EXECUTIVE INSIGHTS

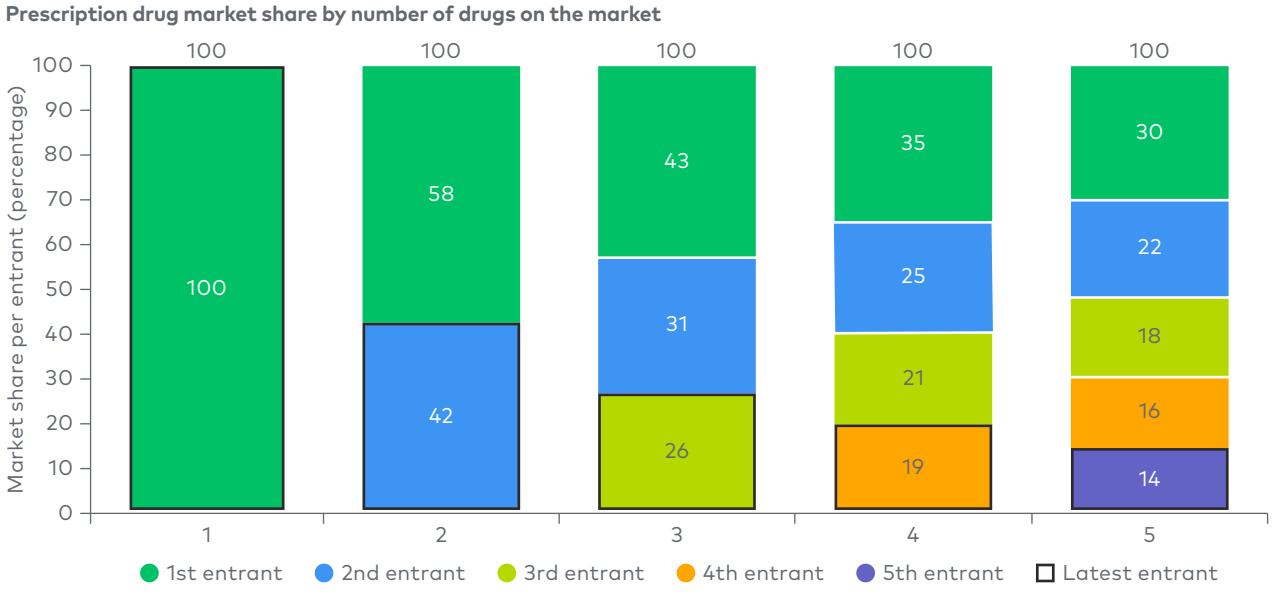
First vs. Best in Class — Simplifying the Equation for Biopharma

Over the past 20 years, there have been a number of attempts to answer the age-old biopharma argument of whether it is better to be first[1] or best in class. The complexity of these analyses has varied from calculating simple averages (e.g., market share by order of entry) to using multivariate equations (i.e., characterizing and weighting the level of differentiation and timing of entry to calculate expected share).[2,3,4] The problem with many of these analyses is that an algorithmic look across a large aggregation of products obscures a key fact: For most products, the outcome is more binary. The idea is analogous to a risk-adjusted revenue forecast — the only certainty is that the risk-adjusted revenue number is unlikely. In reality, revenues will likely be much higher or lower than the risk-adjusted middle ground.

The same shortcoming impacts most order-of-entry-based share projections. While traditional order-of-entry tables are easy- and intuitive-to-use benchmarks, few if any product categories (e.g., classes, markets) approximate the share dynamics that the benchmarks would project. Traditional order-of-entry tables project a steady step-down in share expectations as a product's entry order declines. So, the same product would achieve less share if it were third to market rather than second to market. The tables also predict that the more products there are on the market, the lower the share expectations are for all the products (see Figure 1).

In reality, this is not the case. Order of entry is incredibly important when products are undifferentiated, but aggregate benchmarks underestimate the effect. In fact, in classes where later entrants are not perceived to be differentiated, the first-in-class product often retains more than a 60% share, with later entrants generally capturing less than

Figure 1
Traditional order-of-entry benchmark



Source: Adapted from International GK Associates, Journal of Pharmaceutical and Healthcare Marketing (2008)

