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Review Article

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Lifecycle Management of Generic product in US market

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Abstract

In the US Market, lifecycle management for generic products includes developing and implementing plans to maximize an item's market potential from launch to decline. It starts with market research and approval of regulatory involving submission of an Abbreviated New Drug Application (ANDA) to demonstrate bioequivalence to the branded product followed by comprehensive market analysis to identify opportunities and assess rivals. Companies use aggressive pricing and marketing techniques to swiftly increase their market share after a product is approved. Continuous monitoring and adaptability to changes in the market, updates to regulations, and competitive actions are crucial throughout the lifecycle. This review focuses on Market entry strategy, Product launch, Market landscape of Generic Drugs in US.

Keywords: Generic drugs, lifecycle management, product launch, USFDA, ANDA, OGD, CDER

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1. Introduction

The last years have become very complicated in the generic market of the US. We believe that this is caused because companies take in making developments and applying forms to systems, not taking the generic product as something intrinsic in the business of the company. Large profit margins are made with the development of the new entities, but on the side of the generic, nothing or when a fast fail in the market of some developed products jointly in investments that turn over the plan of businesses of some companies that take portfolios of generic in some of more recurring pathways of the country. To apply time and resources is necessary when developing a generic product in agreement with what calls a project management. For this, many companies create the lifecycle program of management that has the purpose to give it to all the plan of work of the product, involving all the related insuring and activities. (1)

1.1 Overview of Generic products

Generic pharmaceuticals are an important part of maintaining public health. They provide a great way to lower healthcare costs. They are bioequivalent to the originator or reference listed drug. They contain the same active ingredients, possess the same strength, and have the same biopharmaceutical effects. Actually, 52% of all dispensed prescriptions for commercial drugs in the United States are for generic products. Almost 8 out of 10 prescriptions are filled with generic products. Moreover, generic products within the United States markets make up 98% of the volume and are perceived with the utmost safety and efficacy. They are purchased at a price to the patient that saves money in their healthcare budget. At an average of 30% of the branded reference listed products' prices, greater than 236 billion US dollars in cost savings occur every year in the US health systems and in the purchase of 3.3 billion prescriptions. (2)

This document provides the reader with basic information that introduces the concept of generics. It briefly describes the ethical and legal background in the United States and how the present generic regulatory environment was established. This includes abbreviated pathways and arguments that reflect the strength of generic products. It goes on to outline some of the opportunities that exist, along with some of the challenges that generic products and their manufacturers encounter in making and marketing these products. Finally, regulatory comparisons are made that provide insight into variations that different global generic enabling regulations have in common. (3)

In 1984, the federal government made the decision to permit commercial distribution of pharmaceuticals and biological products for human use in interstate commerce. The authority to monitor this process was given to the Food and Drug Administration, an agency of the Department of Health and Human Services. The legislation gave the FDA the responsibility for ensuring

that the products are both safe and effective. This law, the Drug Price Competition and Patent Term Restoration Act, is now best known as the "Hatch-Waxman Act". (4)

1.2 Regulatory Environment

The regulations related with the generic drugs are overseen by the United States agency called food and Drug Administration (FDA). Purpose of FDA is to ensure the quality, safety and efficacy of the new drugs, medical devices and generic drugs. The main part of manufacturing and marketing the generic drug is Abbreviated New Drug Application (ANDA). Manufacturers need to submit the ANDA to FDA. In ANDA it is proven that the bio equivalence of the generic drug is same as the branded drug. (5) The generic drug should be same effective and efficacious as the branded drug. The FDA thoroughly reviews the ANDA checks the bio equivalence and accept the ANDA. As the ANDA is accepted by the FDA then FDA gives the approval to manufacture and market the generic drug. With a combination of quality control, design specifications, and various records matching ability needed for device identification and traceability of a device from its regulatory/unique identifier, through the main stages of its life cycle, the FDA's current "unique device identification" regulations focus on the placement of a UDI, its format, and its direct marking on device packages as well as design and manufacturing specific ID placement on the device itself. These regulatory changes require the greatest amount of system change to support device-specific unique identification and label placement and quality control, with additional testing and associated new telecommunications systems changes also necessary. With current regulations also focused on making this same information accessible to people, reliance on a new critical device information concept is a potential outcome. Although such regulations involve issues of process efficiencies as they currently exist, and further concentrate on securing the health information within the UDI, there is no common repository acknowledgment or remote UDI-specific information sharing with respect to this type of defense information. (6)

