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COST OF GENERIC DRUG DEVELOPMENT AND APPROVAL

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DISCLAIMER

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LIST OF ACRONYMS

AAM	Association for Affordable Medicines
ACA	Affordable Care Act
AG	Authorized Generic
AIPLA	American Intellectual Property Lawyers Association
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
AUC	Area Under the Curve
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
CAPM	Capital Asset Pricing Model
CDMO	Contract Development and Manufacturing Organization
CEO	Chief Executive Officer
CFR	Code of Federal Regulations
CGT	Competitive Generic Therapeutic
CMC	Chemistry, Manufacturing, and Controls
CMO	Contract Manufacturing Organization
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CP	Communication Plan
CRL	Complete Response Letter
CRO	Contract Research Organization
CTD	Common Technical Document
CY	Calendar Year
dOFM	Dermal Open-flow Microperfusion
ENPV	Expected Net Present Value
ERG	Eastern Research Group, Inc.
ETASU	Elements to Assure Safe Use
FD&C	Federal Food, Drug, and Cosmetic
FDA	U.S. Food and Drug Administration
FDARA	FDA Reauthorization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FDF	Finished Dosage Form
FTC	Federal Trade Commission
FTF	First to File
FY	Fiscal Year
GAIN	Generating Antibiotic Incentives Now
GAO	U.S. Government Accountability Office
GDUFA	Generic Drug User Fee Act
GI	Gastrointestinal
GPO	Group Purchasing Organization
GSK	GlaxoSmithKline
OGD	Office of Generic Drugs
HHS	U.S. Department of Health and Human Services
I-MAK	Initiative for Medicines, Access & Knowledge
IP	Intellectual Property
IR	Instant Release
IQR	Interquartile Range
MFE	Most Favored Entry

MFEP	Most Favored Entry Plus
MG	Medication Guide
NBCD	Non-biological Complex Drug
NCE	New Chemical Entity
NCI	New Clinical Investigation
NDA	New Drug Application
NDC	National Drug Code
NIR	Near-infrared Spectroscopy
NSP	National Sales Perspective®
NTI	Narrow Therapeutic Index
ODE	Orphan Drug Exclusivity
OTC	Over the Counter
PAI	Pre-approval Inspection
PAT	Process Analytical Technology
PBM	Pharmacy Benefit Manager
PD	Pharmacodynamic
PED	Pediatric Exclusivity
PI/II	Paragraph I or II
PIII	Paragraph III
PIV	Paragraph IV
PK	Pharmacokinetic
PSG	Product-specific Guidance
QbD	Quality by Design
QIDP	Qualified Infectious Disease Product
REMS	Risk Evaluation and Mitigation Strategies
RLD	Reference Listed Drug
RTR	Refuse to Receive
SSS	Single Shared System
USPTO	U.S. Patent and Trademark Office
XR	Extended Release

EXECUTIVE SUMMARY

The cost of prescription drugs is an ongoing source of concern in the United States. The share of healthcare spending on prescription drugs is expected to increase from 14.5 percent in 2021 to 15.4 percent in 2026 (Roehrig, 2018). In dollar terms, this translates to a rise of $250 billion (from $625 billion in 2021 to $875 billion in 2026) over the 5-year period (Roehrig, 2018). Much of this increase is attributed to new brand drugs with patent protections and increased utilization for existing high-price drugs (Cicchiello & Gustafsson, 2021; Conti, et al., 2021). Several studies have shown that drug prices typically decline after generic entry and this decline is steeper the higher the number of generic entrants to a given market (Gupta, et al., 2019). HHS has an active interest in achieving lower drug prices and greater patient access to prescription drugs as part of its Comprehensive Plan for Addressing High Drug Prices prepared in response to Executive Order 14036, "Promoting Competition in the American Economy," which advocates for the expansion of access to high-quality, safe, and affordable generic medicines (Office of the Assistant Secretary for Planning and Evaluation, 2021). This requires a better understanding of the costs of developing generic drugs, the barriers that may increase these costs, and the policies that may encourage entry.

This study develops an analytical framework for examining the expected net present value (ENPV) (i.e., the difference between the present value of expected revenues over product life and cost of product development and approval) to a generic drug developer in different size drug markets. The developed framework forms the basis for an accompanying operational model that enables the user to specify numerous details of a generic drug development project and provides cost, revenue, and ENPV estimates for the project being examined. The technical factors, development stages, and activities accounted for by the model include:

- **Characteristics or type of drug**—Costs, timelines, and phase transition success probabilities can vary widely depending on the complexity of the drug at issue, from a simple oral tablet to solutions, emulsions, topicals, injectable solutions, narrow-therapeutic index (NTI) drugs, and ophthalmic drugs.
- **Opportunity cost of capital**—This is the annual return (net of inflation) a drug developer could expect from the capital should they not invest in the generic drug project; estimated at 8.82 percent for this model, which represents the average across five studies and information provided by industry representatives interviewed for the study. The model user has the ability to alter this value if desired.
- **Fifteen development stages**—Detailed in Sections 5.3 through 5.8, these development stages include such activities as reverse engineering a reference listed drug (RLD); testing the equivalence of the active pharmaceutical ingredient (API) and the formulation; demonstrating bioequivalence (BE) and stability; intellectual property (IP) challenge and litigation; and preparing and submitting an Abbreviated New Drug Application (ANDA) to the Food and Drug Administration (FDA). Each of these development stages involves a range of activities that the generic drug company spends resources to conduct and spans several months. The stages applicable to any given generic drug project, referred to as "pathway" hereinafter, vary by drug type, whether the RLD is subject to any patents/exclusivities, among other factors all of which can be specified by the model user.
- **Revenue Expectations—**Using IQVIA National Sales Perspective (NSP) data on sales, the model provides estimates of average lifetime expected revenues (years 1 through 5) by type of drug in five different sized markets (extra small, small, medium, large, and extra-

large) where market size was defined as the average generic drug revenues corresponding to 20th, 40th, 60th, 80th, and 100th percentile of the market.

Using the model, where possible, the study then examines the impact of different types of cost factors, barriers to generic drug development and market entry and a range of incentives designed to mitigate these barriers on the ENPV of the generic drug developer (Table E - 1). Given the hundreds of different product-pathway combinations that can be specified in the model, the study examines the impacts shown in Table E - 1 using 18 different product-pathway combination models that range from simple products (e.g., solid oral small molecule drug) to highly complex drugs (e.g., glatiramoids).

Table E - 1. Types of Cost Factors, Barriers, and Incentives Examined

Cost Factors		FDA Abbreviated New Drug Application (ANDA) Review Cycle Changes
		Change in FDA User Fees
		Use of Biowaivers in Lieu of In-vivo Bioequivalence (BE) Studies
Barriers	Intellectual Property (IP) Barriers	Strategic Accumulation of Patents [a]
		Product Hopping [b]
		Settlements and Pay-for-delay [c]
	Other Non-IP Barriers	Formulary Tier Manipulation and Brand Drug Rebates
		Reference Listed Drug (RLD) Labeling Changes Near Patent and/or Exclusivity Expiry
		Authorized Generics (AGs)
Incentives		180-day Exclusivity Modifications
		Additional FDA Product-specific Guidances (PSGs)
		Reference Listed Drug (RLD) Full Ingredient List Disclosure Requirements

[a] Also known as "evergreening."
[b] Refers to the case when a brand manufacturer, in the face of imminent generic competition, brings a "new and improved" variant—often a slight variant—of their brand drug to market, thereby disadvantaging the generic version(s) of the now "old" or "obsolete" drug.
[c] Settlements redistribute producer surplus from the brand company to the generic company and improve the ENPV of the generic drug developer. In this sense, settlements can be viewed as a barrier to lowering generic drug prices but not necessarily a barrier to generic drug development.

The key findings from the analysis of the factors presented in Table E - 1 using the analytical model developed, where applicable, and expert opinion include the following:

- Increasing the rate of FDA first-cycle approvals from its current baseline level of around 20 percent to a high of 66 percent reduces the time to market for the generic drug developer by around 13 months (45 percent) resulting in a $3.5 million decline in expected capitalized costs to the generic applicant across all types of ANDAs.
- The effect of a 50 percent decrease in FDA ANDA submission fees is relatively minor at -1.2 percent expected capitalized costs.
- In-vivo BE studies constitute a major portion of overall development costs. Thus, expanding the use of biowaivers in lieu of BE studies, where possible, saves money and time. On average, the time to market reduces by 10.6 months (11.8 percent) and expected capitalized costs decline by as much as 66.9 percent.
- Based on three case studies (Pennsaid [diclofenac sodium 1.5% topical solution], Doryx [doxycycline hyclate, 50 mg and 200 mg DR tablets], and Copaxone [glatiramer acetate]) and IQVIA NSP sales data, product hopping by the brand company (i.e., the introduction

of a newly patented version of the brand drug, such as an extended-release [XR] version) could reduce the size of the market (in terms of units sold) for the first-to-file (FTF) generic and other generic entrants by up to 29 percent on average within the first year after generic entry and more in subsequent years. Subsequently, this reduction in the volume of units sold over time results in declining revenues for all generics in the market including the FTF from one year to the next until they reach a level that cannot be sustained.

