

Research Report

Marketing of First Generic Drugs Approved by U.S. FDA
from January 2010 to June 2017

November 2021

The FDA logo is a white square containing the letters "FDA" in a bold, blue, sans-serif font. The logo is positioned in the bottom right corner of the page, set against a background of a dark blue gradient with a pattern of light blue dots of varying sizes and opacities, creating a textured, wave-like effect.

Research Report

Marketing of First Generic Drugs Approved by U.S. FDA from January 2010 to June 2017

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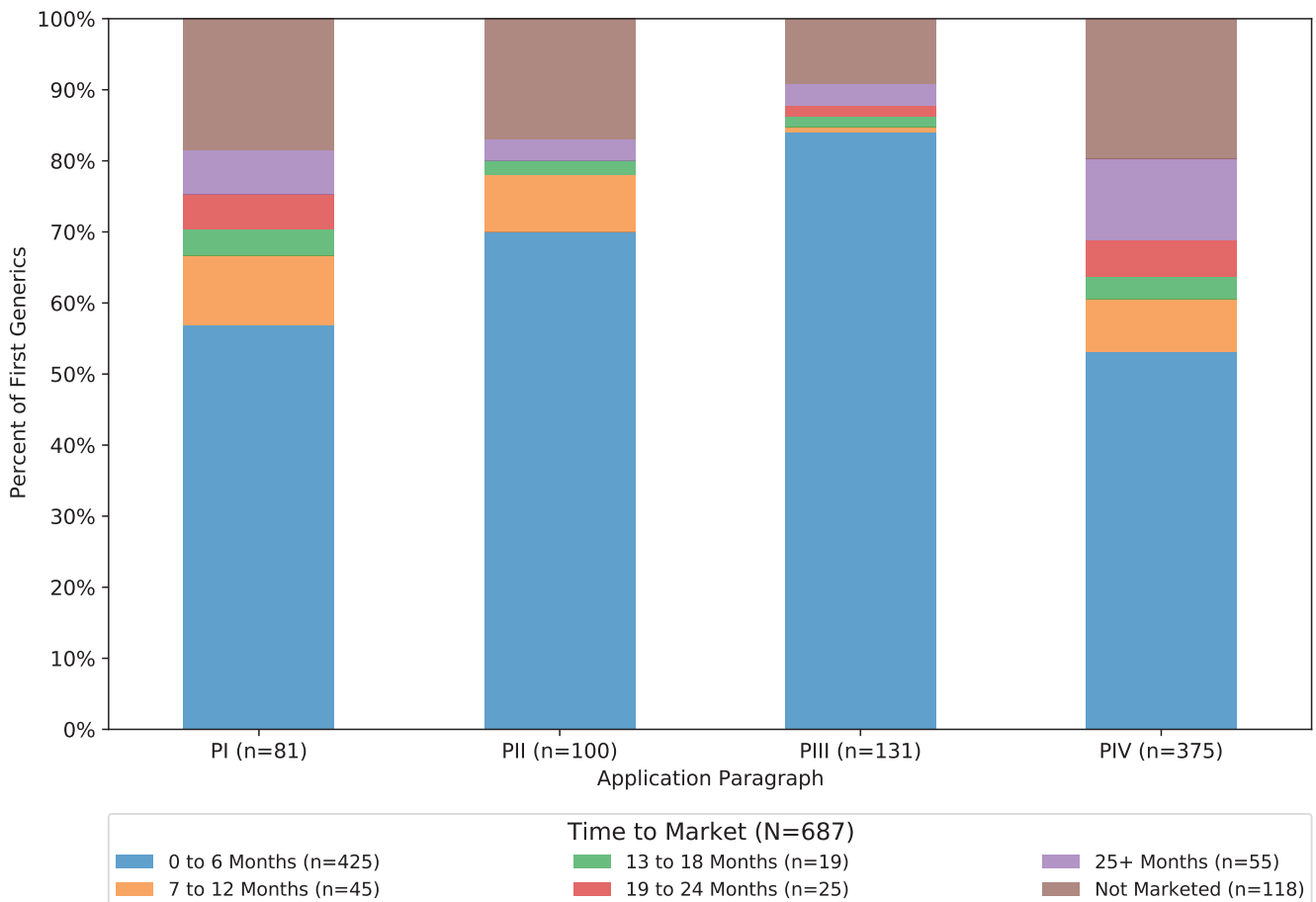
EXECUTIVE SUMMARY

In 1984, U.S. Congress passed the Hatch-Waxman Amendments with the goal of facilitating the availability of prescription generic drugs and thereby decreasing drug costs. A key incentive in this law is the availability of 180 days of marketing exclusivity to certain “first generic” applicants who expose themselves to the risk of patent litigation to compete with their branded counterparts. If 180-day exclusivity applies, the 180-day exclusivity clock starts when the first generic applicant starts marketing (i.e., selling) the drug, not when it is approved by FDA or when the patent issues are settled.

It was assumed that the promise of 180 days of marketing exclusivity would not only motivate generic drug manufacturers to compete for “first generic” status and to challenge patents, but would also motivate these manufacturers to get their generic drugs to market quickly in order to reap profits as soon as possible. To test this assumption, this study reviewed 687 first generics approved by the FDA from 2010 to mid-2017 to assess how fast first generic drugs begin marketing.

Of the 687 first generics, 375 submitted paragraph IV (PIV) certifications challenging patents on the branded drugs in an effort to introduce generics into the market faster than they otherwise could. However, this study found that among these 375 first generics, only 53% were marketed within 6 months of approval, and about 69% had marketed within two years following FDA approval (see **Executive Summary Figure**). Further, of the 375 first generics with PIV certifications, 54% (204) were eligible for exclusive marketing for 180 days at approval. Among these 204 first generics with exclusivity, only 50% had marketed 6 months after approval, and about 70% had marketed two years after FDA approval.

Executive Summary Figure: Marketing of FDA-approved first generics by paragraph certification



The marketing rate was lower yet among PIV first generics for which the branded drug company and the generic drug company settled litigation (as opposed to litigation being decided upon the merits by the courts) – in this group only 38% marketed within six months, and 57% marketed within two years of FDA approval. In contrast, among first generics for which the litigation was decided on the merits by courts (instead of a settlement between the companies), the marketing rate was 65% within six months and 78% within two years of approval.

As discussed in more detail in the “Discussion” section, below, an interplay of dynamics between litigation outcomes and business decisions may account for these unexpected results. In certain instances, settlement of patent litigation between the companies may result in agreements that delay marketing of generic drugs. Such agreements may result in some generic applicants not marketing the first generic, effectively “parking” the exclusivity and preventing other generics for the same branded drug from coming to market. Addressing these outcomes, which undermine competition, may require U.S. Congress to reexamine the statutory provisions governing patent challenges and 180-day exclusivity.

The following report describes how we did the study, provides our detailed results, and includes a discussion of the potential implications.

BACKGROUND

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) aimed to strike a balance between protecting innovation while increasing competition, by using exclusivities and patent extensions to protect innovation and creating the modern abbreviated new drug application (ANDA) approval pathway to facilitate market entry of lower-cost generics.^{1,2} It also created a way for generic applicants to challenge patents on the branded product via litigation prior to ANDA approval, and an incentive for the first applicant(s) to do so. Under the law, if there are patents listed by the branded drug applicant in FDA's "Orange Book," the generic drug applicant must address each patent by "certifying" to the patents when it submits an ANDA with one of four types of certifications referred to as Paragraph I (PI), Paragraph II (PII), Paragraph III (PIII), or Paragraph IV (PIV) certifications.³ The PIV certification indicates to FDA and the brand drug sponsor the generic applicant's intent to challenge one or more patents listed for the brand drug, after which patent litigation may be commenced by the brand application holder (see **Figure 1** for a simplified process). In exchange for taking on the risk of litigation to challenge patents that might otherwise delay generic competition, the first generic applicant(s) to provide a PIV certification could be eligible for 180 days of exclusive marketing in the United States (U.S.).^{4,5} (*See Supplement Section I for a detailed discussion of first generic regulatory pathways.*)

The result of the Hatch-Waxman Amendments is a generic drug market that currently accounts for 90% of dispensed prescriptions in the U.S. and that offers tens of billions of dollars in savings annually as a result of the lower prices charged for generic drugs relative to their branded counterparts.⁶⁻⁹ Further, the congressionally mandated Generic Drug User Fee Amendments, which provide FDA with industry user fees and industry and public stakeholders with the opportunity for input on agreed-upon performance goals, have increased resources for generic drug review and achieved reduced review times and the approval of record numbers of generic drugs.^{2,10}

However, even with the increase in generic approvals, the cost of branded prescription drug products continues to rise, and the U.S. spends more per capita on prescription medicines than any other country.^{11,12}

Barriers to generic competition have been identified as one driver of high drug costs.^{2,12-14} Of importance to decreasing drug costs is the marketing of "first generics" – the first approved generics eligible to compete with their branded counterpart.

Despite their importance to drug competition, the market dynamics of first generics remain understudied, and in particular, how the patent certification and challenge process informs the timing of first generic market entry. In this novel analysis, we seek to systematically quantify and compare the post-approval marketing trajectory of first generic drugs as informed by the four certification types, the status of patent litigations, and the impact of 180-day exclusivity and its forfeiture, where applicable.

METHODS

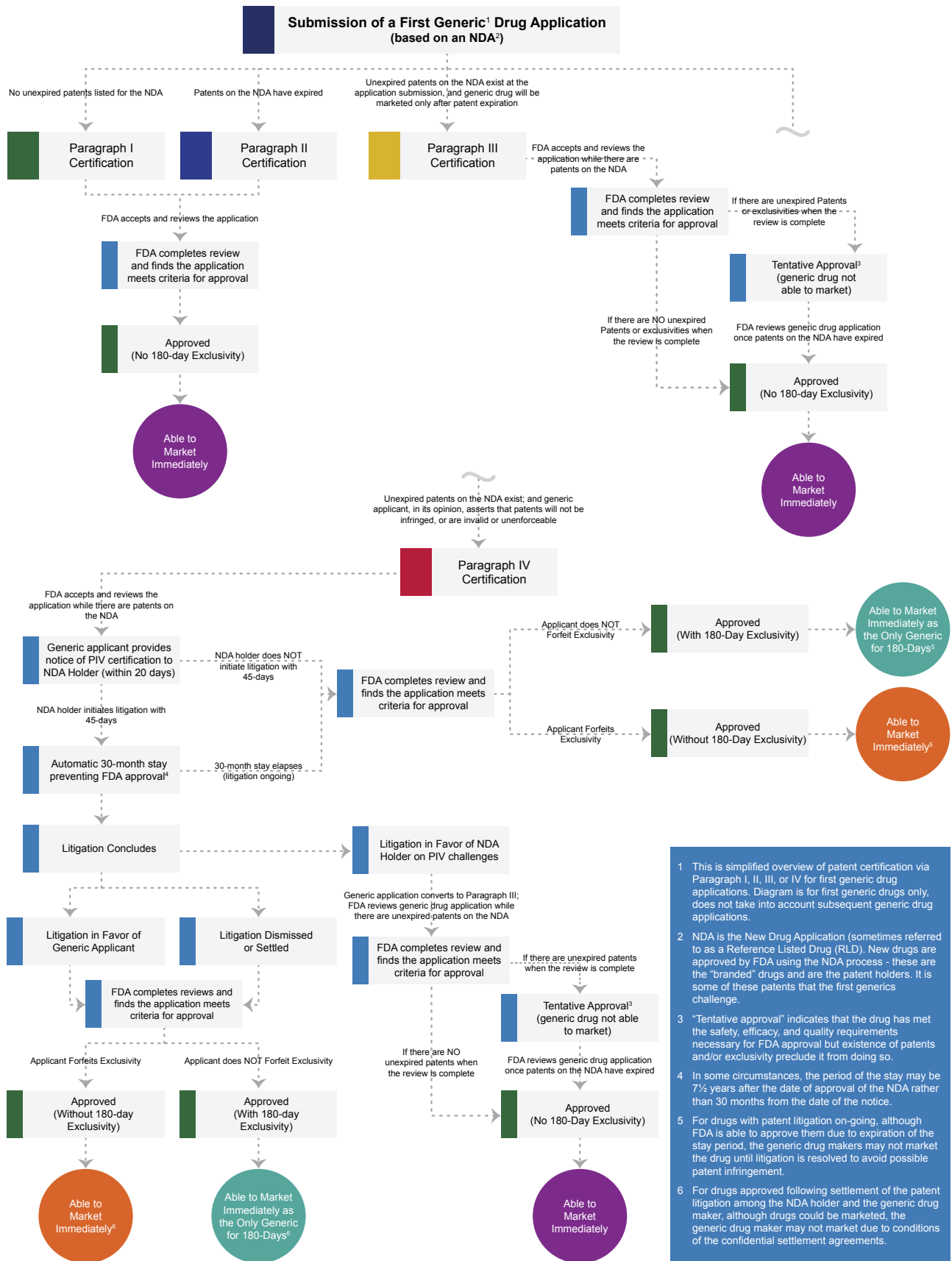
Overview

We conducted a cross-sectional study of first generic drug products approved by FDA between January 1, 2010 and June 30, 2017. Data were collected between June 2018 and January 2020.