The United States Food and Drug Administration (FDA) is the enforcement arm of the United States federal government responsible for national regulations and compliance requirements ensuring that different types of medical devices are both safe and effective. This begins with the concept of filing and documenting unique products as a part of the formal product development process, with current FDA regulations also highlighting the importance of good manufacturing practices and post market surveillance and compliance as potential life cycle support activities. Their definition of what a medical device is, how such devices should be classified, their real-world evaluation, overall design and manufacturing accuracy, and how they should be labeled and marketed, is stipulated within their federally controlled CFR 21 "Code of Federal Regulations". Furthermore, such devices need to be evaluated by all aspects of the Health Care community including the Health Insurance Portability and Accountability Act, other regulatory authorities like HIPAA, which together with their jurisdictions' unique privacy concerns, must be addressed. Overarching these regulations are those of "safety, efficacy, and quality," which generally must be demonstrated before devices can be used to treat patients. (7)

1.3 Overview of the Food and Drug Administration

The US FDA plays a very important role in ensuring that the regulations are being followed by the manufacturers while manufacturing the generic drugs. FDA ensures that the quality, efficacy and safety of the generic is equivalent to their branded counterfeit. The FDAs office of generic drug (OGD) reviews the Abbreviated new drug application and gives the approval to manufacture the generic drug. The office of Generic drug (OGD) is the part of Center for drug evaluation and research (CDER). (8) In ANDA process manufacturers needs to demonstrate the bio equivalence of generic drug is same as its branded drug. The recent surge in attention for drug reimportation, as well as instances of deaths related to unsafe or dangerous uses of drug products, has forced the FDA to step into this arena in an official but time-limited capacity. The agency opposes drug reimportation and promotes the development of a legal framework that would encourage alternatives. Annually, the FDA reviews billions of dollars in Investigational New Drug applications, New Drug applications, and Abbreviated New Drug applications. These applications form the basis for the agency's rulemaking, guidance development, and administrative efforts that encourage manufacturers to innovate, research, and develop products with superior cost-benefit profiles. The agency is an imposing force of cooperation and public interest, but as an investor of substantial supervisory duties, it accepts the role it plays with respect and humility. (9)

The Food and Drug Administration (FDA), a division of the U.S. Department of Health and Human Services, is a regulatory agency dedicated to the promotion and protection of public health in the food, cosmetic, and drug industries. The FDA is responsible for determining the truthfulness of food labeling, quality and purity standards, and positioning of products, and it has the authority to require the prestigious label "FDA Approved." The agency regulates the development and deployment of prescription drugs, including animal drugs. Its role is not generally associated with the regulation of illicit drugs, although it assumes an important role of collaboration and cooperation with other federal and state agencies, including the Drug Enforcement Administration (DEA). (10)

The FDA also enforce the strict regulations related to the manufacturing process. It is mandatory for all the generic drug manufacturers to implement cGMP. The FDA conducts the survey to review and to check that manufacturing facility is clean. FDA also checks that the cGMP practices are implemented and followed. Post marketing surveillance needs to be conducted and it is important for the manufacturers to report the adverse event related to the generic drug and it is also mandatory for the generic drug manufacturer to submit periodic safety reports to FDA. (11)

2. Product Development and R&D Process of Generic Drug

The product development and R&D process for generic drug is critical process, it involves various steps. This R&D and product development process aimed at creating the drug which is therapeutically equivalent to the branded drug. This process starts with selecting the drug from the Reference Listed Drug (RLD) (12) Next the process involves the formulation development, the formulation developed should match in route of administration, dosage form and strength with RLD. As the drug selected its stability and efficacy is ensured, it is really important to verify the stability and efficacy of that drug. The stability and efficacy of the drug is ensured by performing the compatibility studies and optimization. For the generic drug analytical methods are developed. (13) The developed analytical methods are validated according the ICH Q2 (R1) guidelines. Various parameters are used to validate that analytical method. The analytical method is developed and validated to determine drugs properties. The analytical method is used to perform stability studies to determine shelf life. The important study for approval of generic drug is bio equivalence studies, in this study it involves the clinical trial with healthy volunteer. In clinical trial the pharmacokinetic of the generic drug is compared with RLD. In pharmacokinetics studies mainly absorption rates are determined. The absorption rates of the generic drug and RLD should be similar. The data generated from the stability and efficacy studies, bio equivalence studies, pharmacokinetics studies and the data about the manufacturing site, process and also the data about the labelling is combined. This data is combined and submitted to FDA through the Abbreviated New Drug Application (ANDA). FDA reviews the ANDA and gives the approval to the manufacturer to manufacture the generic drug at large commercial scale while compliance to the cGMP practice. The post marketing surveillance ensures the continuous safety and efficacy of the generic drug. The post marketing surveillance also helps to ensure the continuous quality control measure. This process ensures that the generic drug manufactured is safe, effective and best affordable alternative the branded medicine. (14)