- The extent to which PBMs' placement of generics across formulary tiers and the rebate system affect the decision of a generic firm to enter a market, the costs of entering a market, or even the revenue model of entering a generic market is indeterminate. Some generic manufacturer representatives interviewed for this study commented on the decline in anticipated market share for first or early entrants to a market. However, none was able to quantify this impact with any degree of certainty.
- RLD labeling changes by the brand drug company near patent and/or exclusivity expiry can potentially delay market entry of a generic drug. However, the importance of this timing varies widely. A generic company with shared exclusivity could lose valuable weeks of exclusivity in the market if another FTF generic can adjust their label sooner. Contracts with wholesalers or distributors may have to be modified to account for a delay. However, neither the expense nor the potential delay caused by an RLD label change were considered serious barriers by manufacturing representatives interviewed for this study.
- The average market share in terms of dollar sales of an FTF generic is 7 percent higher on average if there are no authorized generics (AGs) during its 180-day exclusivity period. Consequently, the first-year revenues of the FTF generic could be roughly 5 percent higher in the absence of an AG which translates to an average increase of 10.9 percent in the ENPV of an FTF generic company that prevails in its PIV challenge and markets its product without facing competition from an AG during its 180-day exclusivity period.
- The 180-day exclusivity period may not, on average, provide a consistently substantial revenue advantage in the first year after entry over non-exclusive generic entrants into markets of comparable size, however, further analysis is needed with an expanded sample of Paragraph IV (PIV) drugs. We find some evidence that the potential value of an additional month of exclusivity to an FTF generic could be as much as 29.0 percent of the FTF generic's month 6 sales, but it is not clear whether this would translate to an overall gain for the first year.
- Existence of an FDA product-specific guidance (PSG) can save "several years" of development, especially for complex generic drugs and potentially reduce early development as well as BE study costs. We estimate that these savings could reduce the expected capitalized costs of a generic drug developer by 22.3 percent ($25.9 million) on average. Under GDUFA, FDA is committed to issuing PSGs for complex products as soon as scientific recommendations are available. FDA's list of *Planned New PSGs for Complex Generic Drug Products* contains 57 entries as May 19, 2021.
- The full ingredient list disclosure requirement for the RLD could reduce development costs by $3.35 million on average for otic and ophthalmic generic drugs if the expected reduction in Stage 1—R&D to Establish Equivalence for Active Pharmaceutical Ingredient (API)—costs due to the disclosure requirement is 10 percent. By regulation, drugs that are intended for parenteral, otic, or ophthalmic use are required to "contain

the same inactive ingredients and in the same concentration as the reference listed drug" with certain limited exceptions described in 21 CFR 314.94(a)(9)(iii) and (iv). In FY 2020, these types of drugs accounted for approximately one quarter of all ANDAs received (233 out of 830).

We note that the analysis for some of the factors presented in Table E - 1 is qualitative in nature. The experts interviewed for the study were unable to quantify several parameters of interest needed to estimate the expected impact of those factors on a generic drug developer's ENPV using the operational model, such as the expected reduction in market share due to product hopping.

1 INTRODUCTION

The modern generic drug industry in the United States was created with the passage of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act (Boehm, et al., 2013).[1] Passed unanimously by the 98th Congress, the Hatch-Waxman Act amended the patent and the food and drug laws to facilitate the marketing of safe and effective generic drugs while incentivizing brand-name drug companies to innovate (Congressional Research Service, 2016).

Before Hatch-Waxman, there were a few programs and/or initiatives, such as the paper new drug application (NDA) policy,[2] for bringing generic versions of drugs to market but for the most part, a prospective generic drug maker had to plan on following the same FDA approval pathway as the brand drug. This entailed filing an NDA which requires performing a succession of animal studies and human clinical trials to demonstrate the safety and clinical efficacy of the drug. The Hatch-Waxman Act created an Abbreviated New Drug Application (ANDA) pathway for generic drug companies to obtain Food and Drug Administration (FDA) approval for their products. The ANDA requires generic applicants to demonstrate that their proposed generic product has the same active ingredient, dosage form, route of administration, strength as the reference listed drug (RLD), i.e., the brand drug, and the same labeling with, limited exceptions. The ANDA also requires generic applicants to demonstrate scientifically that their product is bioequivalent to the RLD, meaning that once ingested, injected, inhaled, or absorbed, it acts on patients' bodies the same as the brand drug does, within parameters defined by FDA. A generic product must exhibit comparable stability and be manufactured packaged in a manner consistent with established good manufacturing practices and regulations. Thus, generic applicants no longer had to establish their product's safety and efficacy through expensive, time-consuming animal studies and clinical trials, mainly because the brand drug had already done so.

The Hatch-Waxman Act also provided a way for generic applicants to challenge the patents of brand drugs without extreme risk and loss of time. Brand drug patents, like other patents, give the patent holder 20 years of market protection from imitators—but they do eventually expire,[3] which is when generics can freely enter the former patent holder's market. The Hatch-Waxman Act, in the interests of accelerating the timeline for the availability of low-cost generic drugs to consumers, provided that an ANDA applicant could challenge a brand's patent by (1) filing an ANDA, (2) certifying to FDA that the patents listed in the FDA Orange Book protecting the brand drug were either invalid, unenforceable, or would not be infringed by their generic drug, and (3) notifying the brand company of their ANDA filing and their intention to market the generic drug upon approval. These actions by the generic company are collectively referred to as a Paragraph IV (or PIV) certification, after the part of the statute establishing the procedure.

If the patent holder does not bring an infringement action against the generic within 45 days of receiving the PIV notice, FDA is free to approve the generic once it meets all applicable legal

[1] Brand-name drugs (also referred to here as brand drugs or innovator drugs) are pharmaceutical products developed and tested for safety and efficacy by pharmaceutical companies. Generic versions of a brand drug have the same active pharmaceutical ingredient(s) as the brand drug, though generics for some more complex brand drugs are also required by FDA to have the same inactive ingredients (excipients) in the same proportion as the brand.

[2] The paper NDA policy implemented by FDA in 1978 "…permitted an applicant to rely on studies published in the scientific literature to demonstrate the safety and effectiveness of duplicates of certain post-1962 pioneer drug products" (U.S. Food and Drug Administration, 1999).

[3] Drug manufacturers generally apply for patent protection early during product development, which means that the several years required for drug development, animal and clinical trials, and submission to FDA for approval shorten the brand drug's patent protection in the market to less than 20 years.

and scientific requirements. If the brand company does bring an infringement case against the generic company within 45 days, final approval of that generic for which the PIV was submitted will generally be stayed for 30 months, pending the outcome of the legal action.

The stakes are high for all involved in the legal process. The reward established by the Hatch-Waxman Act for patent challenge by a generic company is a 180-day-long period of "exclusivity," starting on the day they first market their product commercially. This means that generally FDA will not approve any other ANDA for that brand drug until 180 days after the first generic challenger (also called the "first to file," or FTF, company) enters the market.[4] These 180 days of exclusivity can be—and were meant to be—a substantial opportunity for the FTF generic. For the brand company, the potential loss of many months or years of monopoly profits could mean billions in lost revenue.

The combination of requiring generics to demonstrate bioequivalence (BE), rather than safety and effectiveness—the ANDA pathway—and the opportunity, through PIV certification, to have weak brand patents declared invalid more expeditiously and with less risk has been highly successful.[5] From 1985 to 2012, FDA approved an average of 284 ANDAs annually (Walker, 2020). Then in July 2012, Congress enacted the Generic Drug User Fee Amendments of 2012 (GDUFA) as part of the Food and Drug Administration Safety and Innovation Act (FDASIA), which was designed to accelerate access to safe and effective generic drugs by allowing FDA to collect fees from drug companies that submit ANDAs "for certain generic human drug applications, certain drug master files, and certain facilities" (U.S. Food and Drug Administration, 2015). Since then, the annual increase in ANDA submissions and approvals peaked in 2017 and somewhat leveled off since then. Over the previous six calendar years (CYs), annual ANDA approvals were, 726 (2015), 813 (2016), 1,027 (2017), 1,021 (2018), 1,014 (2019), and 948 (2020) (U.S. Food and Drug Administration, 2021). This has resulted in significant savings to the U.S. healthcare system. In 2017, generics filled 90 percent of all prescriptions in the U.S., while accounting for just 23 percent of prescription drug spending; generics are estimated to have saved the U.S. healthcare system $1.125 trillion over 5 years from 2013 through 2017 (Association for Accessible Medicines, 2019a). In 2019, generics continued to account for 90 percent of prescriptions filled, but their share of prescription drug spending declined to 20 percent. For the five years from 2015 to 2019, generics are estimated to have saved the U.S. healthcare system $1.334 trillion (Association for Accessible Medicines, 2019a).

The Hatch-Waxman Act drastically diminished the extent and complexity of the testing FDA requires for approval, thereby significantly shortening the time to approval and, inferentially, the costs from initial development to final approval and generic drug market entry. The ANDA pathway to approval also fostered greater competition within many generic markets, diminishing potential

[4] The 180-day exclusivity only blocks other PIV filers but not those ANDAs with a "section viii" carve-out (i.e., a submission in accordance with 21 U.S.C. § 355(j)(2)(A)(viii) in which the applicant has "carved out" the protected condition of use from its product labeling).

[5] Outside of the framework established by Hatch-Waxman, patents are usually challenged by a competitor to the patent holder when the competitor enters the market with a product that the patent holder considers infringing. The patent holder then takes legal action, alleging infringement. The competitor can defend against the allegation of infringement via several methods. Patents can be declared invalid due to obviousness (i.e., the patented feature was not innovative, but was derived from "prior art" or was a simple and logical next step) or unenforceability (which usually means the patent application made inaccurate claims or statements). In the context of drug patent litigation, in certain circumstances generics can also assert non-infringement if their product is approved for fewer than all the uses for which the RLD is approved. Because physicians can prescribe medications for off-label uses, a generic drug can compete with a brand drug even though the generic is not approved for all the same use(s) as the brand.

profitability for all market participants (Rosenberg, 2018).[6] In response, brand drug companies began using a series of strategies to maintain as much of their market share as possible for as long as possible in the face of generic competition. Moreover, even though the overall cost savings due to generics are substantial, individual markets can suffer severe price iniquities. Wang et al. (2018) point out that about 10 percent of branded drugs with expired patents have no generic competitor and that 25 percent of brand drug markets have but one generic competitor. This has led to some well-publicized price increases in some markets.[7]

HHS has an active interest in achieving lower drug prices and greater patient access to prescription drugs. This requires a better understanding of the costs of developing generic drugs, the barriers that may increase these costs, and the policies that may encourage entry. Consideration of the barriers to market entry that may confront a prospective new generic drug is an early-stage exercise for generic companies. If the brand name drug's patents are not expected to expire before market entry, the generic company must assess the strength of the patents and the probability of successfully defending an infringement action, as well as the legal costs involved.

The generic company must also consider the probability and potential costs, or delays associated with other barriers. Among the more serious threats to the overall value of the putative generic is "product hopping" by the brand company—i.e., the introduction of a slightly altered (and newly patented) version of the brand drug, such as an extended-release (XR) version. Product hopping coupled with aggressive marketing of their "new and improved" product by the brand company can saddle the generic company with marketing what many potential customers might consider an obsolescent product. We discuss the effects of brand drug product hopping in more detail in Section 7.1.2.