Inclusion and exclusion criteria

We included first generic applications that were submitted to the FDA after January 1, 2004 and had been approved between January 2010 and June 2017, including drug products that were marketed but discontinued from sale at the time of analysis. We used the investigator defined "first generic action" for our analysis because one generic drug application may in some instances include multiple strengths; and sometimes, these multiple strengths are submitted and/or approved at different times during the study period (*see Supplement Section II*). We excluded over-the-counter drugs, drug products approved in supplemental ANDAs, and all applications subject to different criteria for 180-day exclusivity in effect prior to amendment by U.S. Congress in 2003.¹⁵ First generics that were at one point approved by the FDA, but for which the approval was then rescinded due to a court order (typically resulting from a brand company winning litigation against the generic company on patent challenges) were excluded from analysis. We also excluded first generic actions that may have met our inclusion criteria but were not available to the investigators at the time of data collection.

Figure 1: Simplified overview of patent certification via Paragraph I, II, III, or IV for first generic drug applications



Identification of study drugs and data collection

A list of first generic actions was compiled using FDA's public list of approved first generics and from the Orange Book.^{3,16} For each first generic action, using FDA's internal databases, we collected information on the drug product such as the established name, strength, and dosage form, as well as drug labels, patent and exclusivity information, and applicable litigation history. *See Supplement Section II for a list of all variables collected and their sources.*

We captured the paragraph certification (PI, PII, PIII, or PIV) used when the first generic was initially submitted; and because the certification can be amended at any time during the application review process, we also captured the certification at approval. For example, an application may be submitted as PI (because brand patents were not listed with FDA) but amended to PIV when the brand company later listed patents with the FDA. Or in cases where the branded companies prevail over generic companies in PIV litigation, the first generic may be converted to a PIII from the initial PIV certification if it is found that the generic applicant has infringed on the patent(s). The analyses presented are based only on the paragraph certification of the first generic application at approval.

Exclusivity status of first generics at approval

We collected data on the status of 180-day marketing exclusivity at approval of PIV first generics. At approval, these PIV first generic applicants may have one of multiple exclusivity statuses. First, the applicant could be eligible for exclusivity for the drug products reviewed in the application. Second, the applicant may forfeit the exclusivity because of failure to meet certain milestones. Third, the applicant may forfeit a part of their exclusivity and be eligible for partial exclusivity; eligibility for partial exclusivity occurs when an applicant has filed an application with multiple drug products (i.e., different strengths of the same drug product) but is eligible for exclusivity at approval only on one or some of the products.

Fourth, applicants can have a "pending" determination for forfeiture of exclusivity at approval. A "pending" status indicates that the applicant for the first generic may not have met certain milestones, for example, they may have failed to receive tentative approval (an

intermediate regulatory step to full marketing approval) within a specified period, but that FDA has not made a determination regarding whether they have forfeited eligibility. In such cases, FDA approves the first generic and informs the application holder that the product may be eligible for 180-day exclusivity, but that FDA is not making a formal determination at that time. These first applicants may market the drug and this commercial marketing would trigger the running of any purported 180-day exclusivity period. However, based on future events, FDA may need to complete a forfeiture analysis to formally determine whether the first applicant is eligible for 180-day exclusivity for the product(s) in question. FDA does not undertake a forfeiture analysis until one is necessary; FDA will undertake a forfeiture analysis if another applicant for the same drug product becomes eligible for approval but is blocked from being fully approved because of the exclusivity potential of the first applicant. In our analyses below, we refer to the exclusivity status of this group of first generics as "pending determination of exclusivity."

Fifth, the first approved applicant for a generic drug may be a "subsequent applicant" who was never eligible for the 180-day exclusivity because they were not the first to file a substantially complete application with a PIV certification, and so were not a "first applicant" under the Hatch-Waxman Amendments. These subsequent applicants may end up being the first approved applicant for a particular generic product (i.e., become the first generic) if any "first applicant(s)" for that same drug who were potentially eligible for 180-day exclusivity either forfeited or relinquished that exclusivity before being approved, or exhausted it by marketing an authorized generic under the branded drug's application,¹⁷ and the subsequent applicant's ANDA was then approved before any first applicant's ANDA.

Strategy to determine the litigation status and outcomes

For this study, only first generics with a PIV certification could have relevant litigation, with three possible outcomes: 1) generic company wins (branded drug's patent(s) found to be invalid, non-infringed, or unenforceable); 2) brand company wins (court finds the challenged patent(s) to be valid and infringed); and 3) litigation is terminated due to an agreement between the companies to settle or dismiss the case without a court decision on the merits. Because litigation can

take several years to conclude, including appeals, we captured the most recent court decision or dismissal/settlement outcome available to the investigators during data collection.

When available, we used the applicant-submitted information to determine litigation history and outcomes. However, because applicants are not required to inform FDA of all activities in legal proceedings, we used a commercial database, Docket Navigator,¹⁸ to identify or assess status of litigation on patents addressed with a PIV certification, and used Public Access to Court Electronic Records (PACER)¹⁹ to the extent possible to review court documents to determine the outcome of the cases. The available documents did not always allow us to determine the terms of settlements or dismissals and the companies are not required to submit this information to the FDA. To note, the FDA is not involved in these court cases or in any settlement discussions.

Strategy to determine marketing status of drugs

We used prescription data, obtained from IQVIA's National Prescription Audit (NPA) database, which contains information on prescriptions dispensed in retail and mail-order pharmacies, and in long-term care facilities, as a proxy for first generic marketing.¹⁸ The prescription data were available from January 1, 2006 to November 30, 2019 at the National Drug Code (NDC) level and by month and year in which the prescription was dispensed. [See Supplement Section II for details on IQVIA's NPA database and NDCs.](#)

To establish marketing, we cross-matched each drug product (at the drug strength-level) in each first generic action by comparing the labeler and product code segments of the NDC against the NDCs available in the NPA database. The NDCs were collected from applicant submissions to an internal FDA database of drug listing information and from drug product labeling contained in ANDA files.

If a first generic action had multiple products because the application included more than one strength and each was marketed at different times, we only captured the earliest marketed product to determine marketing. If multiple drug products were marketed at the same time, we selected one product for analysis.

Marketing status was determined as of November 30, 2019 – 119 months after the first and 28 months after the most recent approval action in our sample.

Sensitivity analysis on marketing of drugs

The NPA database does not contain data on drug products dispensed in hospitals and thus may lead to an underestimate of marketing of first generics, because it would not capture some injectables that are only used in hospital settings. Therefore, to assess the impact of injectables in our sample on marketing, we conducted a sensitivity analysis that excluded all injectables (including those that are dispensed in retail settings or long-term care facilities).

Limitations

First, our study is subject to differential follow up; first generics approved earlier in the study timeframe would have had more time to market compared to those approved more recently. We address this by waiting a minimum of 28 months after the latest approval in our study to determine marketing status. Second, our marketing analysis relies on matching NDCs submitted by firms, as identified from certain FDA databases, to those available in a national prescription dataset. Although we used multiple FDA sources to identify NDCs associated with first generics, it is possible that we may not have captured all relevant NDCs (e.g., all NDCs associated with re-packagers, relabelers, or private label distributors of a drug (“resellers”). The effect of this is likely minimal on our findings because we captured all NDCs that ANDA applicants indicated they were using in labeling for first generics; we believe that it is unlikely that a reseller will sell a first generic drug before the first generic applicant who secured the approval. Third, litigation is a lengthy process and often takes many years to conclude, thus litigation related to the earlier first generics in our study would have had more time to conclude compared to those approved more recently. As litigation can last multiple years, we are unable to fully adjust for this, however, given our large sample size spanning approvals over 7.5 years, the effect on the findings, if any, would be minimal. Fourth, we did not study the duration of marketing of first generics. It is possible that some of the drug products in our sample only marketed for a short time before being discontinued from sale.

Data analysis

We used descriptive statistics to analyze first generic actions and the paragraph certification in place at the time of approval. We analyzed marketing of first generics with two methods: first, the fraction that marketed at set time intervals after approval (for example, 6 months after approval) and at any time during the 119-month study period; and second, we used an adapted survival curve analysis with continuous time (in months) to show fraction of first generics marketed over the course of the full study period. We assessed the association of PIV certification, 180-day exclusivity, litigation status, and outcomes of the litigation using relative risk (RR) (chi-squared test and Fisher's exact test) with 95% confidence intervals (95% CI). Similar analyses were conducted for the sensitivity analysis in

which drug products with injectable formulations were excluded. Analyses were conducted in Python, version 3.9 (Python Software Foundation) and Stata, version 16 (StataCorp LLC).

RESULTS

Overview of findings

Our study included 687 first generic actions; at approval, 12% (81/690) were certified as PI, 14% (100) as PII, 19% (131) as PIII, and 55% (375) as PIV (**Table 1**). Among the PIV first generics, 70% (263/375) had litigation between brand and generic companies. Of the 263 first generics that were litigated, litigation for one application was ongoing at the time of this analysis, leaving 262 for further analysis. Of these 262 litigated

Table 1: Characteristics and disposition of first generics approved by FDA between 2010 and June 30, 2017

Type of First Generic Action	First Generic Actions, N (%) ¹	Marketed within 6 Months of Approval Action, n (%) ²	Relative Risk Point Estimate (95% CI) ³	Marketed at Any Time During the Study Period ⁴ , n (%) ²	Relative Risk Point Estimate ⁴ (95% CI) ³
All First Generic Actions	687 (100)	425 (62)	N/A	569 (83)	N/A
First Generic Actions by Paragraph Certification (N=687)					
Paragraph I	81 (12)	46 (57)	0.91 (0.74-1.11)	66 (81)	0.98 (0.88-1.1)
Paragraph II	100 (14)	70 (70)	1.16 (1.1-1.34)	83 (83)	1 (0.91-1.1)
Paragraph III	131 (19)	110 (84)	1.48 (1.34-1.65)	119 (91)	1.12 (1.05-1.2)
Paragraph IV	375 (55)	199 (53)	0.73 (0.65-0.82)	301 (80)	0.93 (0.87-1)
Litigation History of Paragraph IV Actions (N=375)					
Litigation	263 (70)	114 (43)	0.57 (0.48-0.68)	199 (74)	0.83 (0.76-0.91)
No Litigation	112 (30)	85 (75)		102 (91)	
Litigation Outcomes for Paragraph IV Actions (N=262)⁵					
Litigation that was Settled or Dismissed	211 (81)	81 (38)	0.59 (0.45-0.77)	156 (74)	0.88 (0.76-1.01)
Litigation with Judgment on Merits of the Patent	51 (19)	33 (65)		43 (84)	
Exclusivity Status of Paragraph IV First Generics at Approval (N=375)					
First Generics With 180-Exclusivity	204 (54)	102 (50)	0.88 (0.73-1.07)	167 (82)	1.04 (0.94-1.16)
First Generics Not Eligible for Exclusivity ⁶	67 (18)	46 (69)	1.38 (1.13-1.68)	56 (84)	1.05 (0.93-1.19)
First Generics With Pending Determination for Exclusivity ⁷	64 (17)	26 (41)	0.73 (0.53-1)	46 (72)	0.88 (0.75-1.03)
First Generics With Forfeited Exclusivity	35 (9)	21 (60)	1.15 (0.86-1.53)	28 (80)	1 (0.84-1.19)
First Generics With Partially Forfeited Exclusivity ⁸	5 (<1)	4 (80)	1.52 (0.97-2.38)	4 (80)	1 (0.64-1.55)
First Generics Approved WITH vs. WITHOUT Exclusivity (N=271)⁹					
First Generics With 180-Exclusivity	204 (75)	102 (50)	0.73 (0.59-0.9)	167 (82)	0.98 (0.87-1.11)
First Generics Without Exclusivity	67 (25)	46 (69)		56 (84)	
Injectable Formulation (N=687)					
Subcutaneous and Intravenous Injectable Formulation	100 (15)	46 (46)	0.71 (0.57-0.89)	70 (70)	0.82 (0.72-0.94)
Non-Injectable Formulation	587 (85)	379 (65)		499 (85)	

N/A: Not Applicable

1: Column percentages. Percentage may not sum to 100% due to rounding.