Here's are the key stages involved in product development and R&D process:

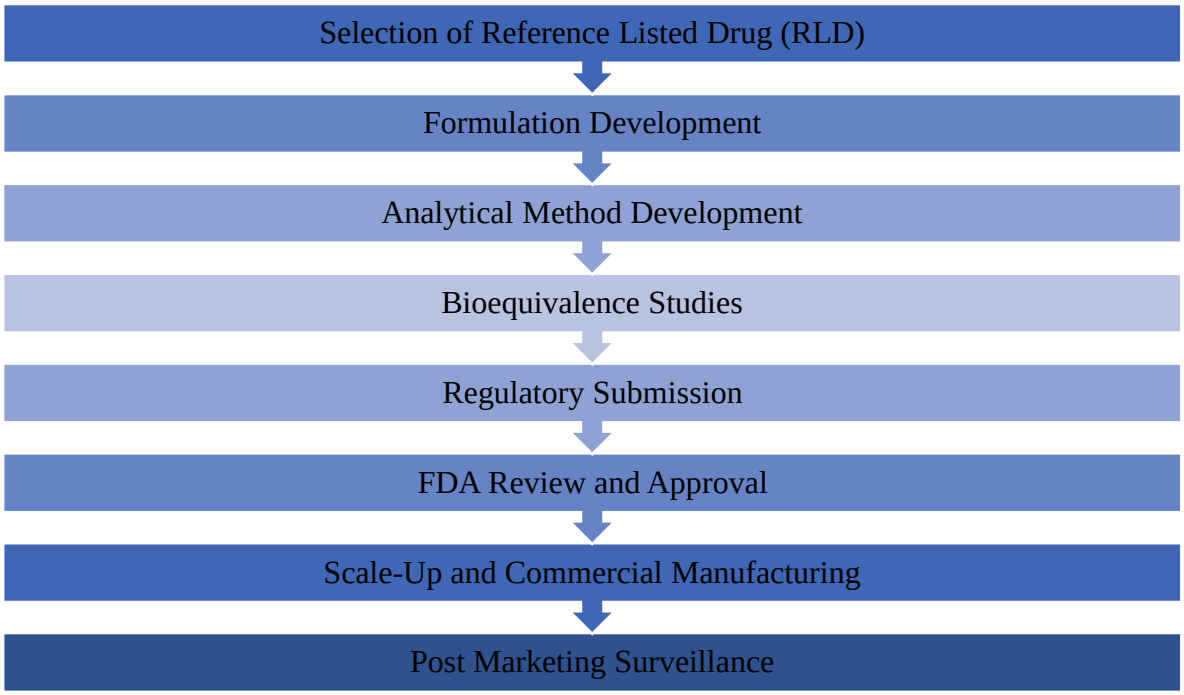

Figure 1. Key stages involved in product development and R&D process

3. Market Entry Strategies as for Generic Drug in US Market

Manufactures in US uses comprehensive strategies to launch the generic drug in the market. To launch these strategies, it involves lot of comprehensive planning for strategies and execution of these planning. These strategies and planning are done to ensure the successful launch of the generic drug and to sustain the competitiveness. These strategies involve regulatory navigation, marketing, pricing, distribution, and partnership development to capture market share effectively and achieve commercial success. (15)

Here are key components of market entry strategy for generic drug:

a) Regulatory strategy:

ANDA submission: It is important to submit the Abbreviated New Drug Application to FDA quite before the expiration of the patent of reference listed drug (RLD) to ensure the early market entry and that will help manufacturer to capture large market.

Compliance with cGMP: For the manufacturer who is manufacturing generic drug it is mandatory to ensure compliance with current good manufacturing

practices cGMP to meet FDA requirements and avoid delays due to regulations.

b) Pricing Strategy

Competitive Pricing: Manufacturers set the prices lower than the branded drug this will attract the cost-conscious consumer, healthcare providers and payers this strategy of lowering prices is called as aggressive pricing.