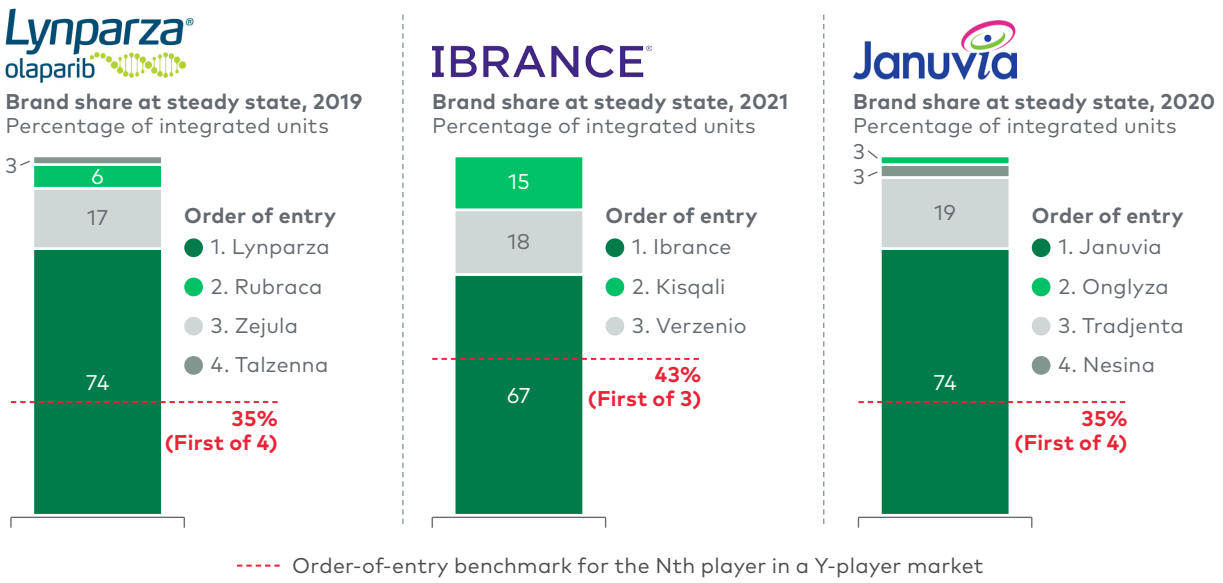
20% and often less than 10% of the class share. Several product classes demonstrate this dynamic, but it can be seen clearly when looking at the poly (ADP-ribose) polymerase inhibitors, the cyclin-dependent kinase 4 and 6 inhibitors, and the dipeptidyl peptidase-4 inhibitors. In each of these classes, traditional order-of-entry tables would have projected that the first-in-class asset would retain considerably less share and, conversely, that later entrants would capture a much larger share of the market than they did in reality (see Figure 2).

Conversely, when a product is truly differentiated, order of entry plays a far lesser role. This phenomenon has been demonstrated across a wide range of disease areas, where a best-in-class product enters the market years after the first-in-class product and still captures majority market share. It is also consistent with L.E.K. Consulting's prior analysis of the makings of a blockbuster, which showed that differentiation was the single greatest predictor of blockbuster revenue outside of company size.[5] Tagrisso, Eliquis, Firazyr and Fasenra are among countless examples of molecules that exceeded order-of-entry benchmark expectations through significant differentiation (see Figure 3). While significant differentiation is most frequently based on efficacy (e.g., Tagrisso), it can also be achieved through other dimensions, such as safety (Eliquis), route of administration (Firazyr) and dose frequency (Fasenra). Such products are often underestimated by analysts with order-of-entry benchmarks.

Figure 2

First-to-market products can maintain market leadership if follow-on entrants offer only modest differentiation

First-to-market product analogs* leading the market with late entrants offering limited differentiation



*Integrated units from Symphony prescription data were adjusted based on formulations, dosing volumes and dosing frequency to reflect the actual annual patient volume

