EVALUATION OF THE GENERIC DRUGS PROGRAM AND GDUFA REAUTHORIZATIONS FOR FISCAL YEARS 2013-2022

by

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(Under the Direction of Michael Bartlett)

ABSTRACT

Name brand drugs have no competition until their patents or other exclusivities run out at which time generic drug products can enter the market. Generic drugs help bring competition to the market driving prices down. However, there are many drugs still without generic competition. This study used an analysis of GDUFA I and GDUFA II ANDA approvals to identify barriers to the generic drug market. Many approvals have been for what are known as "subsequent generics." Subsequent generics are the consecutive versions of a reference listed drug (RLD) after the 3rd and have a diminished effect in market price. Many prescription drugs without generic competition are complex products which can be difficult and expensive to manufacture. These, among other factors, are continuing to prevent adequate competition in the drug market leaving consumers to pay the price.

INDEX WORDS: US Food and Drug Administration, Generic Drug User Fees, Generic Drug Approvals, Abbreviated New Drug Applications, Market Competition

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by

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CHAPTER 1

INTRODUCTION

According to the United States Food and Drug Administration (FDA), 9 out of 10 prescriptions filled in the United States are for generic drugs.[1] The U.S. FDA-approved generic drugs have the same dosage, safety, effectiveness, strength, stability, quality, and route of administration as their reference listed drug at a fraction of the cost. The FDA put forth the legislature for Generic Drug User Fee Amendments (GDUFA) in 2012. This first iteration of GDUFA included an annual list of regulatory science initiatives specific to generic drugs. These initiatives were designed to increase the public's access to safe, affordable, high-quality generic drugs. The Amendments also functioned to reduce the cost of generic drug approval for industry, hoping for a subsequent increase in generic drugs being manufactured and approved for market. GDUFA was reauthorized in 2017 for fiscal years (FYs) 2018-2022 (GDUFA II) and again in 2022 for FYs 2023-2027 (GDUFA III). The reauthorizations of GDUFA are supported by additional policies and guidance published by the FDA to provide industry with relevant information and support.

This research aims to identify and evaluate the effectiveness of the regulatory initiatives, strategies, and incentives put forth in GDUFA I and II. These two authorizations have been completed during the time this research study was conducted. This research also aims to contribute to the discussion surrounding the barriers to increasing competition in the generic drug market. This chapter will introduce the research conducted starting with the necessary

background and context of the study. This will be followed by an explanation of the research aims, the significance of the research, and a discussion of limitations.

1.1 History of Generic Drugs

The 1984 Hatch-Waxman Act established the generic drug product approval pathway, the abbreviated new drug application (ANDA), under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[2] The FD&C Act provides the FDA with regulatory jurisdiction over the products defined in the Act. The Hatch-Waxman Act eliminated the requirements for extensive and expensive pre-clinical and clinical testing of the drug. These tests are replaced with bioequivalence studies to prove that the bioavailability of the generic product is equivalent to the reference (name brand) product. These savings in development costs can then be passed on to the consumer. Generic drug prices range from 80-85% lower than their brand product. [3] The Office of Generic Drugs (OGD) at the FDA is responsible for the oversight of the GDUFA program. This office lies within the Center for Drug Evaluation and Research (CDER).

1.2 Overview of the current market

The rising cost of healthcare in the United States is an ongoing challenge and has many contributing factors. One major area of healthcare that has seen increasingly high prices is prescription drugs. Companies with name brand drugs have all the power in the market to charge any price until their patent or market exclusivity expires. Upon approval, name brand drugs can qualify for different types of market exclusivities based on the characteristics of the drug, their intended treatment population, and other considerations. These exclusivities vary in length and can be combined in certain scenarios. [4]

Once these patents and exclusivities have expired, generic drug companies can proceed to manufacture and market generic versions of the drug. These generic drugs help bring

competition to the market and drive prices down. However, there are many drugs still without generic competition.

There are many barriers that can impede the growth of the generic market. These barriers can come from manufacturing of the active pharmaceutical ingredient (API), the application process, the review process, and market manipulation tactics by brand companies. Alongside the first reauthorization of GDUFA, the FDA announced the Drug Competition Action Plan (DCAP) in 2017. This program was put in place in order to "further encourage robust and timely market competition for generic drugs and help bring greater efficiency and transparency to the generic drug review process, without sacrificing the scientific rigor underlying our generic drug program." [5] The FDA has focused its efforts under the DCAP in three main areas: [5]

1) improving the efficiency of the generic drug development, review, and approval process
2) maximizing scientific and regulatory clarity with respect to complex generic drugs
3) closing loopholes that allow name brand drug companies to "game" FDA rules in ways that delay the generic competition Congress intended.

The efforts put forth in this plan were aiming to remove some of the barriers to entering the generic drug market and further drive competition.

A major hurdle to entering the generic drug market is the manufacturing of complex generics. Many prescription drugs without generic competition are complex products. Complex generics are those that have complex active ingredients, formulations, dosage forms, routes of administration, or are complex drug-device combination products. [6] One or more features of these products are difficult to "genericize" under the traditional approaches familiar to the generic industry. For a generic drug company, these can be difficult and expensive to manufacture. They may also require substantial investments in manufacturing, packaging, and

quality testing equipment that the generic company does not currently have in its possession. This also results in the necessary training of employees on this equipment and the development of standard operating procedures (SOPs) and quality control/quality assurance plans. It is not uncommon for these complex branded products to have their patents and exclusivities expire and still not be subject to generic competition. The FDA provides a list of off-patent, off exclusivity drugs that is updated in June and December every year. [7] For example, as of December 2022, there were four prescription aerosol metered dose products without any patent of exclusivity protections. [7] Three of these products (Nitroglycerin, Mometasone Furoate, and Hydrocortisone Acetate) have been on the list since December 2017. The fourth (Formoterol Fumarate; Mometasone Furoate) was added in December 2020. Additionally, this subset of generics typically has a higher cost than other brand products due to their complex nature. This makes it even more critical to develop generic alternatives for consumers. Under the DCAP and FDA policies, the FDA is aiming to increase the amount of scientific and regulatory information surrounding these complex generic products.

Another barrier from an industry point of view is the application process. The application process is complex and requires technological infrastructure as well as personnel expertise. The ANDA follows the Common Technical Document (CTD) format developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). This format was developed in an effort to streamline the review process across countries and application types. This simplifies the application process and expectations for reviewers on the regulatory end. As of 2017, all ANDAs are submitted in this format as an electronic submission (eCTD). The eCTD contains five modules of information. These modules are: [8]

1) Administrative Information and Prescribing Information
2) Summaries
3) Quality
4) Nonclinical
5) Clinical

As discussed above, the Hatch-Waxman Act eliminated the redundant non-clinical and clinical studies for generic drugs. Therefore, modules four and five look a little different than in a traditional application. Module four, Nonclinical Study Reports, are not typically included in an ANDA submission. There is only data related to specific circumstances regarding impurities, residual solvents, leachables, or excipients. Module five, Clinical Study Reports, contains all of the bioequivalence study data needed to prove that the generic product is bioequivalent to the reference listed drug (RLD).

From the regulator agency point of view, the review process is cumbersome and time-consuming. Incomplete or deficient applications can take up reviewer's time and cause delays in getting generic drug products to the market. In 2018, the FDA released a statement regarding the new steps and strategies that were being put in place to improve the efficiency of the generic drug approval process. [9] At the time of this statement, the average ANDA went through four review cycles before it was approved. These additional review cycles were not a result of deficiencies within the actual product but rather a result of deficiencies in the application. The most common deficiency resulting in the refusal of an ANDA is insufficient bioequivalence data. [10] Bioequivalence is the core of an ANDA. Therefore, the data presented must be thorough and must prove that the generic product is bioequivalent to the RLD. The FDA provides guidance in the application process in order to give generic companies the most relevant

information on the FDA's current thinking that will hopefully result in a complete application with the necessary supporting data.

Barriers to the market do not just exist within the boundaries of generic drugs. The generic drug market is directly influenced by the brand drug market. Companies in both of these markets have long taken advantage of the complexities that are presented in the overlap of the Hatch-Waxman Act, patent laws, antitrust laws, and state drug product selection laws. Over the years since the Hatch-Waxman Act was put in place, brand drug companies have developed multiple strategies to prolong the lifetime of their market exclusivity and delay the availability of generic drugs. Generic drug companies will often work together with a brand company to execute these strategies because they can receive guaranteed compensation. The strategies brand companies use include reverse payment or "pay-for-delay" patent settlements, authorized generics (AGs), product hopping, and buying out the competition. [11]

Patent protection and market exclusivities are used to allow the brand drug companies time to recoup their investment. As part of Hatch-Waxman, generic companies were encouraged to challenge existing drug patents in their ANDA. However, in the "pay-for-delay" strategy brand companies will come to an agreement on a settlement amount to be paid to the generic company that challenged their patent in order to delay the entry of their generic product into the market. This is commonly referred to as reversed payment because in a traditional scenario, the generic company would be paying the brand company in order to enter the market. The reverse payment strategy is a more nuanced alternative to buying out competitors. This strategy is estimated to have costed consumers billions of dollars and prevented access to affordable drugs for the treatment of critical diseases including cancer and Alzheimer's. [11] Perhaps the most notable example of the "pay-for-delay" strategy being used for cancer drugs is the case of

Nolvadex (tamoxifen). Tamoxifen is the most widely prescribed cancer drug in the world. In March 1993, brand-name drug manufacturer AstraZeneca agreed to pay $21 million directly to generic manufacturer Barr Laboratories, in exchange for Barr's consent to not market a less expensive generic version of tamoxifen until AstraZeneca's patent expired in August 2002. [12] Additionally, once the patent expired, Barr could invoke their 180-day exclusivity granted to them in their ANDA submission.