Tiered Pricing: Manufacturers offer benefits and discounts to the large pharmacy depending upon the quantity of the drug purchased. Bulk purchase discounts are given to the pharmacy benefit manager (PBM).

Volume discounts: Manufacturers of generic drug often gives discounts to the large pharmacy chains, healthcare system and wholesalers when they order in bulk. (16)

c) Reimbursement Strategy

Formulary placement: Manufacturers negotiate with the pharmacy benefits managers (PBMs) and payers to secure the favourable formulary placement by this negotiations manufacturer ensure that generis drug includes in insurance plan.

Rebate agreements: Manufacturers gives rebate agreements to the PBMs and payers this will encourage the PBMs and payers to prefer the generic drug over branded drug.

Medicare and Medicaid: manufacturers participate in government programs like Medicare and Medicaid. In Medicaid drug rebate program manufacturers participate and secure the entry in Medicare Part D formularies to increase patient access. (17)

d) Marketing and Education

Direct to consumer marketing: Manufacturers needs to launch the campaigns the purpose behind the campaigns is to educate consumers about the safety and efficacy of the generic drug and also to educate about cost savings of generic drug.

Digital marketing: In the recent era, digital marketing has taken over the world, manufactures needs to utilize digital platforms to reach the targeted patients.

Healthcare provider engagements: Manufactures needs to provide healthcare professionals all the necessary information about the generic drug safety and efficacy and generic drugs are well informed to prescribe and encourage healthcare professionals to recommend it to patients.

Samples and Promotions: Manufacturers often offer samples and promotional materials to the healthcare professionals to encourage the healthcare providers to adopt generic drug.

e) Distribution Strategy

Distribution network: Manufacturers needs to establish strong relationships with pharmacy chains, wholesalers and healthcare providers. The established strong relationship helps the manufacturers to ensure efficient distribution of the generic drug.

Inventory Management: Manufacturers often implement the effective inventory management strategies. These strategy helps manufacturers to prevent the stockouts and maintain the product availability consistently.

f) Strategic Partnerships

Collaborations: Manufacturers of generic drug often partner and collaborate with major pharmacy chains and wholesalers. These collaborations help manufacturers to expand reach and improve penetration into market.

Co- Marketing Agreements: Manufacturers of generic drug often engage in co-marketing agreements with well - established pharmaceutical companies this engagement helps manufacturers of generic drug to use the established networks and resources of that pharmaceutical companies.

Alliance with healthcare systems: Manufacturers of generic drug forms alliance with the hospital systems. This alliance helps to integrate the generic drug into treatment protocols and pharmacies of hospitals.

4. Generic Drug Product Launch

Launching of generic drug product is very formidable process. It involves various steps which makes the launch of generic drug efficient. Here are the steps and regulatory requirements which are needed to launch the generic drug product:

a) Drug Development and Manufacturing

Formulation development: Manufacturers develop the generic version of the branded drug. While developing formulation it is mandatory to ensure that bioequivalent of generic drug is same as the branded drug. The formulation of generic drug developed should be same in route of administration, strength and efficacy as of the branded drug.

Manufacturing process: To ease launching of generic drug product process manufacturers needs the manufacturing process that is complying with the current good manufacturing practices (cGMP). (18)

b) Regulatory Approval

Abbreviated new drug application (ANDA): Manufacturers of generic drug product needs to submit the ANDA to FDA to get the approval to launch generic drug product in the market.

ANDA should contain the following information:

Bioequivalence studies: In this study it is proven that the generic drug has the similar bioavailability as the branded drug.

Quality data: In this section, manufactures needs to provide the data related to drugs chemistry, manufacturing and controls (CMC).

Labelling: While filling this section manufacturers needs to ensure that label matches with the brand

name counterpart, excepting the patent protected elements.

Patent Certification: In this section filer needs to address the patents listed in FDAs orange book. This entail the following one of four certifications:

Paragraph 1: No patents listed.

Paragraph 2: Patents have reached the expiration.

Paragraph 3: Wait for the patients to be expired.

Paragraph 4: Patients that are invalid or not infringed this can lead to litigation.

c) ***Market Preparation:*** Manufacturers to enter the market needs to prepare and plan for the supply chain management, pricing strategy and distribution channel.

Supply chain: Before entering the market manufacturers needs to establish the supply chain to ensure consistent availability of the generic drug product.

