, general and administrative costs may be incurred depending on the timing of failure. This failure scenario must be factored into NPV calculations through risk adjustment, as it represents the most common outcome in drug development.
NPV: Net present value; SG&A: Selling, general and administrative expense.

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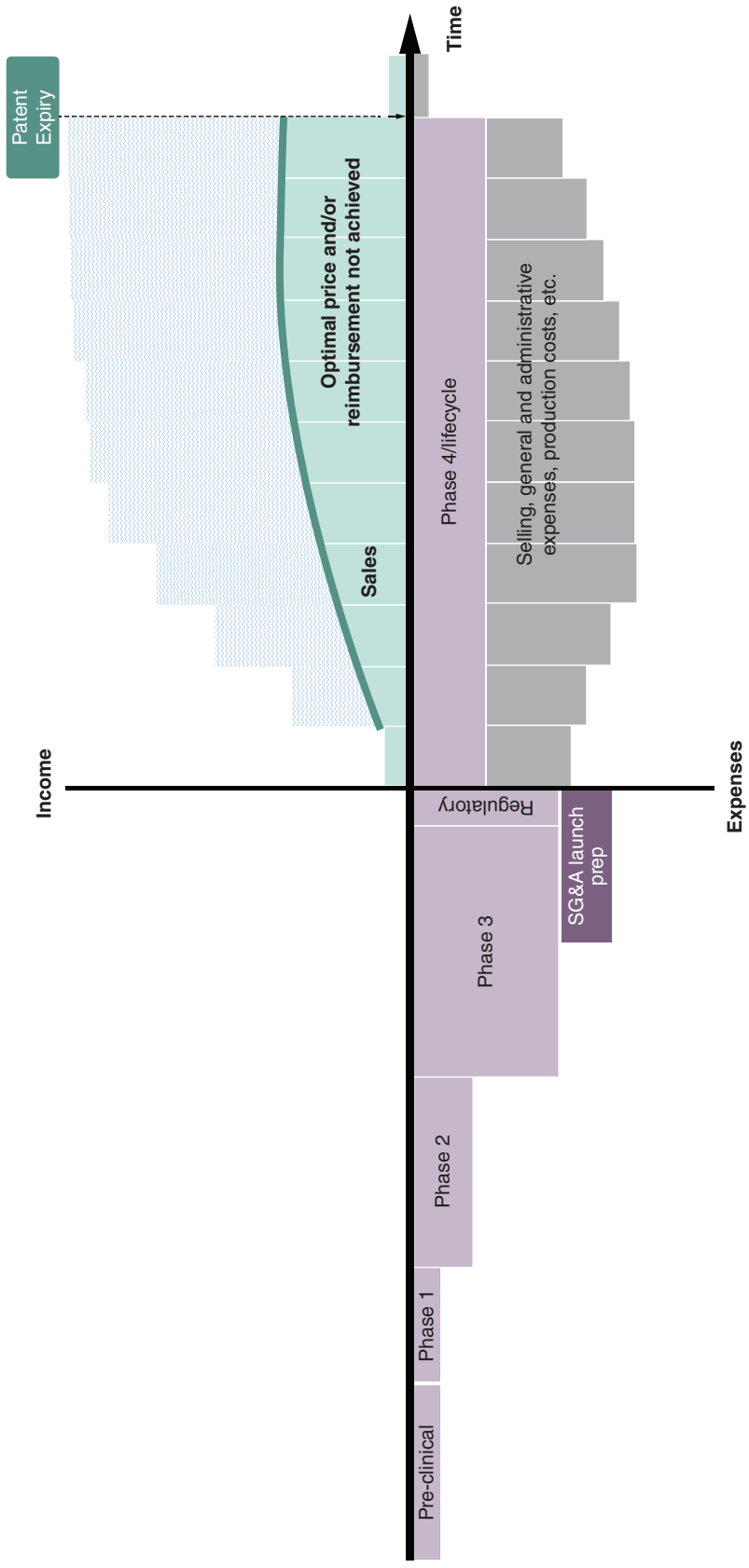

Figure 4. The impact of poor market access on financial cash flows in drug development. The green line demonstrates reduced revenues due to market access challenges. These challenges can include delayed reimbursement approvals, restricted patient populations, lower achieved prices or limited market uptake. The shaded blue area represents lost revenue opportunity due to suboptimal market access. Even after successfully developing a drug and gaining regulatory approval, poor market access can significantly reduce the overall return on investment and may result in a negative NPV despite regulatory success.
NPV: Net present value; SG&A: Selling, general and administrative expense.