Authorized generics (AGs) are another well-known strategy. Under the Hatch-Waxman Act, brand companies are allowed to produce an authorized generic during the 180-day exclusivity awarded to the first generic filing for a brand product. These authorized generics are either produced by the brand company themselves or in collaboration with a generic manufacturer. The introduction of AGs still provides a price cut benefit, but they interfere with the profits of the first generic. This strategy can be combined with the "pay-for-delay" strategy by adding an addendum that once the extended patent protection expires, the brand company provides a promise not to introduce an AG during that generic's exclusivity period. [11]

A third strategy is product hopping, also known as "forced switching" or "evergreening." [11] These are all terms for when a brand company switches the marketed product to a reformulated version shortly before patent expiration date for the brand product. These products typically offer little to no additional therapeutic benefit or advantage. This strategy is often combined with a large promotional push to physicians and consumers to encourage the use of this "new and improved" formulation. [11] In 2015, Actavis attempted to remove an older version of Namenda IR, a drug used in the treatment of Alzheimer's disease, with Namenda XR. [13] The only difference between the two versions was that the new version was to be taken once a day instead of twice. The New York Attorney General blocked this product hopping scheme. It

was estimated that the removal of Namenda IR and subsequent patent extension to 2029 would have led to consumers paying almost $300 million more, third-party payors paying almost $1.4 billion more, and Medicare and its beneficiaries paying a minimum of $6 billion over ten years. [11] These, among other factors, are continuing to prevent adequate competition in the drug market leaving consumers to pay the price.

These strategies typically have an unproportionate effect of the first-to-file or first generics. First generics are the first generic version of a branded product to be approved for the market. These generics are responsible for creating the first competition for a branded product and driving prices down. It is the first, second, and third generic of a reference branded product that have the most significant impact on price competition. As part of DCAP, the FDA has made attempts to close these loopholes that impede the growth of the generic market.

1.3 Purpose of GDUFA

GDUFA aims to facilitate the development and delivery of more generic drugs to the market to combat high prescription and over the counter name brand drug costs for consumers. The GDUFA program and the DCAP were designed not only to alleviate some pressure on the manufacturers and sponsors of the applications, but also to support the FDA in the regulatory review process.

For the majority of generic drugs, the manufacturers have a well-established process for each dosage form they are making. As brand drugs continue to advance and innovate, there is a natural lag in the generic market as these novel manufacturing processes become more commonplace. Through GDUFA II, only 13% of generics approved were considered complex generics. [14] Aside from the manufacturing hurdles and struggles that go along with the production of complex generics, there is also a significant challenge presented in proving

bioequivalence to the RLD. As discussed above, bioequivalence is the most critical aspect of the generic drug application. Oftentimes complex generic drugs can be difficult to measure in the blood because the drug may be administered locally to a particular organ rather than in systemic circulation through the bloodstream. [15] This makes pharmacokinetic studies much more difficult, which in turn makes proving bioequivalence significantly more complicated.

The submission of an Abbreviated New Drug Application (ANDA) is a complicated process, especially for smaller companies. In the first reauthorization of GDUFA, the FDA decided to alleviate some of the financial stress on these smaller companies by establishing a user fee tier system based on the number of ANDAs each company has approved on the market. The generic drug program is all about increasing market competition, and a great way to do that is level the playing field for companies of varying sizes to feel as though the generic drug approval approach is both accessible and a sound financial investment.

One way the FDA worked to provide more financial benefit to those applying to put a generic drug on the market was by providing 180 days of exclusivity for the first generic of a branded drug to submit a complete application that meets all requirements. [4] This exclusivity incentive serves the same function as the exclusivities offered to new drug applications (NDAs). Market exclusivity for first generics encourages companies to make these products for the market with the promise that they will get 180 days on the market without any other generic competition. This gives them time to recoup their investment.

Bioequivalence is a critical part of the generic drug application. The Hatch-Waxman Act eliminated the need for redundant pre-clinical and clinical testing and replaced it with the need for proof of bioequivalence. Because the reference listed brand drug has already been proven to be safe and effective, generic manufacturers and application sponsors only need to prove that

their products have the same rate and extent of absorption into systemic circulation. This is done through pharmacokinetic studies in smaller groups of human subjects. All bioavailability and bioequivalence requirements are detailed in section 21 of the Code of Federal Regulations (CFR) part 320. Section 21 of the CFR is reserved for rules regarding the FDA. This alternative testing process saves a significant amount of time and money for the applicant while still ensuring consumers will receive a safe and effective product. Regardless of whether a complex generic or regular generic product is being tested, some products may require special patient population considerations including gender, age, or presence of target disease.[16] Some medicines can pose a risk to patients that are not in the target population, so subject selection should take that factor into consideration.

First cycle approvals are those applications that are approved for the market after the first round of review. If an application is found deficient in any area, it will have to undergo additional rounds of review until it is deemed sufficient for approval. Depending on the severity of the deficiency, the FDA can refuse to receive the application entirely and the entire process starts over for the generic applicant company. These additional rounds of review take time and resources on both sides, the applicants and the reviewers. In a 2017 statement from the FDA, it was said that before the first authorization of GDUFA the average percentage of first cycle approvals was 1%. [17] In that same statement it was also said that the average percent of first cycle approvals was 9%. [17] Part of the performance goals of the GDUFA program was to increase these first cycle approvals.

The commitment letter for GDUFA does not discuss any specific aims or strategies to increase the number of first generics on the market. The FDA has its control on the regulatory side. Their goal in GDUFA II was to make sure any first generic application was approved by the

first lawful ANDA approval date. While the FDA does not have direct control of drug development and pricing, they can develop guidance and strategies for generic companies to follow. This would result in an increase in generics to the market.

The FDA publishes guidances for industry to provide their current thinking on the application process. These guidances help industry to achieve complete applications. Guidance documents for ANDAs include Generic Drugs Guidances, Biopharmaceutics Guidances, and Product-Specific Guidances for Generic Drug Development. In turn, the FDA can provide an efficient review process. The FDA also provides a dissolution database. The FDA Dissolution Methods Database provides information on dissolution methods presently recommended by the Division of Biopharmaceutics, Office of Pharmaceutical Quality to aid industry personnel in developing generic drug products. [18] The goal is for the consumer to benefit from generic drugs reaching the market at a faster rate.

1.4 Research Problem

GDUFA has resulted in consistent increases in approval numbers each year, but competition in the market is still lagging. A large number of approvals have been for "subsequent generics." Subsequent generics are the consecutive versions of a RLD after the third. [17] After the third generic version of the same drug, the benefit to the market drops off significantly. As part of the first reauthorization of GDUFA (GDUFA II), the FDA publishes annual reports on how their GDUFA science and research-funded projects support the development of generic drug products, generation of evidence needed to support efficient review and timely approval of ANDAs, and the evaluation of generic drug equivalence.

The current literature on this topic spans the global generic market. Some of the categories and deficiencies that are most commonly evaluated are bioequivalence, dosage form,

and therapeutic class.[10] [19] The generic drug market is critical for patients and consumers who need access to traditionally high-cost prescription medications.

We have now seen the conclusion of the second iteration of GDUFA in 2022. The third iteration was just approved for the fiscal years of 2023-2027. During this transition period, it is beneficial to see where the program lies in its current state. By evaluating the current state of the generic program and drug market, we can provide insight into weaknesses or shortcomings that still hinder the process of generic drug approval. These insights and evaluations should contribute to the current body of research in this field as well as prompt additional projects as the GDUFA program continues to employ new strategies with each reauthorization and additional policies and guidances.

1.5 Research Aims and Objectives

This study will contribute to the body of knowledge surrounding the generic drug market, generic drug applications, and the FDA's review and approval process. This research aims to evaluate the GDUFA program, the changes made during the reauthorization in 2018, and their impact on the current market. This research also aims to identify deficiencies in the generic drug program from the point of view of the applicant and the Agency. The major objectives are to evaluate the differences for the metrics outlined in **Table *1***. This table also includes the additional metrics and categories that will be evaluated during this research study regardless of whether the data is available for both authorizations.

Table 1 GDUFA Authorization Comparison Matrix

Category/Metric	GDUFA I	GDUFA II
Fiscal Years	2013-2017	2018-2022
Submission Process [20]	Tiered submission with different cohorts receiving different goals. Challenging for FDA to keep track and resulted in gaps in commitments and expectations.	Eliminated tier system and consolidated review goals. Review goals now measured against commitment letters from FDA.
Agency communication [21]	No teleconferencing for First Cycle review.	Teleconferences for clarification of First Cycle deficiencies. Teleconference: a verbal communication by telephone, and not a written response, unless otherwise agreed to by the applicant.
Withdrawals and Application Refunds [20]	No incentive to withdrawal and correct an application even if it was flawed.	Offered 75% refund of application fee if an application was withdrawn before the applicant receives a notice of receipt by the Office of Generic Drugs.
User Fees [20]	Annual fees on a per ANDA basis.	Annual fees based on the total number of ANDAs the company has. Large program: ≥20 ANDAs Medium program: 6-19 ANDAs Small program: ≤5 ANDAs
	Combined active pharmaceutical ingredient (API) and final dosage form (FDF) facilities had to pay both fees. Fee varied between 15-30k.	API and FDF facilities only pay FDF fee. Fee set at 15k.
Performance Metrics [22]	Monthly and quarterly activities reporting to track performance metrics.	Monthly and quarterly activities reporting to track performance metrics. New and updated performance metrics including addition of First Cycle approval numbers.

