Editorial

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How much do ex-US revenues make a difference for pharmaceutical investment returns?

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"Given the changing policy landscape in the US, where initiatives such as the Inflation Reduction Act and reference pricing proposals may reduce traditional US revenue premiums, comprehensive market access planning that optimizes both pricing and reimbursement outcomes globally may be a strategy that drives higher returns on investment."

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Recent US pharmaceutical pricing changes, including proposals for international reference pricing (Most Favored Nation) and Medicare price negotiations under the Inflation Reduction Act (IRA), have raised concerns about their potential impact on the incentives for pharmaceutical innovation [1–3]. The economic rationale for pharmaceutical investment fundamentally depends on achieving sufficient risk-adjusted returns to justify the substantial costs and uncertainties inherent in drug development [1,2]. Traditional analyses have often assumed that US market revenues represent the primary driver of investment returns, given the historically higher pricing levels obtainable in the US compared with other developed nations. However, the relative contribution of revenues outside of the US and how this differs across therapeutic categories, in particular for treatments addressing rare diseases, has not been analyzed in detail.

To investigate this further we employed net present value (NPV) modeling, a standard technique in pharmaceutical valuations, to examine geographic revenue distribution patterns across a selection of pharmaceutical products spanning different therapeutic areas. The models calculated present values of expected future cash flows over the commercial life of each product, accounting for patent expiry timelines. We utilized historical sales and forecast data from GlobalData to construct the models incorporating regional revenue breakdowns between the US and the rest-of-world (ROW). Gross margin assumptions were applied to estimate gross profit, from which we deducted selling, general and administrative expenses to calculate earnings before interest and taxes. We used pharmaceutical sector-specific data inputs as used in the study by Xie *et al.* [2], including gross margins, corporate tax rates and discount rates across different regions. Net operating profit after tax values were then discounted to present value to quantify the contribution of each region to overall product NPV.

The analysis encompassed products across multiple therapeutic categories: oncology treatments Keytruda®, Blincyto®, Lumakras®, Vectibix®, Alecensa® and Yescarta®, spinal muscular atrophy treatments Zolgensma® and Evrysdi®, and the cardiovascular medication Xarelto®. The products were selected to enable examination of whether and how therapeutic area and disease prevalence influence geographic revenue distribution patterns and overall investment attractiveness. In particular, some rare disease treatments (Yescarta, Alecensa, Vectibix, Lumakras, Blincyto, Zolgensma and Evrysdi) were chosen to compare to known blockbuster medications (Xarelto and Keytruda).

Table 1 shows the total NPV for each product as well as the breakdown of contributions to NPV by geography,

Table 1. Geographic contributions to overall net present value for a selection of treatments.

Drug name	NPV					ASMR assessment in France
	US	NPV (%)	ROW	NPV (%)	Total	
Blincyto®	1225	59%	862	41%	2087	III
Lumakras®	749	62%	454	38%	1203	NA
Vectibix®	644	35%	1171	65%	1815	V
Evrysdi®	1698	36%	3028	64%	4725	III
Alecensa®	1629	32%	3406	68%	5035	IV
Keytruda®	32,389	57%	23,966	43%	56,355	Numerous assessments
Yescarta®	2302	54%	1949	46%	4251	III
Zolgensma®	1962	41%	2854	59%	4817	V
Xarelto®	6996	61%	4557	39%	11,554	IV

The table shows the overall NPV calculated for these treatments, and the breakdown of contributions to NPV from the US and all other markets, ROW. As a proxy for pricing and reimbursement achieved through global health technology assessment (HTA), the improvement in medical benefit rating (ASMR) provided by the French HTA agency Haute Autorité de santé (HAS) was identified. As products may have multiple indications and may be reassessed, the best ASMR was chosen. ASMR I, II and III allows for premium pricing.
ASMR: Amélioration du Service Médical Rendu; NPV: Net present value; ROW: Rest-of-world.

comparing the US to the ROW. The results reveal significant heterogeneity in geographic revenue distribution across therapeutic categories. Products demonstrate US NPV contributions ranging from 32 to 62%, with corresponding ROW contributions spanning 38 to 68%. 'Blockbuster' treatments such as Keytruda and Xarelto demonstrate the classic preponderance of US market revenues for investment returns. Keytruda, with a massive $56.4 billion total NPV, derives 57% from US markets ($32.4 billion) and 43% from ROW markets ($24.0 billion); Xarelto obtains 61% of NPV from the US. This is generally the expectation for pharmaceutical NPV calculations, reflecting the significantly higher per-unit pricing achieved in the US market relative to international markets. However, oncology treatments treating rarer conditions, such as Vectibix and Alecensa, demonstrate greater international dependence; 68% of NPV ($3.4 billion of $5.0 billion total) for Alecensa originates from ROW markets. Spinal muscular atrophy treatments also exhibit this pronounced shift toward international revenue dependence. Zolgensma derives 59% of its NPV ($2.8 billion of $4.8 billion total) from ROW, while Evrysdi shows an even more dramatic pattern with 64% international contribution ($3.0 billion of $4.7 billion total). This reversal of traditional revenue patterns reflects the necessity for global commercialization to achieve sufficient patient scale in rare disease markets, combined with the unmet need for these treatments in their respective markets, potentially supporting premium pricing across multiple jurisdictions.

As a proxy for the pricing achievable in ROW markets, we investigated the French health technology assessment (HTA) agency, Haute Autorité de santé (HAS), medical benefit rating (ASMR) for the products analyzed. ASMR ratings I–III allow for premium pricing to existing comparators. While there is no clear trend in this limited analysis (which has the limitation of being from a single HTA body, as well as not factoring in sales volume), Evrysdi, Blincyto and Yescarta were able to achieve ASMR ratings of III which must have helped for ROW revenues.

There are limitations to this analysis in terms of the number of products selected. The products have differences in terms of the unmet need in their respective indications (and number of indications they cover) and the clinical benefit provided, which preclude direct comparisons. We also do not have the data to understand the specific country contributions to ROW revenues, and have used sales forecast data which will, by definition, not be able to incorporate any unexpected changes to sales revenues. Further, to simplify the modeling we applied a uniform selling, general and administrative assumption of 25% and did not consider post launch research and development expenses. Nevertheless, the findings provide two general conclusions.

First, assuming an average cost of approximately $1 billion to bring a new drug to market [4,5], a reduction in US revenues would potentially make some of the drugs investigated unlikely to have been attractive investment opportunities (e.g., Blincyto, Lumakras and Vectibix). As noted by others, policy interventions that significantly reduce US pricing may therefore have pronounced negative effects on investment incentives for drug development [2,6,7]. Second, for NPV calculations, revenues outside the US may be the predominant driver of NPV for some indications. Given the changing policy landscape in the US, where initiatives such as the Inflation Reduction Act and reference pricing proposals may reduce traditional US revenue premiums, comprehensive market access planning that optimizes both pricing and reimbursement outcomes globally may be a strategy that drives higher

returns on investment. Early consideration of the evidentiary requirements to demonstrate value for HTA agencies across multiple jurisdictions, and strategic global commercialization (including consideration of launch sequencing) may be able to compensate for the loss of revenues previously achievable in the US. While mature HTA markets may classically be viewed as having onerous requirements, they are perhaps more predictable in terms of pricing and reimbursement outcomes in the current environment. For pharmaceutical companies and investors, while it is hoped that US policy changes do not significantly reduce the incentives for pharmaceutical innovation, this analysis underscores the fundamental importance of optimizing revenue potential across the globe to drive returns, derisk investments and support the pharmaceutical innovation ecosystem.

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