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Evaluating Fda Generic Approval After 2017 Agency Initiatives

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Abstract

Importance: Generic drugs play an essential role in the US healthcare system, providing less costly alternatives to branded drugs that are equally effective and safe. The US Food and Drug Administration (FDA) regulatory policies influence the standards for generic drug approval. In 2017, the FDA instituted several initiatives to promote generic drug approval, particularly focused on those with limited competition.

Objective: To determine whether the initiatives begun by FDA in 2017 were associated with greater numbers of approvals of generic drugs with limited generic competition and histories of drug shortage.

Study Sample and Design: We conducted a cross-sectional study of new drug applications (ANDA) approved by FDA during two one-year periods: July 1st, 2016 to June 30th, 2017 (before the initiatives) and January 1st, 2018 to December 31st, 2018 (after the initiatives). ANDAs were also characterized on the basis of their initial approval year, priority review status and orphan designation status for the original new drug, World Health Organization (WHO) essential medicine status, therapeutic area, drug complexity.

Main outcomes and measures: We determined (1) generic competition at the time of ANDA approval; (2) history of drug shortage during the five years before ANDA approval.

Results: A total of 1,410 ANDAs were identified, 661 prior to the FDA's initiatives, 749 afterwards. Overall, there were 336 (23.8%) ANDAs originally approved with priority review status, 183 (13.0%) ANDAs previously approved with orphan drugs status. 262 (18.6%) ANDAs were listed as essential medicine by WHO, and 265 (18.8%) generic approvals were categorized as complex generic drugs. In the pre-period, 234 (35.4%) of the ANDAs approved were determined to have limited competition (≤3 ANDAs), as compared to 237 (31.6%) afterwards (p=0.14). Similarly, 242 (36.6%) of the ANDAs approved in the pre-period had been in shortage during the five years before ANDA approval, as compared to 282 (37.7%) afterwards (p=0.69). In multivariate analysis, approval of generics with limited competition was significantly less likely during the period after the FDA's initiatives when compared to before (OR=0.76; 95% CI, 0.60-0.97; p=0.02), but there was no significant difference in the approval of generics with histories of drug shortage (OR=1.09; 95% CI, 0.86-1.38; p=0.46).

Conclusion and relevance: The FDA's initiatives in 2017 to promote generic drug approvals had limited impact on the approval of ANDAs for drugs that lacked generic competition and had histories of drug shortage. Additional efforts are needed to promote approval of generic drugs with limited competition.

Introduction

Generic drugs play an essential role in the US healthcare system, providing less costly alternatives to branded drugs that are equally effective and safe. The 1984 Hatch-Waxman Act formalized the generic approval pathway, which aims to limit patent terms of the brand-name drugs and promote generic approvals. Generic drugs accounted for 90% of total prescriptions in the United States in 2017[1]. Despite this, there has been evidence that the generic drug market was experiencing insufficient competition and long approval times, with a backlog of applications, potentially limiting cost savings to patients and the healthcare system[2,3]. In response, Congress and the US Food and Drug Administration (FDA) have continued to promote policies to foster generic drug approvals. 971 ANDAs were approved or tentatively approved in FY 2018, up from 937 ANDAs in FY 2017 and 835 ANDAs in FY 2016[4].

As a marker of competition in the generic drug market, since 2016, the FDA has been tracking and publicly reporting rates of first generic drug approvals[5] , which is the first generic drug marketed, and therefore breaks the monopoly of brand name drugs. Research has shown that 1 generic manufacturer only lowers the price of the brand name drug by 13%, while significant savings are achieved only after 3-4 generic manufacturers are available on the market[6]. Another study demonstrated high market competition level (at least 2 manufacturers) was associated with price decrease over time[7]. This showed that the first generic approval alone, although symbols a good start, may not be enough to achieve significant savings. Having multiple generic drug manufacturers is important not only for drug prices, but also to prevent drug shortages. Previous research has shown that drug shortages are internally related to the price increase and may result in disruptions in hospitals and pharmacies operation[2,8]. In addition, research suggested the number of manufacturers was associated with market status, and prioritizing approval of drugs with 3 or fewer generics were necessary[9].

