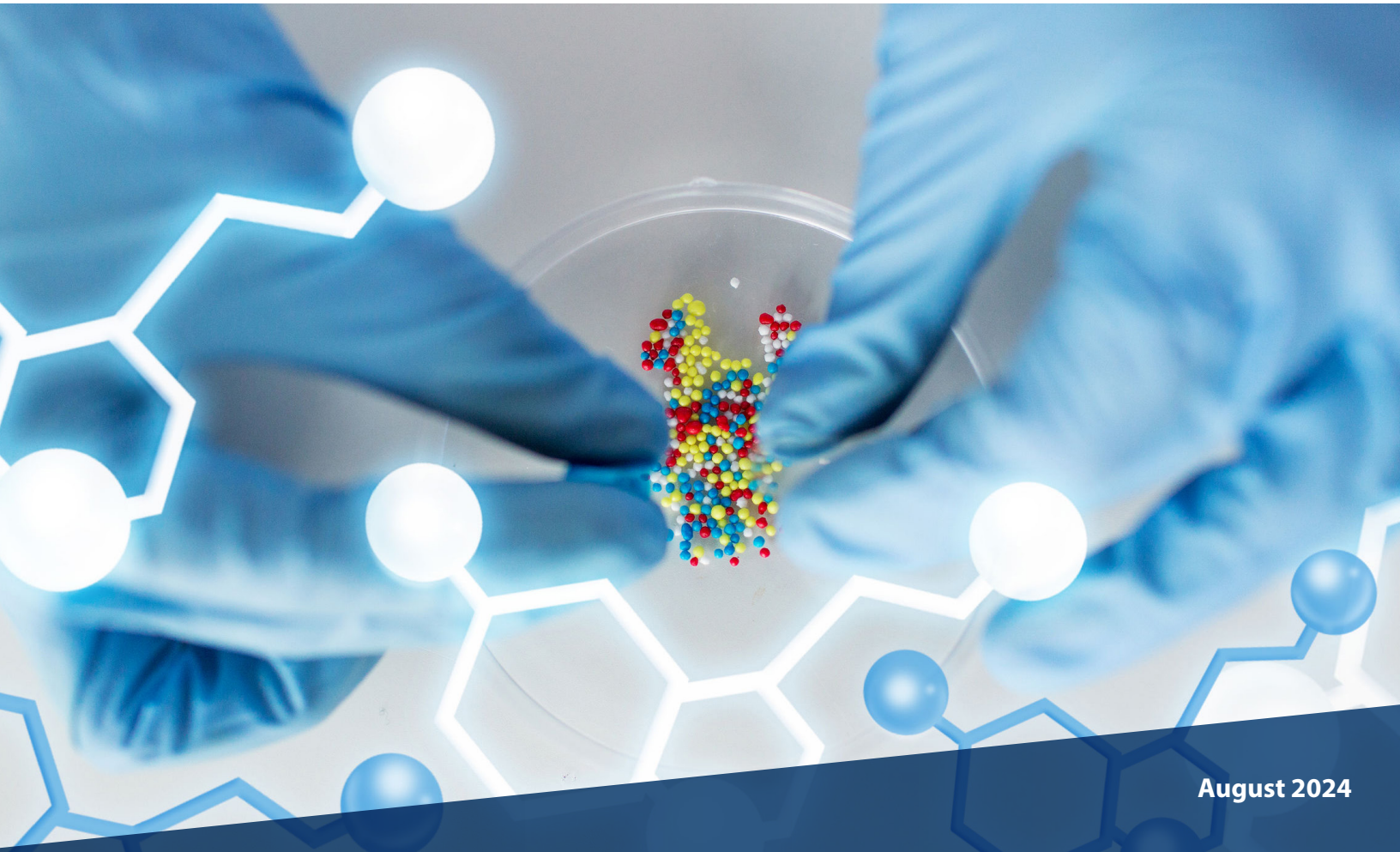
TRINITY

ADVISORY BRIEF

The "Molecular Optimizer" Archetype: A Strategy for First-Launch Companies to Streamline Their Path to Market

Colin DiBenedetto • Susheel Sukhtankar • Amid Zand • Suraj Bharadwaj • Riya Gohel



August 2024

Executive Summary

» The "molecular optimizer" archetype is a strategy utilized by first-launch companies to optimize existing molecules when developing their first product

» Companies using this approach tend to be small and emerging biotech firms that are seeking a foothold to enter the market

» Primary benefit of this approach is that the method offers a higher probability of regulatory approval and streamlines the manufacturer's path to commercialization

» With these benefits come some challenges related to access and pricing of a new product leveraging an existing molecule

» The "molecular optimizer" archetype presents an attractive option for first-launch companies seeking to overcome funding limitations and secure a foothold in the market, with the potential to pave the way for more innovative pipeline assets in the future

Introduction

A number of small and emerging biotechs have encountered a range of challenges while striving to introduce highly innovative, novel therapies to the market. Launching a novel therapy with the financial support of investors is already challenging for emerging biotech firms, but it becomes even more daunting when limited funding makes the success of the product and the company intertwined. In such times, companies that debut by creating advanced versions of existing molecules may have a greater likelihood of achieving commercial success. This "molecular optimizer" archetype has been observed in previous companies and products, as we will discuss later on.