2: Row percentages. Percentage may not sum to 100% due to rounding.

3: For single rows, the relative risk calculations are conducted for first generics in that row for the listed category vs. all other first generics in that category. For example, under the "First Generic Action by Paragraph Certification" – the relative risk calculations are for first generics approved with each paragraph certification vs first generics approved with all other paragraph certifications (paragraph I vs the combined first generics approved with PII, PIII, and PIV).

4: Study period is from January 2010 to November 2019. These columns show status of marketing of first generics and related relative risk over the full 119-month study period.

5: Excludes one first generic for which the litigation was ongoing at the time of analysis.

6: Paragraph IV first generics that were subsequent applications (not the first filed) thus were ineligible to receive the 180-day exclusivity, but they were the first generic to be approved.

7: Paragraph IV first generics that had failed to obtain tentative approval within the specified timeframe. However, they still may have been eligible for 180-day exclusivity, and due to the lack of other generics ready for approval FDA had not had to complete a forfeiture analysis at the time the approval was issued. FDA does not undertake a forfeiture analysis until one is necessary – i.e., a subsequent applicant for the same drug product becomes eligible for approval but could be blocked from being fully approved because of the exclusivity potential of a first applicant

8: Paragraph IV first generics partially forfeited 180-day exclusivity for some products in the application.

9: This analysis only includes paragraph IV first generics that either had been found to be eligible for 180-day exclusivity on all products in the application or they were not eligible for exclusivity at approval. It excludes first generics with a "pending" determination, those that forfeited exclusivity for all products or partially forfeited exclusivity for some products in the application.

actions, 81% (211) resulted in dismissals following settlements or other agreements between the brand and generic companies, while the remaining 19% (51) had court decisions on the merits of the case. Among the PIV first generics, 54% (204/375) received 180-day exclusivity at approval. And 15% (100/687) of the first generics were for injectable formulations.

Overall, 62% (425/687) of first generics had marketed at least one drug product within 6 months of FDA approval; the percent marketed increased to 83% (569) over the course of the full 119-month study timeframe.

Status of 180-day exclusivity at approval

Among the 375 first generics approved with a paragraph IV certification, 54% (204/375) received exclusivity at approval. However, 35 first generic applications had forfeited exclusivity for all drug products in the application based on a forfeiture event that took place before approval and 5 had forfeited exclusivity for some of the drug products (i.e., partial forfeiture). The forfeiture or partial forfeiture of the 180-day exclusivity for these 40 applications occurred based on two primary reasons: failure to obtain tentative approval (an intermediate regulatory step to full marketing approval)

within a specified time period and expiration of the patent(s) that were the basis of exclusivity eligibility before the drug was fully approved (**Table 2A**).

Additionally, for 17% (64/375) of the first generics the forfeiture status was undetermined (or “pending”) at the time of approval; these were applications that had failed to obtain tentative approval within the specified timeframe. However, they still may have been eligible for 180-day exclusivity, and due to the lack of other generics ready for approval FDA did not need to complete a forfeiture analysis at the time the approval was issued. (FDA does not undertake a forfeiture analysis until one is necessary – i.e., until a subsequent applicant for the same drug product becomes eligible for approval but may be blocked from being fully approved because of the exclusivity potential of a first applicant) (**Table 2B**).

The remaining 18% (67/375) of PIV first generics were subsequent applicants who were never eligible for 180-day marketing exclusivity at approval. These 67 subsequent applications became eligible for approval as first generics primarily because the first applicants who were potentially eligible for 180-day exclusivity for the

Table 2: Status of 180-day exclusivity at time of approval of the first generics with paragraph IV certification

	First Generic Actions, N (%) ¹	Marketed within 6 Months of Approval Action, n (%) ²	Marketed at any time During the Study Period, n (%) ²
(A) 180-Day Exclusivity Forfeited, Relinquished, or Extinguished at Approval³			
No Tentative Approval within Specified Timeframe	23 (58)	12 (52)	17 (74)
Exclusivity Dependent PIV Patent Expired Prior to Approval	15 (38)	12 (80)	13 (87)
Exclusivity Relinquished by Applicant	1 (3)	0	1 (100)
Exclusivity Triggered by sale of Authorized Generic Prior to Approval	1 (3)	1 (100)	1 (100)
Total	40 (100)	25 (63)	32 (80)
(B) 180-Day Exclusivity Forfeiture Status Pending at Approval⁴			
No Tentative Approval within Specified Timeframe	63 (98)	25 (40)	45 (71)
Failure to Market; No Tentative Approval within Specified Timeframe	1 (2)	1 (100)	1 (100)
Total	64 (100)	26 (41)	46 (72)
(C) First Generics Not Eligible for 180-Day Exclusivity at Approval⁵			
Exclusivity Forfeited by Another Applicant	54 (81)	35 (65)	43 (80)
Exclusivity Relinquished by Another Applicant	8 (12)	6 (75)	8 (100)
Exclusivity Triggered by Sale of Authorized Generic Prior to Approval	4 (6)	4 (100)	4 (100)
Applicant did not Certify to Late-Listed Patent ⁶	1 (1)	1 (100)	1 (100)
Total	67 (100)	46 (69)	56 (84)

1: Column percentages. Percentage may not sum to 100% due to rounding.

2: Row percentages. Percentage may not sum to 100% due to rounding.

3: Includes 5 first generics with partial loss of exclusivity (1 for Exclusivity Dependent PIV Patent Expired Prior to Approval and 4 for No Tentative Approval within Specified Timeframe)

4: Paragraph IV first generics that had failed to obtain tentative approval within the specified timeframe. However, they still may have been eligible for 180-day exclusivity, and due to the lack of other generics ready for approval FDA had not had to complete a forfeiture analysis at the time the approval was issued. FDA does not undertake a forfeiture analysis until one is necessary – i.e., a subsequent applicant for the same drug product becomes eligible for approval but could be blocked from being fully approved because of the exclusivity potential of a first applicant.

5: Paragraph IV first generics that were not first applicants (i.e., subsequent applicants), and thus were ineligible to receive 180-day exclusivity but were the first generic to be approved. The reasons listed in section C indicate why the subsequent applicant was approved before any first applicant for the particular drug product at issue. For example, 81% (54/67) of the subsequent applicants were approved before any first applicant because the first applicants had forfeited their eligibility for exclusivity.

6: A late-listed patent is one for which the brand drug company submits the patent for listing later than required by statute or regulations. Generics with pending applications are not required to submit a patent certification to address a patent that is late-listed with respect to their pending application, and a first applicant's PIV certification to that patent, and any related 180-day exclusivity, would not block approval of the application for which the patent is late-listed and for which, as a result, no patent certification is required.

same drug product had either forfeited (81%, 54/67) or relinquished (12%, 8/67) the exclusivity (**Table 2C**).

Association of certifying paragraph with marketing of first generics

Table 1 shows percent of first generics actions that marketed within six months of approval and during the full study timeframe. Marketing of first generics that contained a PI or PII was not found to be significantly higher or lower relative to first generic drug products approved with other paragraph certifications. However, compared to first generics with PI, PII, and PIV certifications, PIII drugs, which are approved once the relevant patents expire, had significantly higher marketing at both six months (84% [110/131], relative-risk (RR) 1.48, 95% confidence interval (CI) 1.34-1.65) and during the full study period (91% [119/131], RR 1.12, 95% CI 1.05-1.2). PIV first generics, however, were significantly less likely to market, relative to first generics approved with PI, PII, and PIII, at six months after approval (53% [199/375], RR 0.73, 95% CI 0.65-0.82); however, the difference in marketing between these two groups was not significant during the full study period (80% [301/375], RR 0.93, 95% CI 0.87-1).

Figures 2 through 6 show the trends in marketing over the study period. Relative to other certification types of first generics, PIII first generics reached the market quickly with 76% percent marketed at time 0 (first month after FDA-approval) and remained the most marketed throughout the study timeframe (**Figure 2**).

In contrast, PIV first generics trail other first generics, with 39% marketing in the first month and lagging for 86 months before catching up (**Figure 3**).

Supplement Table 3 and *Supplement Figure 1* categorize the first generic marketing status first in 6-month intervals up to two years after approval, then those that marketed two years after approval and those that did not market during the full 119-month study timeframe.

Association of litigation and litigation outcomes with marketing of first generics

Among first generics approved with a PIV certification (375/687), generics that experienced litigation by the brand company (263), compared to generics that did not have litigation (112), were found to have significantly lower marketing at both six months after approval (43% vs 75%, RR 0.57, 95% CI 0.48-0.68) and during the full study timeframe (74% vs 91%, RR 0.83, 95% CI 0.76-0.91) (**Table 1, Figure 4**).

Furthermore, among those litigated that had an outcome (262), first generics for which litigation was settled or dismissed by an agreement between the companies (81%, 211/262) compared to litigation that was ruled on by the court on the merits (19%, 51/262), were significantly less likely to market within six months of approval (RR 0.59, 95% CI 0.45-0.77). However, over the course of the full study time frame, that is at month 119, the difference in marketing between the first generics that had settled litigation

Figure 2: Percent of FDA-approved first generics marketed between January 2010 to November 2019, by certifying paragraph

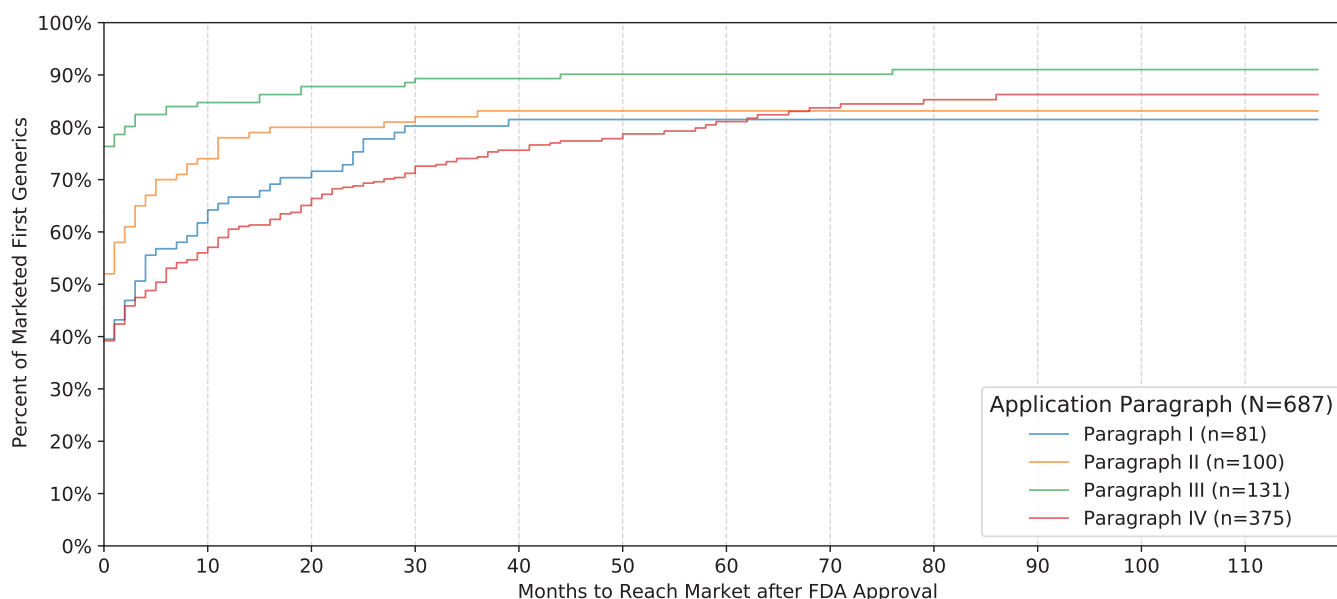
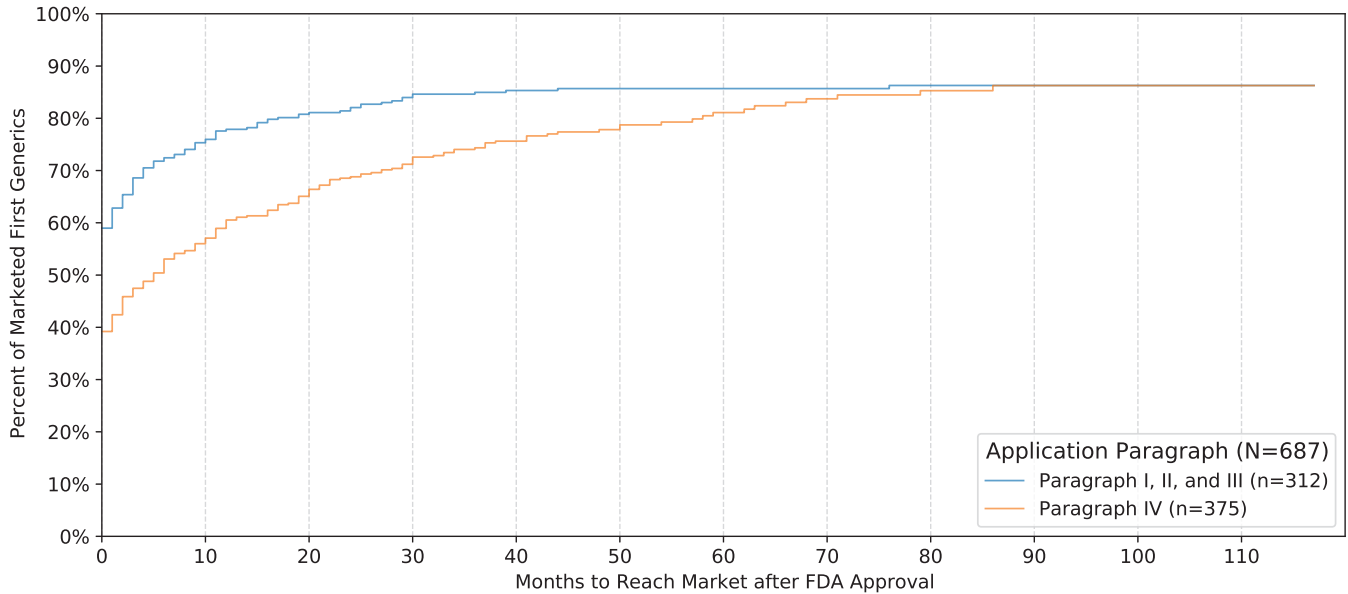