In 2017, the FDA established a series of initiatives to promote the approval and availability of generic drugs. First, the agency successfully negotiated the authorization of GDUFA II with the pharmaceutical industry, which provided the FDA with more financial resources to increase review capacity and commit to approval timelines. Secondly, FDA Commissioner Scott Gottlieb introduced the Drug Competition Action Plan (DCAP) which explicitly acknowledged the importance of approving drugs with less than three generics by prioritizing their review by the agency when ANDAs are submitted[10]. Lastly, as a part of the FDA Reauthorization Act (FDARA), the FDA was able to expedite the ANDA review process if there is only one approved drug in the active section of the Orange Book[11], which is a publication that identifies drug products approved by the FDA.

A recent Pew report evaluated FDA's achievement during GDUFA I, and found that although approval numbers increased during 2012-2017, the proportion of generic approvals with limited competition did not increase[12]. The report also suggested that new initiatives in 2017 had more focus on drugs with limited competition. In order to better understand the early impact of the FDA's 2017 initiatives, this study characterized generic drug approvals by the FDA during two one-year time period between 2016-2018. The objective of this study was to determine whether the FDA's efforts were associated with an increase in the number of generic drug approvals with limited generic competition and that had previously been in shortage. Results from this study will inform future regulatory and policy efforts to promote approval of generic drugs with limited competition.

Method

Sample construction

We used the Drugs@FDA database to identify all abbreviated new drug applications (ANDA) approved by FDA in two one-year time periods: July 1st, 2016 to June 30th, 2017 (prior to FDA's initiatives) and January 1st, 2018 to December 31st, 2018 (after the FDA's initiatives). We excluded all ANDAs approved between July 1st, 2017 and December 31st, 2017 as a wash-out period to allow the FDA's initiatives to take effect. We excluded tentative approvals, biological treatments, over-the-counter products, and discontinued products.

Generic competition

Our primary outcome measure was the level of generic competition at the time of approval. For a specific generic drug, we used the Drugs@FDA database to identify all drugs with the same active pharmaceutical ingredient and dosage form of that drug. We then counted the number of ANDA approved at the time of approval for a generic drug, excluding discontinued products, tentative approvals, and over-the-counter products. To determine the level of generic competitions, we categorized ANDAs as having limited generic competition if there were 3 or fewer generic drug manufacturers with FDA approved ANDAs at the time of the ANDA approval; ANDAs with 4 or more generic drug manufacturers were not considered to have limited competition. This approach is consistent with the FDA consideration, which was outlined in the Drug Competition Action Plan, that the FDA will expedite the review of generic drug applications until there are three approved generics[10].

History of drug shortage

Our second outcome measure was history of drug shortage during the five years before ANDA approval. We used the University of Utah's Drug Information Service drug shortage database. The database adopts the American

Society of Health-System Pharmacists (ASHP, http://www.ashp.org/ shortages) definition of shortage, which is defined as a supply issue that affects how a pharmacy prepares or dispenses a drug product that influences patient care when prescribers must use an alternative agent. The Drug Information Service receives voluntary reports of drug shortages, which are confirmed by clinical pharmacists, who contact all manufacturers of a reported drug to determine if there is a national shortage. A shortage is considered resolved when all manufacturers have all drug products available, have discontinued their products, or the FDA reports on its website that the shortage has been resolved.

For each drug in the sample, we searched for any shortage for the same active ingredient and dosage form in the database that lasted longer than 1 month within the previous five years of the approval.

Covariates of Interest

Initial approval year

We determined the initial approval years for each drug in the sample. We used the Drugs@FDA database to search for the first drug approved for the same active ingredient and dosage form. The year of approval for the first drug was considered the initial approval year.

Priority review

We used the Drugs@FDA database to determine whether the initial new drug application for an ANDA received priority review status. Priority review is granted to drug applications by the FDA and usually reflects that the new drug presents significant improvements in the safety or effectiveness compared to standard treatments[13]. Upon giving the status, the FDA will commit to complete the review in 6 months compared to the standard review time of 10 months.

Orphan drug status

Drug makers can seek their developing drugs to receive orphan designations from FDA, as long as the drugs intended to treat diseases which affect less than 200,000 people in the US[14]. Orphan designation database is publicly available[15], and we used the database to determine whether the NDAs for a generic drug received orphan designations. The orphan designation is based on indications, and one drug can receive multiple designations for different indications. We consider the drug has orphan status in this study as long as the drug has a designation for any indication.