In recent years, the high unpredictability associated with developing new pharmaceutical products has raised the stakes among private equity firms when considering their investment in small and emerging biotech companies. Further, the evolving regulatory landscape has led to fewer FDA approvals of novel therapies in recent years. In 2022, the FDA approved 37 novel drugs, a relatively low number compared to the past 5 years, across which there was an average of 51 FDA approvals per year. To address this issue, some pharmaceutical companies are opting to optimize existing molecules rather than discovering and commercializing entirely new molecules, streamlining the path to market. This strategy is particularly advantageous for first-launch companies seeking to establish themselves in the market. In a time when funding is limited and a small company's future hinges on the launch of its first product, these "molecular optimizer" companies can leverage this strategy to increase their probability of success.

In this advisory brief, Trinity Life Sciences will explore the "molecular optimizer" archetype — a strategy utilized by first-launch companies to focus on the optimization of an existing molecule as their first product. Additionally, we will delve into the advantages and disadvantages of employing this approach.

Examples of First-Launch Companies Utilizing the "Molecular Optimizer" Archetype

PharmaEssentia's BESREMi® (ropeginterferon alpha-2b-njft)

BESREMi is a long-acting interferon taken once every two weeks to treat polycythemia vera (PV). BESREMi is an updated version of the molecule ropeginterferon alfa-2b, first approved as PegIntron in 2001. PharmaEssentia leverages the pre-existence of interferons in their marketing, describing interferons as being "among the most recognized and well-studied therapies for a range of malignant diseases," and positioning BESREMi as "a fresh approach" to treating PV.

Ascendis Pharma's SKYTROFA® (lonapegsomatropin)

SKYTROFA is a human growth hormone (GH) indicated for the treatment of pediatric patients with growth failure due to inadequate secretion of endogenous GH. Ascendis' TransCon technology, a drug-delivery platform designed to enhance the overall benefit of a given molecule without compromising safety, allowed Ascendis to create a "long-acting" growth hormone product that, once injected, gradually releases in the body. The product is a differentiated version of the existing molecule somatropin, which was first approved in 1997. In the Ascendis press release regarding SKYTROFA's approval, CEO Jan Mikkelsen frames the product as an innovation that can "replace daily somatropin injections that have been the standard of care for more than 30 years."

MannKind's AFREZZA® (insulin human)

In 2014, MannKind launched AFREZZA, the only ultra-rapid-acting inhaled insulin that can lower blood sugar levels in approximately 12 minutes for adults with type 1 or type 2 diabetes. By leveraging the established human insulin molecule, MannKind developed a powder formulation that can be delivered through a cartridge and inhaler system, providing a new option for diabetic patients.

Heron Therapeutic's SUSTOL® (granisetron)

In 2016, Heron Therapeutics launched SUSTOL for the treatment of acute and delayed phases of chemotherapy-induced nausea and vomiting (CINV). SUSTOL is a long-acting formulation of the molecule granisetron, which was first approved in 1993. Heron Therapeutics used their Biochronomer polymer-based drug delivery technology to create an extended-release formulation of granisetron that maintains therapeutic levels for five or more days, allowing the product to address both the acute and delayed phases of CINV.

Advantages of the "Molecular Optimizer" Archetype

Use of this strategy can bring a number of benefits to the manufacturer as they develop and prepare for the launch of their product.

1 Proven Efficacy/Safety

With the exploration of an existing molecule, the burden of proof is not on the drug but rather the alteration made to it. Efficacy and safety that are "as good as" the earlier versions of the drug, as opposed to "significantly better" will often get the new product across the finish line. Proving "as good as" safety is especially important when bringing products forward for sensitive populations, in which higher priority is placed on tolerability. The leveraging of proven efficacy can be seen in MannKind's AFREZZA, for which the company could take advantage of the existing knowledge of human insulin's efficacy and focus on demonstrating the incremental improvement of the product's efficacy compared to previous mealtime insulin products.

2 Familiar Mechanism of Action

Focusing on an established molecule reduces the burden of convincing doctors about the product's mechanism before launching it. Additionally, patients may feel more comfortable taking a "proven" therapy versus an experimental one. This allows the company to concentrate on highlighting the distinctive and differentiating features of the new product rather than having to shape the market to accept a new agent and market the branded product during their outreach efforts. For example, PharmaEssentia's framing of BESREMi as a "new perspective on interferons," leveraging the pre-existing knowledge base and allowing the company to focus on adjusting the perceptions of interferons rather than having to introduce an entirely new product.