1.6 Research Scope, Impact, and Limitations

The scope of this research focuses on the evaluation of the changes made during the first GDUFA transition period. Within this is an evaluation of the effectiveness of the changes through analysis of performance metrics common to both the original authorization and the reauthorization. The data will be collected for each reauthorization as well as the breakdown for each fiscal year 2013-2022. The fiscal year (FY) of the generic drug program runs from October through September of the next year. For example, FY 2022 ran from October 2021 through September 2022. The performance metrics being evaluated for these authorizations and the comparison between them are displayed in **Table *1***. The primary methodology used for this research is data collection and analysis from FDA databases and resources published to their website. This data was compiled using Microsoft Office Excel to organize and perform analysis. Any statistical analyses performed on the data were performed in Excel.

Due to the changing authorizations and efforts for improvement, there were many performance metrics that were not recorded or published early on in the program. For this reason, it can be difficult to compare the two authorizations to each other. With that in mind, this research focuses on the metrics and trends that can be directly evaluated and compared based on the data available.

For the purposes of this research, only original ANDA approvals were evaluated. Any supplemental ANDA submissions were not included in the data collection or analysis. Original ANDA submissions are those initial applications by a generic company for a generic drug product. Supplemental ANDA submissions are those submitted to propose a change to the product relating to manufacturing process, product specifications, container closure system, labeling, formulation, or other miscellaneous changes. [23] Any changes considered major by the

FDA in any of these categories require approval before the actual product can be marketed. These are known as prior approval supplements (PAS). Any changes deemed moderate by the FDA require a supplemental submission before the changes are put into effect. Changes considered minor by the FDA do not require a supplemental submission, but they are included in the annual report on the drug product from the applicant. Original ANDA submissions can either receive full approval or tentative approval based on the content of the application and any exclusivities or patents that belong to the RLD. Tentative approvals are issued when the application is approvable prior to the expiration of any patents or exclusivities that are assigned to the RLD. When granted a tentative approval, the applicant cannot market the product and must wait for final approval when all patents and exclusivities have expired.

Time is a significant limitation for this research study. While GDUFA has been approved since 2012, there has only been one complete reauthorization to date. This means there has only been one set of data from GDUFA I that was evaluated and revised to begin GDUFA II in 2018. After the first reauthorization, there have only been four years for changes and strategies to be implemented and evaluated for impact. In regard to time, it is also critical to look at the timeline of the COVID-19 public health emergency in relation to the first reauthorization of GDUFA (GDUFA II). The day-to-day operations of the FDA, manufacturers, applicants, and other participants were adjusted due to the effects of the pandemic. The FDA had a serious focus on public health and safety which included the approval for emergency use of COVID-19 tests and vaccines. Now that we are transitioning out of the pandemic and into the second reauthorization of GDUFA (GDUFA III), we will be able to evaluate whether the trends in this study are a result of the effects of the pandemic or if they will continue.

For a program as far reaching and complex as generic drug approvals, this is not a significant amount of time to be able to evaluate the full potential of these changes. That being said, the purpose of this research is to see which changes and strategies have already seen their intended impact or are headed in that direction. It is also important to keep in mind what strategies may need to be revised in future reauthorizations.

It should also be noted that other than data that came directly from an FDA resource, some data collection and compilation was performed by hand. Active steps were taken to review each month of approvals exported from the Drugs @ FDA database to ensure that all NDAs and BLAs were removed. When transcribing route of administration, dosage form, and market status, the drug name and ANDA number were verified before the data was recorded. This verification was replicated for all other manual data transcription.

The hope is that this research will provide a foundation for further independent study and analysis of the efforts of the GDUFA program. Generic drug competition is critical to the design of the drug market. Barriers to generic drug approval and marketing can cost consumers billions of dollars. Lagging approvals can also prevent consumer access to life-changing medications for diseases such as cancer and Alzheimer's. [11] The generic drug market is essential for providing safe and cost-effective options to patients. Therefore, it is essential that this process be as efficient as possible for both the applicant and the reviewer.

The following chapters will detail the research methods used in order to accomplish the aforementioned research aims and objectives. This will be followed by a presentation and analysis of the results obtained through the execution of these methods. These results will be further discussed and summarized in the context of the study and their role in impacting the

generic drug market for consumers. The final section will discuss the future work that would be beneficial to perform based on the research results and analysis of the generic drug market.

CHAPTER 2

METHODS

2.1 Introduction

The primary objective of this research was to evaluate the differences between GDUFA I and GDUFA II performance metrics. This research began with extensive review of FDA resources including commitment letters, annual reports, activities reporting, relevant guidance documents, congressional hearing reports, and statements released by the FDA. The results of this research were compiled into a comparison matrix highlighting the major changes and improvements being made in the transition period between the two authorizations. A portion of this matrix was included in **Table *1*** with the contents focusing on the research objectives. Further aims of this research were to identify any trends in the types of drugs being approved, market status of approved drugs, first generic options of brand drugs being brought to market, and barriers that are preventing the growth of the generic drug market. The methods described below detail the process of data collection and analysis performed to meet these research objectives.

2.2 Authorization Transition Period

The first step in comparing GDUFA I and GDUFA II was to review the original goals and purposes of the program and compare those to the GDUFA II commitment letter. [24] Prior to GDUFA, data and analytics on the generic drug program were not recorded or published in detail. Additionally, as time went on, the FDA began to include different metrics in their annual,

quarterly, and monthly performance reports. For this reason, some performance metrics cannot be directly compared due to a lack of data in the earlier years of GDUFA.

The FDA website provides monthly activities reports for each fiscal year (FY) of GDUFA starting in FY 2013. [22] One of the metrics that is available across all FYs is the number of withdrawals. The withdrawal number available on these reports included all withdrawals for original ANDAs that were approved and unapproved. As mentioned in the introduction and **Table *1***, one of the improvements made to the GDUFA II authorization was the addition of a refund with an application withdrawal. The withdrawal number from each FY from 2013-2022 were collected. It was important to see if the difference in withdrawals from GDUFA I and GDUFA II were statistically significant, so a two-sample t-test was performed. The two-sample t-test was chosen as it is designed to identify if there is a statistically significant difference between the two groups. The two-tailed test was run at an alpha value of 0.05 to see if the two populations, GDUFA I withdrawals and GDUFA II withdrawals, were different. The one-tailed test was also a part of the analysis which is used to see if one population mean is greater or less than the other. The two-sample t-test was run assuming unequal variances. Variances are assumed unequal when the ratio of variances of the two groups is greater than 4:1. These variance values are displayed in **Table *5***.

The monthly and quarterly activities reports also include the number of first cycle approvals for GDUFA II (FY 2018-2022). These values were not provided in the activities reports for GDUFA I. Using an FDA statement regarding the average first cycle approval before GDUFA and during GDUFA I, these values were compared to the average first cycle approvals calculated from the GDUFA II activities reports.

2.3 FDA Database Search

The Drugs @ FDA database was integral to the collection of ANDA approval data. Using the function to search by month and year, each month was exported as an excel file. When the months are exported, the file includes all original and supplemental applications for New Drug Applications (NDAs), Biologics Licensing Applications (BLAs), and Abbreviated New Drug Applications (ANDAs). The data was sorted to separate the original and supplemental applications. Once the original submissions were isolated, any NDAs or BLAs had to be removed. After the original ANDAs had been completely isolated, the months were organized by FY on excel sheets for further analysis. A total of 7,441 original ANDA approvals from FY 2013 through FY 2022 (October 2012 through September 2022) were evaluated. This number includes 1,084 tentative approvals.

Table 2 Number of Original ANDA Approvals FY 2013-2022

	FY	Original ANDA Approvals + Tentative	Original ANDA Approvals
GDUFA I	2013	446	441
	2014	436	410
	2015	537	503
	2016	691	638
	2017	830	769
	TOTAL	**2940**	**2761**
GDUFA II	2018	885	796
	2019	1052	938
	2020	854	744
	2021	809	687
	2022	881	731
	TOTAL	**4481**	**3896**

Using the aforementioned Excel sheets of all original ANDA approvals for each FY and the Drugs @ FDA platform search function, each individual ANDA number was searched, and the dosage form and market status were recorded. As discussed in the introduction, the number of approvals has increased over the years of GDUFA, but the market has still not seen significant

benefits. Therefore, market status was an important metric to see how many of the approved drugs were still available on the market. The market status categories are shown below in **Table *3***.

Table 3 Market Status Term Definitions

Term	Definition
On Market	At least one dosing option included in the ANDA available on the market. Includes prescription and over-the-counter products.
Discontinued	No dosing option included in the ANDA available on the market.
Tentative Approval	Still under tentative approval, not available on the market.

The dosage form data was compiled and evaluated for trends in the types of products that are most commonly approved. The research focused on the frequency of each route of administration and dosage form. Using the FDA's route of administration resource, each one was defined and the dosage forms that fall into those categories were grouped together. [25] If a dosage form was listed for multiple routes of administration (ROAs) (ex. solution; oral, rectal), then the dosage form was included in the count for each of those ROAs. For some approvals, the ROA was listed as "unknown." All data has remained the same since the time of collection, no updates were made regarding approval or market status.

The FDA uses the Wayback machine archive function for many resources on its website. One of the ways we used this resource in the research study was to access the first generic approvals for the years 2012 through 2015. The FDA publishes the list of first generics approved each calendar year, but only 2016 through 2022 were available directly on the website. [26] The archived years had monthly lists that were individually opened, and the number of approvals

were recorded in the appropriate fiscal year. For 2016 through 2022, the first generic approval numbers were compiled for the entire calendar year. The approvals for each calendar year were separated into their appropriate fiscal year based on the provided month of approval and the data was recorded.