The changing market access environment

The importance of market access has been further underscored by recent changes in major markets. One such major change, the introduction of the US Inflation Reduction Act (IRA), has added a layer of complexity to NPV calculations. The IRA introduces predictable but significant revenue impacts at different time points depending on molecule type [8]. Compared with pre-IRA when drug prices naturally fall at the end of the patent period due to generic entry, now small molecule drugs face price negotiations after seven years after first FDA approval, with implementation of negotiated prices by year nine, typically resulting in a 25–40% revenue reduction. Biological products receive a longer period before negotiations begin at eleven years after first FDA approval, with implementation by year thirteen. This creates an earlier cliff effect in NPV calculations, where future revenues must be adjusted downward at specific time points. For instance, a small molecule drug generating $1 billion annually might see revenues reduced to $600–750 million after year nine (Figure 5). In addition, the exact methodology for determining the final Medicare 'fair price' is not described in legislation, but instead is left to the discretion of the Secretary for Health and Human Services, a political appointee, meaning that companies must do what they can to prepare evidence to support pricing negotiations with no guidance. Given impacts on revenues and therefore NPV, the IRA has catalyzed significant restructuring of R&D priorities. A number of areas are experiencing reduced investment: companies are shifting from the development of oral small molecules to injectable biologics, leveraging the Medicare's 4-year negotiation delay for biologics (the so called 'pill penalty'); post-approval phase IV research now has a significantly diminished return on investment given Medicare negotiation timelines begin from the date of FDA approval of the first indication, this will particularly impact oncology indication expansion (the testing of an approved drug's efficacy in additional tumor types and disease stages beyond what it was initially approved for). Companies are now prioritizing the indication which has the largest market size opportunity; orphan drug development for secondary indications has decreased due to Medicare negotiation exemption only for orphan drugs with single-indications; pediatric research investment has declined given extended development timelines as compared with adult studies (pediatric studies would only complete close to or at time of Medicare negotiations leaving little time for return on investment to be achieved); and finally reduced focus on therapies with high Medicare/Medicaid patient populations given IRA inflation penalties and Medicare price negotiation.

In Europe, we are also seeing major changes with the implementation of the Joint Clinical Assessment from 2025. This EU wide requirement has introduced substantial new complexities to market access planning [9]. Companies must now address multiple population, intervention, comparator and outcomes frameworks across member states, meaning that evidence generation plans need to incorporate value demonstration against multiple comparators [10]. These additional requirements must be factored into development planning and corresponding NPV calculations (in terms of costs of any additional evidence generation as well as impacts on time to and breadth of reimbursement).

An effective market access strategy secures optimal pricing, reimbursement and access across diverse global healthcare systems and payer environments. This can be achieved by generating clinical, economic and humanistic evidence to demonstrate product value for multiple stakeholders, and planning for country-specific regulatory frameworks, HTA requirements and pricing mechanisms. We are already seeing the impact from the IRA on what assets are taken forward for development/further investment. Successful market access requires early planning as not meeting payer requirements can delay time to revenue and/or result in a sub-optimal price. Where an initial price achieved is lower than expectations, there is seldom an opportunity in Europe to have this revisited and increased when more data on product value is generated, so getting things right at the first opportunity is important. While payer evidence requirements are crucial, additional studies must be justified by clear commercial benefits: reducing the probability of poor access, securing better pricing, increasing physician adoption or expanding patient populations. Not all market access requirements need to be addressed through expensive clinical trials – companies can optimize NPV by prioritizing evidence that delivers the greatest commercial value. For example, rather than conducting large comparative trials for all markets, companies might focus on key comparators and end points for major markets while addressing smaller markets through indirect comparisons or real-world evidence. Trade-offs may be required as costs or time required for further evidence generation may impact revenue achievable- accepting restricted access in some markets in exchange for faster launch in key territories, or initially targeting a narrower patient population where value is most clearly demonstrated are scenarios that a comprehensive market access strategy will cover.