Pricing strategy: Manufacturers needs to develop the pricing that competitive and will help to capture the large market share while maintaining the good profitability.

Distribution channel: Manufacturers needs to develop the distribution channel to reach consumer through the large pharmacy chains, wholesalers, hospitals and other relevant channels.

d) ***Marketing and Sales:*** Manufacturers before entering the market needs to do the analysis the market to understand the demand of generic drug, needs to develop good sales strategy.

Market Analysis: Manufacturers before launching generic drug product in the market need to conduct the deep market research which will help to understand demand, competition and potential market of generic drug.

Branding and Packaging: Manufacturers needs to create the packaging that meets the regulatory requirements and that packaging should appeals the consumers.

Sales strategy: Manufacturers needs a team which will develop the good sales strategy that will join in the healthcare providers, Pharmacist and direct consumers.

Key consideration while launching the generic drug into the US market

FDA Compliance: Manufacturers needs to strictly follow the FDA guidelines and strict adherence with the FDA timeline is critical.

Legal Challenges: Manufacturers needs to be prepared for the potential patent litigations, particularly focusing the Paragraph 4 certifications.

Market Dynamics: Manufacturers before entering the market needs to understand the competitiveness in the market and essentially understand the payer dynamics.

Supply chain robustness: Manufacturers must ensure the ability to scale up productions and manage the disruptions in the supply chain. (19)

5. Market Landscape of Generic Drugs in the US

The generic drug market in US is very competitive because there are many players in the market who are manufacturing the generic drug products. The generic drug market in US is very substantial and is characterized by various factors and key players. Here is the current landscape of generic drug:

a) Market Size and Growth

Market value: The generic drug market of United States of America is one of the biggest and largest globally. The generic drug market of US is valued at more than $90 billion dollar annually, it is one of the competitive market globally.

Growth Rate: The growth of the US market is linear and increasing exponentially. The factors which are contributing in growth area patent expiration of the one of the famous and blockbuster drugs, cost saving measures taken by the healthcare providers and initiatives taken by the government bodies to minimize healthcare cost. (20)

b) Key Players

Major companies: In US, the generic drug market is mainly dominated by the several large pharmaceutical companies which includes Teva Pharmaceuticals, Mylan (now mylan is part of Viatris), Sandoz (Novartis Division), and Sun Pharma. These are the major companies which contributes the most in the generic drug market of US.

Emerging Players: There are also new companies and smaller firms which also plays a role in case of generic drug market of US. These smaller companies and firms often focus the niche and less competitive areas.

c) Regulatory Environment

FDA Oversight: The FDAs Abbreviated New Drug Application is one of the process used in US to regulate the approval and monitoring of the generic drug. Once the ANDA is approved by FDA the manufactures then can manufacturer generic drug on commercial scale.

Legislative Support: The Law such as Hatch – Waxman Act is used in US to make possible the approval of generic drug by permitting the filing of the ANDA. The Hatch - Waxman Act also facilitate the establishment of the orange book for patent listing.

d) Market Dynamics

Cost Savings: The branded drugs are so expensive and generic drug in comparison with branded drug are lower in cost. Typically, the generic drug is 80-85% lower in cost than the branded drug. The lower price of the generic drug attracts the cost sensitive consumer and increase the demand of generic drug.

Patent Cliff: The expiration of the patent for the major branded drug is referred as the patent cliff. This patent cliff becomes the right set of circumstances and provides the golden opportunity for generics.

Biosimilars: The generic version of biologic drug is called as the biosimilar. The biosimilar is the expanding segment. But the biosimilars will have to face more complex regulatory process and will have to endure the market challenges compared to the traditional generic drugs.

e) Competitive Landscape

Price Competition: The generic drug market is very competitive, the generic drug manufacturers are battling on cost so that they can win contracts with large pharmacy chains, hospitals and healthcare providers. The generic drug market is highly price sensitive manufacturers need to take care of the price while maintain the profitability.

Product Differentiation: The generic drug manufacturer companies need to focus on hard to manufacturer generics and also need to take special care while planning to manufacture the complex formulation.