2.4 FDA Resources

The first reauthorization of GDUFA provided tiered fees based on a company's size. When the monthly drug approvals were exported from Drugs @ FDA to Excel, the applicant companies were included in the listed information for each ANDA. This column was analyzed for the frequency of each company's occurrence on the list. Using the company tier list for fiscal years 2018-2022, the applicant companies were ranked to evaluate any impact on smaller companies entering the generic landscape. This tier list information came from an Excel file that was shared by Karl Hill Sr., a management analyst at the FDA. This file provided all program fee tier information for FY 2018-2022 including the parent company name, their assigned GDUFA tier in that FY, and total ANDAs claimed as of that FY. Given the large number of different applicant companies, the data was organized to display the top twenty companies with the most ANDA approvals that FY. It was chosen to look at the top twenty companies, because in most cases the top ten all fell into the large program tier and looking at twenty would give a better view overall.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Chapter Introduction

The overarching goal of this research is to identify what strategies are effective for increasing generic market competition and what strategies are not as effective. In order to evaluate the effectiveness of the changes between GDUFA I and GDUFA II, the FDA reported resources and databases were critical. Beyond the hard data reporting, it was immensely important to review the statements made by the FDA which reflect their current thinking as well as information that is not directly reported. With further evaluation and analysis, the results in this chapter will contribute to the conversation surrounding efficient generic drug development and approvals and be a resource for developing new strategies. This chapter will detail the results of the execution of the research methods described in chapter two.

Table 4 Routes of Administration and the Dosage Forms Included in Each Category

Route of Administration	Definition	Dosage Forms
Oral	Administration to or by way of the mouth.	Capsule (extended release, delayed release, delayed release pellets), chewing gum, concentrate, drops, elixir, for solution, for suspension, granule, liquid, powder, solution, suspension (extended release, delayed release), syrup, tablet (extended release, delayed release, chewable, orally disintegrating (ODT), delayed release ODT, film coated), troche/lozenge
Buccal	Administration directed toward the cheek,	Film, tablet

	generally from within the mouth.	
Sublingual	Administration beneath the tongue.	Film, metered spray, tablet
Dental	Administration to a tooth or teeth.	Paste, solution
Parenteral	Administration by injection, infusion, or implantation.	Injectable, liposomal, solution, powder, sterile liquid
Subcutaneous	Administration beneath the skin; hypodermic. Synonymous with the term Subdermal.	Injectable, solution, powder
Intracavitary	Administration within a non-pathologic cavity, such as that of the cervix, uterus, or penis, or such as that which is formed as the result of a wound.	Powder
Intrathecal	Administration within the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles.	Injectable
Intravesical	Administration with the bladder.	Powder, solution
Intravenous	Administration within or into a vein or veins.	Powder, solution, injectable
Intramuscular	Administration within a muscle.	Powder, solution, suspension (extended release), injectable
Intraosseous	Administration into the medullary space of the bone.	Solution
Intraspinal	Administration within the vertebral column.	Injectable
Endotracheal	Administration directly into the trachea	Solution
Topical	Administration to a particular spot on the outer surface of the body.	Aerosol foam, cream, drops, foam, for solution, gel, jelly, lotion, ointment, oil, patch, shampoo, solution, spray
Transdermal	Administration through the dermal layer of the skin to the systemic circulation by diffusion.	Film (extended release), gel, system, solution

Auricular (Otic)	Administration to or by way of the ear.	Solution, suspension, drops, oil
Ophthalmic	Administration to the external eye.	Emulsion, solution, drops, solution (gel forming)
Nasal	Administration to the nose; administered by way of the nose.	Spray, metered spray
Vaginal	Administration into the vagina.	Cream, gel, ring, tablet
Rectal	Administration to the rectum.	Powder, solution, suppository
Respiratory (Inhalation)	Administration within the respiratory tract by inhaling orally or nasally for local or systemic effect.	Aerosol (metered), gas, liquid, powder, solution, suspension
Unknown	Route of administration is unknown.	N/A

3.2 Presentation and Analysis of Findings

Throughout the two authorizations of GDUFA, there have been a variety of routes of administration and dosage forms manufactured and approved. **Table *4*** lists all the routes of administration and the dosage forms that were available for both authorizations of GDUFA. The following charts display the frequency of each route of administration for GDUFA I and GDUFA II. Unsurprisingly, the largest group of approvals fall under the oral route of administration. Within this route of administration, the largest group of dosage forms are tablets and capsules. These dosage forms are also available in extended and delayed release formulations. When it comes to manufacturing, tablets and capsules are some of the most well-established methods. The equipment and processes used are well documented and all good laboratory practices (GLP) and good manufacturing practices (GMP) are outlined in detail by the FDA. Parenteral dosage forms are the second most frequent route of administration. These

processes are well established, but there are additional stability and sterility requirements that must be met.

Figure 1 Number of Approvals in Each Route of Administration Category for GDUFA I

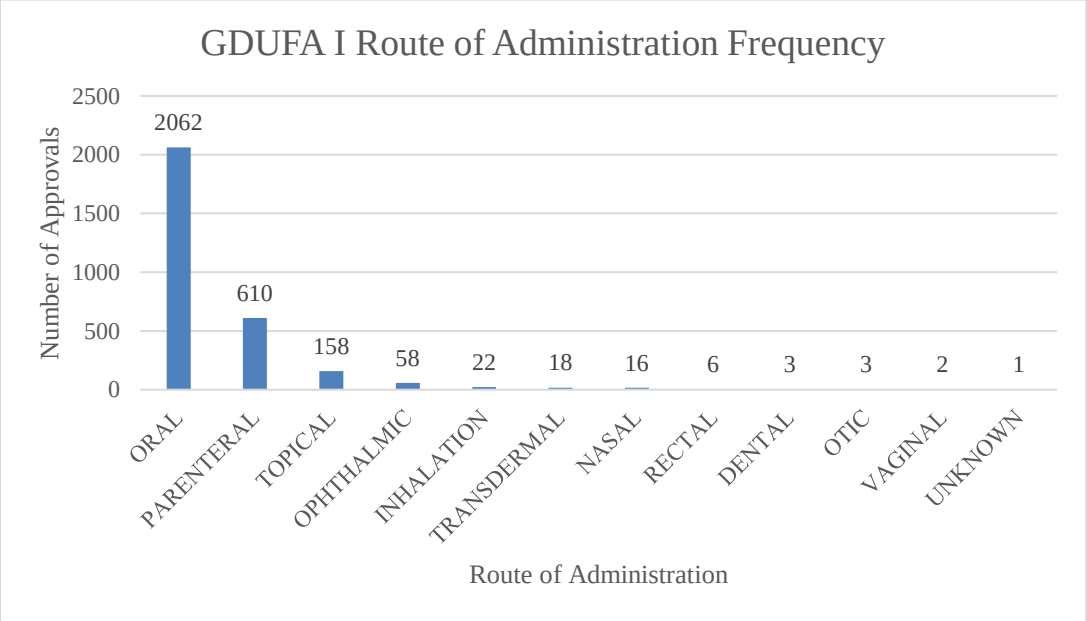


Figure 2 Number of Approvals in Each Route of Administration Category for GDUFA II

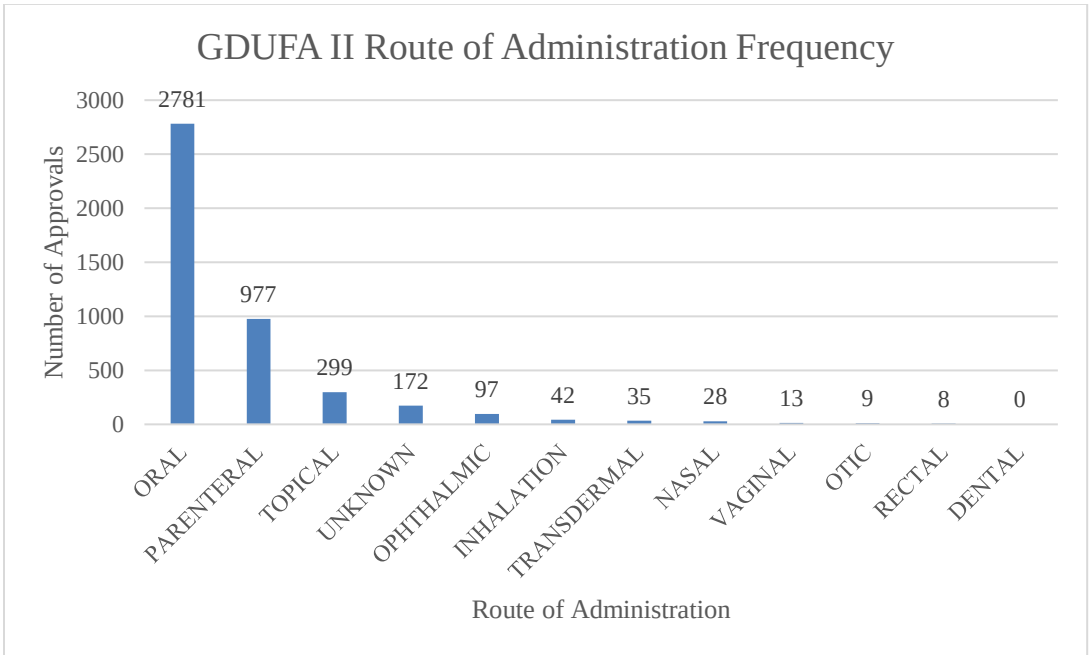
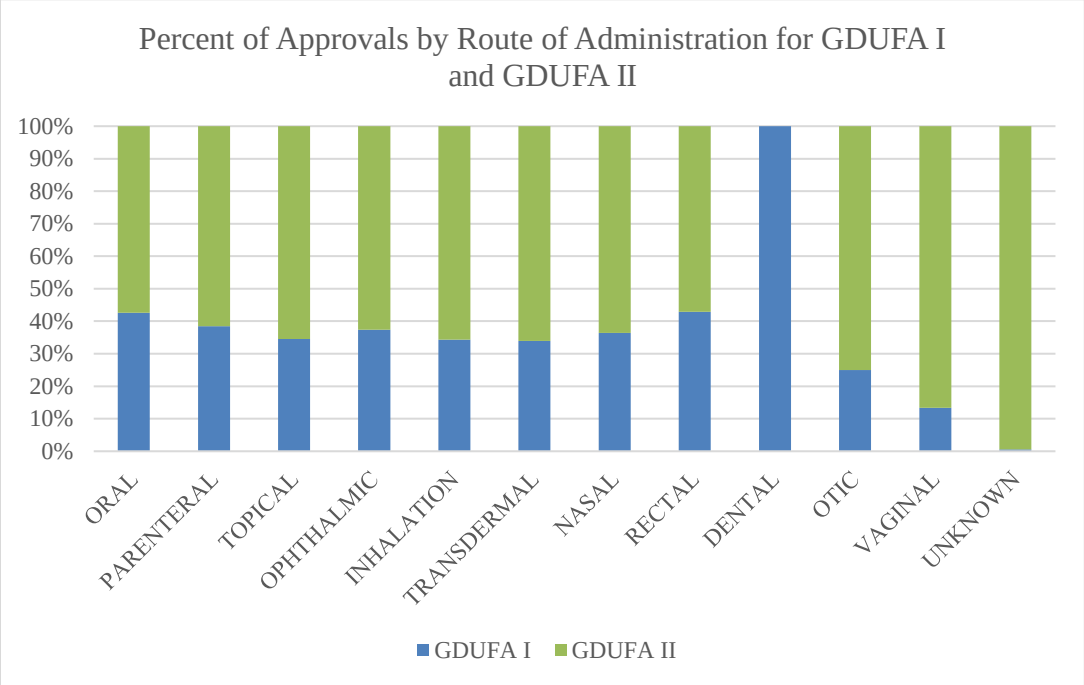