Figure 3: Percent of FDA-approved first generics marketed between January 2010 to November 2019, for paragraph IV vs paragraph I, II, and III products



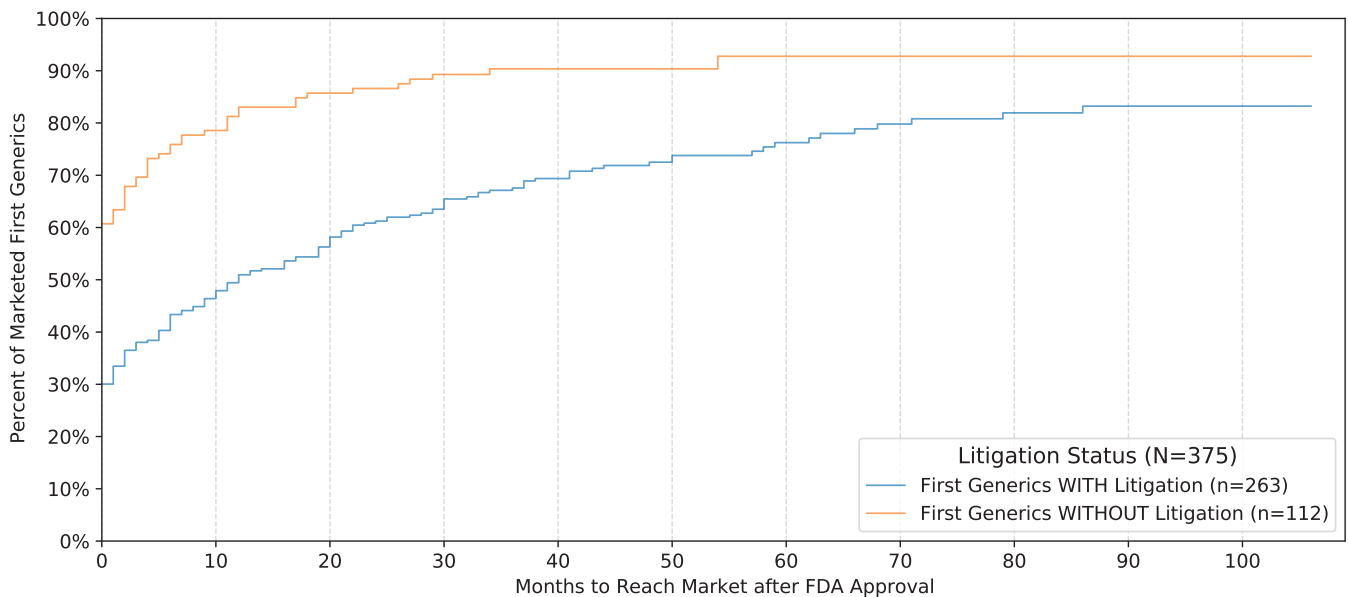
versus those ruled on by the courts on merits of the case was not significant (Figure 5).

Association of 180-day exclusivity with marketing of first generics

Approval of first generics with 180-day marketing exclusivity was not associated with faster entry into market. We found that first applicants who were approved with exclusivity (50%, 102/204), were significantly less likely to market than first approved

applicants who were ineligible for exclusivity (i.e., subsequent applicants) (69%, 46/67) within six months of approval (RR 0.73, 95% CI 0.59-0.90) (Table 1, Figure 6). Not only were fewer first generics with exclusivity marketed in the first month after approval compared to first generics ineligible for exclusivity (37% vs 49%), it also took the two groups about 86 months to reach parity. However, at the end of the full study timeframe (at month 119), this difference in marketing between the groups was not statistically significant.

Figure 4: Percent of FDA-approved first generics marketed between January 2010 to November 2019, with and without litigation



The first generics with a “pending” determination of exclusivity at approval had the lowest marketing rate (31%) in the first month after approval; and relative to other groups, it remained the lowest marketed group until after 70 months into the follow up period.

Sensitivity Analysis

After exclusion of 100 first generic actions for injectable drug products, 85% (587/687) of the first generics were eligible for sensitivity analysis. We found

Figure 5: Percent of FDA-approved first generics marketed between January 2010 to November 2019, by outcome of litigation

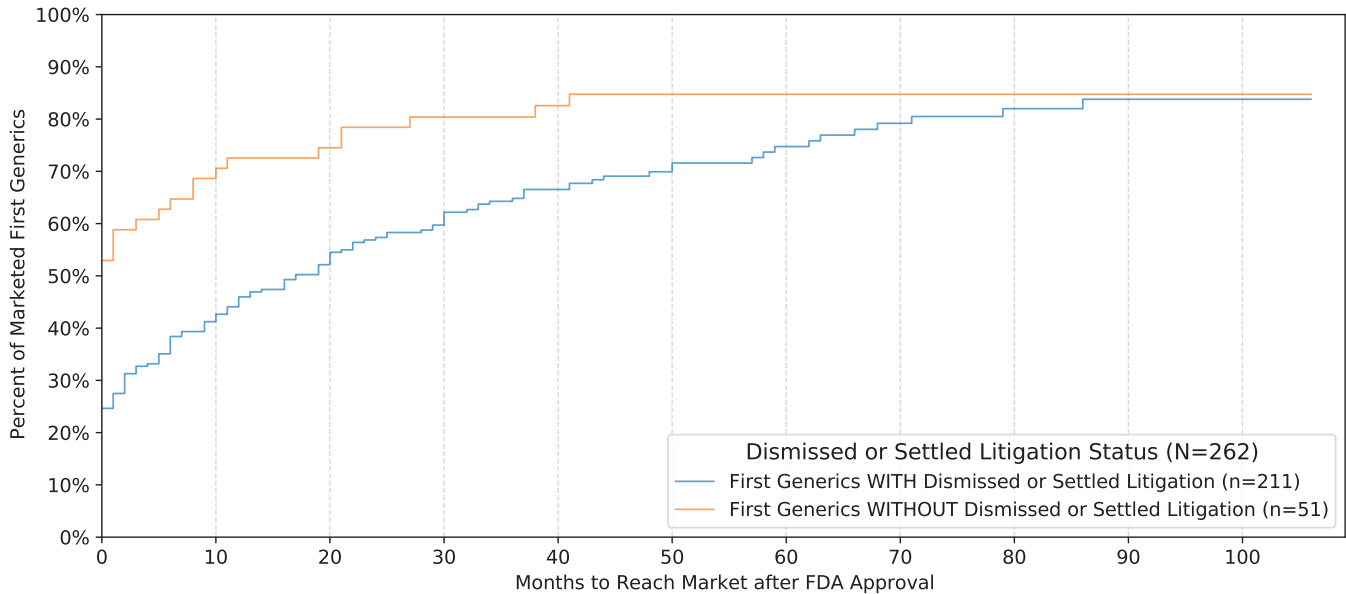


Figure 5 note: Litigation outcomes data excludes one first generic for which the litigation had not concluded at the time of analysis.

Figure 6: Percent of FDA-approved first generics marketed between January 2010 to November 2019 by 180-day marketing exclusivity status at approval

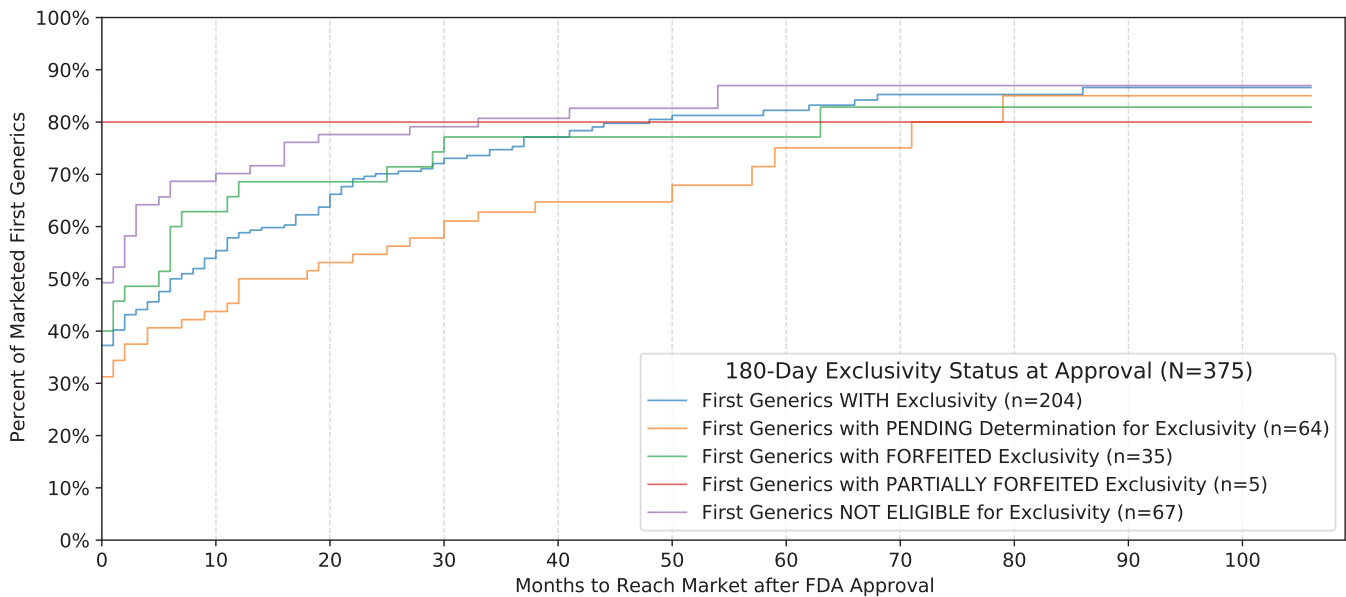


Figure 6 notes: 1) “PENDING Determination for Exclusivity” means the Paragraph IV first generics had failed to obtain tentative approval within the specified timeframe. However, they still may have been eligible for 180-day exclusivity, and due to the lack of other generics ready for approval FDA had not had to complete a forfeiture analysis at the time the approval was issued. 2) “PARTIALLY FORFEITED” means that paragraph IV first generics forfeited 180-day exclusivity for some products in the application. 3) “NOT ELIGIBLE for Exclusivity” means the paragraph IV first generics that were subsequent applications (not the first filed) and thus were ineligible to receive 180-day exclusivity but were the first application to be approved as a generic.