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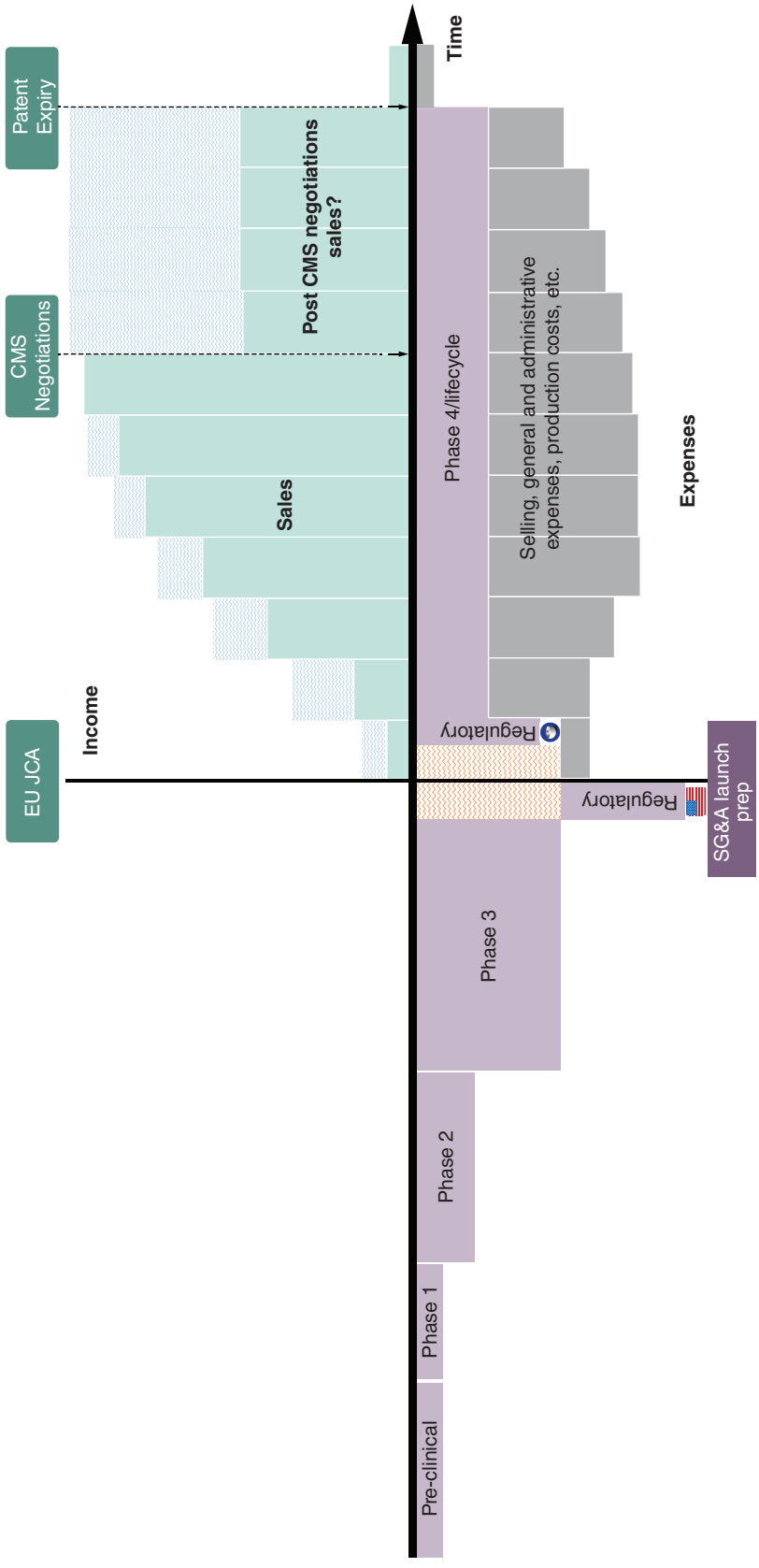

Figure 5. The impact of EU Joint Clinical Assessment and US Inflation Reduction Act on financial cash flows in drug development. The EU JCA affects the early part of the commercial phase by potentially increasing development costs and/or delaying time to or limiting revenue generation due to additional evidence requirements (orange shading indicates additional costs for evidence generation). The IRA creates a 'cliff effect' where revenues decline sharply at a specific point – after 7 years for small molecules (with price negotiations implemented by year 9) and after 11 years for biologics (implemented by year 13). The shaded blue area represents lost revenue opportunity due to both of these policy changes, which must be factored into NPV calculations.
CMS: Centers for Medicare & Medicaid Services; JCA: Joint Clinical Assessment; NPV: Net present value; SG&A: Selling, general and administrative expense.

Conclusion

Looking to the future, the integration of market access considerations into revenue forecasting and ultimately NPV calculations will become, if it is not already, of fundamental importance to all investors and drug developers. More and more markets are implementing formal HTA processes, and existing processes are becoming more sophisticated. Even where HTA is not a formal requirement, these methodologies are now used extensively if non-transparently for decision making, for example by US payers. The use of novel payment models, such as outcomes-based contracts or installment payments, adds another layer of complexity to NPV calculations. Companies must now consider not only the magnitude of potential revenues but also their timing and certainty. As investors become more sophisticated in evaluating market access strategies, the quality of market access planning will become as important as clinical data in determining which products receive funding. Companies that treat market access as a strategic function rather than a tactical one, who believe that market access is a science that requires years of experience and expertise to perform, and who engage market access expertise early in development are better positioned to secure investment and achieve commercial success for their assets.

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Competing interests disclosure

The authors all consult to the life sciences industry. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

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