Another potentially serious barrier that the generic company must assess is the possibility that the brand company will introduce an authorized generic (AG) into the market. An AG is the same product as the brand drug, usually manufactured by the brand drug company but marketed in different packaging. The AG enters the market under the approved NDA (without filing an ANDA), as it is the exact same product already approved by FDA. The AG is therefore not restricted from entering the market during the 180-day exclusivity period recognized for FTF generic drugs under Section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic (FD&C) Act. We discuss the impact of AGs on the price, market share, and profitability of generics in further detail in Section 7.2.3. Although generic companies surely can make reasonable estimates of their direct costs and potential revenues, based on their experience with drug development, knowledge of their distribution networks, market conditions, etc., for regulators, information on some of these issues has been sparse. For example, there are only three published estimates of generic drug development and approval costs, with figures ranging from as low as $250,000 to $25 million (Morton & Fiona, 1999; Reiffen & Ward, 2005; Federal Trade Commission, 2009). These estimates are out of date and do not provide sufficient detail to design targeted policies to encourage generic entry. The analytical model and the accompanying operational model that allows for an

[6] Some observers have noted that this procompetitive trend may be reversing in some markets. Rosenberg (2018) asserted that generic drug consumer characteristics (particularly high sensitivity to price and low brand identification), intense competition, and low profitability prompted many companies to exit the generic marketplace, merge into larger companies, or attempt to collude on prices with supposed competitors.

[7] Two of the most widely publicized brand drug price increases are (1) Mylan's EpiPen epinephrine self-injector, which went from $57 (per two-pack) to over $600 during the 10 years after Mylan acquired the rights to it (Silverman, 2016); and (2) Turing's Daraprim, the standard treatment for toxoplasmosis, which went from $13.50 to $750 per tablet immediately after Turing was acquired by a former hedge fund manager in 2015 (Pollock, 2015).

examination of barriers and potential incentives designed to alleviate them presented herein provide more comprehensive information that can help policymakers to effectively target efforts to increase generic competition.

2 STUDY OBJECTIVES

The primary objective of this study is to develop an analytical framework for examining the expected net present value (ENPV) (i.e., the difference between the present value of expected revenues over product life and cost of product development and approval) to a generic drug developer in different size drug markets. The framework will form the basis for an operational model with which the user would be able to create a scenario to examine, alter any default parameter values, and run the calculations to compute the ENPV of the generic drug developer.

A second objective of the study is to examine the impacts of different types of barriers to generic drug development and market entry and a range of incentives designed to mitigate these barriers on the ENPV of the generic drug developer. In addition to those mentioned in the introduction, the barriers identified through a literature review and discussions with industry include product hopping, strategic accumulation of patents by the RLD company, changes in product approval standards, and uptiering of generic drugs in PBM-designed formularies, that increase cost of development and/or reduce market returns. The different incentives considered upon consultation with the U.S. Department of Health and Human Services (HHS) and FDA include modifications to the 180-day exclusivity, provision of additional FDA product specific guidances, and full ingredient list disclosure requirements for certain types of RLDs. Where possible, the goal is to quantify the potential impacts of these barriers and incentives with the use the operational model developed.

3 DATA SOURCES

We conducted a literature review, structured interviews with industry representatives, and an analysis of IQVIA National Sales Perspectives® (NSP) data on monthly drug sales from January 2013 through June 2021 to collect the information needed for the study.

Our literature search targeted several categories of literature: peer-reviewed articles in scientific journals, unpublished papers and presentations, white papers, gray literature, and news stories and occasional pieces appearing in newspapers and magazines or other print media outlets. While our literature search focused primarily on studies published in 2010 onward, we included select studies of high relevance that were published as early as 2004. Our search methodology featured systematic inquiries of Google Scholar, PubMed, and ScienceDirect using keywords such as "generic drug development AND cost*," "generic drug AND formulary placement," "generic drug market" among others. We also reviewed relevant government publications, presentations, and data sets, including FDA Product-Specific Guidances (PSGs) for Generic Drug Development, FDA List of PIV Certifications, FDA List of Authorized Generic Drugs, GDUFA performance reports, drugs@FDA, clinicaltrials.gov, and various other FDA guidance documents and white papers. Where an article was particularly useful, we also employed a "snowball" type search strategy and reviewed the sources cited and the sources citing that article.

PIV patent certifications and subsequent litigation (collectively referred to here as "IP litigation") comprise an important innovation of the Hatch-Waxman Act, potentially enabling generic market entry many years before patents on the brand drug expire. The potential costs of this litigation to the generic company can be its greatest expense in bringing their generic product to market. The American Intellectual Property Lawyers Association (AIPLA) surveys its membership biennially on numerous aspects of their practices. The survey asks several questions on the costs of Hatch-Waxman litigation at various stages, from early mediation and settlement through trial and appellate processes. We purchased a year-long membership in AIPLA to obtain

the median Hatch-Waxman cost estimates provided by IP law firms in several recent AIPLA surveys.

Our structured interviews included representatives from 20 industry-related organizations—manufacturers, wholesalers/distributors, contract manufacturing organizations (CMOs), a contract development and manufacturing organization (CDMO), a group purchasing organization (GPO), a trade association, and independent industry experts, as presented in Table 1. Our interviewees were experienced industry professionals, including company founders and chief executive officers (CEOs), and executives overseeing regulatory affairs, product development, manufacturing, analytical operations, or supply chain services.

Table 1. Interviews Conducted, by Type of Entity

Entity Type	Entity Size	Citation
Contract Development and Manufacturing Organization (CDMO)	NA	CDMO A
Group Purchasing Organization (GPO)	Small	GPO B
Wholesaler/Distributor	Small	Wholesaler/Distributor C
	Large	Wholesaler/Distributor S
	Large	Wholesaler/Distributor T
Generic Drug Manufacturer	Small	Small Manufacturer D
	Small	Small Manufacturer E
	Small	Small Manufacturer F
	Small	Small Manufacturer G
	Small	Small Manufacturer H
	Mid-size	Medium Manufacturer I
	Large	Large Manufacturer J
	Large	Large Manufacturer K
	Large	Large Manufacturer L
Trade Association	NA	Trade Association M
Contract Research Organization (CRO)	NA	CRO N
	NA	CRO O
	NA	CRO P
Independent Industry Expert	NA	Expert Q
	NA	Expert R

Our interview questions focused on the decision process for entering and withdrawing from a market, costs of and barriers to entry, and industry dynamics that impact entry/exit decisions, as well as development costs and revenue expectations. The questions were targeted to each type of entity. Additionally, we obtained information from FDA's Office of Generic Drugs (OGD) on ANDA review cycle times, number of resubmissions, Risk Evaluation and Mitigation Strategies (REMS) programs, and other topics of interest throughout the study.

We used IQVIA NSP data on monthly dollar and unit sales of drugs in the U.S. for January 2013 – June 2021 to generate estimates of market size by type of drug. The database includes national estimates of all drugs sold (in dollars and units) directly from drug manufacturers and indirectly through wholesalers into retail and non-retail channels of distribution in the U.S and is considered the industry standard for measuring pharmaceutical sales. The NSP measures sales at actual transaction prices but does not capture off-invoice discounts, such as rebates to plans or pharmacy benefit managers (PBMs), that reduce the amount received by manufacturers (IQVIA Institute for Human Data Science, 2019; Conrad & Lutter, 2019).

4 ANALYTICAL MODEL FRAMEWORK

Figure 1 lays out the process steps associated with bringing a new generic drug to market based on information we gleaned from the peer-reviewed and gray literature; FDA guidances, white papers, and presentations; and expert interviews.

The framework covers such activities as reverse engineering an RLD (Stages 1 and 2); testing the equivalence of the API and the formulation (Stage 3); demonstrating BE (Stages 5, 7, and 8) and stability (Stages 4 and 6); and preparing and submitting an ANDA to FDA (Stages 12 and 13). Each development stage, i, depicted in the figure involves a range of activities that the generic drug company spends resources to conduct, C_i and spans several months, t_i. The ability of the generic drug company to proceed to the subsequent development stage, $i+1$, requires successful completion of development stage i, which is associated with a transition success probability of p_i.

In this framework, which is similar to that of DiMasi, et al. (2016) for new drugs, if the company fails a given stage, the development effort is, in theory, abandoned. We recognize that, in reality, a company may not necessarily abandon development and may choose to tweak the formulation or other aspects of the product to re-try. To the extent possible, our baseline model captures some, but not all, of these re-try attempts (e.g., bridging study, resubmission) in the form of alternative pathway scenarios. However, our theoretical model abstracts from most of these re-tries to make the baseline model computationally tractable. We argue that once substantive changes are initiated, the product is no longer the same one the manufacturer started with and hence a new decision tree is activated.

In Figure 1, the expected average cost of entering a generic market depends on the pathway the generic drug applicant takes from biobatch manufacturing for stability and BE testing stage onward, which in turn is dependent on drug type, whether the RLD is subject to any patents/exclusivities, among other factors. For example, development stages 5 through 8, 10, 13, and 15 in the figure are not relevant for the applicant of a generic version of an off patent, simple immediate-release oral RLD that is eligible to have in vivo testing waived by FDA in favor of successful in vitro tests[8], and for which FDA does not require a Risk Evaluation and Mitigation Strategy (REMS) submission or a pre-approval inspection (PAI). In contrast, all development stages depicted in the figure (with the exception of stage 11) could be relevant for the applicant of a generic version of a non-biological complex[9], patent-protected RLD that requires a pilot BE study[10] followed by a successful BE study on patients, a bridging study[11] due to stability issues encountered, a REMS submission, and an FDA PAI.

