WHITE PAPER

Creating shareholder value in pharma with optimal portfolio strategy

Using current signals to predict tomorrow's growth markets today

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> **"The pessimist complains about the wind; the optimist expects it to change; the realist adjusts the sails."**
>
> – William Arthur Ward

Flying from New York to San Francisco often takes more than an hour longer than doing the reverse. That's because it takes more time, not to mention fuel, to fly against a jet stream than with one. If pharma innovation can be compared to aeronautics, then new molecular entities (NMEs) are the planes, R&D spend is the fuel and complex, ever-shifting market forces are the jet streams—those macro-environmental factors that can function either as tailwinds behind or headwinds against commercial success.

For pharma companies making big R&D investments over long horizons, predicting future headwinds and tailwinds can be just as important as finding the right planes to fly in them. So, what's the optimal pharma portfolio strategy? It depends. For pharma companies looking to place long-term bets, there's no blanket "right" answer. In fact, if every company were to look at the facts and draw the same conclusions about where to invest, the markets they selected would quickly lose their luster.

Find the strategy professor at any halfway decent business school, and they'll lay out the principles of a good corporate strategy, regardless of industry: Focus capital allocation on creating competitive advantage and position yourself in economically favorable markets where this advantage can create value. Our argument is no different, with one exception: Pharmaceuticals is not a single market. It is many markets, and companies get to choose which markets to be in. But not all therapeutic areas (TAs) are created equal, and each pharma company must build a portfolio investment strategy tailored to its unique capabilities and market position. Predicting which TAs are more likely to experience tailwinds or headwinds, and the implications for where to focus investment, is a critical capability every pharma company must now master—and it's the subject of this whitepaper.

The value—and challenge—of focus for portfolio investment strategy

As future drug revenue comes under pressure from the largest pipeline of clinical-stage NMEs in history, a diminishing number of high-prevalence diseases with suboptimal standard of care (SOC), an impending patent cliff and now the Inflation Reduction Act (IRA), concentrating R&D and business development activity into a focused set of TAs will become increasingly important to pharma's financial success. Why? Because we know that companies outperform the industry when they achieve leadership through focused investment in a limited number of therapeutic areas.[1] In the 10 years preceding the COVID-19 pandemic, top-20 pharma companies that achieved above-average TA focus[2] and leadership[3] generated more than double the total shareholder return of their peers.

One way to measure the current wind direction in a TA is by looking at the revenue per branded product (RBP) approved in that TA. In other words, how much revenue is being generated by branded pharmaceuticals, and how many products are splitting the opportunity? Financial markets reward companies that draw more of their revenue from TAs with above-average and growing RBP—TAs with tailwinds, in other words—than from TAs with below-average and shrinking RBP—TAs with headwinds. The difference is significant: The top-20 pharma companies with above-average tailwind-to-headwind ratios have a revenue multiple 60% higher than their peers.

For pharma companies gambling at scale, assuming your product development bets will be systematically immune to market headwinds is hubris. While a great product can underperform in a bear market and a good one can overperform in a bull market, the average "me too" drug in a high-RBP therapeutic area has been worth 40% more than a first-in-class drug in a low-RBP therapeutic area[4] (Figure 1).

[1] TAs are defined by the American Medical Association, according to the specialty of the primary prescribing physician (such as hematology oncology).

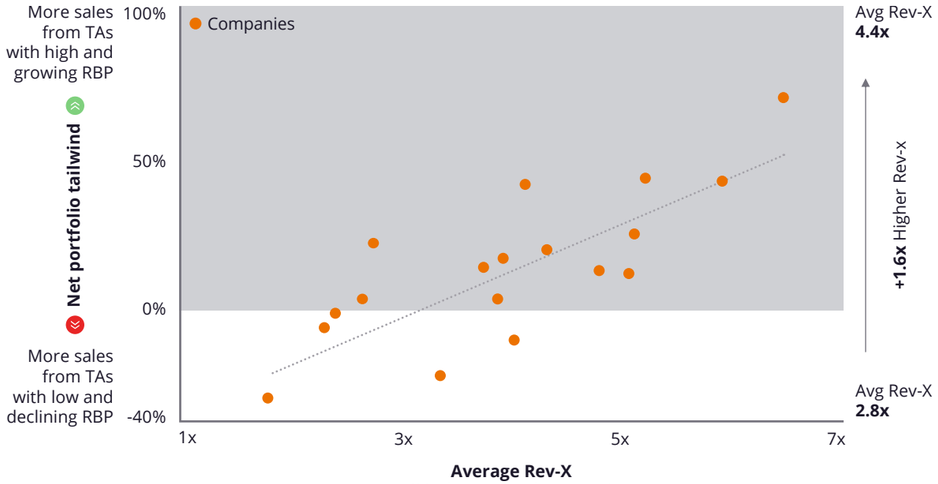
[2] "TA focus" = % of company's sales in their top 3 TAs (ranked by sales)