Figure 3 Comparison of Percent of Approvals by Route of Administration Between GDUFA I and GDUFA II



Looking at the two authorizations of GDUFA, the percent distribution of routes of administration is similar for both. During GDUFA II we saw the disappearance of the dental route of administration. We also saw an increase in the number of approvals with a route of administration/dosage form listed as unknown. GDUFA I saw 1 approval designated as unknown while GDUFA II saw 172. This represents an increase from 0.03% of all approvals to 3.86%. The final dosage forms are available via the approval letters from the FDA to the applicant, so the reason for this designation of unknown dosage forms is unclear at this time.

Figure 4 Current Market Status of ANDA Approvals Made Under GDUFA I

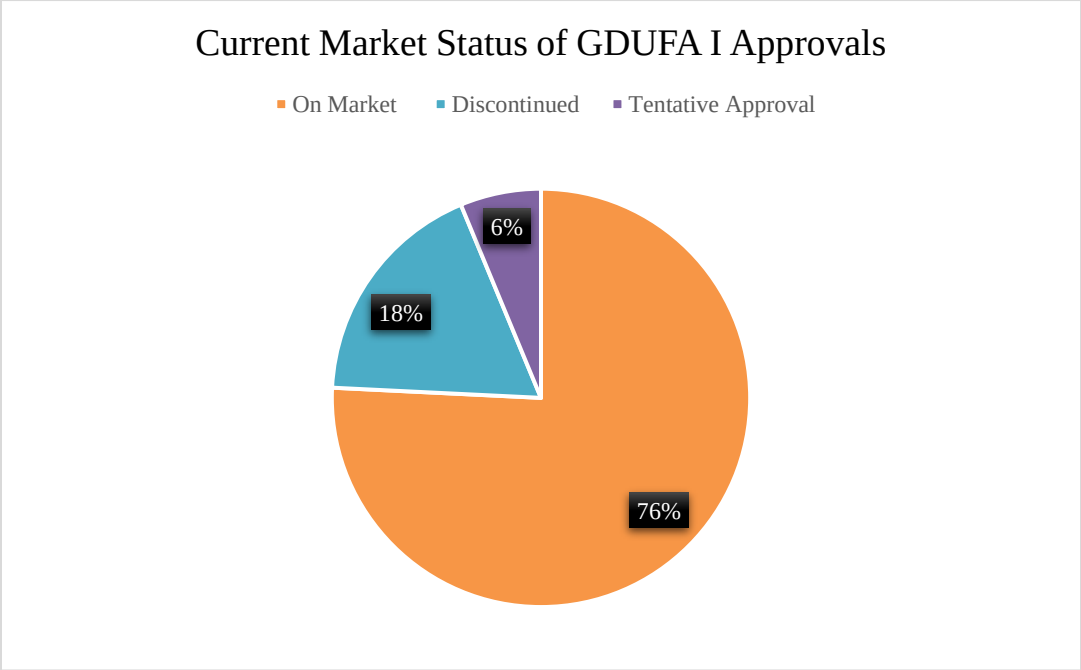
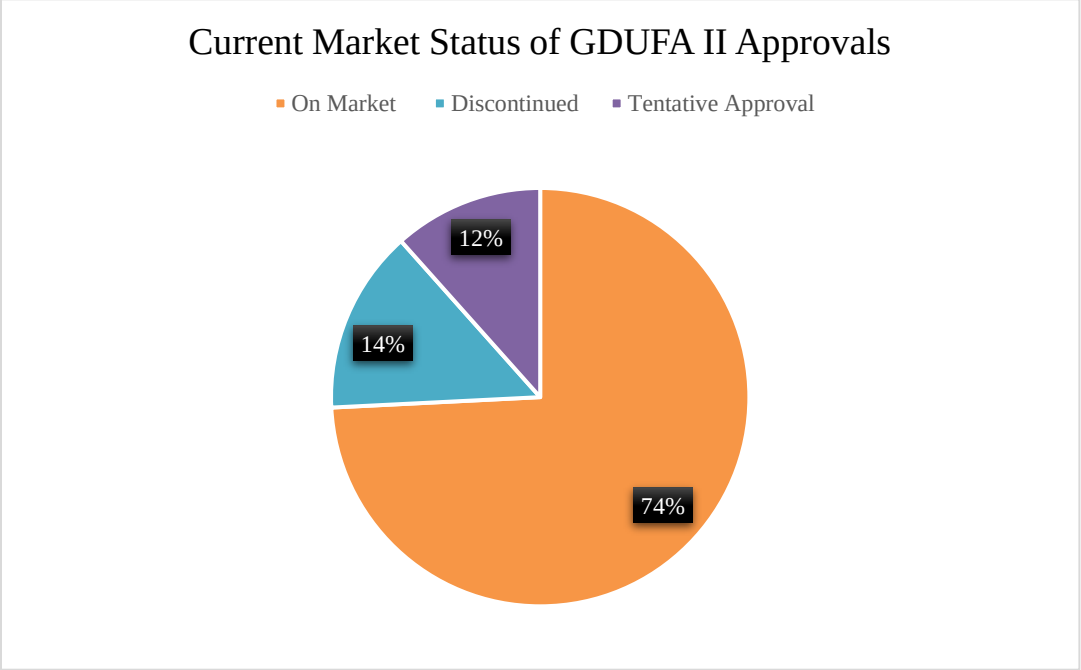


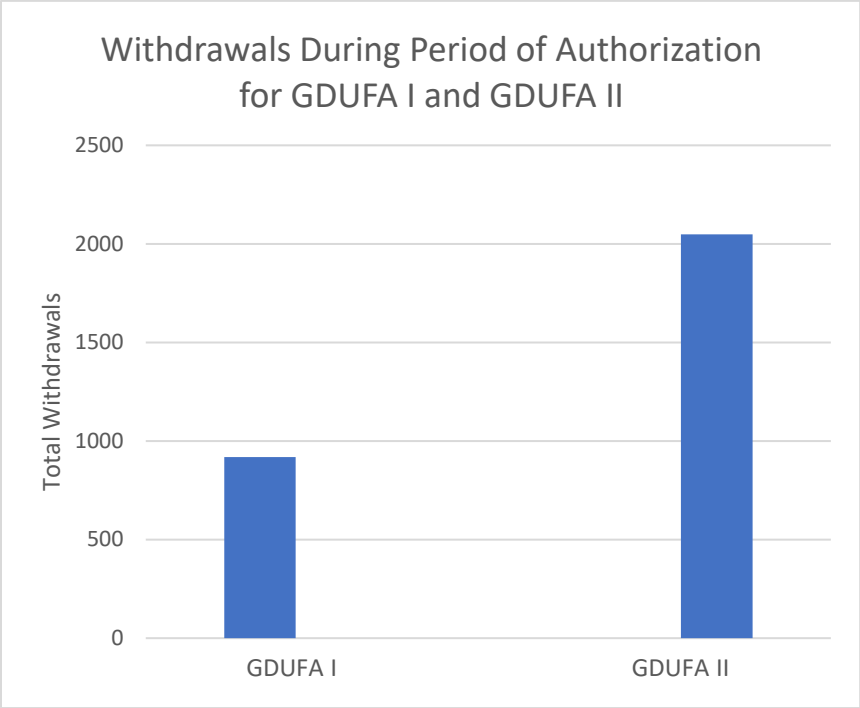
Figure 5 Current Market Status of ANDA Approvals Made Under GDUFA II



The market status of the approved ANDAs was an important metric chosen for this research. We can see the number of approvals increasing, but we wanted to see how many of those products actually remained on the market for consumers. At the time that data collection was completed, approximately 75% of approved generic drugs under GDUFA I and GDUFA II remained on the market. In order for market competition to be active and benefit the consumer, there have to be drugs available on the market. Tentative approvals represent a large portion of generic drug products that are not on the market in both GDUFA I and GDUFA II. About one fifth of approved drugs were discontinued and are no longer available on the market. Products being discontinued from the market could be a result of safety, efficacy, profitability, or other issues. Not all generic products are removed due to their own product faults. As a generic product, their approval is based on the bioequivalence to the reference brand product. If a reference listed drug is removed from the market due to product safety concerns, it is likely that the generic drug will also be removed from the market.