WHO essential medicine status

WHO periodically publishes a list of Essential Medicine, which includes medicines that satisfy the priority health care needs of the population[16]. The list is updated once every two years, and the most current version is published in 2017. Medicines on the list are fundamental and should always be available with the appropriate dosage forms, adequate quantity, affordable price, and proper quality. We recorded drugs in our sample that are on the essential medicine list, based on active ingredients.

Therapeutic area

Drugs in our sample were categorized based on the WHO Anatomical Therapeutic Chemical Classification System (ATC code)[17]. We determined the therapeutic area based on the active ingredient and dosage form listed in the ATC code system. To simplify categorization, we further grouped the ATC codes into eight therapeutic areas: alimentary tract and metabolism, cardiovascular system, dermatologicals, genito-urinary system and sex hormones, infectious disease, hematology-oncology, nervous system and sensory organs, others. If there is more than one ATC codes correspond to one drug, we will refer to the initially approved indication for the active ingredient of that drug.

Complexity

We determined if the generic drug is considered a complex generic, based on a previous study[3]. The criteria include whether a specific attribute make it difficult to manufacture the drug or establish bioequivalence, such as complex active pharmaceutical ingredients such as peptide, polymer, naturally-derived complex mixtures, metal complex; complex formulations such as liposomes, emulsions, gels; complex routes of delivery such as topical or ophthalmic; complex dosage forms such as long-acting injectable or transdermal; complex drug-device combination such as autoinjector. One author (KJ) independently reviewed each drug in the sample, and inconclusive drugs were classified by another (RG).

Statistical Analysis

We used descriptive statistics to characterize the ANDAs approved by the FDA in both time periods, using $\chi 2$ tests to determine if there were differences in the characteristics of the two samples. We then used the $\chi 2$ test to assess whether there were differences in approval of ANDAs with limited generic competition and with a history of drug shortage during the five years before ANDA approval before and after the FDA initiatives. Next, we conducted independent nominal logistic regression analyses for each outcome measure as the binary dependent variable, time period (before/after FDA initiatives) as the main independent variable, initial approval year (categorical), priority review (binary), orphan drug status (binary), WHO essential medicine status (categorical), therapeutic area

(categorical), complexity (binary) as covariables. We reported odds ratios (OR) with 95% confidence intervals for each of the parameters; all characteristics were kept in the model, because they were considered highly relevant to the outcomes. All statistical tests were 2-sided and used a P value of 0.05 for significance. We created and cleaned the sample with SAS 9.4 (SAS Institute Inc) and Excel 2019 (Microsoft Corp), and used JMP Pro 13 (SAS Institute Inc) to conduct all the statistical analyses.

Result

During the 2 periods examined, a total of 1,410 ANDAs were approved by the FDA, covering 473 different active ingredients (Table 1). There were 661 ANDA approvals during the 1-year period before the agency's initiatives and 749 ANDA approvals during the 1-year period afterwards. Among these ANDAs, the most common original drug initial approval year was 1995-2004, including 302 (45.8%) before agency initiatives and 299 (39.9%) afterwards. Priority review for the original drug accounted for 135 (20.4%) ANDAs before agency initiatives and 201 (26.8%) ANDAs afterwards. Orphan drug status was less common, with 62 (9.4%) ANDAs before agency initiatives and 121 (16.2%) ANDAs afterwards. Before the FDA's initiatives, 111 (16.8%) were included in the WHO essential medicine list, 151 (20.2%) afterwards. Drugs for nervous systems and sensory organs were most prevalent in both the first time period (173 [26.2%]) and the second time period (151[20.2%]), followed by cardiovascular drugs (102[15.4%] vs. 99[13.2%]) and infectious disease drugs (69[10.4%] vs. 111[14.8%]). Complex generic drugs accounted for 118 (17.9%) ANDAs before the FDA initiatives and 147 (19.6%) ANDAs after the initiatives.

There were significant differences between the ANDAs approved before and after the FDA's initiatives, as more ANDAs were for drugs initially approved via priority review (p=0.005) and with an orphan designation (p<0.001) after the FDA's initiatives, and there were similarly changes in the therapeutic areas for which the drugs were initially approved; there were no significant differences in initial approval year (p=0.17), WHO essential medicine status (p=0.10) and drug complexity status (p=0.39).