[3] "TA leadership" = % of a company's sales in TAs where they are market leaders (top 2 by sales)

[4] ZS analysis of Evaluate Pharma data, accessed September 2022, https://www.evaluate.com.

FIGURE 1:

Net portfolio tailwind versus revenue multiple



Climate vs. weather: The art—and science—of predicting market attractiveness

According to the National Oceanic and Atmospheric Association, a 10-day forecast is right only about half the time. However, scientists can (and do) use sophisticated climate models to predict how jet streams will impact climate over the course of decades. Likewise, no one can predict with precision how valuable a therapeutic class currently under development will be in 10 years, given the multivariate uncertainty between now and then. But that doesn't mean we can't foresee the risks of shifting headwinds and tailwinds to pharmaceutical innovation in specific TAs. To support better foresight, we have developed a model that uses today's signals to predict the shifting climes likely to impact TAs tomorrow. When considering the value of investing in future innovation, we recommend pharma companies evaluate TAs along three axes: macro forces that will exert future headwinds or tailwinds, cost of market entry, and a company's position and unique capabilities.

Headwind and tailwind forces

A TA's future growth depends on its degree of unmet need and the volume of new product innovation in the pipeline targeting this need. However, the formula isn't this simple. For chronic diseases with an established standard of care—the context for many new product launches—a safe and moderately effective SOC with generic pricing will be hard to dislodge. Even with a novel product that's proven safe and effective, health technology assessments and payers will have the leverage to contain utilization or negotiate lower prices.

This means that a market's exposure to generic competition and the remaining economic burden that pharma can address are important leading indicators as well. The IRA, which will disproportionately affect TAs with a high concentration of Medicare patients and innovation centered on small molecules, will create headwinds for some TAs due to its price negotiation provisions. Finally, even a great product is worth less to its owner when lifetime value will be stunted by subsequent innovation, so the speed at which new products are being followed by the next wave of innovation is an important consideration.

Cost of entry and company situation

Companies also must look at market attractiveness through the lens of their own ability to create and sustain competitive advantage. In many therapeutic areas, having existing commercial scale and significant pipeline activity is itself a competitive advantage: From 2005 through 2015, companies that launched products in TAs in which they had an existing multibillion-dollar business attained average peak-year sales for these launches two to three times higher than for launches in TAs for which they lacked existing commercial presence. This is thanks largely to the depth and history of customer and scientific community relationships that incumbents enjoy, as well as their ability to lock in preferential tiering for new U.S. products via discounting established brands, such as AbbVie has done with Humira.

How drug pipelines foretell market attractiveness

In 2021, the vaccines jet stream accelerated rapidly, but only those few companies that moved fastest to apply mRNA technology to the novel coronavirus benefited. Although pandemic readiness will become a growth market, we wouldn't recommend big pharma base its portfolio investment strategies on a once-in-a-century pandemic. Beyond vaccines, jet streams in 2021 were highly variable; TAs with the highest RBP outperformed those with the lowest by a factor of five.[5]

The challenge with using RBP as a leading indicator for R&D or business development and licensing decisions, however, is two-fold. First, a company can't easily overhaul its portfolio in a year. And second, RBP isn't stable. A TA will typically shed or gain a third of its RBP value every 10 years.[6] To proactively shift the composition of an investment portfolio of new products without relying on expensive late-stage business development, pharma companies must understand what drives RBP over time.

A powerful predictor of RBP change is the composition of new products being developed in each therapeutic area. To best discern the effects of new product development on RBP, we must first sort them into three categories:

- **Pioneers.** These are products that launch into indications with no approved branded treatments
- **Disrupters.** These are products that launch into indications with existing treatment options but which offer a new mechanism of action.
- **Bandwagoners.** These are products that launch into indications with an incumbent product with the same mechanism of action.