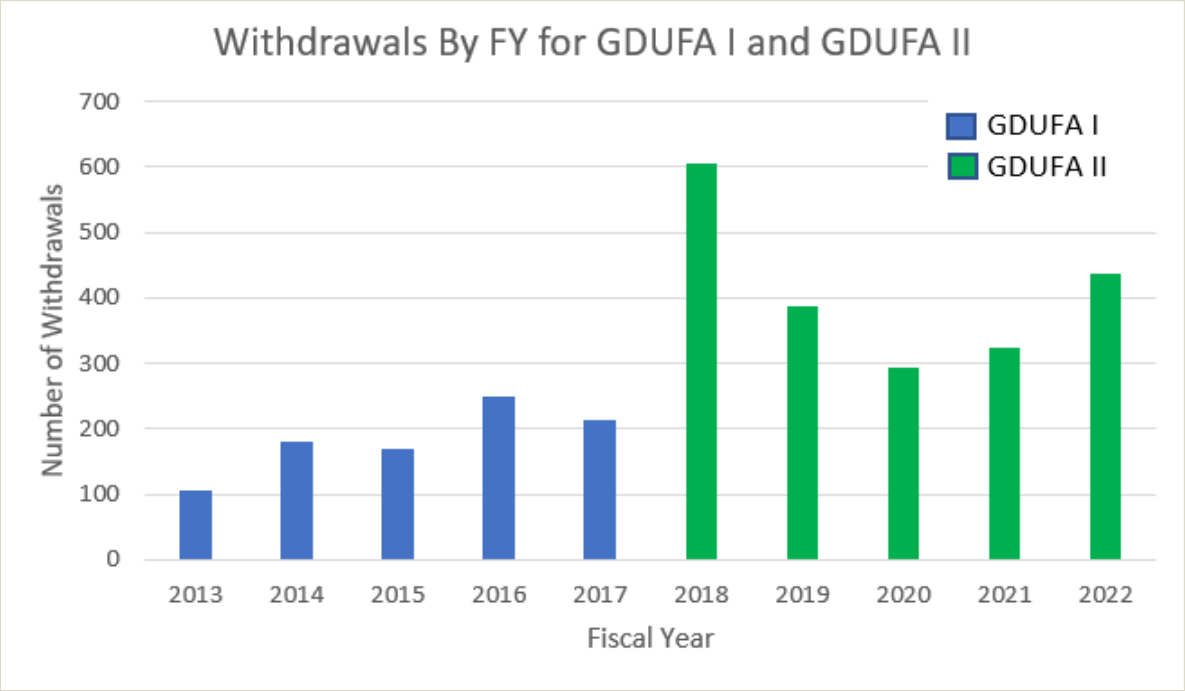
Timely processing of tentative approvals only goes so far, the final approval and market availability then is dependent on the patent or market exclusivity expiration date. Additionally, as was mentioned in the introduction, there are external forces at play for any first to file generics that may delay or completely prevent their arrival to the market.

Figure 6 Total Number of Withdrawals During the Periods of Authorization for GDUFA I and GDUFA II



After visualizing the notable increase in the total number of withdrawals from GDUFA I to GDUFA II, the withdrawals were divided by fiscal year and displayed in **Figure *7***. The figure above, **Figure *6***, shows that there were approximately 123% more withdrawals in GDUFA than in GDUFA I. Both representations of the data showed a clear increase in the number of withdrawals, but it took further testing to see if that observation was statistically significant.

Figure 7 Total Number of Withdrawals During the Periods of Authorization for GDUFA I and GDUFA II by Fiscal Year



The statistical testing of the withdrawal data yielded the following results as shown in **Table *5***. The two-tailed, two-sample t-test presented a P-value of 0.012913789 which is less than the α value of 0.05. Therefore, we can reject the null hypothesis as there is sufficient evidence that the two populations are different. The two-tailed, two-sample t-test also presented a critical value of 2.570581836 which is less than the test statistic (t Stat). When the critical value is less than the test statistic, we can reject the null hypothesis as there is sufficient evidence that the two groups are different from each other. This same trend in the data can be observed in the one-tailed, two-sample t-test results.

Table 5 Statistical Analysis of Withdrawals in GDUFA I and GDUFA II

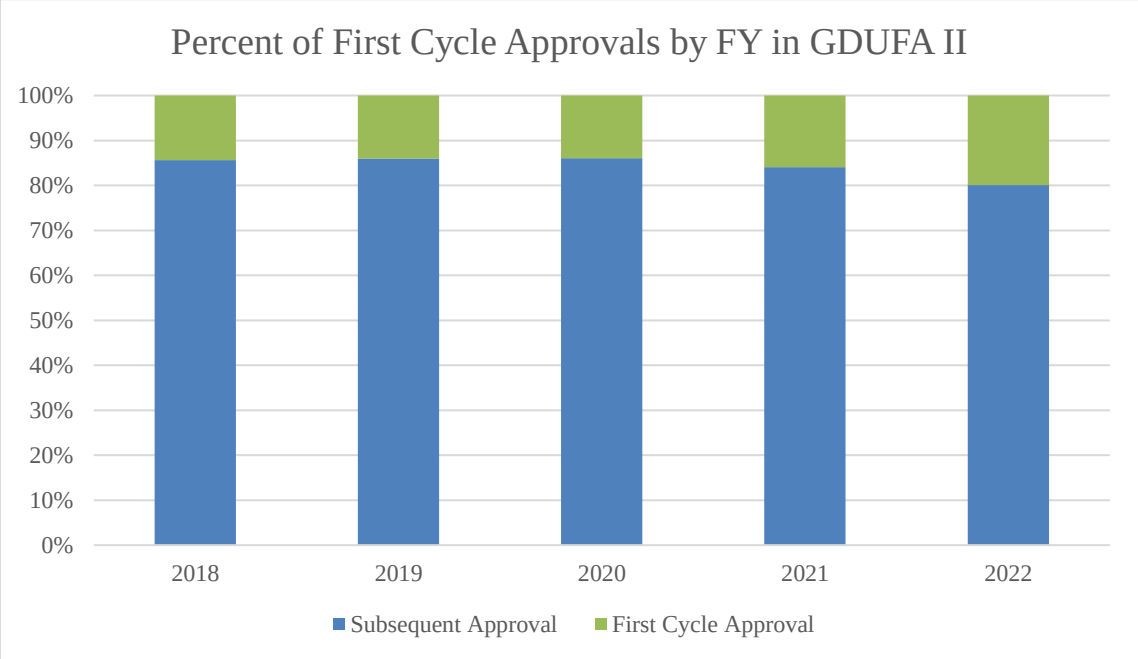
t-Test: Two-Sample Assuming Unequal Variances	Withdrawals	
	GDUFA 1	*GDUFA 2*
Mean	183.6	409.8
Variance	2786.3	15135.7
Observations	5	5
Hypothesized Mean Difference	0	
df	5	
t Stat	-3.778194977	
P(T<=t) one-tail	0.006456895	
t Critical one-tail	2.015048373	
P(T<=t) two-tail	0.012913789	
t Critical two-tail	2.570581836	

This statistical analysis supports that the number of withdrawals is significantly different between the first authorization of GDUFA and the first reauthorization. This increase can be attributed back to changes made in the GDUFA II commitment letter. For GDUFA II, the FDA offered a partial refund of the application fee if the application was withdrawn before the applicant received notice of receipt by the FDA. This provided an incentive for companies to withdrawal an incomplete or flawed application before the FDA began the review process. This change not only benefited the industry by issuing a partial refund, but it was a major improvement from a regulatory standpoint. Since companies would withdrawal their applications before review without concern for serious financial loss, the FDA saves a significant amount of time, money, and manpower that would have gone towards reviewing an incomplete or flawed application.

Theoretically, with this new withdrawal incentive, we would see an increased number of first cycle approvals. Without the first cycle approval numbers from GDUFA I being readily available, it is impossible to make any conclusions on whether first cycle approval numbers

increased or if the withdrawal incentive supported that increase. The first cycle approvals were a part of the activities reporting for GDUFA II. These values are reported as percentages of the number of original ANDA approvals in **Figure *8***.

Figure 8 Percent of First Cycle Approvals by Fiscal Year During GDUFA II



In all FYs in GDUFA II, the first cycle approvals were less than a quarter of approvals. While this research study does not currently contain the individual data on first cycle approvals for each FY under GDUFA I, we are aware that the average percentage of first cycle approvals was 9%. We are also aware that this value was closer to 1% before the first GDUFA authorization. The average percent of first cycle approval was approximately 16%. From the start of the first authorization of GDUFA we have seen a sixteen-fold increase in the average percentage of first cycle approvals. Additionally, there was an almost two-fold increase in the average percentage of first cycle approvals from GDUFA I to GDUFA II. Not only have these percentages increased, but the number of approvals they represent has increased because the number of total approvals each FY has increased under GDUFA I and GDUFA II.

While the effort to make the generic application process more financially accessible to companies of all sizes is important, there are a few considerations that should be made regarding the grouping of these programs. A small program has no more than five ANDAs, a medium program has between six and nineteen, and a large program has at least twenty. Looking at the original tier sizes, they look reasonable. That is until you look at the companies that are dominating the market. Looking at the companies with the highest frequencies of approvals each FY, the large companies that corner the market can have as many as 1500 ANDAs. In **Table *6*Table *6* Top Twenty Applicant Companies with the Highest Number of ANDA Approvals in FY 2018**, Mylan Labs LTD received 60 ANDA approvals in FY 2018. Under GDUFA II, a large company is one that has at least twenty ANDAs claimed to its program. Each year these companies receive approvals on ANDAs that are equivalent to one or multiple large companies.