Market Consolidation: There has been notable unification in the pharmaceutical market, many pharmaceutical industries collaborate and merge into one another many giant pharmaceuticals acquire the small pharmaceutical firms and all this leads to the competitive landscape. (21)

Table 1. Summary of Anticipated Implementation Dates in US

Type	Anticipated implementation type	Guideline approval timeline
AR	Upto 1 year before submission	N/A
CBE-0	On receipt of submission by FDA	N/A
CBE-30	30 days after receipt of submission	6 months
PAS	Upto 6 months after submission	4 months

6. Challenges and Opportunities in Generic Drug Lifecycle Management

Managing the lifecycle of generic drug involves the various challenges generic drug manufacturers needs to face and over these challenges. While navigating the lifecycle of the generic drug the manufacturers get no of opportunities which helps in incorporating profitability in the business. Here are the challenges and opportunities:

Challenges:

a) Regulatory Hurdles

ANDA approval: To manufacture generic drug on large scale manufacturers needs to get approval from the FDA through ANDA process. This process of filing an ANDA to FDA to secure the approval can be time consuming and complex. This process is mainly time consuming for the biosimilar and complex generic formulation.

Compliance: Manufacturers need to comply with the current good manufacturing practices (cGMP). Continuing this compliance is very challenging for the generic drug manufacturers. (22)

b) Patent Litigation

Paragraph IV certification: A generic drug manufacturer while filing ANDA to FDA with the Paragraph IV certification leads to the patent infringement. This patent infringement lawsuit is filed by the branded drug manufacturers and this delays the market entry of generic drug.

Legal Cost: When the branded drug manufacturers file the patent infringement lawsuit on the other firm this kind of lawsuits are costly and very time consuming.

c) Market Competition

Price Wars: In US there is very competition the field of generic drug, this intense competition leads to price attrition and this intense competition and price attrition affects the profitability.

Market Saturation: In US, the generic drug market is oversupplied that many generic manufacturing companies struggle to capture the market share and this saturation leads to loss.

d) Supply Chain Management

Quality Control: When supplying the generic drugs not only in US but exporting it globally makes difficult and challenging for the generic drug manufacturer to ensure the consistent quality of active pharmaceutical ingredient (API) and of the finished drug product.

Disruptions: Geopolitical issues, natural disasters, pandemics causes the disruptions in the supply chain of the generic drug it also affects the production chain.

e) Pricing Pressure

Reimbursement Rates: In US, the government and some insurers makes pressure on the generic drug manufacturers to lower the prices of the generic drug and lower the recompense rates this squeeze the profit margins of the manufacturers.

Cost Management: For the manufacturers in US it is mandatory to maintain the high quality of the generic medication but while maintaining the high quality and managing the cost it becomes critical and challenging.

Opportunity:

a) Patent Expiration

New Generics: As the expiration of patients for famous and winner drugs continuous it provides

growing opportunity for the generic manufacturers to introduce new generics to market.

First to file: When any pharmaceutical company in the US first files the ANDA for the generics and secures the first to file status for the generics it grants that company 180 days of market exclusivity and provides the main competitive advantage.

b) Biosimilar

In the US the market for biosimilar generics is emerging and growing rapidly. It offers generic manufacturers an opportunity to enter that market. The FDA demands clarity in case of the biosimilar in generic manufacturing company manages to provide that clarity this will enhance the chances to gain profitability in biosimilar generics.

c) Technological Advancements

Advanced Manufacturing: There have been many innovations in the manufacturing process of pharmaceuticals worldwide and in US. This innovation includes the continuous manufacturing can help to improve the efficiency of production line reduce the cost of production.

d) Strategic Partnership

Collaboration: As the pharmaceutical companies collaborate with other manufacturing to enhance the production capabilities. Also collaborate with contract research organization (CRO), contract manufacturing organization (CMO) this enhances their production ability and expatiate market reach.

Licensing Deals: The generic manufacturers often look for the licensing deals with innovators of the drug. The innovator of drug issues the license to the generic manufacturer for authorized generics and this licensing helps the generic manufacturer to access the market immediately and it also reduce the infringement risks and also terminate the lawsuit expenses. (23, 24)

7. Conclusion

In the US market, maximizing profitability and maintaining competitive advantages depend on the generic product life cycle management. Feom every step of the process, from novel development and regulatory approval to market launch and continuous management. To remain in the market, one must keep an eye on market changing aspects and adjusts tactics in reaction to rivalry and patent expirations. A well-managed lifecycle ensures that the product remains related and profitable throughout its time in the market, while also assisting a smooth transition during market withdrawal. By employing a strategic approach, companies can optimize their generic products success and can achieve long-term business goals. The life cycle management of generic products in the U.S market demands a multifaceted approach to navigate the complexities of development, regulatory compliance and market dynamics.

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Conflict of Interest

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