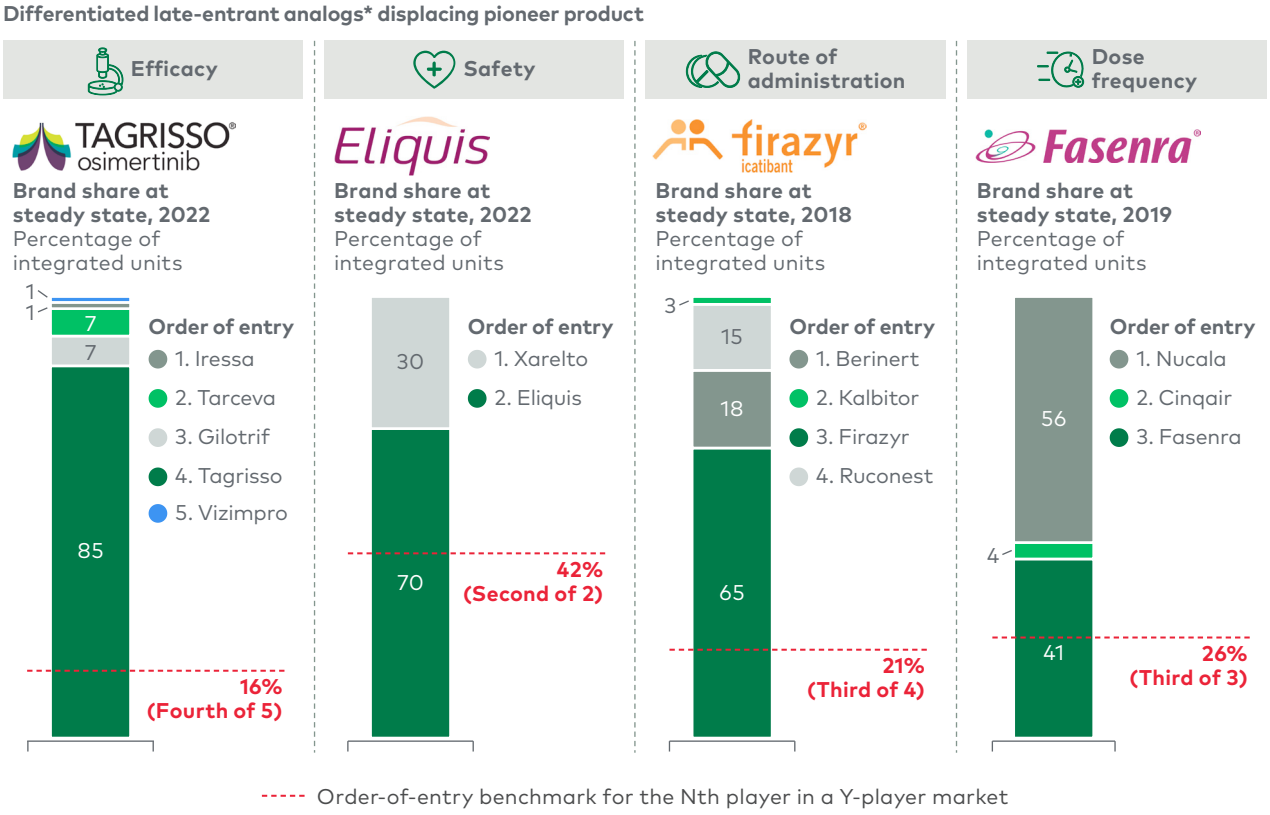
Source: Bloomberg Symphony; Food and Drug Administration (FDA) labels; Datamonitor; Cowen (October 2022, March 2023); GK Associates

Applying this more binary approach to estimating share seems simple until one tries to define "differentiation." There are several confounding factors when looking to define differentiation, such as evolving market access dynamics, biomarker strategies, commercial model innovation and even legislation/public policy. Still, one of the most important and avoidable factors is lacking a transparent and objective assessment of what differentiation means within a specific disease area, patient population and competitive landscape. For example:

- In one tumor type, a physician may find a few months' improvement in overall survival to be highly differentiating; in another tumor type, greater improvement may be required.
- In a slowly progressing disease with safe and efficacious options delivered via monthly infusion, a twice-yearly infusion with similar efficacy may be highly differentiating, whereas in a rapidly progressing disease requiring frequent monitoring, extended dosing may be less differentiating.
- Reducing gastrointestinal (GI) adverse events may be highly differentiating for an oral product that must be taken daily for a chronic disease, while that same reduction in GI adverse events may not move the needle for a product that is taken for a short period of time to address a life-threatening disease.

Figure 3

Product differentiation can overcome order-of-entry dynamics to achieve impactful market share



*Integrated units from Symphony prescription data were adjusted based on formulations, dosing volumes and dosing frequency to reflect the actual annual patient volume

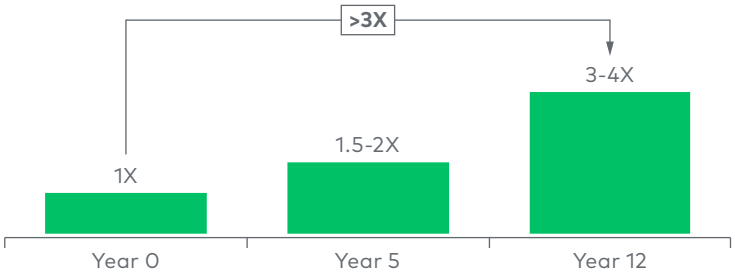
Source: Bloomberg Symphony; FDA labels; Datamonitor; Cowen (October 2022, March 2023); GK Associates

Furthermore, new entrants will need to consider market expansion, which is not captured by order-of-entry benchmarks. In addition to capturing share from the existing standard of care, new market entrants, especially differentiated ones, often attract broader adoption for the class. This is exemplified by many autoimmune diseases, such as psoriasis. New advanced therapies (i.e., biologics, novel orals) have grown the number of patients on such therapies, more than tripling the advanced therapy penetration rate over the past decade (see Figure 4).