Table 6 Top Twenty Applicant Companies with the Highest Number of ANDA Approvals in FY 2018

Applicant Company	ANDA Approvals FY18	GDUFA Tier FY18	Claimed ANDAs FY18
MYLAN LABS LTD	60	Large	697
AMNEAL	55	Large	159
AUROBINDO PHARMA LTD	51	Large	327
ZYDUS PHARMS	43	Large	151
CIPLA	24	Large	109
FRESENIUS KABI USA	22	Large	187
TEVA PHARMS USA	21	Large	1506
STRIDES PHARMA	18	Large	18
LUPIN LTD	18	Large	207
PRINSTON INC	15	Large	49
SAGENT PHARMS INC	13	Large	53
TELIGENT	13	Medium	19

ACCORD HLTHCARE	13	Large	83
MACLEODS PHARMS LTD	12	Large	53
EUGIA PHARMA	12	Unlisted	Unlisted
CADILA	11	Medium	11
AKORN	10	Large	189
TARO	10	Unlisted	Unlisted
TORRENT	10	Large	64
GLAND PHARMA LTD	9	Large	34

Table 7 Top Twenty Applicant Companies with the Highest Number of ANDA Approvals in FY 2019

Applicant Company	ANDA Approvals FY19	GDUFA Tier FY19	Claimed ANDAs FY19
AMNEAL PHARMS CO	45	Large	303
ALKEM LABS LTD	44	Large	45
ZYDUS PHARMS	42	Large	204
SUN PHARM	34	Large	576
ALEMBIC PHARMS LTD	27	Large	63
LUPIN LTD	26	Large	226
MYLAN	25	Large	750
TEVA PHARMS USA	24	Large	1386
DR REDDYS LABS LTD	24	Large	160
TARO	21	Unlisted	Unlisted
GLENMARK PHARMS LTD	21	Large	133
APOTEX	20	Large	270
AUROBINDO PHARMA LTD	19	Large	386
EUGIA PHARMA	18	Unlisted	Unlisted
MICRO LABS	18	Medium	14
CIPLA	17	Large	125
NOVAST LABS	16	Large	42
STRIDES PHARMA	15	Large	59
ACCORD HLTHCARE	13	Large	95

NOVITIUM PHARMA	12	Small	2

Table 8 Top Twenty Applicant Companies with the Highest Number of ANDA Approvals in FY 2020

Applicant Company	ANDA Approvals FY20	GDUFA Tier FY20	Claimed ANDAs FY20
AMNEAL	29	Large	344
ZYDUS PHARMS	28	Large	250
GLAND PHARMA LTD	25	Unlisted	Unlisted
FRESENIUS KABI USA	23	Large	201
MSN	23	Medium	13
DR REDDYS	23	Large	217
ALEMBIC PHARMS LTD	21	Large	89
MYLAN	21	Large	785
SUN PHARM	21	Large	611
ALKEM LABS LTD	18	Large	66
APOTEX	18	Large	246
GRANULES	16	Medium	15
AUROBINDO PHARMA LTD	15	Large	392
STRIDES PHARMA	15	Large	69
ACCORD HLTHCARE	15	Large	108
HETERO LABS LTD III	15	Large	79
HIKMA	13	Large	508
EUGIA PHARMA	12	Unlisted	Unlisted
AJANTA PHARMA LTD	10	Large	31
CIPLA	10	Large	142

Table 9 Top Twenty Applicant Companies with the Highest Number of ANDA Approvals in FY 2021

Applicant Company	ANDA Approvals FY21	GDUFA Tier FY21	Claimed ANDAs FY21
ALKEM LABS LTD	28	Large	78

ZYDUS PHARMS	27	Large	271
DR REDDYS LABS LTD	26	Large	237
LUPIN LTD	23	Large	253
EUGIA PHARMA	22	Unlisted	Unlisted
TEVA PHARMS USA INC	21	Large	1186
GLENMARK PHARMS LTD	18	Large	158
MYLAN	17	Large	791
GLAND PHARMA LTD	16	Unlisted	Unlisted
AMNEAL	16	Large	371
SUN PHARM	16	Large	626
MEITHEAL	15	Unlisted	Unlisted
ALEMBIC PHARMS LTD	15	Large	112
AUROBINDO PHARMA LTD	14	Large	419
FRESENIUS KABI USA	14	Large	214
SANDOZ INC	13	Unlisted	Unlisted
BRECKENRIDGE	13	Large	39
ACCORD HLTHCARE	13	Large	113
STRIDES PHARMA	10	Large	103
SCIEGEN PHARMS INC	10	Large	37

Table 10 Top Twenty Applicant Companies with the Highest Number of ANDA Approvals in FY 2022

Applicant Company	ANDA Approvals FY22	GDUFA Tier FY22	Claimed ANDAs FY22
AMNEAL	38	Large	388
ZYDUS PHARMS	35	Large	290
TEVA PHARMS USA	32	Large	1093
APOTEX	28	Large	237
DR REDDYS	26	Large	255
MSN	26	Large	29
PRINSTON INC	24	Large	58

ALEMBIC PHARMS	24	Large	131
EUGIA PHARMA	21	Unlisted	Unlisted
LUPIN LTD	20	Large	260
NOVITIUM PHARMA	17	Large	36
ALKEM LABS LTD	17	Large	102
GLAND PHARMA LTD	16	Unlisted	Unlisted
MEITHEAL	13	Unlisted	Unlisted
SANDOZ INC	12	Unlisted	Unlisted
ANNORA PHARMA	12	Unlisted	Unlisted
FRESENIUS KABI USA	12	Large	215
ACCORD HLTHCARE	11	Large	124
HIKMA	11	Large	532
MANKIND PHARMA	11	Medium	7

Over all five FYs of GDUFA II, only seven of the top twenty companies (by number of ANDA approvals) were not a large company. This number was made up of six medium programs and one small program. These larger programs and companies have the ability to produce these high approval numbers for a number of reasons. Two of those being funding and infrastructure. These companies have a long and reputable history with the FDA and have the personnel expertise and infrastructure to execute these ANDAs. Another reason is the establishment of their manufacturing processes. These companies have a well-established manufacturing and quality program that supports their operation and applications. While it would be impossible for smaller, start-up companies to compete at this level, it could be more achievable if these tiers were re-evaluated and expanded.

It is widely known that smaller companies and start-up companies are often focused on novel technology and breaking into new and innovative therapeutic spaces. This kind of research and development is critical to the growth of the generic program. One of the barriers to defeating the rising cost of prescription drugs is the rapid innovation happening on the branded drug market that generic companies struggle to keep up with, such as new complex products. By re-evaluating this tier system further and providing new strategies and incentives for these innovators to make it to the approval process and to the market, the market can be impacted significantly for the benefit of consumers.

First generics are a critical turning point in the generic market. By being the first to file a complete application for the generic of a branded product, these first generics provide the first significant impact to market price. The FDA has published a list of all first generic approvals each calendar year including 2012-2022. [26] Using the Wayback archive machine the monthly reports for 2012-2015 were accessed and the monthly first generics numbers were recorded in their appropriate FY. For 2016-2022, the FDA published the list for the year as a whole. This list included the dates of approval which allowed for separation into their appropriate FY. These values are presented in the charts below.

Figure 9 Total Number of First Generic Approvals During GDUFA I and GDUFA II

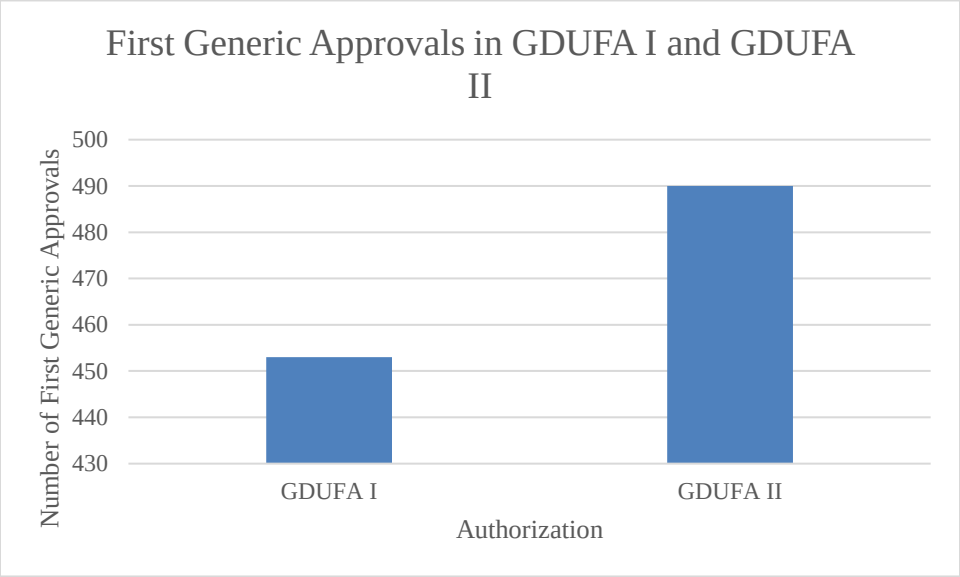
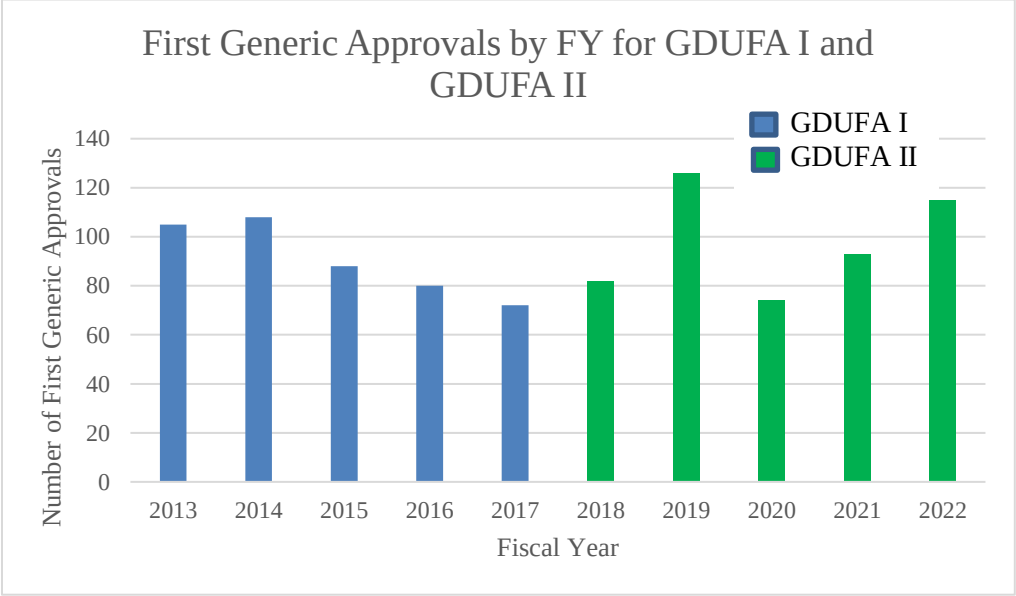