Generic competition

Before the FDA's initiatives, 234 (35.4%) of the ANDAs approved had limited competition (≤3 generics), compared to 237 (31.6%) ANDAs afterwards (p=0.14) (Table 2). In multivariable analysis, controlling for priority review status, orphan drug status, initial approval year, WHO essential medicine status, therapeutic area and drug complexity, approvals for ANDAs with limited competition were significantly less likely after the FDA's initiatives when compared to before (OR=0.76; 95% CI, 0.60-0.97; p=0.02) (Table 3).

History of drug shortage

Before the FDA's initiatives, 242 (36.6%) of the ANDAs approved had experienced a shortage in the previous five years, compared to 282 (37.7%) afterwards (p=0.69) (Table 2). In multivariable analysis, there was no significant difference in approvals for ANDAs with a prior history of drug shortage (OR=1.09; 95% CI, 0.86-1.38; p=0.46) (Table 4).

Discussion

We conducted a cross-sectional study of 1,410 ANDAs approved before and after the FDA initiatives in 2017. Our primary result indicated that ANDA approvals for drugs with limited competitions were less likely after the initiatives, while no difference was found in approvals for drugs with prior drug shortage history. Our findings suggest that the FDA's initiatives, during the early period right after they went into effect, have not been effective in promoting the approval of generic drugs with limited competition. The agency should continue to foster approvals for generic drugs with limited competition, as well as generic drugs with prior shortage history.

Over the past 5 years, drug pricing has been the focus of significant public attention. High-profile incidents like Turing Pharmaceuticals raising the price of Daraprim by over 50 times or Marathon hiking the price for Duchenne Muscular Dystrophy drug provoked society's thought about drug pricing and competition[18,19]. Adequate generic competition is among the few ways to bring down drug prices and prevent "drug ventures" to raise drug prices without reason. In response, prioritizing generic approval has been the center piece of the FDA's agenda. Former commissioner Scott Gottlieb has been vocal about promoting generic approvals[20]. In addition, the Congress has also provided important support, both through legislations like FDARA, which provided new tools to the agency such as priority review and market exclusivity for drugs with limited competition, as well as bipartisan political support to the FDA. It is crucial that the agency continue toward promoting approvals for drugs with limited generic competition, especially since our study found that it was less likely for such drugs to receive approval in 2018. The agency could increase transparency around the status of priority reviews, for example by publishing a list of generic approvals that have received priority review from limited generic competition and disclosing number of applications involved with limited generic competition monthly or quarterly.

At the same time, we also need to recognize that the drug approval is only one piece of the puzzle toward drug availability. Recent report from Kaiser Family Foundation found 43% of the generics approved since 2017 were not marketed till January 2019[21]. This means the effect of generic drug approvals may be understated if few approvals

lead to an actually marketed and available generic drug as expected. Meanwhile, drug shortages also represent a major influence in availability as its limited patient and physician choice of drugs, have ripple effect to put strain on other manufacturers and even impact supply of substitution drugs. Market supply and demand should be the foundation of economy, and drug shortages could mean market failure. It is therefore important for the FDA to take actions, not only in notification system currently in place, but also looking into prioritizing approvals for drugs with constant shortage issues. New manufacturers could bring in new supplier for active ingredients, new manufacturing site for drugs, and at minimum companies that show interest in making the drugs. The agency could take previous shortage history into consideration, and prioritizing reviews for those generics with the most shortage occurrences and durations.

Limitations

This study has important limitations to consider. First, we only examined generic approvals, but many generic drugs secure approval by the FDA but the ANDA sponsor does not bring the product to market after approval. We had no data for the actual marketing status, so the impact of the approvals for limited competition generics was not well understood. Second, while we focused on aspects of the generic drug market that have been explicitly mentioned by the FDA as generic market factors that the agency's initiatives would address, including competition level and history of shortages, there are other aspects we did not examine, such as price.

Conclusion

In 2017, the FDA established a series of initiatives to promote the approval and availability of generic drugs, particularly those with limited competition. Our analysis of the early impact of these initiatives found that they had limited impact on the approval of ANDAs for drugs that lacked generic competition and had histories of drug shortage, as approvals for generics with limited competition were actually less likely. Additional efforts are needed to promote approval of generic drugs with limited competition.