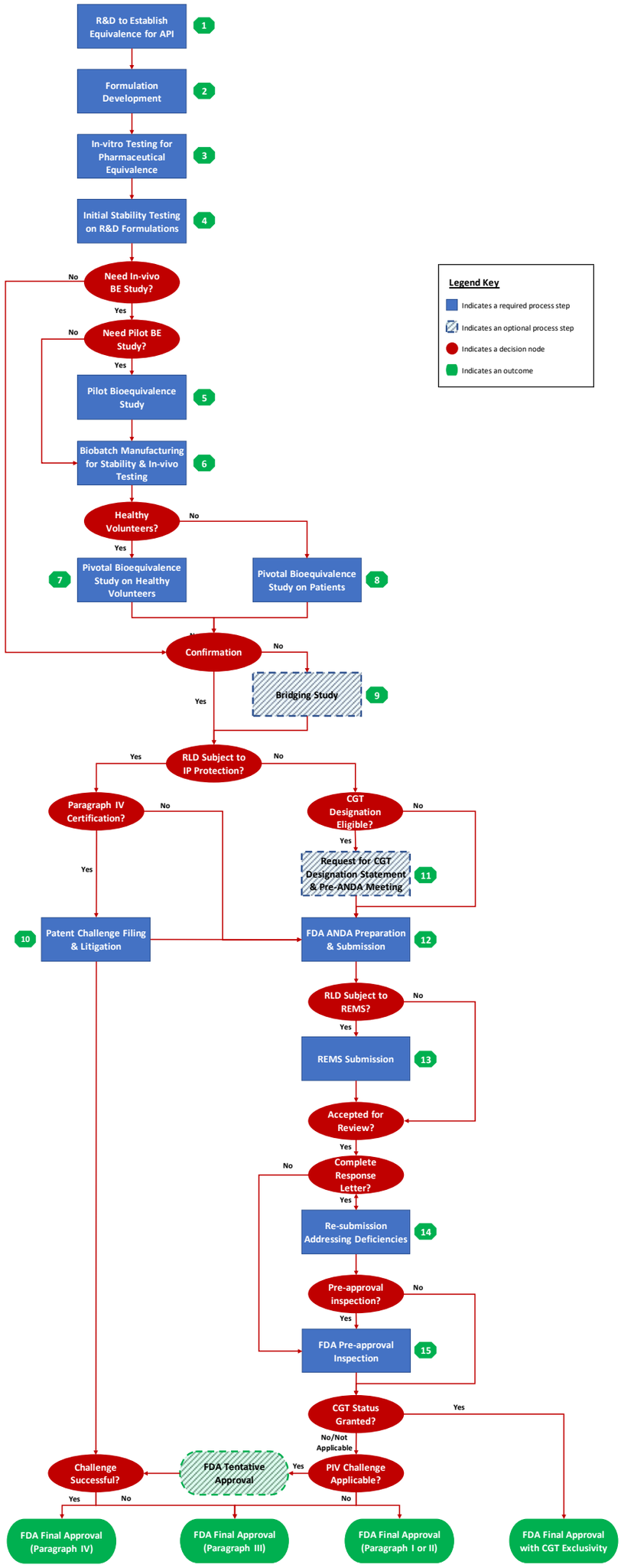
[8] Drugs not eligible for a biowaiver must perform a BE study on either healthy volunteers or patients to show that the generic is bioequivalent to the brand drug.

[9] A non-biological products complex generic drug product includes those with (1) complex active ingredients (e.g., peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients); (2) complex formulations (e.g., liposomes, colloids); (3) complex routes of delivery (e.g., locally acting drugs such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions or gels); (4) complex dosage forms (e.g., transdermal drugs, metered dose inhalers, extended release injectables); (5) complex drug-device combination products (e.g., auto injectors, metered dose inhalers); and (6) other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement. (U.S. Food and Drug Administration, 2020b).

[10] The generic drug applicant often initiates one or more smaller-scale pilot studies before the full-scale BE study to ensure safety and improve chances of success.

[11] See Section 5.5 for an explanation of bridging studies in the ANDA context.

Figure 1. Generic Drug Development and Approval Process Map



Using the approach of DiMasi, et al. (2016), we estimate the expected average cost of developing a generic drug by considering the cost, duration, the probability of successfully transitioning from one development stage, *i*, to the next applicable stage, and the opportunity cost of capital. If the cash outlay associated with a given development stage *i* is C_i, then the expected cost, $E(C_i)$, that incorporates failures can be computed by dividing this cost by the transition success probability from stage *i* to launch, p_i, i.e.,

$$E(C_i) = \frac{C_i}{p_i} \tag{1}$$

Assuming that development stage costs are distributed uniformly over the length of the applicable stage, t_i,—a simplifying but necessary assumption to make model calculations tractable—the capitalized cost, CC_i, that accounts for the opportunity cost of the investment in the generic drug is given by:

$$CC_i = \int_{t_i^e}^{t_i^b} \left(\frac{C_i}{t_i}\right) e^{rt} dt \tag{2}$$

where *r* is the opportunity cost of capital (net of inflation) that captures the time value effect; t_i^b is the time from the beginning, *b*, of the given development stage to product launch, and t_i^e is the time from the end, *e*, of the given development stage to product launch. Equation 2 then becomes:

$$CC_i = \left(\frac{C_i}{t_i}\right)\left(\frac{1}{r}\right)\left(e^{rt_i^b} - e^{rt_i^e}\right) \tag{3}$$

Given equations 1 and 3, we can then compute the expected capitalized cost of development stage *i* that accounts for the cost of failures and the cost of capital as:

$$E(CC_i) = \frac{CC_i}{p_i} \tag{4}$$

Then the total expected capitalized cost of development for a generic drug, $E(CC)$, is the sum of the expected capitalized cost of each applicable development stage *i*, for the drug in consideration.

$$E(CC) = \sum_{i=1}^{n} E(CC_i) = \frac{1}{p_i}\left[\left(\frac{C_i}{t_i}\right)\left(\frac{1}{r}\right)\left(e^{rt_i^b} - e^{rt_i^e}\right)\right] \tag{5}$$

In Table 2, we present a sample calculation for the applicant of a generic version of an out-of-patent, simple immediate-release oral RLD that is eligible for a biowaiver, and for which a REMS submission or an FDA PAI are not needed. In this simple case, while the average cash outlay for the applicant is around $2.6 million, the average expected capitalized cost computed using equation 5 that accounts for failures and cost of capital is $6.5 million, about 2.5 times higher.

Table 2. Sample Calculation for Estimating the Development Cost of a Simple Small Molecule Generic Drug

Type of Drug	Small Molecule					
In vivo Bioequivalence (BE) Study Needed?	No					
Is a Bridging Study Needed Based on Stability Testing Results?	No					
RLD Subject to Intellectual Property (IP) Protection?	No					
Competitive Generic Therapeutic (CGT) Designation Sought?	No					
RLD Subject to REMS?	No					
Finished Dosage Form (FDF) Facility Location?	Domestic					
Pre-approval Inspection (PAI) Needed?	No					
Opportunity Cost of Capital (%)	8.82%					
Applicable Development Stage	**Average Cost ($)**		**Average Duration (in Months)**	**Average Transition Success Probability (%)**	**Average Transition Success Probability to Launch [b]**	**Expected Capitalized Average Cost ($) [c]**
	Total	**Per-month [a]**				
Stage 1 - R&D to Establish Equivalence for API	$1,000,000	$181,818	5.5	90%	53%	$2,824,509
Stage 2 - Formulation Development	$350,000	$16,667	21.0	90%	59%	$807,918
Stage 3 - In-vitro Testing to Establish Equivalence for Formulation	$30,000	$30,000	1.0	90%	66%	$57,428
Stage 4 - Initial Stability Testing on R&D Formulations	$100,000	$100,000	1.0	95%	73%	$171,024
Stage 6 - Biobatch Manufacturing for Stability & In vivo Testing	$525,000	$262,500	2.0	95%	77%	$843,636
Stage 12 - FDA ANDA Preparation & Submission - Biowaiver	$421,899	$21,875	28.4	81%	81%	$576,973
Total	**$2,426,899**	**NA**	**58.9**	**NA**	**NA**	**$5,281,488**

NA = Not applicable

[a] The average cost per month is computed by dividing the average total cost of the development stage by stage duration.

[b] The average transition success probability to launch for a given development stage, *i*, is computed as the product of the transition success probability for that stage and each successive stage, $i + 1$. For example, the average transition success probability for Stage 6 (Biobatch Manufacturing for Stability & In vivo Testing) is 73 percent, which is the product of 90 percent for successfully transitioning from Stage 6 to Stage 12 and 81 percent for successfully transitioning from Stage 12 to approval.

[c] Calculated using equation 5.

In deciding whether to enter a given market, the generic applicant compares the expected cost, *E(CC),* to the expected present value of the revenues, *E(R)*, that it could recoup. Then the expected net present value, *ENPV*, of investing in the development project is given by:

$$ENPV_i^k = E(R^k) - E(CC) \tag{6}$$

where k = extra small, small, medium, large, and extra-large size market in terms of dollar volume. Thus, the generic applicant, for whom the average expected capitalized cost of development, *E(CC)*, is $6.5 million in the example above, will enter a given market, if the expected present value of revenues over the lifetime of its generic, *E(R)*, is $6.5 million or greater. The market share for a first-approval generic drug is often estimated as 50 to 80 percent of total annual sales of the RLD. Saha et al. (2006) reported a median market share of 55 percent for the first generic after one year; Grabowski et al. (2013) reported an average brand drug unit share one year after first generic entry at 16 percent. However, as more generic drugs enter a given market, the expected revenues for a generic company diminish. Thus, generic drug companies re-evaluate their market position continuously and may exit a market if sales volume is insufficient for profitability.

The present value of lifetime revenues for a generic manufacturer in a market sized k is given by:

$$E(R^k) = \sum_{t=1}^{T} E\left[\frac{R_t^k}{(1+r)^t}\right] \tag{7}$$

where r is the opportunity cost of capital (net of inflation) as before; R_t are revenues in year t with $t = 1,\ldots, T$ (time that the generic company exits the market).

As expected, the revenues in a given year will be inversely related to the number of generic competitors in the market. In a 2018 study, Olson & Wendling estimated the impact of generic competition on generic drug prices (see Table 3) during the 180-day exclusivity and outside the 180-day exclusivity periods (Olson & Wendling, 2018). Additionally, Berndt, et al. (2017) estimated that the median number of generic drug manufacturers in a market for a given molecule to be between 2 and 3.

Table 3. Relative Price of Generic Drug Compared to Pre-Entry Brand Drug Price in Percentage Terms

Number of Generic Competitors	During 180-Day Exclusivity	Outside Exclusivity
One Generic Manufacturer	74%	43%
Two Generic Manufacturers	64%	37%
Three Generic Manufacturers	38%	29%
Linear Trend Line where: x = Number of Generic Entrants y = Relative Generic Drug Price	y = -0.196x + 0.984 $R^2 = 0.974$	y = -0.219x + 0.851 $R^2 = 0.764$

Source: Tables 1 and 2 in Olson & Wendling (2018)

While these published estimates are informative, they are not sufficiently granular or provide the needed estimates for our analytical model purposes. To be able to project expected revenues in the analytical model, we need estimates of expected sales (in dollars and units) by type of drug and market size (e.g., extra small, small, medium, etc.) that take into account average number of companies (i.e., generic, AG, and brand) expected to serve those markets over time.

