Investing in Pharma: The Drug Lifecycle

Arelis Agosto
aagosto@globalxetfs.com

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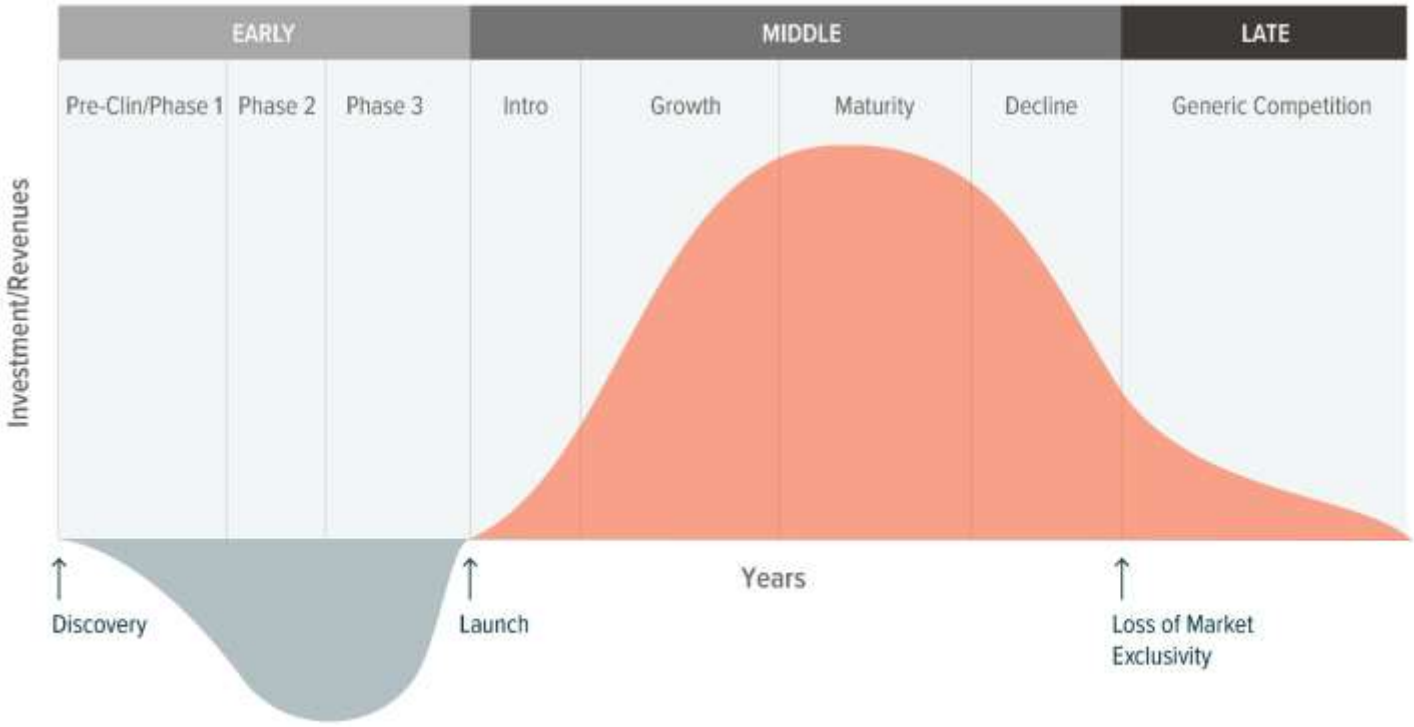
Drug development pipelines are the lifeblood of the pharmaceutical industry. It is crucial for investors to understand milestones like FDA approvals and the impact of losing exclusivity on profits to navigate the dynamic healthcare sector. This piece provides an investment-focused overview of a typical drug's lifecycle.

This piece is Part 1 in a 2-part series on the fundamentals of investing in pharmaceutical companies. The second part will delve into the key characteristics that can help inform an investigational treatment's success.



For illustrative purposes only.

Key Takeaways

- The regulatory process for investigational drugs is long and costly, but the rewards for successfully bringing a new drug to market can be vast.
- There are numerous potential pathways to accelerate the drug discovery process, which may notably impact a new drug's return on investment.
- Generic competition can quickly eat into sales and reduce profit margins, leading investors to keep a close eye on new drug development.