Table 3: Characteristics and disposition of non-injectable first generics approved by FDA between 2010 and June 30, 2017

Type of First Generic Action	First Generic Actions, N (%) ¹	Marketed within 6 Months of Approval Action, n (%) ²	Relative Risk Point Estimate (95% CI) ³	Marketed at Any Time During the Study Period ⁴ , n (%) ²	Relative Risk Point Estimate ⁴ (95% CI) ³
All First Generic Actions	587 (100)	379 (64)	N/A	499 (85)	N/A
First Generic Actions by Paragraph Certification (N=587)					
Paragraph I	60 (10)	35 (58)	0.89 (0.72-1.12)	51 (85)	1 (0.89-1.12)
Paragraph II	77 (13)	60 (78)	1.25 (1.09-1.43)	70 (91)	1.08 (1-1.17)
Paragraph III	115 (20)	101 (88)	1.49 (1.35-1.65)	105 (91)	1.09 (1.02-1.17)
Paragraph IV	335 (57)	183 (54)	0.7 (0.62-0.79)	273 (81)	0.91 (0.85-0.97)
Litigation History of Paragraph IV Actions (N=335)					
Litigation	233 (70)	106 (45)	0.6 (0.5-0.72)	181 (78)	0.86 (0.78-0.95)
No Litigation	102 (30)	77 (75)		92 (90)	
Litigation Outcomes for Paragraph IV Applications (N=232)⁵					
Litigation that was Settled or Dismissed	188 (81)	76 (40)	0.59 (0.45-0.77)	143 (76)	0.88 (0.76-1.02)
Litigation with Judgment on Merits of the Patent	44 (19)	30 (68)		38 (86)	
Exclusivity Status of Paragraph IV First Generics at Approval (N=335)					
First Generics With 180-Exclusivity	188 (56)	96 (51)	0.86 (0.71-1.05)	157 (84)	1.06 (0.95-1.18)
First Generics Not Eligible for Exclusivity ⁶	55 (16)	38 (69)	1.33 (1.08-1.65)	45 (82)	1 (0.88-1.15)
First Generics With Pending Determination for Exclusivity ⁷	58 (17)	25 (43)	0.76 (0.55-1.03)	42 (72)	0.87 (0.73-1.03)
First Generics With Forfeited Exclusivity	29 (9)	20 (69)	1.29 (0.99-1.69)	25 (86)	1.06 (0.91-1.24)
First Generics With Partially Forfeited Exclusivity ⁸	5 (1)	4 (80)	1.47 (0.94-2.31)	4 (80)	0.98 (0.63-1.53)
First Generics Approved WITH vs. WITHOUT Exclusivity (N=243)⁹					
First Generics With 180-Exclusivity	188 (77)	96 (51)	0.74 (0.59-0.93)	157 (84)	1.02 (0.89-1.17)
First Generics Without Exclusivity	55 (23)	38 (69)		45 (82)	

N/A: Not Applicable

1: Column percentages. Percentage may not sum to 100% due to rounding.

2: Row percentages. Percentage may not sum to 100% due to rounding.

3: For single rows, the relative risk calculations are conducted for first generics in that row for the listed category vs. all other first generics in that category. For example, under the "First Generic Action by Paragraph Certification" – the relative risk calculations are for first generics approved with each paragraph certification vs first generics approved with all other paragraph certifications (paragraph I vs the combined first generics approved with PII, PIII, and PIV).

4: Study period is from January 2010 to November 2019. These columns show status of marketing of first generics and related relative risk over the full 119-month study period.

5: Excludes one first generic for which the litigation was ongoing at the time of analysis.

6: Paragraph IV first generics that were subsequent applications (not the first filed) and thus were ineligible to receive 180-day exclusivity but were the first application to be approved as a generic.

7: Paragraph IV first generics that had failed to obtain tentative approval within the specified timeframe. However, they still may have been eligible for 180-day exclusivity, and due to the lack of other generics ready for approval FDA had not had to complete a forfeiture analysis at the time the approval was issued. FDA does not undertake a forfeiture analysis until one is necessary – i.e., a subsequent applicant for the same drug product becomes eligible for approval but could be blocked from being fully approved because of the exclusivity potential of a first applicant.

8: Paragraph IV first generics partially forfeited 180-day exclusivity for some products in the application.

9: This analysis only includes paragraph IV first generics that either had been found to be eligible for 180-day exclusivity on all products in the application or they were not eligible for exclusivity at approval. It excludes first generics with a "pending" determination, those that forfeited exclusivity for all products or partially forfeited exclusivity for some products in the application.

that even with exclusion of injectable drug products, the findings very closely mirrored the full dataset (Table 3, Figure 7). Overall, the sensitivity analyses indicate that inclusion of injectable drug products in the full analysis, potentially including drug products that may be limited to hospital settings, did not significantly influence the study findings.

DISCUSSION

FDA-approved first generics offer potential savings to the U.S. health care system and its patients. However, for the savings to be maximized, the generic drugs must be marketed in a timely manner after approval. Our study found that this is not case with all first generics. Specifically, ANDA applicants that include PIV certifications and receive 180-day exclusivity are slow to market despite the fact they, as first generics

challenging brand products still protected by patent, can have the greatest impact on reducing prescription drug costs.

Key findings

As expected, because PIII first generics are approved upon expiration of patents on the branded drug, they were the fastest to reach market to compete with higher priced brands in an environment in which there is little to no competition. In contrast to PIII first generics, PI and PII first generics were slower to market, however, still ahead of the PIV first generics. It is not immediately clear why PI and PII first generics – drugs that are not constrained by patents on branded drugs (either because the patents were not listed with the FDA or had expired at time of submission) – are slower to market compared to PIII first generics (which could

Figure 7: Percent of non-injectable FDA-approved first generics marketed between January 2010 to November 2019

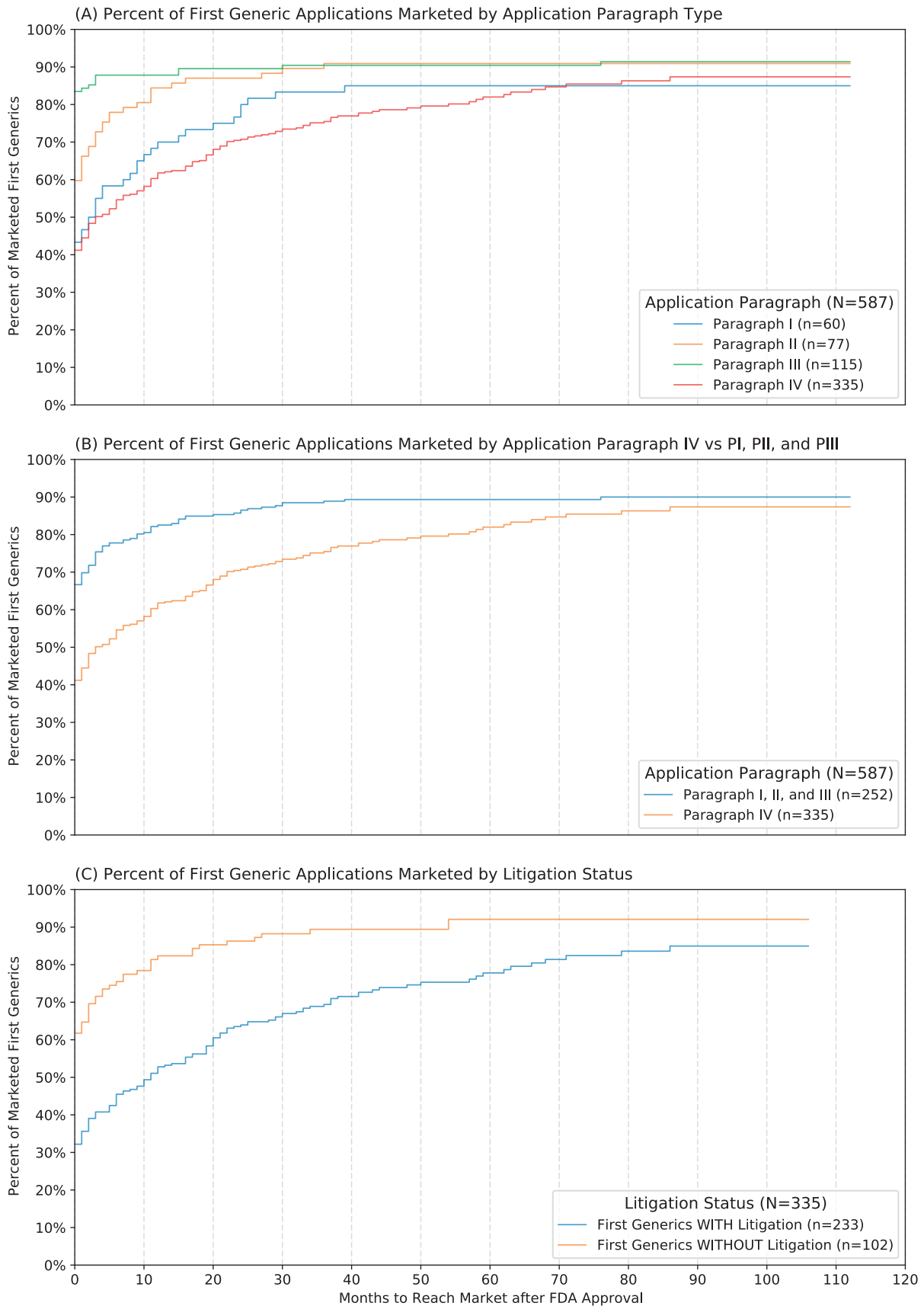


Figure 7 (continued): Percent of non-injectable FDA-approved first generics marketed between January 2010 to November 2019

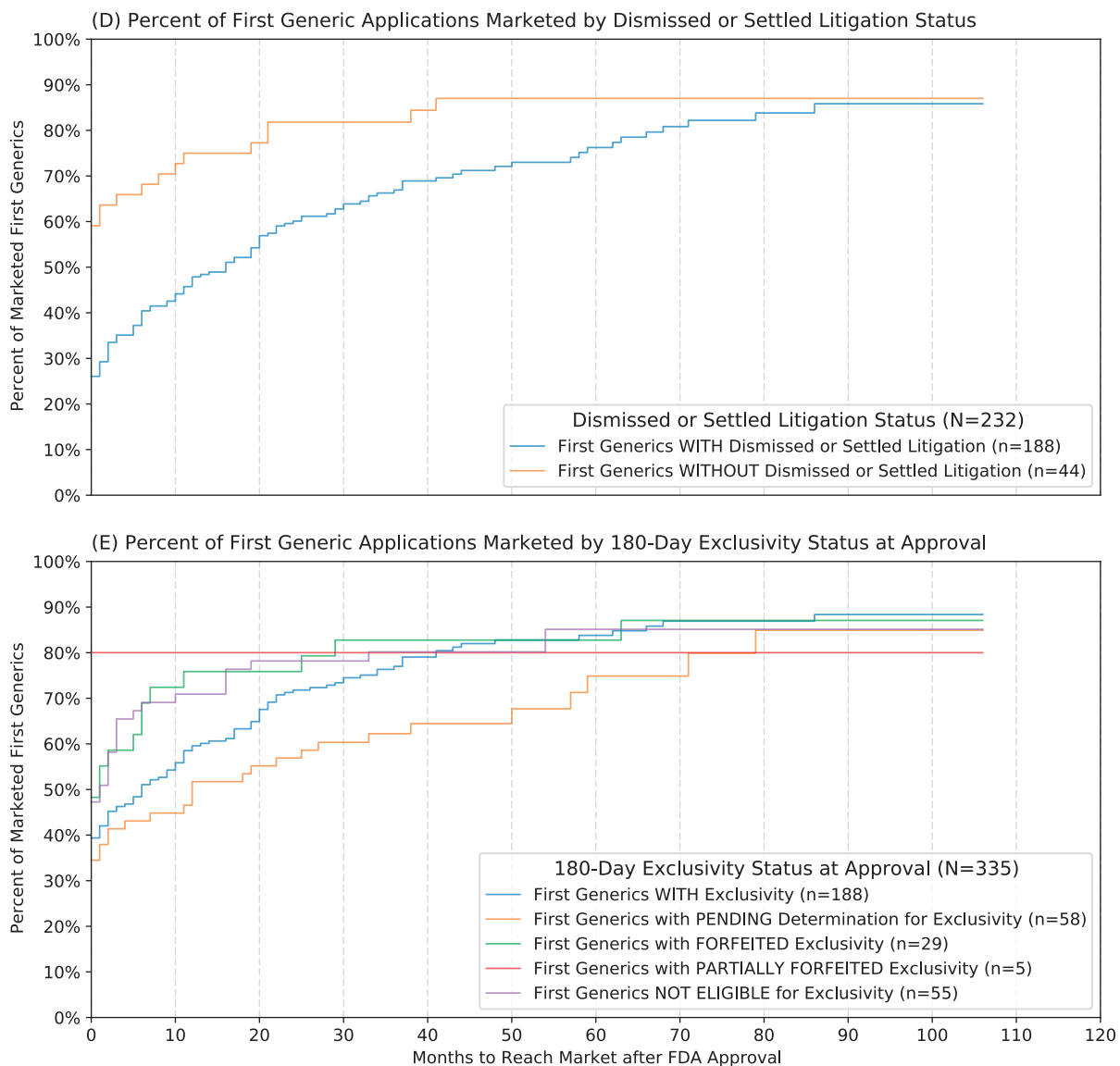


Figure 7 notes:

Figure 7(D): Litigation outcomes figure excludes one first generic for which the litigation had not concluded at the time of analysis.