From the perspective of a generic company contemplating entry into a market, best predictor of the expected number of competitors and market share are historical estimates of these parameters from data, such as IQVIA NSP, readily available to the potential entrant. Thus, we used data from the IQVIA NSP, to empirically estimate expected revenues over time, by type of drug in five different sized markets (extra small, small, medium, large, and extra-large) where market size was defined as the average generic drug revenues corresponding to 20^{th}, 40^{th}, 60^{th}, 80^{th}, and 100^{th} percentile of the market, which accounted for the expected number of companies that would be serving each of those markets over time. The approach to estimating average market size is discussed in greater detail in Section 5.9.

5 MODEL PARAMETERS AND ASSUMPTIONS

To be able to operationalize the model described in Section 4, we need estimates of cost, duration, and transition success probability associated with each development stage as well as average annual revenues over time upon entry by type of generic drug. Table 4 presents the model parameter estimates and assumptions.

Table 4. Development Stages 1 through 9 – Baseline Model Parameter Estimates, by Type of Generic Drug

Development Stage	Baseline Model Parameter		Small Molecule Drugs	Topical Drugs	Narrow Therapeutic Index (NTI) Drugs	Inhalers	Liposomes, Dendrimers, Polymeric Micelles	Iron Carbohydrate Complexes	Glatiramoids	Ophthalmic Emulsions
Opportunity Cost of Capital (%)			8.82%							
Stage 1 – R&D to Establish Equivalence for API	Cost (in $ 2020)		$1,000,000	$1,000,000	$1,000,000	$1,000,000	$1,500,000	$2,000,000	$2,000,000	$1,500,000
	Duration (in Months)		5.5	5.5	5.5	5.5	9.0	9.0	9.0	9.0
	Success Probability (%)		90%	90%	90%	90%	78%	78%	78%	78%
Stage 2 – Formulation Development	Cost (in $ 2020)		$350,000	$350,000	$350,000	$350,000	$525,000	$700,000	$700,000	$525,000
	Duration (in Months)		21.0	21	21	21	34.4	34.4	34.4	34.4
	Success Probability (%)		90%	90%	90%	90%	85%	85%	85%	85%
Stage 3 – In-vitro Testing to Establish Equivalence for Formulations	Cost (in $ 2020)		$30,000	$30,000	$30,000	$30,000	$45,000	$60,000	$60,000	$45,000
	Duration (in Months)		1.0	1.0	1.0	1.0	1.6	1.6	1.6	1.6
	Success Probability (%)		90%	90%	90%	90%	85%	85%	85%	85%
Stage 4 – Initial Stability Testing on R&D Formulations	Cost (in $ 2020)		$100,000	$100,000	$100,000	$100,000	$150,000	$200,000	$200,000	$150,000
	Duration (in Months)		1.0	1.0	1.0	1.0	1.6	1.6	1.6	1.6
	Success Probability (%)		95%	95%	95%	95%	82%	82%	82%	82%
Stage 5 – Pilot Bioequivalence (BE) Study [e]	Healthy Volunteers	Per-subject Cost ($) [a]	$2,000	$19,000	$18,000	$25,000	$15,000	$23,000	$27,000	$27,000
		Number of Subjects	10	15	6	10	6	6	15	15
		Duration (in Months)	1.6	3.5	1.6	3.0	1.6	1.6	3.5	3.5
		Success Probability (%) [b]	65%	55%	60%	50%	60%	50%	50%	50%
	Patients	Per-subject Cost ($) [a]	$3,000	$38,000	$27,000	$50,000	$30,000	$46,000	$54,000	$54,000
		Number of Subjects	10	15	6	90	6	6	90	90
		Duration (in Months)	1.6	6.0	1.6	6.8	1.6	1.6	6.8	6.8
		Success Probability (%) [b]	65%	55%	60%	50%	60%	50%	50%	50%
	Patients & Clinical Endpoint	Per-subject Cost ($) [a]	$3,000	$38,000	$27,000	$50,000	$30,000	$46,000	$54,000	$54,000
		Number of Subjects	15	28	9	180	9	9	180	180
		Duration (in Months)	1.6	6.0	1.6	6.8	1.6	1.6	6.8	6.8
		Success Probability (%) [b]	65%	55%	60%	50%	60%	50%	50%	50%
Stage 6 – Biobatch Manufacturing for Stability & In vivo Testing	Cost (in $ 2020)		$525,000	$525,000	$525,000	$525,000	$787,500	$1,050,000	$1,050,000	$787,500
	Duration (in Months)		2.0	2.0	2.0	2.0	3.3	3.3	3.3	3.3
	Success Probability (%)		95%	95%	95%	95%	82%	82%	82%	82%
Stage 7 – Pivotal Bioequivalence (BE) Study on Healthy Volunteers [e]	Healthy Volunteers	Per-subject Cost ($)	$2,000	$19,000	$18,000	$25,000	$15,000	$23,000	$27,000	$27,000
		Number of Subjects	50	75	30	50	30	30	75	75
		Duration (in Months)	3.3	7.0	3.3	6.0	3.3	3.3	7.0	7.0
		Success Probability (%) [g]	65%	55%	60%	50%	60%	50%	50%	50%
	Patients	Per-subject Cost ($)	$3,000	$38,000	$27,000	$50,000	$30,000	$46,000	$54,000	$54,000

Development Stage	Baseline Model Parameter		Small Molecule Drugs	Topical Drugs	Narrow Therapeutic Index (NTI) Drugs	Inhalers	Liposomes, Dendrimers, Polymeric Micelles	Iron Carbohydrate Complexes	Glatiramoids	Ophthalmic Emulsions
Stage 8 - Pivotal Bioequivalence (BE) Study on Patients [e]		Number of Subjects	50	75	30	450	30	30	450	450
		Duration (in Months)	3.3	12.0	3.3	13.5	3.3	3.3	13.5	13.5
		Success Probability (%) [g]	65%	55%	60%	50%	60%	50%	50%	50%
	Patients & Clinical Endpoint	Per-subject Cost ($)	$3,000	$38,000	$27,000	$50,000	$30,000	$46,000	$54,000	$54,000
		Number of Subjects	75	140	45	900	45	45	900	900
		Duration (in Months)	3.3	12	3.3	13.5	3.3	3.3	13.5	13.5
		Success Probability (%) [g]	65%	55%	60%	50%	60%	50%	50%	50%
Stage 9 – Bridging Study	Healthy Volunteers	Cost (in $ 2020)	$20,000	$285,000	$108,000	$250,000	$90,000	$138,000	$405,000	$405,000
		Duration (in Months)	1.6	3.5	1.6	3.0	1.6	1.6	3.5	3.5
		Success Probability (%)	98%	98%	98%	98%	98%	98%	98%	98%
	Patients	Cost (in $ 2020)	$30,000	$570,000	$162,000	$4,500,000	$180,000	$276,000	$4,860,000	$4,860,000
		Duration (in Months)	1.6	6.0	1.6	6.8	1.6	1.6	6.8	6.8
		Success Probability (%)	98%	98%	98%	98%	98%	98%	98%	98%
	Patients & Clinical Endpoint	Cost (in $ 2020)	$45,000	$1,064,000	$243,000	$9,000,000	$270,000	$414,000	$9,720,000	$9,720,000
		Duration (in Months)	1.6	6.0	1.6	6.8	1.6	1.6	6.8	6.8
		Success Probability (%)	98%	98%	98%	98%	98%	98%	98%	98%
Stage 10 – Patent Challenge and Litigation Phase			See Table 8							
Stage 11 – Request for CGT Designation Statement & Pre-ANDA Meeting	Cost (in $ 2020)		NA							
	Duration (in Months)		0.5							
	Success Probability (%)		56%							
Stage 12 – FDA ANDA Preparation and Submission	Cost (in $ 2020)	With In vivo Studies [c] [f]	$471,899							
		With Biowaiver [d] [f]	$421,899							
	Duration (in Months)		28.4							
	Success Probability (%)		81.3%							
Stage 13 – REMS Submission	Cost (in $ 2020)		$100,000							
Stage 14 – Resubmission Addressing ANDA Deficiencies			NA							
Stage 15 – FDA Pre-approval Inspection (PAI)	Cost (in $ 2020)		$20,000							
	Success Probability (%)		90%							

Sources: ERG interviews with industry representatives; Shur, (2019); Hussaarts et al. (2017); Davit et al. (2008); Also refer to the model application in Excel for more detail on the source of each model parameter noted.
NA = Not applicable
[a] Assumes that the per-subject cost for a pilot study is equivalent to that for a pivotal study.
[b] Assumed that the probability of successfully transitioning to Stage 6 (Biobatch Manufacturing for Stability & In vivo Testing) is equivalent to the phase transition success probability of Pivotal BE Study stage (Stage 7 or Stage 8, whichever is applicable).

Development Stage	Baseline Model Parameter	Small Molecule Drugs	Topical Drugs	Narrow Therapeutic Index (NTI) Drugs	Inhalers	Liposomes, Dendrimers, Polymeric Micelles	Iron Carbohydrate Complexes	Glatiramoids	Ophthalmic Emulsions

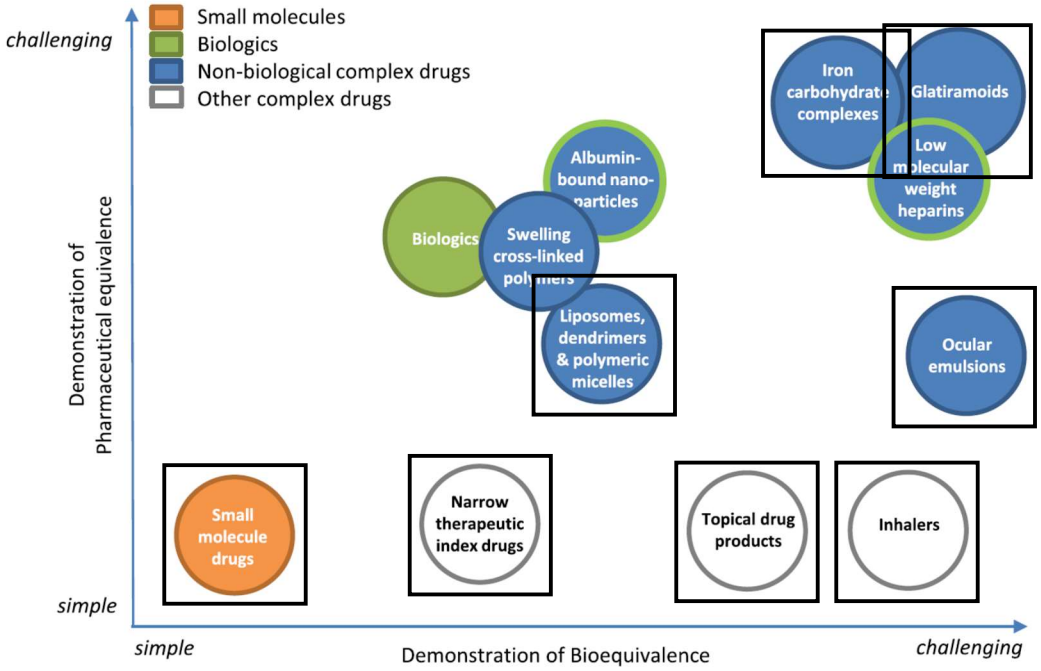
[c] Includes the FDA user fee of $371,899 for an applicant with a domestic FDF facility as described in Section 5.8.1 plus an ANDA preparation cost of $100,000.
[d] Includes the FDA user fee of $371,899 for an applicant with a domestic FDF facility as described in Section 5.8.1 plus an ANDA preparation cost of $50,000.
[e] The costs are for studies conducted in the U.S. The per-subject costs for studies conducted in India are estimated to be 60 percent of those in U.S.
]f] The average FDA user fees are for domestic facilities. The fees for foreign facilities are higher as described in Section 5.8.1.
[g] The industry representatives interviewed did not provide different estimates of phase transition success probability for BE studies on healthy volunteers and patients. They thought the primary driver of phase transition success probability is product type.