Drug Discovery & Development Process of an Investigational Drug

Investigational new drugs go through a rigorous process to ensure efficacy and safety. In the U.S., this process takes, on average, 10 to 15 years to ensure approved treatments are beneficial and safe for patients.[1] Key regulatory steps include:

REGULATORY PROCESS FOR INVESTIGATIONAL DRUGS

Sources: Food & Drug Administration. (n.d.). The Drug Development Process. Accessed March 15, 2024.

Drug Discovery & Design	**Purpose**: Identifying, designing, and testing potential therapeutic compounds to develop novel treatments.
Preclinical Studies	**Purpose**: Evaluate efficacy and safety of the investigational treatment by testing the therapy in isolated cells in a laboratory (in-vitro) or by administering to animals (in-vivo).
Regulatory Review: Should the treatment be tested on humans?	Based on preclinical data, regulatory bodies (e.g., U.S. Food & Drug Administration, European Medicines Agency) sign off that thetreatemnt is safe for testing in people. Sponsor firms also submit detailed outlines for planned clinical studies to ensure patient safety and data accuracy. In the U.S., sponsors submit an Investigational New Drug (IND) Application to the FDA.
Phase I: Is the treatment safe?	**Study Participants**: 20 to 100 healthy volunteers or people with disease/condition **Length of Study**: Several months **Purpose**: Evaluate safety and determine dosage Approximately 70% of drugs move to next phase
Phase II: Does the treatment work?	**Study Participants**: Up to several hundred people with disease/condition **Length of Study**: Several months to 2 years **Purpose**: Evaluate efficacy and establish side effects Approximately 33% of drugs move to next phase
Phase III: Is it better than what's already available?	**Study Participants**: 300 to 3,000 volunteers with disease/condition **Length of Study**: 1 – 4 years **Purpose**: Efficacy and monitoring of adverse effects and tolerability compared to standard of care. Approximately 25- 30% of drugs move to next phase
Regulatory Review: Can the treatment be marketed and sold to patients?	If the treatment shows that it is more effective or safer than the current treatment, regulatory bodies evaluate it for commercial approval. In the U.S., sponsors must submit a New Drug Application (NDA) or a Biologics Licence Application (BLA) to the FDA. During the evaluation process, the FDA might convene an Advisory Committee (AdComm) Meeting to help decide if approval of the drug is warranted. AdComms consist of external experts in various fields such as medicine, ethics, and patient advocacy. Their input helps the FDA make an informed decision, though the ultimate authority for approval rests with the FDA. In other words, the agency may choose to approve or deny a product, independent from the AdComm vote.
Phase IV: Is the therapy performing as expected?	**Study Participants**: Thousands **Purpose**: Evaluates long-term efficacy and safety of the drug

Pathways to Accelerate the Drug Development Process

Though the process for all investigational drugs is largely the same, regulatory bodies have outlined potential accelerated pathways to speed up the availability of drugs that treat serious diseases.[2] When granted, these decisions can notably impact the return on investment for investigational drugs and can thus have a significant impact on biotech stock prices.[3] The U.S. FDA has four key such designations:[4]

- Fast Track: Designed to streamline the development and review process of drugs targeting serious conditions with high unmet medical needs. Among other things, pharmaceutical sponsors have more frequent interactions with the FDA throughout the development process and can submit regulatory filings on a rolling basis.
- Breakthrough Therapy: Designed to streamline the development and review process of drugs that may demonstrate substantial improvement over available therapies. Like Fast Track designations, this process allows for increased interactions with the FDA and rolling reviews.
- Accelerated Approval: Designed to accelerate the development process of drugs that address illnesses with high unmet medical needs. This pathway allows for greater flexibility in evidence requirements for approval, as many illnesses (e.g., Alzheimer's) progress slowly and waiting for clinical outcomes data can take years.
    - Allows clinical trials to utilize "surrogate endpoints" for clinical trials. Surrogate endpoints are markers or measurements that are considered reasonably likely to predict a real clinical benefit. These are common in cancer clinical trials, for example, where measuring tumor shrinkage can occur far sooner than waiting to learn if a patient lived longer.

- May also require fewer clinical trials upfront. These treatments can, for example, be conditionally approved after a phase II clinical trial. In these instances, a phase III clinical trial is typically required to confirm the drug's effectiveness and safety. The FDA can then decide to grant full approval to the drug or, in instances where the confirmatory trial fails, to modify or withdraw the drug's approval.

— Priority Review: Designed to accelerate the review process of investigational drugs that may demonstrate substantial improvement over available therapies. Once granted, the FDA agrees to take action on an application within six months, compared to 10 months under standard review.