Appendix

Table 1. Unadjusted associations between sample characterics and study timeframes

Sample Characteristic	**7/2016 – 6/2017 (N/%)**	**1/2018 – 12/2018 (N/%)**	**P value**
Initial Approval Year			0.17
Before 1984	131 (19.8)	168 (22.4)	
1984-1994	104 (15.6)	123 (16.4)	
1995-2004	302 (45.8)	299 (39.9)	
2005-2015	124 (18.8)	159 (21.2)	
Priority Review			0.005
Standard	526 (79.6)	548 (73.1)	
Priority	135 (20.4)	201 (26.8)	
Orphan Drug Status			<0.001
Standard	599 (90.6)	628 (83.8)	
Orphan	62 (9.4)	121 (16.2)	
WHO Essential Medicine			0.10
No	550 (83.2)	598 (79.8)	
Yes	111 (16.8)	151 (20.2)	
Therapeutic Area			0.004
Alimentary tract and metabolism	54 (8.2)	73 (9.7)	
Cardiovascular system	102 (15.4)	99 (13.2)	
Dermatologicals	44 (6.7)	72 (9.6)	
Genito-urinary system and sex hormones	63 (9.5)	54 (7.2)	
Infectious disease	69 (10.4)	111 (14.8)	
Hematology-oncology	69 (10.4)	96 (12.8)	
Nervous system and sensory organs	173 (26.2)	151 (20.2)	
Others	87 (13.2)	93 (12.4)	
Complexity			0.39
Non-complex	543 (82.2)	602 (80.4)	

Complex	118 (17.9)	147 (19.6)

Table 2. Unadjusted associations between outcome measures and study timeframes

Sample Characteristic	**7/2016 – 6/2017 (N/%)**	**1/2018 – 12/2018 (N/%)**	**P value**
Generic Approvals at Launch			0.14
1-3 Approvals	234 (35.4)	237 (31.6)	
>4 Approvals	427 (64.6)	512 (68.4)	
Shortage within 5 years			0.69
No	419 (63.4)	467(62.4)	
Yes	242 (36.6)	282 (37.7)	

Table 3. Multivariable logistic regression model of sample characteristics associated with generics competition level

Sample Characteristic	**OR (95% CI)**	**P value**
Sample time period	0.76 (0.60,0.97)	0.02
Initial Approval Year		
Before 1984	1.00	
1984-1994	0.62 (0.42,0.94)	0.02
1995-2004	0.74 (0.54,1.03)	0.07
2005-2015	2.64 (1.85,3.77)	<0.001
Priority Review	0.88 (0.64,1.23)	0.47
Orphan Drug Status	1.24 (0.86,1.81)	0.24
WHO Essential Medicine	0.57 (0.40,0.81)	0.002

Therapeutic Area		
Alimentary tract and metabolism	1.00	
Cardiovascular system	0.81 (0.49,1.35)	0.42
Dermatologicals	1.30 (0.75,2.27)	0.35
Genito-urinary system and sex hormones	0.96 (0.55,1.67)	0.87
Infectious disease	1.35 (0.80,2.28)	0.26
Hematology-oncology	1.27 (0.76,2.14)	0.36
Nervous system and sensory organs	0.67 (0.42,1.07)	0.09
Others	0.88 (0.53,1.46)	0.62
Complexity	0.88 (0.65,1.19)	0.41

Table 4. Multivariable logistic regression model of sample characteristics associated with prior drug shortage history

Sample Characteristic	**OR (95% CI)**	**P value**
Sample time period	1.09 (0.86,1.38)	0.46
Initial Approval Year		
Before 1984	1.00	
1984-1994	0.83 (0.57,1.21)	0.33
1995-2004	0.51 (0.37,0.70)	<0.001
2005-2015	0.30 (0.20,0.44)	<0.001
Priority Review	1.06 (0.76,1.46)	0.73
Orphan Drug Status	1.14 (0.78,1.66)	0.51
WHO Essential Medicine	2.38 (1.71,3.33)	<0.001
Therapeutic Area		
Alimentary tract and metabolism	1.00	
Cardiovascular system	3.33 (1.94,5.73)	<0.001

Dermatologicals	0.51 (0.25,1.05)	0.07
Genito-urinary system and sex hormones	2.02 (1.10,3.71)	0.02
Infectious disease	2.88 (1.66,5.00)	<0.001
Hematology-oncology	3.01 (1.72,5.29)	<0.001
Nervous system and sensory organs	5.12 (3.07,8.54)	<0.001
Others	3.55 (2.05,6.13)	<0.001
Complexity	1.04 (0.77,1.39)	0.80

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