Figure *9* represents the total number of first generics approved in both GDUFA I and GDUFA II. There were only thirty-seven more first generic approvals during GDUFA II than in GDUFA I. The following figure, **Figure *10***, represents the first generic approvals by FY.

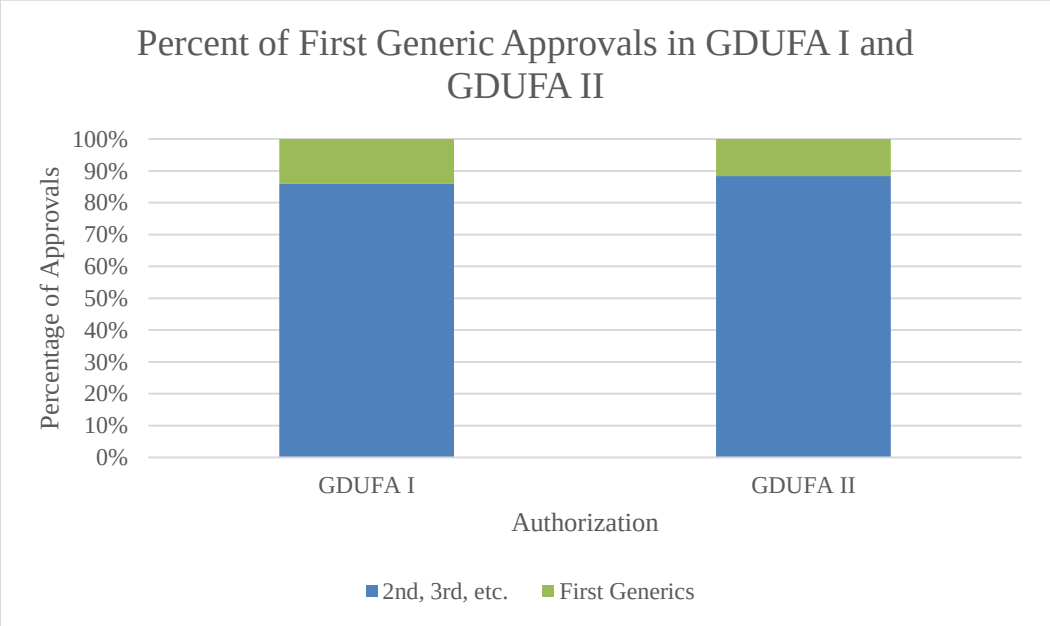
Figure 10 Total First Generic Approvals During GDUFA I and GDUFA II by Fiscal Year



Comparing the two authorizations and their first generic approval numbers, there is no discernible relationship or trend between the two groups. This is an issue that continues to plague

the generic market. The majority of approvals are made up of what are referred to as subsequent generics. This term describes any generic of a branded drug beyond the third approved product. In both authorizations, less than 15% of approvals were for first generics. Even though we observed an increase in the number of first cycle approvals by thirty-seven in GDUFA II, the larger number of overall approvals still resulted in a decrease in the percent of first generic approvals. It is also important to note that the information collected does not discern between tentative approvals and discontinued products. Therefore, the number of first generic approvals does not necessarily reflect the number of first generics available on the market.

Figure 11 Percent of First Generic Approvals During GDUFA I and GDUFA II



This area of the market is not progressing like regulators and consumers would have hoped. Part of this is due to the manufacturing and research and development barriers presented to the generic market. These processes can consume large amounts of time and money. Meanwhile, the development of a generic product that already has a first generic (or more) on the market is a simpler process. Subsequent generics can rely on well-established manufacturing

information as well as market information. Since this generic product has already been made available on the market for some time, the generic companies producing subsequent generics know what the market value of the product is going to be. First generics not only have to establish the manufacturing and quality requirements for the first generic product, but they also have to deal with the legal issues such as patent infringement of the branded product. As discussed in the introduction to the market, there are many strategies that brand companies use to prevent these first generics from reaching the market in a timely manner. These strategies eventually cost consumers billions of dollars and prevent access to critical medications.

CHAPTER 4

SUMMARY AND FUTURE DIRECTIONS

4.1 Summary

This research is still in its beginning stages. At the time of completing this study, only two authorizations of GDUFA have been completed. It is also important to consider that the COVID-19 public health emergency occurred during the timeframe of GDUFA II. During this time the FDA had a critical role in activities regarding COVID-19 tests and vaccine emergency use approvals while balancing their other responsibilities and activities. Many programs, including the generic drug program, saw a downturn in activity. Besides the FDA activities, manufacturers and applicants were also affected which slowed the pipeline of generic drug approvals overall. Therefore, when we look at this data, it may not be representative of actual trends, and it will take more time to understand the pandemic's effects on the program. The

generic drug program and market are immensely complex. As this program moves forward it will be essential to follow the subsequent reauthorizations, their performance metrics, and the state of the generic drug market.

While this research has a limitation of time, it is still important to see the beginning stages of the program and what changes that are already making an impact even if they have only been in place for four years. This research was able to highlight some improvements that have already been shown to have had an impact on the generic drug program such as the increase of withdrawals with the addition of a refund incentive. With the time and work saved by the FDA by preventing them from spending time on an incomplete application, application reviewers can spend their time on complete applications and get generics approved for the market.

New and more detailed metrics were recorded and reported for GDUFA II. It will be both interesting and important to follow these metrics as time passes into GDUFA III. This is especially true for metrics such as first cycle approvals and company size. According to the GDUFA III reauthorization, the program tier sizes have remained the same. Therefore, it is unlikely that we will see any significant increase in the appearance of medium and small companies in the top twenty companies by number of approvals within the next five years.

The newest reauthorization of GDUFA (GDUFA III) also came with the promise of more funding. As the FDA relies primarily on government funding and user fees, additional resources will contribute to acquisition of additional review staff. Having a more robust staff will allow for an increased number of applications being simultaneously evaluated. It will also increase the availability of FDA staff to meet with applicants and answer questions regarding applications. This should increase efficiency in the review process as well as increase the number of complete and flawless applications.

Even if all of the strategies put forth by GDUFA and guidance by FDA were executed efficiently, there are other forces within the marketplace that contribute to the lagging market competition. While consumer benefit is the ultimate goal of the generic drug program, this is still a for-profit industry where a lot of investment money and sales opportunity are on the line. It is not uncommon for companies to exploit loopholes and strategies in the system in order to protect their investment. Without effective monitoring, these strategies cannot be prevented, and the patients and consumers will be left to pay the price.

4.2 Future Directions

GDUFA was reauthorized for the second time for FYs 2023-2027. The reauthorization commitment letter details the changes and updates to the program. The drug market is incredibly complex, and generic drugs are no exception. It would be beneficial to continue evaluating the effectiveness of these new changes and improvements to the program. This most recent commitment letter included a specific section for performance metrics. [27] This section has significant importance given the inconsistent metrics that have been recorded and reported over the periods of GDUFA I and II.

For the goals and purposes of this research, it was decided to focus on original ANDA approvals. It would be interesting to evaluate the supplemental ANDA approvals available through Drugs @ FDA. These supplemental applications are categorized based on the change the company is making to the product. It would be beneficial to evaluate the types of supplemental applications that are the most common or reoccurring. Using this information, both the FDA and future applicants can put new processes in place to prevent any need for these moderate changes if they relate to a product that is seeking market approval.

Market competition that drives prices down is the ultimate goal of GDUFA and the generic drug program as a whole. Approximately 75% of all approved drugs since the inception of GDUFA are available on the market at the time of data collection. The rest of these products have been discontinued. For these discontinued products it would be valuable to determine the reason for these products being taken off the market. Using this information regulators could provide strategies or guidance on any preventable issues that could require a drug's removal from the market. On the applicant's end, any foreseeable issue with the marketed product could be mitigated.

The FDA consistently updates its list of off-patent and off-exclusivity drugs.[7] It would be interesting to evaluate these drugs and see any trends in the dosage forms or routes of administration. As was discussed in the introduction, it is very common for complex generics to have all patents and exclusivities expired and still remain on the market without any competition. Therefore, it is likely that these complex products make up a large portion of these lists. This group of products represents a significant hurdle to generic manufacturers and the FDA can only provide guidance on how to go about the scientific and regulatory processes. It is up to the generic manufacturers to invest the time and money into the process of making a complex generic product and applying for market approval. As the generic program continues to grow, expand, and improve, it will be critical to develop strategies and incentives for the development of these products.

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