Given the cost of drug development and commercialization, it is critical to understand both whether a product is truly differentiated and whether the market is likely to expand in order to accurately gauge its commercial potential. Errors could have immense consequences, such as striving for a value proposition that does not resonate with key stakeholders, or deprioritizing an asset that would have been differentiated and missing out on a potential blockbuster. Over 60% of all innovative branded products approved between 2004 and 2018 failed to reach $250 million in U.S. revenues.[6] Most of these

Figure 4
New entrants, especially differentiated ones, can expand the market

Advanced therapy-treated psoriasis patients (US)
Indexed to Year 0



Unique MOAs	2 (TNF, IL-12/23)	4 (+PDE4, IL-17)	6 (+IL-23, TYK2)
Endpoint evolution	PASI 75 (primary)	PASI 75 (primary) PASI 90 (secondary)	PASI 90 (primary) PASI 100 (secondary)
Safety	No black box (decreasing number of label warnings/precautions)		
ROA/dosing	Q12W SC	Oral	

Note: MOA=mechanism of action; PASI=Psoriasis Area and Severity Index (e.g., PASI 75 is a 75% or greater reduction in PASI scores from baseline); ROA=route of administration
Source: L.E.K. analysis and directional triangulation of EvaluatePharma, Symphony, Cowen reports and claims data

products underperformed expectations, often because a team did not understand which endpoints were most important or what performance thresholds were required across these endpoints, or was not realistic about the probability of achieving such thresholds.

The Inflation Reduction Act,[7,8,9] which may incentivize companies to accelerate development given a potentially shorter drug life span, could further exacerbate companies' inability to accurately gauge their products' market potential. However, striving for faster development pathways should not come at the expense of understanding the target product profile required for commercial success. Still, many organizations are using outdated approaches to assess both internal and external product opportunities.

So, what's the solution? With hundreds of millions of dollars hanging in the balance, how should investment and attention be focused on the winners?

- **Have a clear target product profile** with both R&D and commercial input. Make sure it is based on performance thresholds across key endpoints that will enable share capture and that the R&D team feels are achievable.
- **Focus on differentiation that addresses an unmet need**, not just numerical advantages. It is critical to understand which endpoints are valued and what performance is impactful if achieved. This can only be done through open and objective discussions with physicians, payers and patients.

- **Do not rely on mechanistic rationale** as the differentiator. While a difference in binding affinity could create promise of differentiation, commercial uptake will follow only if that mechanistic advantage drives better clinical performance on endpoints that physicians feel are important.
- **Be honest about the probability of achieving the target product profile** once performance thresholds have been defined. Often teams rely on traditional probability-of-success benchmarks, which typically reflect the probability of approval but not necessarily the probability of achieving a commercially successful product profile.
- **Learn from analogs** to sense-check assumptions. For instance, looking at analogs with L.E.K.'s proprietary Launch Monitor tool would highlight that a 40% share estimate for a late-to-market product with only minor advantages in side effects physicians are not worried about should raise red flags.

If you would like to discuss these findings further, please contact lifesciences@lek.com.

We would like to thank David Knoff, Grace Mizuno and Jiayang Chen for their contributions to this piece.

Endnotes

[1]Lek.com, "First-in-Class Products for Biotech." https://www.lek.com/insights/hea/us/sc/first-class-products-biotech

[2]Nature.com, "What matters most in commercial success: first-in-class or best-in-class?" https://www.nature.com/articles/nrd4035

[3]Nature.com, "First-in-class versus best-in-class: an update for new market dynamics." https://www.nature.com/articles/d41573-023-00048-2

[4]Emerald.com, "The order of entry effect in prescription (Rx) and over-the-counter (OTC) pharmaceutical drugs." https://www.emerald.com/insight/content/doi/10.1108/17506120810865415/full/html

[5]Lek.com, "Key Indicators of a Successful Biopharmaceutical Product Launch." https://www.lek.com/insights/hea/us/ei/key-indicators-successful-biopharmaceutical-product-launch

[6]Ibid

[7]Lek.com, "The Inflation Reduction Act: Implications for Drug Delivery Innovation." https://www.lek.com/insights/hea/us/ei/inflation-reduction-act-implications-drug-delivery-innovation

[8]Lek.com, "Initial Drugs Selected for Medicare Price Negotiation: Emerging Perspectives." https://www.lek.com/insights/hea/us/ei/initial-drugs-selected-medicare-price-negotiation-emerging-perspectives

[9]Lek.com, "How the Inflation Reduction Act Will Impact the Biopharmaceutical Industry." https://www.lek.com/insights/ei/how-inflation-reduction-act-will-impact-biopharmaceutical-industry

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