Figure 7(E): 1) "PENDING Determination for Exclusivity" means the Paragraph IV first generics had failed to obtain tentative approval within the specified timeframe. However, they still may have been eligible for 180-day exclusivity, and due to the lack of other generics ready for approval FDA had not had to complete a forfeiture analysis at the time the approval was issued. 2) "PARTIALLY FORFEITED" means that paragraph IV first generics forfeited 180-day exclusivity for some products in the application. 3) "NOT ELIGIBLE for Exclusivity" means the paragraph IV first generics that were subsequent applications (not the first filed) and thus were ineligible to receive 180-day exclusivity but were the first application to be approved as a generic.

only enter the market upon expiration of certain patents on the branded drugs). One plausible explanation is that PI and PII generic drugs contend with a less attractive market since they may be older drugs that are no longer widely used and can face competition from other generics at any time, leading to a lower incentive to sell. The extent of competition between first generic drugs was outside of the scope of this study.

The observed trends on marketing of first generics

containing a PIV at the time of approval, including those with 180-day exclusivity, however, are contrary to what is expected. Because PIV first generics challenge patents on branded drugs in a bid to enter the market faster than they otherwise could, they would be expected not only to reach the market quickly after approval, but also outpace their entry into the market relative to generics approved without patent and/or exclusivity protection on the branded drug. Similarly, a drug's eligibility for 180-day exclusivity could also be expected to have an

accelerating effect on time to market, as these applicants could be expected to market their products quickly in order to reap the benefits of this marketing exclusivity. Neither was the case in our study. In our analysis, fewer PIV first generic drug products marketed at approval, and they were slower to attain the same levels of marketing as observed with first generics approved with PI, PII, and PIII certifications.

The paradoxical trends could, in part, be explained as a consequence of litigation by brand drug companies against PIV first generics, including those with 180-day exclusivity, for patent infringement. In our study, compared to applications that did not undergo litigation, fewer of the first generics with litigation were marketed over the study period. This could be because litigation is a lengthy process, and even if a generic is approved by FDA while litigation is pending (after the statutory 30-month stay expires), companies may choose not to market the drug until the litigation is complete – either by a court decision or through a settlement. Although companies can market after FDA approval even if litigation is pending, this is considered “at-risk” marketing, meaning that if the courts ultimately rule against the generic, they may be required to pay damages to the brand and potentially withdraw the drug from the market.¹⁹

Another factor that may explain the paradoxical trend is the litigation outcome. In our study, the vast majority (81%) of litigation was settled following confidential agreements between the companies, while only 19% of the litigation was decided by the courts on the merits. The first generics associated with settled litigation had slower marketing compared to first generics with decisions on the merits. Although the investigators could not study settlement conditions, the settlements between the companies often include clauses to delay market entry of first generics and could be accompanied by compensation, either cash or non-cash, from brand to generic companies.^{20,21} According to the U.S. Federal Trade Commission (FTC), in fiscal year 2016, of the 76 settlements between brand and first generic companies, all but three explicitly restricted the generic’s ability to market the drug. Among those with marketing restrictions, 16 provided compensation to generics in the form of litigation costs and 9 contained “possible compensation to the generic.”¹⁹ The delays resulting from such agreements can have significant implications for competition, especially if 180-day

exclusivity is implicated as it can result in “exclusivity parking.”²² Exclusivity parking occurs when the first generic drug product with the exclusivity delays marketing for an extended period of time, preventing FDA from approving a subsequently submitted generic for the same product containing a PIV certification – effectively blocking all generic competition.²

Policy implications

The findings of this study have potential policy implications for FDA, other federal agencies, and policy makers. Based on our observations in this study, three factors are heavily implicated in the bottleneck from first generic submission to approval to marketing: 1) whether a product is eligible for 180-day exclusivity, 2) whether the brand and generic companies engage in litigation in response to PIV certifications, and 3) whether the brand and generic companies settle litigation on relevant patents instead of it being decided on the merits.

First, while 180-day exclusivity is intended to encourage faster market entry of generics by incentivizing generic applicants to challenge patents on innovator drugs that might otherwise delay generic market entry, in some instances the exclusivity instead serves to hinder competition in circumstances where companies choose to park the exclusivity (that is, delay marketing for an extended period of time after gaining FDA approval). Evidence from this study indicates that the current statutory framework may be insufficient to discourage exclusivity parking by first generic applicants approved with eligibility for 180-day exclusivity. As mentioned above, such parking effectively blocks any subsequent applicant that could otherwise be eligible for FDA approval and thus could, upon approval, potentially market to compete with the branded drug. Some stakeholders have suggested that policy makers explore changes to the exclusivity eligibility and forfeiture features to strike a better balance between encouraging development and ensuring competition.²³ However, others have argued that such changes to the exclusivity provisions could disincentivize generic companies from challenging brand drug patents.²⁴ Legislation has been introduced in the U.S. Congress in this space, specifically to facilitate generic competition in situations where the first applicant is parking their exclusivity prior to approval (i.e., the first applicant substantially delays seeking final approval of their application, whether as a result of significant deficiencies in the application

or for their own business reasons) and is blocking subsequent generic competitors.²⁵ As described above, exclusivity parking can also occur after approval of the exclusivity-eligible first generic (i.e., through a first generic delaying marketing for an extended period of time after gaining FDA approval).

Generic companies are also continuing to gain experience with the 2017 statutory framework for Competitive Generic Therapies (CGT), which targets drug products that have inadequate generic competition (that is, only one or no companies marketing a drug product).²⁶ Although the CGT framework applies to drugs without existing exclusivities or patents on the reference drug, it may still offer lessons to address the limitations of first generic exclusivity identified in this study. First approved applicants for CGTs are also eligible for 180 days of marketing exclusivity, but two features of CGT exclusivity actively encourage rapid marketing following approval: First, generics approved with eligibility for CGT exclusivity must market within 75 days after the date of approval or they forfeit the exclusivity; and second, FDA can continue to approve other applications referencing the same branded drug until the applicant of the generic approved with the CGT exclusivity eligibility begins marketing.²⁶ This combination of provisions appears to be working to promote competition; a recent analysis shows that half of the drug products approved with CGT exclusivity had marketed within 2.5 days and 75% marketed within 9.5 days of approval.²⁷

Second, public stakeholders have also opined that because PIV litigation is a lengthy and an expensive process, it may lead to delays in generic marketing.^{28,29} This study's findings indicate that first generics that entered into litigation on relevant patents were slower to reach market. Thus, these findings may also be applicable to the U.S. Patent and Trademark Office (USPTO) in that the USPTO's Patent Trial and Appeal Board (PTAB) could offer a more efficient and less expensive forum for the resolution of certain types of patent disputes that implicate generic drug competition. While litigation can cost upwards of \$5 million for each party and take around 30 months to conclude (excluding appeals), the "inter partes review" (IPR), an administrative process under the PTAB established under the America Invents Act of 2011, costs around \$450,000 for each party and could be resolved in about 12 to 18 months (excluding

appeals).^{30,31} Further, compared to litigation, IPR's evidentiary standard, which could be easier to satisfy for the generic company, may allow additional avenues for a generic company to argue its case.³¹ Finally, the IPR can be started before generic applications are submitted to the FDA, as opposed to litigation under Hatch-Waxman, which can only start after generic application submission.³¹ However, the current IPR process may not support certain benefits of Hatch-Waxman Amendments to brand or generic companies, for example, the benefit of a 30-month stay of generic approval for the brand, or the 180-day exclusivity eligibility for the first generic company to file.^{32,33} Although IPR has been adopted broadly by generic companies to litigate drug patents,³⁴ it is still used heavily in parallel with litigation. Concurrent litigation with IPR is as high as 90% for Orange Book patents,³⁵ and there is limited evidence to determine whether the IPR has had any meaningful effect on generic drugs' time to approval.³⁴ Thus, policies to encourage IPR, in lieu of litigation, could be explored. As full discussion of the IPR is beyond the scope of this study, our findings only support that to improve generic drug competition, a quicker, more efficient process to resolve patent disputes needs to be examined by policy makers.

Third, some stakeholders have suggested that policy makers should explore options to explicitly prohibit anti-competitive settlements that require delays in generic marketing as a condition, either with or without compensation by brand companies to generic drug makers.³⁶⁻⁴⁰ The findings of this study indicated that first generics that entered into a confidential settlement to dismiss the litigation with the brand company were slower to market. Although direct cash payments to delay generic marketing have decreased significantly, as they are subject to anti-trust review by the FTC, other forms of compensation (such as an agreement by the brand company to not launch an authorized generic) may still play a role in these settlements, and provide incentives to delay generic marketing, including the marketing of first generics.¹⁹ The U.S. Congress is considering legislation that, among other aspects, would make it unlawful for brand and generic companies to enter into agreements that "limit or forego research on, or development, manufacturing, marketing, or sales, for any period of time."⁴¹

CONCLUSION

The results of this analysis can inform efforts to enhance generic drug competition. Policy makers should examine options to address delays in the marketing of first generics that are associated with the 180-day exclusivity provisions and paragraph IV litigation provisions under the Hatch-Waxman Amendments.

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Technical Supplement to Marketing of First Generic Drugs Approved by US FDA from 2010 to June 2017

November 2021

<u>Table of Contents</u>	24
List of Tables	24
List of Figures	24
I. Supplement Section I – Background	25
A. Overview of generic drug applications	25
II. Supplement Section II – Methods	26
A. Overview	26
B. Identification of study drugs and data collection	27
C. FDA National Drug Code (NDC) level data	28
D. IQVIA National Prescription Audit™ (NPA) – NDC level data	30
III. Supplement Section III – Results	31
A. Marketing of First Generics	31
IV. References	33
<u>List of Tables</u>	
Supplement Table 1: Variables collected and their sources for this analysis	27
Supplement Table 2: Converting NDCs from 10-digits to 11-digits	30
Supplement Table 3: Marketing status of FDA-approved first generics in defined time intervals, stratified by application characteristics ¹	31
<u>List of Figures</u>	
Supplement Figure 1: Marketing of FDA-approved first generics within defined time intervals	32

I. SUPPLEMENT SECTION I – BACKGROUND

A. Overview of generic drug applications

When submitting an Abbreviated New Drug Application (ANDA) for a generic drug, the generic applicant must address patent and exclusivity information which protects the branded drug (also called reference listed drug or RLD, typically filed as a New Drug Application (NDA) with the FDA) and provide a certification in its application according to one or more of four types of patent certification schemes.¹ The generic drugs need only provide certifications for patents listed in FDA’s Orange Book for the RLD, not all patents that may have been issued by the US Patent Office; it is incumbent on the brand company to request listing of relevant patents in the Orange Book (relevant patents are drug substance, drug product, and method of use patents).^{2,3} The certification schemes, which determine when FDA may legally approve an ANDA, are named after the paragraph numbers appearing in the law setting forth the FDA submission requirements with which they are associated (see **Figure 1** in the main report for a simplified process).^{1,4}

A Paragraph I certification applies to generic drug applications for which no patents on the RLD have been filed with the FDA by the NDA holder. FDA may receive and approve ANDAs containing Paragraph I certifications without delay and the product can be marketed upon approval.¹ A Paragraph II certification applies to generic applications for which the patent on the RLD has expired. FDA may receive and approve these ANDAs without delay.¹ A Paragraph III certification applies to generic applications for which one or more patents on the RLD have not expired. FDA may receive these applications but may not approve them until the relevant patents have expired.¹ Finally, a Paragraph IV (PIV) certification applies to generic applications for which one or more patents on the RLD have not expired, but the generic applicant is asserting that the relevant patent is invalid or will not be infringed by the manufacture, use, or sale of the proposed generic drug.¹ Applications submitted with PIV certifications are unique in that the products covered by these applications may, under certain conditions, be marketed well before patents on the RLD expire.