The estimates reflect information provided by the industry representatives interviewed, published studies, and analysis of IQVIA NSP data from January 2013 through June 2021. Where we did not have information on a particular type of drug or stage, we worked with a subject matter expert[12] to extrapolate missing values from the available data. The following sections provide further detail on how we estimated each of the model parameters. The parameter estimates are based on our synthesis of available information from disparate data sources described in Section 3 unless attributed to a specified source explicitly. The operational model developed allows the user to easily alter model parameters to evaluate special cases, specific generic drug markets, as well as the impact of different types of policies on generic drug developer returns. The user can also easily override certain assumptions of the model, such as re-try attempts that may not require a generic developer to repeat all development stages after a failure.

5.1 Types of Generic Drugs

Hussaarts et al., (2017) visualized the generic drug landscape by classifying drugs across two dimensions, demonstration of BE to RLD and demonstration of pharmaceutical equivalence (i.e., same active ingredient, dosage form, strength, and route of administration) to RLD, that range from simple to challenging (Figure 2).

Figure 2. Generic Drug Landscape



Source: Hussaarts et al. (2017)
Note: The black box indicates that the product type is included in the operational model.

[12] The subject matter expert consulted is Dr. Leon Shargel, founder and manager of Applied Biopharmaceutics, whose areas of experience and expertise include: planning, budgeting, and executing BA, BE, and PK studies in support of ANDA and NDA submissions; evaluating biopharmaceutic properties of drug products, including IVIVC; evaluating PK, BA and BE data; reviewing clinical and analytical research reports; auditing and monitoring CROs for FDA compliance; interacting with FDA, USP, and other regulatory agencies; and providing expert legal testimony in patent disputes. He has authored and co-authored several books and textbooks, including *Shargel and Yu's Applied Biopharmaceutics & Pharmacokinetics, 8th Edition; Comprehensive Pharmacy Review for NAPLEX; Generic Drug Product Development: Specialty Dosage Forms;* and *Generic Drug Product Development: Solid Oral Dosage Forms.*

The upper right quadrant of the figure includes those products with complex active ingredients and/or complex formulations for which demonstration of both BE and pharmaceutical equivalence are challenging. The remaining products in the figure include those with complex routes of delivery, dosage forms, or complex drug–device combinations, for which either the demonstration of BE or pharmaceutical equivalence is difficult. We adopted a modified version of this classification scheme for the model, excluding biologics, albumin-bound nanoparticles, swelling cross-linked polymers, and low molecular weight heparins. These categories were excluded because they overlap with biologics and/or represent a drug technology rather than a drug type.

There potentially is a third dimension to this figure (Figure 2) applicable to complex drug-device combination products which may pose engineering challenges and may require additional studies, such as comparative use human factor studies, to ensure that the product "…is safe and effective for use by the intended users, uses, and environments" (U.S. Food and drug Administration, 2018). While we did not explicitly incorporate this consideration into the baseline model, the user of the operational model could accommodate the additional costs associated with these studies by allocating higher costs to the early R&D stages (Stages 1 through 4 in Figure 1) and/or altering the per subject costs for BE studies (Stages 5, 7, and 8 in Figure 1). Comparative use human factor studies can be explicitly incorporated into the future versions of the operational model if needed.

5.2 Opportunity Cost of Capital

Opportunity cost of capital, r, represents the rate of return (net of inflation) that the generic drug company would otherwise be able to earn per year at the same risk level as the investment in the new generic drug selected. The value of r is expected to vary by company-specific factors, such as existing product portfolio and size of company, as well as other exogenous factors, such as economic and regulatory climate for generic drug development. Table 5 presents estimates of real opportunity cost of capital from different sources. From the table, the value of r ranges from a low of 4.75 percent to a high of around 10.49 percent, with an average value of 8.82 percent. In the model, we use the average value, 8.82 percent, as our baseline estimate.

Table 5. Opportunity Cost of Capital (r) Estimates

Data Source	Firm Size	Type of Model	Study Period	Opportunity Cost of Capital
DiMasi, et al. (2016)	All	CAPM	2010	9.40%
Damodaran (2019)	All	CAPM	2018	10.49%
Damodaran	All	CAPM	2019	8.51%
Damodaran	All	CAPM	2020	4.75%
Harrington (2012)	All	CAPM	2006-2008	9.30%
	Large	CAPM	2006-2008	9.50%
	Small	CAPM	2006-2008	8.60%
ERG expert interviews	All	NA	NA	10.00%
Average	**NA**	**NA**	**NA**	**8.82%**

NA = Not applicable/available
CAPM = Capital asset pricing model

5.3 Initial Research and Development Phase (Stages 1 through 6)

During the initial research and development phase, the generic drug company typically must undertake to:

- Obtain API to be used for prototype development and obtain API used by brand drug (RLD) (Stage 1).

- Perform analytical tests on generic and brand APIs to assure equivalence between the two (Stage 1)—If the RLD is a complex novel product requiring specialized analytical methods, it may be necessary for the generic manufacturer to develop the analytical methods needed to demonstrate equivalence for the API. However, for most small molecule drugs, this process involves a generally simple structural characterization.
- Obtain samples of RLD to reverse engineer and develop one or more formulations of the generic drug (Stage 2) —The generic manufacturer may need to develop and validate a different drug release mechanism if the RLD has patents around its drug release mechanism. This may require specialized equipment and knowhow that may require outsourcing this activity to a CRO.
- Perform in vitro bench testing of generic formulation(s) to evaluate pharmaceutical equivalence between the RLD and the generic formulation(s) (Stage 3)—The generic formulation(s) may have a different drug release mechanism than the RLD due to RLD's patents. Therefore, the drug release profile in vitro may not be the same as the RLD. However, the formulation(s) can still be bioequivalent in vivo.
- Initiate short-term, bench testing of stability of prototype generic formulation(s) batches to identify any shelf-life problems before producing greater quantities for use in in vivo studies and stability testing (Stage 4).

  If needed, conduct a pilot study on the R&D batches of the prototype generic formulation(s) to determine if the formulation, or which of the formulations if more than one is developed, is a close match to the RLD (Stage 5). Occasionally, a generic drug company undertakes one or more pilot studies of a generic drug candidate before entering into a full-scale BE or clinical endpoint study. Pilot BE studies are implemented using between 10 to as high as 200 subjects depending on the type of generic drug, usually not long after the generic emerges from preliminary stability testing conducted during R&D. Pilot studies are "…used to validate analytical methodology, assess variability, optimize sample collection time intervals, and provide other information" (U.S. Food and Drug Administration, 2013). The pilot study replicates the method and procedure of the planned BE study as closely as feasible in order to identify any issues that could compromise the results of the full-scale study. The pilot study also ideally provides a preview of how the generic will do in the full-scale study relative to the RLD, either achieving comparable clinical results or comparable maximum concentration (C_{max}) and area under the curve (AUC) ratios. Research on the topic has shown that 12-subject studies were good predictors of the AUC ratio but did not correlate very well for the C_{max} (Moreno-Arza, et al., 2015; Moreno, et al., 2016). If the procedures and results of the pilot study do not provide company personnel with confidence that the candidate generic can emerge successfully from the BE study, further R&D will be needed to find and correct any problems, naturally adding to the cost of development.
- Manufacture three biobatches (around 100,000 doses per batch) of generic formulation selected that is representative of the eventual commercial product, for use in in-vivo studies and stability testing (Stage 6).
- Initiate meetings with FDA to seek guidance and clarification, especially if the generic formulation is a non-biological complex product (Stages 1 through 6).

The cost, duration, and the probability of successfully transitioning to the next stage of development associated with each of these development stages, as well as this phase as a whole,

will vary based on the type of drug, the degree of difficulty of obtaining necessary quantities of the API and RLD, and the availability of analytical methods, specialized equipment, and experience appropriate to the tasks.

As noted above, the company also initiates stability testing of manufactured biobatches during this stage. The purpose of stability testing is to evaluate, improve, and develop a formula that provides a consistent therapeutic effect throughout its shelf-life. Techniques for testing stability include exposure to high temperatures, light, transport stresses, and other forms of forced degradation designed to accelerate the testing. Analytical methods include chromatography, spectroscopy, and micrography. The generic drug company may conduct their own stability testing or engage a contractor. Because stability testing can take from 6 months to 18 months, some companies will initiate their full-scale in vivo testing before the final results of the stability tests are recorded.

5.4 In Vivo Testing Phase (Stages 7 and 8)

In a successful research and development phase, the generic drug company will have established equivalence of its API and formulation; gained some assurance of the formulation's stability and, optionally, its BE to the RLD through a pilot study; and manufactured biobatches of the formulation. The company will then begin testing its generic formulation in human subjects to establish BE through scientific evidence.

In accordance with FDA guidance, in vivo studies need to be conducted in individuals 18 years or older who can give informed consent. In general, the study population should be representative of the general population with respect to gender, age, and race, to avoid results distorted by an unrepresentative sample. If other types of populations are considered, such as the elderly or patients, the study designs must account for the "…subjects' stress, blood loss, the status of chronic disease, and pharmacokinetic (PK) effects of altered organ function … as these factors may alter the drug absorption profiles [and/or inflate intra- and inter-subject variabilities]" (Chow, 2014).