3 Potential of Transferable Science

Contract Manufacturing Organizations (CMOs) and potential pharmaceutical partners typically possess the necessary resources and expertise to produce existing biological and chemical entities. This capability can enable companies to better manage production costs while also creating opportunities for licensing. This also helps companies to globalize their product when partnering with companies outside of the U.S.

4 Increased Predictability in Uptake

Leveraging a new product founded on earlier molecules offers the advantage of increased predictability in uptake. The legacy product already has an established market share that is easily targetable to switch to the updated version of the molecule, provided reasonable pricing and limited access restrictions. Additionally, the company can leverage competitor sales data to target potential prescribers, properly structure and size field resources and enhance the accuracy of its forecast for the uptake of the new product. For example, at launch, Ascendis Pharma utilized a targeted field team to engage the highest volume prescribers of somatropin to encourage switching, yielding to rapid uptake of SKYTROFA.

5 Blueprint of Past Commercialization Efforts

Building on the successful strategies of the legacy agent, the company can establish a strong foundation for commercialization and further customize it to showcase the unique aspects of the new asset. As there are likely to be few differences in product manufacturing, distribution and sales, the pre-established commercialization efforts of the legacy product offer the opportunity for the new company to understand what worked well (and what didn't) to inform their go-to-market strategy and commercialization model. Other companies can be used as benchmarks to develop a customized launch readiness playbook and assess any gaps and risks along the way.

Disadvantages of the "Molecular Optimizer" Archetype

While optimizing an existing molecule can provide benefits, it can also have a few drawbacks.

1 Potential Access Constraints

The introduction of a product using the same molecule as an existing asset may present access challenges for physicians and patients. Formularies and associated controls may require use of a step therapy (due to the availability of the lower cost generic) before allowing use of the new asset. However, this obstacle can potentially be overcome through negotiation and discounting to minimize the gap in formulary placement of the generic benchmark and the new product. These constraints can also be maneuvered by motivating physician champions to push on payers to allow them access to the product, even if only as an exception on a case-by-case basis. Further, a best-in-class patient support program can assist patients/caregivers who demand access to a novel compound.

2 Narrow Pricing Flexibility

Part and parcel to navigating access is negotiating the pricing of a new product entering the market. Launching a new product with an existing molecule may establish the legacy product as the industry benchmark for that mechanism of action. This can lead to limitations on pricing flexibility for the new agent since a significant price difference may result in greater restrictions on its use. Further, many of these products utilize innovative technology that is more costly to produce than the generic option, leading to a higher gross-to-net.

3 Limited Organic PR

The enhancement of an established product might not generate the same level of excitement as an entirely new innovation. Consequently, the burden of creating awareness and enthusiasm about the product rests more prominently on the manufacturer's shoulders. This is especially true for first-launch companies with no established name recognition. With competing priorities internally on cash burn (clinical development programs, manufacturing commitments and infrastructure build), these companies must weigh the costs and benefits of investing in a variety of promotional channels to raise awareness, including non-personal promotion.

4 Standard Regulatory Review

It is unlikely for an improved version of an existing molecule to be granted fast-track approval status (e.g., breakthrough, priority or orphan). Thus, the product will most likely have to undergo the standard regulatory review process to obtain approval. Any delays in regulatory approval can cripple a company like this, therefore consistent financial stewardship and diligence is required. For example, the FDA announced a three-month extension related to its review of SKYTROFA's Biologics License Application (BLA) and SKYTROFA was ultimately approved two months after the original PDUFA date. In this case, the financial stewardship in place since 2007 enabled Ascendis Pharma to successfully weather the brief delay.

5 Adjusted Risk/Reward for Investors

It is unlikely for a new product with an existing mechanism of action (MOA) to be paradigm changing. Therefore, the investment opportunity is limited to the current market state with some incremental gain. However, it could serve as a gateway to more innovative pipeline assets in the future. MannKind, for example, is now applying the Technosphere drug delivery technology used in AFREZZA to "a number of therapeutic areas that are both in high demand for innovation, and in need for a different kind of treatment option for people living with these conditions." Its pipeline agent MNKD-101 (clofazimine inhalation suspension) is being studied in a rare lung condition, nontuberculous mycobacterial (NTM) infection; a program made possible, at least in part, by agents that came before it. During a recent earnings call MannKind CEO, Michael Castagna, noted that "we achieved our eighth consecutive quarter of revenue growth," and "received Fast Track designation and clearance of the IND for MNKD-101 which may allow us to bring this innovative product to patients more quickly."