The Federal Food, Drug, and Cosmetic Act describes

only one circumstance in which an ANDA applicant need not certify to a timely listed patent. Specifically, when a patent is listed only for a method of use, an ANDA applicant seeking to omit that approved method of use from the generic drug’s labeling can submit a “section viii” statement, acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval.

A specified process must be followed for PIV applications. By law, within 20 days of FDA acceptance of an original generic application with a PIV challenge, the generic applicant must provide notice of the PIV challenge to the NDA holder or patent owner—the owner of the branded drug.^{1,5} The 20-day timeline applies only to patents listed by the NDA holder at the time the generic application was submitted. In some cases, the NDA holder may list the patents after the generic application is submitted – in these cases, the patents are considered “later listed.” If a patent is timely submitted for listing in the Orange Book after an ANDA is submitted but before it is approved, the applicant for the pending ANDA generally must amend its application and provide an appropriate patent certification or statement to the newly listed patent; however, no 30-month stay will be available in this circumstance.

The NDA holder then has 45 days to file a lawsuit to initiate suit against the generic applicant’s claims of patent invalidity, unenforceability or non-infringement.¹ The generic applicant has ample incentive to file a PIV certification notwithstanding risk of litigation from the NDA holder, as the first generic drug applicant(s) to file a substantially complete application containing a PIV certification to a listed patent may be eligible to exclusively market the drug product for 180-days, this is known as the “180-day exclusivity.”¹ During this time, FDA may not approve another application for the same drug product blocked by this exclusivity. If only one such ANDA is filed on the first day, there is only one first applicant; if two or more such ANDAs are filed on the first day, the ANDA applicants share first-applicant status, as well as the 180-day exclusivity.

The judicial outcome of a PIV challenge, however, is uncertain. If the NDA/patent owner sues the generic applicant in court, approval of the ANDA generally will be stayed for 30 months from the later of the date of receipt of the notice by any owner of the patent or

the NDA holder or such shorter or longer time as the court might order. If the 30-month period expires before litigation has concluded, barring any other reasons, FDA may approve the generic application. However, under this scenario, if the ANDA applicant markets their approved product, it would be at-risk marketing for the generic company; should the litigation ultimately resolve in favor of the NDA holder, the generic company may be liable for patent infringement and monetary damages. If, during this 30-month period, the court rules in favor of the generic company, marketing of the generic drug may proceed upon FDA approval. Alternatively, should the court rule in the NDA holder's favor within the 30-month period, the drug may not be approved until the date identified by the Court. In general, if the PIV challenge is successful in court, the generic drug maker can be approved and bring the drug to market earlier than would normally be the case.¹

However, generic drug applicants and NDA holders have often concluded litigation over PIV challenges by entering into confidential settlements delaying the marketing of generic drugs, including drugs eligible for 180-day exclusivity.^{6,7} These settlements can involve some form of consideration from the brand company in exchange for settling the litigation and agreeing on a date the generic can begin marketing. For example, an NDA holder may pay a generic applicant's litigation costs and agree not to launch its own authorized generic during the 180-day exclusivity period, in exchange for delayed launch of the generic drug until a certain date.^{6,7} Authorized generics, when sold by the NDA holder, its subsidiaries or a sub-licensee, can reduce profits for the generic drug by up to 60%.⁸ When generic applicants eligible for 180-day exclusivity enter into such settlements, marketing of generic drugs is generally delayed, as no other generic companies with a PIV may be approved and enter the market until 180 days after the first applicant commences commercial marketing of the drug.

II. SUPPLEMENT SECTION II – METHODS

A. Overview

We conducted a cross-sectional study of first generic drugs approved by FDA between January 1, 2010 and June 30, 2017. The time period was selected for its convenience and relevance to the questions being

studied and for availability of data. The investigators selected the start date of January 1, 2010 to ensure that the applications studied 1) would provide relevant insights to the current first generic environment (thus excluding older drugs); and 2) had electronic documentation available to collect relevant data because older drugs may not have all documents in electronic format in the database systems used by the investigators. The end date of the study period was set to June 30, 2017 to allow enough lag time to collect marketing data.

The unit of analysis for this study is the investigator defined “first generic action.” In the context of this study, a “first generic action” refers to FDA’s approval action on a product in a generic drug application. Some applications for generic drugs may contain multiple strengths. Each strength is a distinct drug product and for any number of reasons, including the complexities related to either litigation or exclusivity landscape, or both, different strengths may be approved at different times. A simplified example is one in which Applicant A submits a generic drug application containing one or more PIV certifications for atorvastatin 5 mg and 10 mg; this application is the earliest one received for the 10 mg strength, but Applicant B submits an application with a PIV certification for atorvastatin 5 mg the day *before* Applicant A. Applicant B’s submission is the earliest one received for the 5 mg strength – in this case, Applicant A would be considered the first applicant for atorvastatin 10 mg, while Applicant B will be considered the first applicant for atorvastatin 5 mg. Assuming that both Applicant A and Applicant B maintained valid paragraph IV certifications, then Applicant A is only eligible for approval for the 10 mg strength initially due to Applicant B’s eligibility for 180-day exclusivity on the 5 mg strength. But it is possible that Applicant B may either forfeit or relinquish the exclusivity and may not be the first to receive approval for the 5 mg strength, paving the way for FDA to approve Applicant A for atorvastatin 5 mg, which would make Applicant A’s 5 mg strength the first approved generic.

B. Identification of study drugs and data collection

The table below lists the variables collected and their sources for this analysis.

Supplement Table 1: Variables collected and their sources for this analysis

Variable Number	Category	Variable Name	Variable Definition/Content	Data Source(s)
1	Identifier	First_Generic_Action_ID	Unique integer number assigned to each First Generic approval action	Manually Assigned
2	General Characteristics	ANDA_Number	Application Number; and linked to internal FDA drugs database (CDER Informatics Platform)	CDER Informatics Platform; Orange Book
3		Established_Name	Generic drug name with dose strength and formulation	CDER Informatics Platform; Orange Book
4		Sponsor	Name of the generic applicant at time of approval	CDER Informatics Platform; Orange Book
5		Complex_Drug	If, per GDUFA II definition, the drug is considered "complex."	Internal FDA Complex Drug Database
6		Therapeutic_Class	High-level therapeutic class of the drug	CDER Informatics Platform
7		FDA_Received_Date	Date application was received/accepted by the FDA for review	Document Archiving, Reporting, and Regulatory Tracking System (DARRTS)
8		Approval_Date	Date application was fully approved for marketing by FDA	CDER Informatics Platform; Orange Book; Approval Letter
9		Current_Status	Current status of the application (approved, tentatively approved, discontinued)	CDER Informatics Platform; Orange Book
10		Current_Status_Date	Current status date	CDER Informatics Platform; Orange Book
11		Patent Challenge	NCE_1	If the application was NCE-1
12	Paragraph_At_Submission		Paragraph certification at time of submission	Filing Review; Application Submission Documents
13	Paragraph_At_App		Paragraph certification at time of Approval	Approval Letter; Approval Routing Summary
14	Litigation	Litigation	Litigation by RLD holder on PIV challenge w/in 45-days	Approval Letter; FDA's Review Documents; Docket Navigator
15		Dismissed_Settled_PIV_Litigation	PIV challenge litigation dismissed or settled by the two parties	Approval Letter; FDA's Review Documents; Docket Navigator; PACER (Court Documents)
16		PIV_Litigation_Outcome	If not dismissed or settled, who won the PIV challenge generic or brand company	Approval Letter; FDA's Review Documents; Docket Navigator; PACER (Court Documents)
17		StayExpire	Expiration of statutory delay (30 months or 7.5 years)	Approval Letter
18		StayPeriod	Type of Stay Period (30-month, 7.5 years)	Approval Letter
19	LoseWinAfterApproval	If the generic lost or won the PIV challenge after approval following stay expiration provision	Patent and Exclusivity Filings; TA/Rescind Letter	
20	RescindApp	If application approved with stay expiration provision converted to TA due to PIV challenge loss	TA/Rescind Letter	
21	RescindDate	Date application approval was rescinded	TA/Rescind Letter	

22	Ex180Day	180-day exclusivity at time approval	Approval Letter
23	ExForfeitAtApp	If exclusivity forfeited or pending assessment time approval	Approval Letter; FDA Internal Forfeiture List
24	ExForfeitNoExAtAppRsn	Reason for exclusivity forfeiture, pending assessment at time of approval, or reason why no exclusivity granted to PIV application (other than forfeiture)	Approval Letter; FDA Internal Forfeiture List
25	Partial180Day	If only certain products on an application received exclusivity	Approval Letter
26	Shared180	If exclusivity was shared among multiple sponsors	Approval Letter
27	FDANDC	The labeler- and product-code segments of a National Drug Code (“NDC-9”) associated with a drug product approved in a first generic action in a specified ANDA.	FDA’s Electronic Drug Registration and Listing System (eDRLS); Prescribing Information (package insert) and /Drug Labels from ANDA files
28	IQVIANDC	All prescriptions available in IQVIA between January 1, 2006 to November 30, 2019 in IQVIA’s National Prescription Audit database at the NDC-9 level (labeler- and product-code segments)	IQVIA National Prescription Audit
29	FirstMarketDate	Initial/first Month and Year in which the first FDANDC (NDC associated with a drug product approved in a first generic action in a specified ANDA) is observed in IQVIA’s NPA dataset (this is used as a proxy to estimate marketing of first generic drug products).	IQVIA National Prescription Audit

C. FDA National Drug Code (NDC) level data

The National Drug Code is a unique numeric identifier for a drug, the format of which is governed by FDA regulations that apply to the approved generic drugs that were the subject of our study (among other drugs). We describe the details of NDC format below. FDA uses NDCs for a number of regulatory purposes, and this results in regulatory submissions by firms to FDA in which the submitter associates one or more specific NDCs with a product the submitter reports as approved in a specific ANDA. In addition, NDCs are used by other entities such as dispensers and payors, and thus provide a means for us to identify first marketing from commercial data.

For the drugs in our study, FDA regulations indicate an NDC should consist of three segments that total 10 digits in one of several segment-length combinations (4-4-2, 5-4-1, 5-3-2). The first NDC segment (labeler code) is a unique identifier obtained from FDA and associated with a specific person who engages in manufacturing, repacking, relabeling, or private label distribution (i.e., commercially distributing a drug

under their label or trade name without engaging in any manufacturing, repacking, relabeling, or salvaging of the drug) of a drug. Other than the labeler code, the specific digits that comprise a full NDC are selected by the firm, who combines their labeler code with two additional segments formatted in accordance with FDA regulations. Under those regulations, the second segment (product code) associates the overall NDC with a particular drug product of that labeler (with the product being characterized and distinguished from other of that labeler’s products by elements including active pharmaceutical ingredient (API) identity and strength, and dosage form). The third segment (package code) further associates the whole NDC with a specific package size and type of that labeler’s drug product.

By limiting consideration to the labeler and product code segments of an NDC, one can capture data regarding multiple package configurations of the same drug product from the same labeler (e.g., the same manufacturer, repackager, or private label distributor). Even excluding the package code segment, however, a single product that we consider a “first generic drug” for purposes of our study can have multiple NDCs. For example, if a drug product approved in an ANDA is

commercially distributed under the label or trade name of one or more private labeler distributors (in lieu of or in addition to its manufacturer), or is repackaged, the NDCs for each of these versions of the drug would begin with a distinct “labeler code” and thus result in a distinct NDC. Further, the NDC associated with a product over the course of that drug product’s life can change or additional codes can be associated with that product because of changes in ownership or other events.

For our study, we sought to identify NDCs associated with each strength of drug product that was approved in a first generic action. For example, if the first generic action for a specific ANDA approved only a 5 mg tablet, we looked for NDCs associated with that single drug product to allow us to identify the first instance of its marketing. If instead, the first generic action under a specific ANDA approved two drug products of different strengths (e.g. a 5 mg tablet and a 10 mg tablet), these two products were considered “first generic drugs” and we looked for the NDCs to allow us to identify the first instance of marketing of either drug product. We sought to identify for each first generic drug all the associated NDCs beginning on the date of the relevant first generic action through November 2019, the last period for which we examined marketing data.