On average, bandwagoners achieve sales equal to just 40% of RBP in their TAs. Disruptors, on the other hand, average almost 120%.[7] Pioneers have a roughly neutral effect on RBP, but since these historically represent just one in 10 launches, they are not a primary revenue driver in most TAs.[8,9] What this means is that a TA pipeline oversaturated with bandwagoners is likely to see a future drop in RBP—as was the case for pain between 2005 and 2014, when bandwagoners represented roughly half of launches and RBP sank by roughly half. During this same period, TAs with disrupter-heavy pipelines saw the majority of RBPs rise. In medical oncology, for instance, disruptors accounted for around three-quarters of launches, and RBP rose by more than 70%.[10]

[5] ZS analysis of Evaluate Pharma data, accessed September 2022, https://www.evaluate.com.

[6] Ibid

[7] Ibid

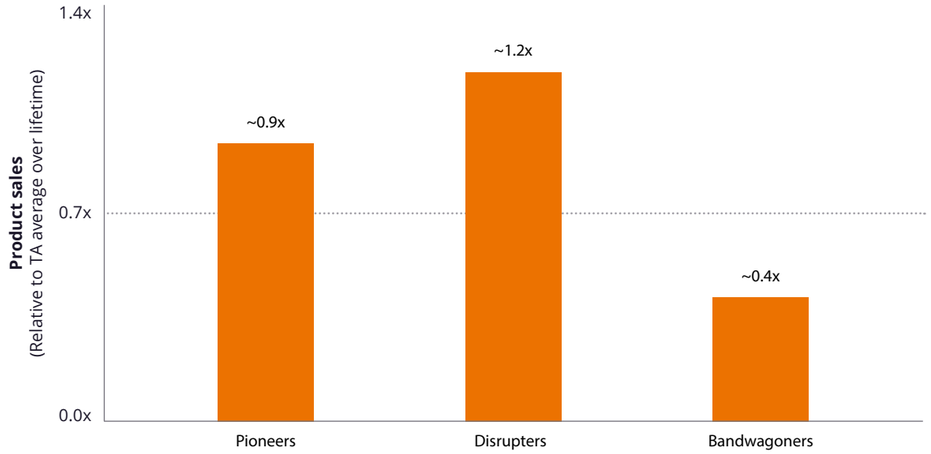
[8] The pioneer result might seem counterintuitive because pioneers always add net-new sales to their TA , as opposed to cannibalizing existing sales. But pioneers only increase RBP if they earn more than the average product in the TA.

[9] ZS analysis of Evaluate Pharma data, accessed September 2022, https://www.evaluate.com.

[10] Ibid

FIGURE 2:

Average product sales by launch archetype



Source: ZS analysis of Evaluate Pharma data, accessed September 2022, https://www.evaluate.com.

Using today's signals to predict tomorrow's growth markets

So how can pharma use today's signals to make informed predictions about which therapeutic areas will experience future headwinds or tailwinds? These examples each use a different set of present-day signals to predict environmental shifts in one of three therapeutic areas: medical oncology, rheumatology and cardiovascular.

Medical oncology and the risk of herd mentality

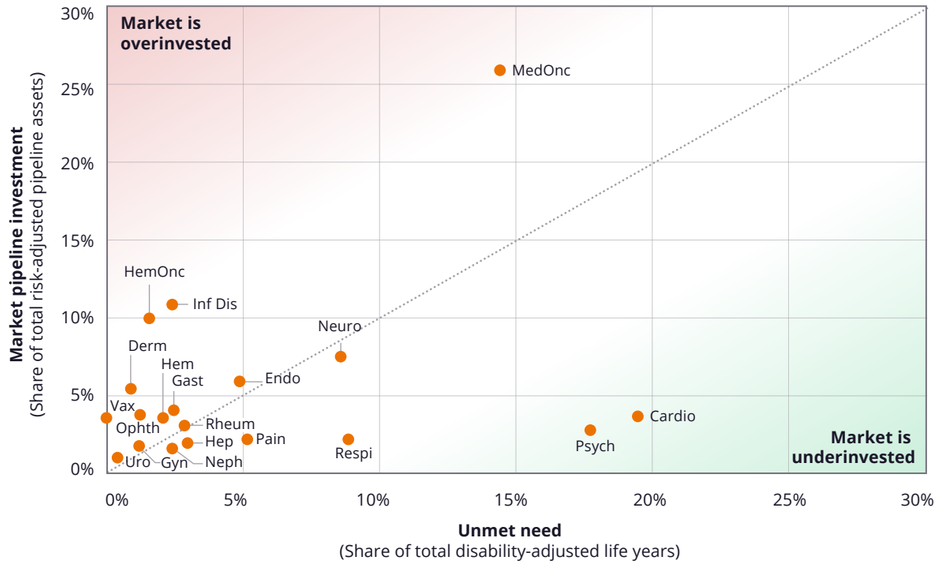
Pipeline investment is rife with herding behavior, with individual firms making decisions inspired by the same breakthroughs and behaviors of their peers. This phenomenon can be seen in the exuberance around specific biological targets, emerging approaches to drugging those targets and even whole diseases and TAs.