In vivo BE studies can be based on PK, pharmacodynamic (PD), or clinical endpoints. PK endpoint BE studies are often performed on healthy subjects and are "…based on the assumption that the therapeutic effect of a drug product is a function of the systemic exposure or excretion profile of the active ingredient" (Zou & Yu, 2014). However, PK endpoint studies are not "…applicable when: (1) the drug and/or metabolite concentrations in plasma and/or urine are negligible; (2) drug and/or metabolite concentrations cannot be reliably measured based on currently available analytical methods; or (3) the measured drug concentration is not an indicator of efficacy and safety of a particular drug product." (Zou & Yu, 2014) These types of products require PD or clinical endpoint studies to demonstrate BE, often requiring a patient population with symptoms that the tested drug is designed to treat. For certain drug products, however, comparative clinical endpoint studies are currently the only acceptable approach to assess BE.

The type of study population, healthy volunteers versus patients, is one of the primary drivers of BE study cost, duration, and phase transition success probabilities. Industry representatives also indicated that the cost of conducting these studies in India is 40 to 50 percent lower than in the U.S. Thus, we estimated that in vivo studies conducted in India cost 60 percent of those conducted in the U.S., overall.

5.4.1 Pivotal Bioequivalence (BE) Study on Healthy Volunteers (Stage 7)

BE studies on healthy subjects (fasting or not) involve PK endpoints and compare the systemic effects and bioavailability of the candidate generic with the RLD by comparing specific relevant parameters. Frequently, these are: maximum concentration of the measured analyte in

plasma (C_{max}) and the area under the plasma drug concentration-time curve (AUC). Time required to reach C_{max} (T_{max}) may also be assessed. AUC reflects the body's actual total exposure to the drug after administration of a drug product and C_{max} reflects the rate of drug exposure.

The number of healthy subjects used in BE studies varies considerably. The optimum number recommended by FDA depends on several statistical variables, high within-subject PK variability being an important factor. Davit, et al. (2008) examined the sample sizes in BE studies from FDA's 2003 to 2005 data set and reported that: "For drugs that were highly variable in C_{max}, the number of study subjects ranged from 18 to 134, with an average of 46 subjects per study. For drugs with lower variability in C_{max}, the number of study subjects ranged from 12 to 113, with an average of 31 subjects per study. For drugs that were highly variable in $AUC_{0\rightarrow t}$, the number of study subjects ranged from 24 to 134, with an average of 55 subjects per study. For drugs with lower variability in $AUC_{0\rightarrow t}$, the number of study subjects ranged from 12 to 113, with an average of 32 subjects per study."

Based on that report, we judged that the number of healthy subjects needed for a BE study ranges from 30 for narrow therapeutic index (NTI) drugs to as high as 75 for more complex drugs, such as ophthalmic emulsions. The cost per subject, which includes recruitment, volunteer costs (e.g., meals, lodging, travel, stipend), blood, urine, or other types of needed tests, RLD drug costs, packaging, clinical facilities, data internalization, bioanalytical analysis, PK and statistical analysis, and report generation, varies from $2,000 for simple small molecule drugs to as high as $27,000 per subject for more complex formulations. In theory, these could be built up and easily altered in the model to accommodate higher/lower than expected per-subject costs. A BE study on healthy volunteers could last from 3.3 months to 7 months (inclusive of statistical analysis and reporting), although one interviewee noted that these could be performed on an expedited basis depending on the circumstances. The average success rate for a pivotal BE study on healthy volunteers ranges from 50 to 65 percent depending on the type of drug. There is some evidence that conduct of a pilot BE study (see Section 5.3) improves the design of pivotal studies and allows for faster screening of formulations, saving time and resources (Best Practices, LLC, Undated). Thus, in the model, we assumed that the conditional probability of success for a pivotal BE study, given that a pilot BE study has been performed, is 25 percent higher than those presented in Table 4 for the pivotal BE study stage (Stages 7 and 8).

5.4.2 Pivotal Bioequivalence (BE) Study on Patients (Stage 8)

As noted above, when PK endpoint studies are not appropriate, PD or clinical endpoint BE studies are warranted. These types of BE studies are conducted on patients, and they compare the therapeutic effects of the generic formulation and the RLD. They are often needed if the drug in question has a localized effect (e.g., diminishing psoriatic plaque, shrinking a tumor).

PD endpoint BE studies are appropriate (Zou & Yu, 2014):

- If quantitative analysis of the API and/or metabolite(s) in plasma or urine cannot be performed with sufficient accuracy and sensitivity based on the currently available analytical methods.
- If measurements of API concentrations cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular drug product.
- For locally acting drug products, such as human gastrointestinal (GI) tract locally acting drugs, topically applied dermatologic drugs, and oral inhalation drugs.

There are, however, certain drugs for which a comparative clinical endpoint BE study is the only acceptable approach for demonstrating BE. Such products include some topical formulations, e.g., adapalene, ciclopirox, and diclofenac sodium; ophthalmic solutions, e.g., cyclosporine,

brinzolamide, and ciprofloxacin hydrochloride; and vaginal formulations, e.g., clindamycin phosphate, dinoprostone, and terconazole, among others (U.S. Food and Drug Administration, 2020d). Comparative clinical endpoint BE studies are "appropriate for dosage forms intended to deliver the active moiety locally, forms that are not intended to be absorbed, or drug products for which traditional [PK] studies are not feasible" (U.S. Food and Drug Administration, 2017b) and PD endpoint-based studies are not applicable.

The contrast between healthy-subject BE studies and those that require patients[13] is stark. The latter are costlier and are likely more susceptible to inconclusive or negative results. PD endpoint BE studies on patients are less expensive than comparative clinical endpoint BE studies, which often need to recruit several hundreds of subjects, due in part to more complex experimental designs involving a placebo group and the need to assume a large number of patients dropping out. For example, Shur (2019) reported that the cost of a comparative clinical endpoint BE study for an inhaled drug was around $45 million and involved more than 900 subjects (i.e., $50,000 per subject). Recruitment for both types of BE studies on patients can be difficult because the universe of potential subjects is limited, and many patients are naturally reluctant to be involved in testing an as-yet unapproved formulation that does not promise to be superior to the brand drug already available to them. All these factors combine to make BE studies on patients far more costly than healthy subject BE studies.

We judged that, on average, the per-subject costs for BE studies on patients are 50 percent higher than those involving healthy volunteers, ranging from $3,000 per subject for simple small molecule drugs to $54,000 for highly complex formulations. Similarly, these studies are generally longer for certain types of drugs, e.g., topical drugs and inhalers. While the number of subjects needed for a clinical endpoint BE study on patients is expected to be similar to that for a PK BE study on healthy volunteers, comparative clinical endpoint BE studies likely require more patients (estimated at 50 percent more than an endpoint BE study on patients).

5.5 Bridging Study (Stage 9)

FDA defined comparability bridging study as, "A study performed to provide nonclinical or clinical data that allows extrapolation of the existing data from the drug product produced by the current process to the drug product from the changed process." (U.S. Food and Drug Administration, 2005). In the context of generic drug development and testing for BE, a bridging study may be deemed necessary if BE studies and stability testing are under way and the generic sponsor needs to change their product's formulation. This can occur due to changes in the supply chain of excipients or even the API, or, more frequently, because stability testing of the generic formulation begins to reveal signs of early deterioration. Although the in vivo BE study is in progress, the company will nevertheless have to reformulate the generic drug to address the stability issue(s) that have arisen. To avoid the cost of suspending the BE study and starting from scratch with the reformulated product, the manufacturer can perform a bridging study to show that the reformulated product has the same PK properties as the original and that the only difference between the two is improved stability. Forced degradation techniques in stability testing can expose stability issues while the batch being used in the BE study remains stable. Thus, the bridging study can preserve the validity and reliability of the BE data.

Bridging studies are not commonly done for the majority of generic drugs. They are occasionally done for complex combination products (e.g., metered dose inhalers or dry powder inhalers), and such products comprise a small portion of the total ANDA submissions to FDA.

[13] BE studies on subjects diagnosed with the condition that the proposed generic drug is intended to treat may be necessary if the drug acts locally and not systemically, or if the drug could have serious adverse effects on the health of asymptomatic (i.e., healthy) subjects.

Hence, none of our interviewees were able to offer an estimate of how much such studies cost on average and how long they last. Thus, we assumed that the cost and duration of a bridging study is similar to that of a pilot BE study in the model. We further gauged that these studies, when needed, likely have a high success rate (98 percent) irrespective of pilot BE study type (e.g., healthy volunteers, patients, or patients with clinical endpoint).

5.6 Patent Challenge and Litigation Phase (Stage 10)

A generic company can pursue FDA approval for a generic drug before the patents related to the RLD that the generic company is aiming to reverse engineer are expired. To do this, the generic company must provide certification in its ANDA "…that a patent submitted to FDA by the brand-name drug's sponsor and listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book)[14] is, in the generic applicant's opinion and to the best of its knowledge, invalid, unenforceable, or will not be infringed by the generic product." This is a "paragraph IV certification," or a PIV certification (U.S. Food and Drug Administration, 2021). The first company (or companies) to successfully submit a "substantially complete" ANDA containing a PIV certification to "…at least one of the patents listed in the Orange Book is generally eligible for the exclusive right to market the generic drug for 180 days." (U.S. Food and Drug Administration, 2021) When a generic drug company decides to file a PIV patent certification, they weigh the probability and value of eligibility for 180 days of exclusivity in the generic market and the value of a potential settlement with the brand company against the litigation costs, the cost of potential delay of market entry caused by the legal action, and the cost of losing the challenge (or infringement suit) outright.

A PIV certification can have a substantial impact on a drug development project's timeline and projected expenses. A 180-day exclusivity resulting from a patent challenge, however, can provide 90 percent or more of the total revenue of the generic drug over its marketed life and hence could raise the ENPV of the project despite the added expense of litigation. The actual "certification" is a statement from the generic applicant, submitted with the ANDA application, that a patent submitted to FDA by the brand drug's sponsor and listed in FDA's Orange Book is, "in the generic applicant's opinion and to the best of its knowledge, invalid, unenforceable, or will not be infringed by the generic product" (U.S. Food and Drug Administration, 2021), and must be accompanied by a statement that the generic applicant will provide notice to the RLD application holder (i.e., brand company) and any patent owner(s) detailing certain information, including the factual and legal basis of the applicant's opinion that the patent is invalid, unenforceable, or will not be infringed. The brand company then has 45 days to file an infringement suit against the generic company. This filing triggers a 30-month stay in the ANDA approval.