As further described below, we drew on FDA databases of two types of submissions to identify the NDCs for our study. One was a database of the drug listing submissions required under legal authorities.⁹ The other was an internal FDA database of ANDA files comprising submissions by ANDA holders that include labels and labeling, which also frequently identify NDCs that are in use for the finished products marketed under that ANDA.¹ These databases allowed us to identify NDCs that firms represented that they used for first generic drugs. Because both databases are dependent on industry submissions to FDA, they cannot be assured to be comprehensive of all NDCs that distributors of first generic drugs have associated with those drugs but using both sources increased the likelihood of our identifying relevant NDCs.

To elaborate, first, we used FDA’s electronic Drug Registration and Listing System (eDRLS) to collect product specific NDCs that drug firms associated with

first generic drugs in drug listing submissions made to FDA. Under FDA regulations, drug listing submissions are required to include NDCs associated with repackers, relabelers, and private label distributors of a drug, if any, as well as with manufacturers. Our search indicated that some ANDAs from our sample were not included in any drug firm listing submissions in the study period.

For ANDAs that did not have any associated NDCs in eDRLS, we manually searched a database of industry submissions to ANDA files and added NDCs seen in labels and labeling beginning with the initial approval for that ANDA and extending through November 2019 for the drug products that had been approved in a first generic action. This review allowed us to identify NDCs that ANDA sponsors indicated they were using in labeling for these products throughout the study period, and which prescribers and dispensers may therefore have seen in the marketplace. Although we searched all accessible labeling in these ANDA files, it is possible that we may have missed some NDCs associated with first generic drugs in our sample. We may have missed NDCs associated with re-packagers, relabelers, or private label distributors, as these may not be readily identifiable in the application-specific labeling that we searched. These omissions, if any, are unlikely to affect our marketing analysis because it is reasonable to assume that the first generic applicant that obtained approval for the initial labeling for the drug product is likely to market before resellers and re-packagers.

Further, while we identified NDCs from FDA databases in 10-digit format, as noted previously, applicable FDA regulations permit a number of configurations with different lengths of the individual labeler, product, and package code segments. Other entities that use NDCs, such as insurance companies, use 11-digit NDCs in a uniform 5-4-2 segment configuration. Each 11-digit NDC is the result of transformation to the 10-digit NDC formatted in accordance with FDA regulations, as shown in Supplement Table 2.

We used IQVIA National Prescription Audit (NPA) database to crossmatch NDCs identified from FDA databases at the product level (i.e., the first two segments). However, NPA also uses 11-digit NDCs. Therefore, we first converted each 10-digit NDC to 11-digit NDC and used the first two segments (NDC-9)

¹ Under FDA regulations for prescription drug labeling, NDCs are generally included in the “How Supplied” section of the prescribing information. See 21 CFR 201.57(c)(17)(iii); 21 CFR 201.80(k)(3). In addition, NDCs are requested but not required, to appear on drug labels (labels on the immediate container and carton). See 21 CFR 201.2.

Supplement Table 2: Converting NDCs from 10-digits to 11-digits

10-Digit Format on Package	10-Digit Format Example	11-Digit Format	11-Digit Format Example	Actual 10-digit NDC Example	11-Digit Conversion Example
4-4-2	9999-9999-99	5-4-2	<u>0</u> 9999-9999-99	0002-7597-01	<u>0</u> 0002-7597-01
5-3-2	99999-999-99	5-4-2	99999- <u>0</u> 999-99	50242-040-62	50242- <u>0</u> 040-62
5-4-1	99999-9999-9	5-4-2	99999-9999- <u>0</u> 9	60575-4112-1	60575-4112- <u>0</u> 1

Source: Maryland Department of Health.¹⁰

to match study data to NPA. Each NDC for every first generic action was manually cross-checked against IQVIA data to confirm accuracy.

D. IQVIA National Prescription Audit™ (NPA) – NDC level data

The IQVIA National Prescription Audit (NPA) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S.¹¹ The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

In December 2019, we obtained NDC-level NPA data for all prescription dispensed between January 1, 2006 to November 30, 2019, which indicated the month and year when a prescription was dispensed.

To determine if a first generic drug had been marketed and when it was first marketed, we cross matched each drug product (at the drug strength-level) in each first generic action using the product specific NDC-9 that we identified from FDA databases as previously described against the NDCs available in the NPA

database. If a first generic action included approval of multiple strengths and each product was marketed at a different time, we only captured the earliest marketed product to determine marketing. If multiple products were marketed at the same time, we selected one product for analysis.

III. SUPPLEMENT SECTION III – RESULTS

A. Marketing of First Generics

Supplement Table 3 below categorizes the first generics marketing status first in 6-month intervals up to two years after approval, then those that marketed two years after approval and those that did not market during the full 119-month study timeframe.

Supplement Table 3: Marketing status of FDA-approved first generics in defined time intervals, stratified by application characteristics¹

Type of First Generic Action	All First Generic Actions, N (%) ²	Timeframe for Marketing of First Generics after FDA Approval					Not Marketed during the Study Timeframe ³ , n (%)
		0 to 6 Months, n (%)	7 to 12 Months, n (%)	13 to 18 Months, n (%)	19 to 24 Months, n (%)	25+ Months, n (%)	
All First Generic Actions	687 (100)	425 (62)	45 (7)	19 (3)	25 (4)	55 (8)	118 (17)
First Generic Actions by Paragraph Certification (N=687)							
Paragraph I	81 (12)	46 (57)	8 (10)	3 (4)	4 (5)	5 (6)	15 (19)
Paragraph II	100 (15)	70 (70)	8 (8)	2 (2)	(0)	3 (3)	17 (17)
Paragraph III	131 (19)	110 (84)	1 (1)	2 (2)	2 (2)	4 (3)	12 (9)
Paragraph IV	375 (55)	199 (53)	28 (7)	12 (3)	19 (5)	43 (11)	74 (20)
First Generic Actions by Paragraph I, II, and III vs. Paragraph IV (N=687)							
Paragraph I, II, and III	312 (45)	226 (72)	17 (5)	7 (2)	6 (2)	12 (4)	44 (14)
Paragraph IV	375 (55)	199 (53)	28 (7)	12 (3)	19 (5)	43 (11)	74 (20)
Exclusivity Status of Paragraph IV Actions (N=375)							
First Generics With 180-Exclusivity	204 (54)	102 (50)	18 (9)	7 (3)	16 (8)	24 (12)	37 (18)
First Generics Not Eligible for Exclusivity	67 (18)	46 (69)	1 (1)	4 (6)	1 (1)	4 (6)	11 (16)
First Generics With Exclusivity Determination Pending	64 (17)	26 (41)	6 (9)	1 (2)	2 (3)	11 (17)	18 (28)
First Generics With Forfeited Exclusivity	35 (9)	21 (60)	3 (9)	(0)	(0)	4 (11)	7 (20)
First Generics With Partially Forfeited Exclusivity	5 (1)	4 (80)	(0)	(0)	(0)	(0)	1 (20)
Litigation History of Paragraph IV Actions (N=375)							
Litigation	263 (70)	114 (43)	20 (8)	9 (3)	18 (7)	38 (14)	64 (24)
No Litigation	112 (30)	85 (76)	8 (7)	3 (3)	1 (1)	5 (4)	10 (9)
Litigation Outcomes for Paragraph IV Applications (N=262)⁴							
Litigation that was Settled or Dismissed	211 (80)	81 (38)	16 (8)	9 (4)	15 (7)	35 (17)	55 (26)
Litigation with Judgement on Merits	51 (19)	33 (65)	4 (8)	(0)	3 (6)	3 (6)	8 (16)

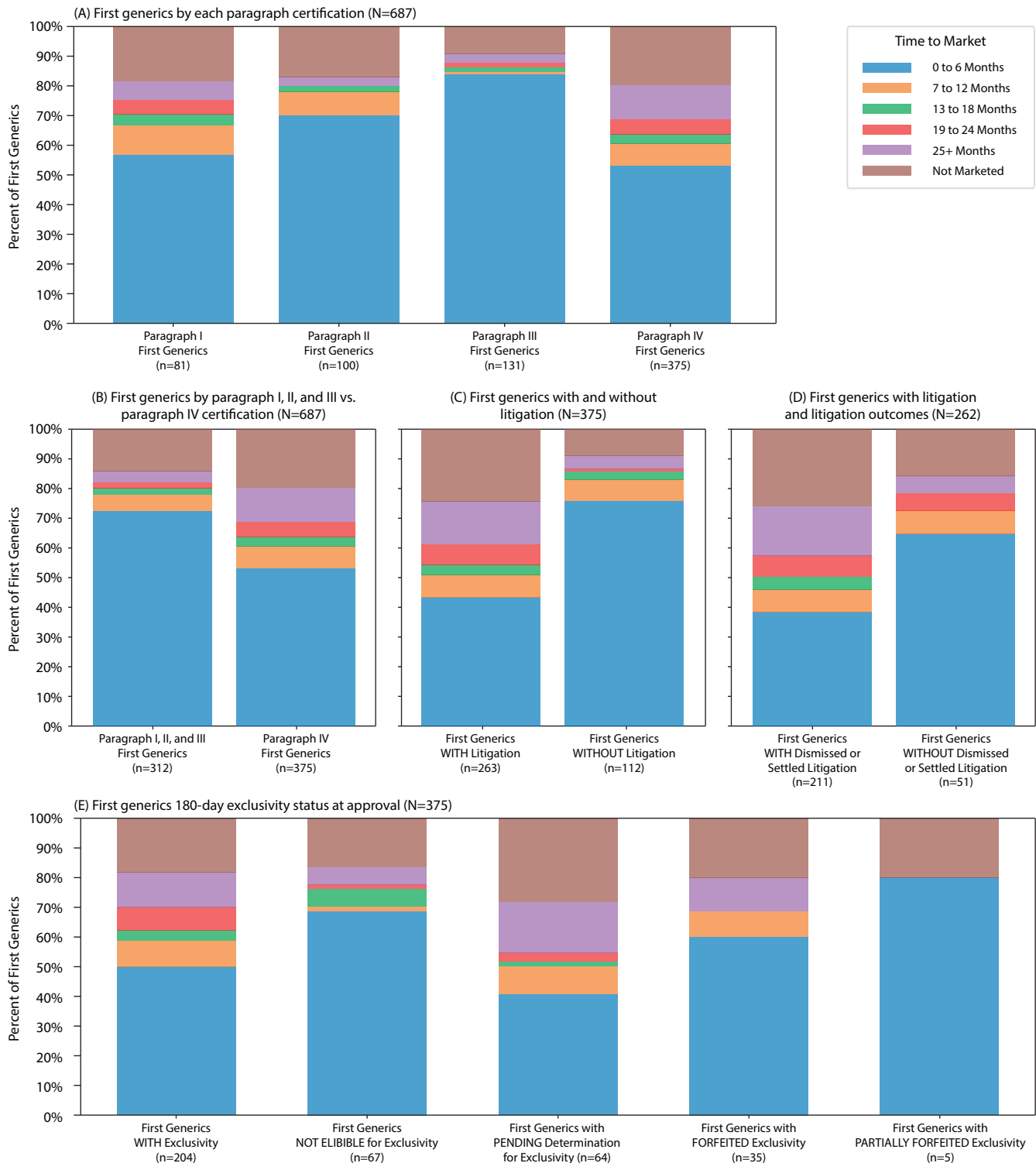
1: Unless otherwise notes, the table uses row percentages. Percentage may not sum to 100% due to rounding.

2: Percentages are column-based.

3: Study period is from January 2010 to November 2019. This column shows the status of marketing of first generics over the full 119-month study period.

4: Excludes one first generic for which the litigation was ongoing at the time of analysis.

Supplement Figure 1: Marketing of FDA-approved first generics within defined time intervals



Supplement Figure 1 note:

Supplement Figure 1(D) Litigation outcomes analysis excludes one first generic for which the litigation had not concluded at the time of analysis. Supplement Figure 1(E): 1) "PENDING Determination for Exclusivity" means the Paragraph IV first generics had failed to obtain tentative approval within the specified timeframe. However, they still may have been eligible for 180-day exclusivity, and due to the lack of other generics ready for approval FDA had not had to complete a forfeiture analysis at the time the approval was issued. 2) "PARTIALLY FORFEITED" means that paragraph IV first generics forfeited 180-day exclusivity for some products in the application. 3) "NOT ELIGIBLE for Exclusivity" means the paragraph IV first generics that were subsequent applications (not the first filed) and thus were ineligible to receive 180-day exclusivity but were the first application to be approved as a generic.

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