Nowhere is this more evident today than in medical oncology, which represents more than a quarter of all risk-adjusted assets in the pharma's clinical pipeline.

While unmet need is unquestionably high,[11] the level of clinical investment has significantly outstripped this need relative to other TAs. Consequently, the medical oncology market basket is primed to expand by 250% over the next decade,[12] far and away the highest figure of any TA.

FIGURE 3:

Unmet need versus pipeline investment volume



··· **Proportional Investment:** In theory, TAs on this line have investment proportional to unmet need.

To date, the business case for oncology investment has become detached from the TA's level of relative unmet need because it benefits from smaller clinical trials, attractive regulatory pathways, higher prices and stronger resistance to rebating pressure in the U.S. All this allows oncology to transcend many of the forces driving down overall R&D ROI.

[11] We focused on U.S. disability-adjusted life years (DALY), as the U.S. typically represents more than 50% of worldwide sales for a multinational pharma company and is often a driver of pipeline investment decisions. DALY data sourced from the World Health Organization, accessed September 2022, https://www.who.int.

[12] ZS analysis of Evaluate Pharma data, accessed September 2022, https://www.evaluate.com.

However, this protection has begun to fray, with examples of companies discontinuing clinical programs not because a drug didn't work but because of anticipated recruiting challenges post-accelerated approval or growing signs of rebating and utilization control creeping into oncology. The IRA also will have an outsized impact on oncology. In the law's first five years, the Centers for Medicare & Medicaid Services will negotiate 100 of the top 200 products by Medicare spend; more than 80% of oncology sales today come from products in this bucket.

Currently, medical oncology boasts the highest RBP of any TA,[13] excluding vaccines, as it has for the past decade, making it an attractive market today. But it is also tied for the highest spend on pharmaceuticals as a percent of total healthcare system costs of any TA, suggesting the market may soon bump up against a natural ceiling as an unprecedented number of new products enter the market this decade. Will health systems around the world, including in the U.S., continue to allow oncology drug development and market economics to remain disconnected from relative unmet need? We believe there will be a correction.

Rheumatology and the danger of linear projection

With the sixth-highest current RBP of any TA[14] and a decade of consistent growth, rheumatology has proved to be one of pharma's most consistently valuable markets. It was the primary revenue driver behind Humira, one of the most lucrative pharma products in history and one that has earned AbbVie nearly $200 billion in sales over the past two decades. Rheumatology's historical tailwind has driven most top pharma manufacturers to invest; emerging signals, however, suggest the winds may be shifting.

Looming loss of exclusivity (LOE) events for major rheumatology drugs threaten nearly 70% of the TA's total branded sales over the next five years, per ZS analysis,[15] representing the highest exposure of any TA. This risk will come into clear focus as biosimilars begin to launch in the U.S. in 2023, boosting competition and applying downward pressure on the price of current and future drugs. Mounting competitive headwinds on future RBP will be further exacerbated by rheumatology's clinical development pipeline, which features the second largest proportion of bandwagoner drugs of any TA, and a high barrier to entry and threshold for attaining leadership.

One of the keys to blockbuster building in rheumatology, and immunology more broadly, has been to begin with a rare disease for faster market entry and to anchor at a higher price point before adding indications later in a product's patent life. Stelara, for example, has accumulated seven approvals since launching in 2009. Indication volume per product is consistently higher in rheumatology than in other TAs. The IRA, however, will hinder this strategy as the price negotiation clock will now start ticking at first approval, shrinking by as much as half the window for companies to realize returns from follow-on indications.