Pharmaceutical sponsors can also, subject to FDA approval, design combined or hybrid clinical trials (e.g., phase 1/2, or phase 2/3) that can reduce the time and resources required for drug development. Combined trials can also allow for faster patient recruitment and more efficient utilization of data while collecting all the necessary data required for regulatory review. Regulatory agencies like the FDA closely review the clinical trial design and results to ensure they meet the necessary standards for approval.

Post-Approval Exclusivity: The Period of Peak Profitability

Once a treatment is approved, the drug receives market exclusivity for a certain period. Different types of products receive different exclusivity timelines, though in most cases, a five-year exclusivity is provided. The FDA can provide certain extensions to exclusivity, including treatments for orphan diseases (those with less than 200,000 patients in the U.S.) and treatments for pediatric illnesses. A treatment can also receive additional exclusivity after its approval if it receives subsequent approval for a new illness or in a new delivery form (e.g., a pill rather than an injection).

Loss of Exclusivity: Entry of Generic and Biosimilar Competition

Once the exclusivity period concludes, competition is allowed to enter the market, usually at a discounted price. These are equivalent products approved through abbreviated pathways. Depending on the technology, the equivalent product is referred to as a:

— Generic: For drugs with specific chemical structures, generics are created to be the same as an already approved brand-name product. The generic must be the same dosage form, strength, quality, and intended use to ensure the generic treatment works in the same way and provides the same benefit as the branded drug.

— Biosimilars: Biosimilars are highly similar to large molecule drugs – also referred to as biologics. Biologics are molecules derived from living organisms and include, for example, vaccines. Corresponding biosimilars have no clinically meaningful difference from the biologic, meaning they have the same effectiveness and safety profile. There are currently 46 approved biosimilars in the U.S.[5]

When equivalent products enter the market, prices for the drugs decrease significantly. A single generic competitor can lead to price reductions of 30%, while five competing generics can lead to price reductions of nearly 85%.[6]

Manufacturers of the branded drug face what is colloquially referred to as a "patent cliff" once a drug faces generic competition, as sales of the branded product may decline up to 90%.[7] To replenish sales, pharmaceutical firms often rely on expected drug launches and mergers and acquisitions (M&A).

GENERICS & BIOLOGICS: KEY FACTORS

Source: NIH. (2013). The Economics of Biosimilars. Pfizer. (n.d.). Let's See How Biosimilars Are Developed. Accessed March 15, 2024. McKinsey. (2022, August 19). Three imperatives for R&D in biosimilars.

	Small Molecule	Generic	Biologic	Biosimilar
Development Cost	-	$1 - 2 million	-	$100 - 300 million
Time to Market	8 - 10 years	2 years	8 - 10 years	6 - 9 years
Clinical Studies	Phase I - III studies efficacy and safety.	Bioequivalence studies in healthy volunteers.	Phase I - III studies efficacy and safety.	Pharmacokinetics comparison studies in Phase III
Post-Authorization Requirements	Phase IV, risk management plan including pharmacovigilance	Pharmacovigilance	Phase IV, risk management plan including pharmacovigilance	Phase IV, risk management plan including pharmacovigilance

Conclusion

The pharmaceutical space is highly specialized, often relying on complex chemistry and biology. However, there are also some basic tenants of the drug discovery process that can be useful to investors when examining the industry, deciphering clinical updates, or understanding the catalysts behind stock-price movements.

Related ETFs

GNOM – Global X Genomics & Biotechnology ETF

AGNG – Global X Aging Population ETF

Click the fund name above to view current performance and holdings. Holdings are subject to change. Current and future holdings are subject to risk.

Footnotes

1. National Institutes of Health. (n.d.). The Pathway from Idea to Regulatory Approval: Examples for Drug Development. Accessed March 15, 2024.
2. Food and Drug Administration. (2023, June 12). Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review.
3. Nature. (2023, August 7). New drugs and stock market: a machine learning framework for predicting pharma market reaction to clinical trial announcements.
4. Food and Drug Administration. (2023, June 12). Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review.
5. Food and Drug Administration. (2024, February 26). Biosimilar Product Information.
6. Food and Drug Administration. (2022). The Generic Drug Approval Process.
7. University of Southern California. (2023, April 13). Mitigating the Inflation Reduction Act's Adverse Impacts on the Prescription Drug Market.

Glossary

Pharmacokinetics (PK): study of how the body interacts with administered substances for the entirety of exposure.
Pharmacovigilance (PV): science of monitoring the safety of medicines in the human body.