Conclusion

The "molecular optimizer" archetype is a viable strategy that first-launch companies are utilizing to improve their chances of success in the market. By focusing on optimizing existing molecules, companies can leverage the benefits of the legacy product to support the development of their improved asset. The strategy also comes with drawbacks, including access and pricing limitations. Despite these drawbacks, the "molecular optimizer" archetype represents an attractive option for first-launch companies seeking to overcome limited availability of funding and secure a foothold in the market, with the potential to pave the way for more innovative pipeline assets in the future.

References:

- https://us.pharmaessentia.com/interferon-therapy-mpn/
- https://investors.ascendispharma.com/news-releases/news-release-details/ascendis-pharma-announces-us-commercial-launch-skytrofar/
  - https://investors.ascendispharma.com/news-releases/news-release-details/ascendis-pharma-announces-european-commission-approval
- https://investors.ascendispharma.com/news-releases/news-release-details/ascendis-pharma-announces-strategic-partnership-teijin-limited
- https://investors.mannkindcorp.com/news-releases/news-release-details/mannkind-corporation-announces-fda-approval-afrezzar-novel-rapid
- https://investors.mannkindcorp.com/news-releases/news-release-details/mannkind-corporation-reports-2024-first-quarter-financial
- https://mannkindcorp.com/pipeline/

Authors

Colin DiBenedetto | Partner and Head, Strategic Advisory

Colin boasts a rich professional background spanning over 15 dynamic years in life sciences consulting, a journey marked by innovation and strategic insight. He and his team sit within the Strategic Advisory group and work with their clients to identify opportunity spaces for new products, quantify and describe product potential, set strategies and tactics to realize product possibilities, and support various marketing activities. His client base is diverse and inclusive of small and mid-size biotechs bringing paradigm-changing products to the areas of oncology, hematology and central nervous system disorders. Prior to his tenure at Trinity, Colin held leadership positions at healthcare-centric organizations including BluePrint Research Group, RG+A and Ipsos.

Susheel Sukhtankar | Partner, Commercial Analytics

Susheel heads Trinity's Commercial Analytics practice and provides strategic and operational support on forecasting, sales analytics and marketing analytics to our partners in the life sciences industry. Susheel started his consulting career in pharmaceutical data management and reporting before going on to lead engagements leveraging primary research and secondary data with a focus on commercial operations and analytics. With in-depth knowledge of the pharmaceutical, biotech and medical device industries, Susheel has worked in multiple therapeutic areas including immunology, oncology, neurology and rare diseases. He holds a Bachelor's degree in Biomedical Engineering from the University of Mumbai and a Master's degree in Bioinformatics from Georgia Tech.

Amid Zand | Director, Commercial Analytics

Amid is a Director in Trinity's Commercial Analytics practice. Since joining Trinity in 2017, Amid has partnered with our clients across the breadth of Trinity's Analytics capabilities with a key focus on field team planning, incentive compensation and performance analytics. Amid leverages his deep understanding of life sciences data along with a holistic view of our customers' strategic objectives to provide tailored field team plans, insights and recommendations. Amid holds a B.S. In Biomedical Engineering from WPI and an MBA from Boston University.

Suraj Bharadwaj | Engagement Manager, Strategic Advisory

Suraj possesses 6+ years of strategic and insights experience supporting the development and commercialization of therapeutics in Oncology, Hematology, CNS, Rare Disease, and Infectious Disease. He has supported multiple emerging biotech companies across a range of Commercial functions and capabilities including Insights & Analytics, Marketing, Forecasting, and New Product Planning. He has leveraged his breadth of experience to support C-suite executive at biotechs, serving as a proxy SI&A department as they begin ramping up commercialization efforts. Suraj holds a Masters in Biotechnology from the University of Pennsylvania.

Riya Gohel | Senior Consultant, Strategic Advisory

Riya is a Senior Consultant in Trinity's Strategic Advisory practice with extensive market research experience across Oncology, Hematology, and Orphan Diseases. At Trinity, she has led numerous global qualitative and quantitative projects, including patient journey mapping, message testing, and demand assessments. She has also contributed to strategic planning initiatives, including dynamic competitive simulations. Riya holds a Bachelor's degree in Health and Societies from the University of Pennsylvania..

About Trinity

Trinity Life Sciences is a trusted strategic commercialization partner, providing evidence-based solutions for the life sciences industry. With nearly 30 years of experience, Trinity is committed to revolutionizing the commercial model by providing exceptional levels of service, powerful tools and data-driven insights. Trinity's range of products and solutions includes industry-leading benchmarking solutions, powered by TGaS Advisors. To learn more about how Trinity is elevating life sciences and driving evidence to action, visit trinitylifesciences.com.

For more information, please contact us at info@trinitylifesciences.com.