Cardiovascular and the allure of unmet need

Cardiovascular represents a very different business case for portfolio development. It has the highest disability-adjusted life years (DALY) of any TA[16] as well as the largest headroom for pharmaceuticals to defray healthcare system costs and absorb a portion of that value. Why? Because only 6% of total spend on patients with cardiovascular disease is on branded drugs. With less than 5% of the industry's total clinical activity, cardiovascular is also the most underinvested TA relative to unmet need.[17]

[13] ZS analysis of Evaluate Pharma data, accessed September 2022, https://www.evaluate.com.

[14] Ibid

[15] Ibid

[16] Obesity DALYs reflected across all relevant TAs with obesity-associated downstream diseases, such as cardiovascular and endocrine, and not allocated to a single TA alone.

[17] ZS analysis of Evaluate Pharma data, accessed September 2022, https://www.evaluate.com.

This means pharmaceutical innovation can address ample unmet need, and it will face comparatively less competition when it comes to market.

When cardiovascular underwent significant genericization in 2011-12, following the loss of exclusivities of mega-blockbusters Lipitor and Plavix, big pharma players and private capital shifted investment to other therapy areas. In addition, it's one of the most expensive TAs in which to conduct clinical research, it's due for another wave of patent expiration this decade and its risk exposure to new IRA-introduced price negotiations is higher than for any other TA.

Despite all this, cardiovascular has several factors working its favor, namely: major outcomes gaps, evidenced by its status as the leading cause of death in the U.S.; evolving knowledge of disease biology and novel drug targets; and promising clinical-stage innovation in some patient populations. While some big pharma players are shifting investment back into cardiovascular, it doesn't feature the same degree of top-heavy market dominance from a few key players as we observe in other TAs, such as rheumatology and medical oncology. This leaves space for new entrants to carve future leadership positions.

Every therapeutic area has a unique story of coming headwinds and tailwinds. Companies need a clear and objective perspective on these signals and an understanding of how to balance known opportunity for innovation against long-term risk.

Doing the 'impossible': Keeping the wind always at your back

There is no historical precedent for a pharma company that can systematically, and in a differentiated way, discern future winning drugs from losers, regardless of TA. This power of omniscience would translate into gravity-defying financial returns. Over the past decade, the biggest creators of shareholder value in pharma have disproportionately created this value in TAs where focus has given them a competitive advantage. For pharma companies operating within the normal laws of physics—that is, all of them—it is imperative to be selective with TAs when building a portfolio investment strategy.

Pharma companies can create competitive advantage by taking three steps:

1. Develop the organizational muscle of future-back market prediction and scenario planning. For many companies, this will require a new capability or the evolution of existing ones, which tend to focus on present-forward and product-level forecasting. It is also critical that this capability be embedded in decision frameworks and mindset from product teams to senior management.
2. Align the enterprise around which TAs the company will target for investment, and make sure R&D and business development and licensing get behind the strategy. Just as important: Companies must decide which TAs in the existing portfolio should be sunsetted and which should be monitored for signs of future opportunity. When this thinking is siloed within functions—research, development, medical and commercial—portfolio focus will drift.
3. Embed these principles on TA value in pipeline governance and budget allocation decisions to ensure portfolio investment strategy aligns with long-term bets the company is making on key TAs. As attractive but isolated opportunities arise beyond core therapeutic areas, it is important to build a mechanism into ongoing decision-making to maintain focus.

Predicting which markets will drive future business is critical to portfolio investment strategy and long-term shareholder value creation. Many companies do future-back market prediction with insufficient evidence or structure—and they do it in ad hoc, rather than systematic, fashion. For most companies, driving cross-division alignment on resource priorities across TAs is a big challenge; adhering to these priorities as leaders make program-level decisions is even harder. But the opportunity makes the challenge worth overcoming. Track the jet streams as they shift, adjust the controls and may the wind be always at your back.

About the author

Joshua Hattem is part of ZS's pipeline and launch strategy practice, leading the Philadelphia-based team within the practice as well as ZS's portfolio strategy service line. He has supported product development, launch and portfolio strategy in 40-plus disease areas with more than a dozen pharma and medical devices companies. He specializes in cross-functional challenges such as market mapping and market shaping, portfolio prioritization, market segmentation, value proposition development and evidence generation strategy.

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