The generic company may incur litigation costs if the brand company files an infringement lawsuit. Because the filing can trigger a 30-month stay of FDA's approval, this may extend the time to market for the generic.[15] Although 95 percent of all patent litigation ends in settlement (Bernard, 2014), this is not true of Hatch-Waxman litigation. According to Grabowski, et al. (2017), only 39 percent (ranging from 26 to 42 percent depending on the type of patent challenge) of Hatch-Waxman related cases were settled (Table 6) for the top quintile of drugs (by U.S. sales) from 1994 to 2006 and 37 percent of cases resulted in a win for generic applicants. Estimates of outcomes

[14] Section 21 CFR 314.53(b), brand drug holders need to list the following types of patents in the Orange Book: (1) drug substance (ingredient); (2) drug product (formulation and composition); and (3) method of use. FDA does not allow listing of process patents and patents claiming packaging, metabolites, or intermediates.

[15] The 30-month stay only delays the final approval of the ANDA, not the scientific review. FDA can issue a tentative approval (as shown in Figure 1) if the review is completed before the 30-month stay expires.

data by Grabowski, et al. (2017), however, stand in contrast to an earlier report prepared by the Federal Trade Commission (FTC) which showed that "generic applicants have prevailed in 73 percent of the cases in which a court has resolved the patent dispute [between 1992 and 2000]" (Federal Trade Commission, 2002). More recently, Jacobo-Rubio, et al., (2020) examined all PIV certifications from 1985 to 2010, which they filtered to 274 cases involving different APIs. They found that, of the 274 cases, 18 percent were uncontested by the brand company; 36 percent were settled before or during litigation, but before a court decision; and 46 percent were litigated to a decision. We used the estimates from Grabowski, et al. (2017) shown in Table 6 in the model as the authors broke down the likelihood winning/losing/settling a PIV challenge by type, i.e., drug substance, method of use, and drug product.

Table 6. Outcomes of Paragraph IV (PIV) Actions for the Top Quintile of Drugs by Dollar U.S. Sales, 1994-2006

Type of Patent Challenge	Brand Win		Generic Win		Settled		Total Number (N) [a]
	N	%	N	%	N	%	
Drug Substance (Active Ingredient)	18	55%	1	3%	14	42%	33
Method-of-use	9	19%	16	33%	22	46%	47
Drug Product (Formulation Only)	1	3%	25	71%	9	26%	35
Overall	**28**	**24%**	**42**	**37%**	**45**	**39%**	**115**

Source: Grabowski, et al. (2017)
[a] Excludes cases that were ongoing at the time of analysis.

AIPLA conducts a biennial economic survey of its members (American Intellectual Property Law Association, 2019). Among several areas of inquiry is a series of questions on the cost of Hatch-Waxman litigation by stage of litigation, including through trial and appeal. The median estimates for the cost of Hatch-Waxman litigation for cases with greater than $25 million at risk are presented in Table 7.[16] From the table, the median cost of litigation if the case goes to court is $3.5 million including pre- and post-trial expenses as well as cost of any appeals. These costs could be much higher for high-value RLDs as the RLD owner brand companies will be more likely to defend the patents of such high-value RLDs aggressively. The operational model allows the user to alter litigation costs for those cases if desired.

Several variables affect the potential costs to a generic company of patent litigation. One factor driving costs is whether the litigation is settled out of court through mediation. Another very significant factor involves the role a given generic company plays in the litigation. Because two or more generic companies can have FTF status—and thus be eligible to participate in the 180-day period of market exclusivity—there are often multiple FTF generic litigants. In these cases, one of the litigants typically takes the lead role in the litigation, while others "piggyback" on their efforts (assuming they are making similar non-infringement and/or invalidity claims for their generic versions). One IP attorney interviewed for the study opined that the cost to the piggybacking

[16] The normal context of patent infringement litigation is one in which the alleged infringer has gone to market at risk and the patent holder sues them for damages i.e., lost revenue due to the infringer's presence in the market. Because the alleged infringer in Hatch-Waxman litigation has rarely ever entered the market at the time of trial, the patent holder in the Hatch-Waxman context has not yet lost any revenue. The "amount at risk" in the usual sense may be low, as the profits for the generic company and the lost revenue for the brand company are as yet theoretical; nevertheless, the stakes can be enormous. We interpreted as related to the combined revenue potentially lost by both litigants should judgment go against them. As a proxy for this sum, we used 80 percent of the brand drug's annual revenue for the year before generic entry. For the brand drugs we are examining, just four show year-before-generic-entry revenues under $31.25 million ($25 million/0.80), so we decided to apply the litigation costs associated with the highest dollars-at-risk category of the AIPLA survey questionnaire (adjusted on the advice from our Hatch Waxman expert attorney).

company(ies) is about one-tenth of the cost to the company leading the litigation, with the legal work increasingly performed by smaller regional firms. This expert also observed that it is now virtually unheard of for there to be just one FTF generic company when a new chemical entity (NCE) first becomes subject to a PIV certification challenge. We estimated that the cost of piggybacking is 50 percent lower than leading the litigation when the case results in a win or loss. For those cases that end in settlement, we estimated the cost of piggybacking only includes that of initial case management and mediation.

Table 7. Estimated Costs of Hatch-Waxman Litigation by Stage for Those Cases where Greater Than $25 Million is at Risk [a]

Stage of Litigation [b]	Median Cost ($)	Adjusted Median Cost ($) [c]
Initial Case Management	$400,000	$280,000
Inclusive of discovery, motions, and claim construction	$3,000,000	$2,100,000
Inclusive of pre- and post-trial, and appeal (when applicable)	$5,000,000	$3,500,000
Cost of mediation	$150,000	$105,000

Source: American Intellectual Property Law Association (2019)
[a] "At risk" refers to the financial impact of an adverse judgment.
[b] The figures represent the median of values reported by respondents to question 36 of the AIPLA survey: What is your estimate of the total cost of patent infringement action of the following varieties: (i) Through the initial case management, (ii) Inclusive of discovery, motions, and claim construction, (iii) Inclusive of pretrial, trial, post-trial, and appeal (when applicable), and (iv) For actions in which the dispute was resolved through mediation, what was the cost of the action up through mediation?
[c] ERG adjusted the AIPLA reported costs for 2019 down by 30 percent based on an interview in 2021 conducted with an IP attorney highly experienced in Hatch-Waxman PIV litigation.

The type of PIV challenge, patent invalidity versus non-infringement, also serves as a determining factor for the decision to lead or follow. Our interviewee noted that patent non-infringement typically will preclude the ability to piggyback as each litigant would need to demonstrate that their version of the drug does not infringe on the RLD patent(s). In contrast, a challenge to the validity of an RLD patent provides litigants with the option to follow or lead. Table 8 presents the estimated IP litigation-related parameters by type of patent challenge, type of PIV challenge, litigation strategy, and outcome. According to an analysis by the FTC of 104 PIV suits filed during the 1992-2000 period, it took an average of 25 months and 13 days (25.4 months) for a district court to reach a decision on a patent infringement lawsuit. The time from filing to a court of appeals decision was 37 months and 20 days (37.7 months) (Federal Trade Commission, 2002). FTC (2002) also predicted that future litigations may take longer to resolve, especially if multiple patents are applicable.

Table 8. IP Litigation Model Parameters and Assumptions

Type of Patent Challenged	Type of Paragraph IV (PIV) Certification	Litigation Strategy	Outcome	Average Total Litigation Cost ($) [a]	Average Litigation Duration (in Months) [b]	Average Litigation Outcome Probability (%) [c]
Drug Product (Formulation and Composition)	Patent Noninfringement	Lead	Win	$3,500,000	45.10	71%
			Settle	$2,205,000	30.87	26%
			Lose	$3,605,000	45.10	3%
	Patent Invalidity	Lead	Win	$3,500,000	45.10	71%
			Settle	$2,205,000	30.87	26%
			Lose	$3,605,000	45.10	3%
		Follow	Win	$1,050,000	45.10	71%
			Settle	$385,000	30.87	26%
			Lose	$1,102,500	45.10	3%
	Both Patent Invalidity and Noninfringement	Lead	Win	$3,500,000	45.10	71%
			Settle	$2,205,000	30.87	26%
			Lose	$3,605,000	45.10	3%
Drug Substance (Active Ingredient)	Patent Noninfringement	Lead	Win	$3,500,000	45.10	3%
			Settle	$2,205,000	30.87	42%
			Lose	$3,605,000	45.10	55%
	Patent Invalidity	Lead	Win	$3,500,000	45.10	3%
			Settle	$2,205,000	30.87	42%
			Lose	$3,605,000	45.10	55%
		Follow	Win	$1,050,000	45.10	3%
			Settle	$385,000	30.87	42%
			Lose	$1,102,500	45.10	55%
	Both Patent Invalidity and Noninfringement	Lead	Win	$3,500,000	45.10	3%
			Settle	$2,205,000	30.87	42%
			Lose	$3,605,000	45.10	55%
Method-of-use	Patent Noninfringement	Lead	Win	$3,500,000	45.10	34%
			Settle	$2,205,000	30.87	47%
			Lose	$3,605,000	45.10	19%
	Patent Invalidity	Lead	Win	$3,500,000	45.10	34%
			Settle	$2,205,000	30.87	47%
			Lose	$3,605,000	45.10	19%
		Follow	Win	$1,050,000	45.10	34%
			Settle	$385,000	30.87	47%
			Lose	$1,102,500	45.10	19%
		Lead	Win	$3,500,000	45.10	34%

Type of Patent Challenged	Type of Paragraph IV (PIV) Certification	Litigation Strategy	Outcome	Average Total Litigation Cost ($) [a]	Average Litigation Duration (in Months) [b]	Average Litigation Outcome Probability (%) [c]
	Both Patent Invalidity and Noninfringement		Settle	$2,205,000	30.87	47%
			Lose	$3,605,000	45.10	19%

[a] Figures are based on the adjusted median cost ($) reported in Table 7.
[b] We assumed that the litigation duration is equivalent to the 30-month stay granted by the FDA when the brand company whose patent is challenged files suit in response to an ANDA submission with PIV certification by the generic applicant. The actual duration of litigation can be shorter or longer than 30 months depending on the case.

Jacobo-Rubio, et al., (2020) found that, from PIV filing, it takes 30.87 months to get a decision at the district court, and 45.1 months for a decision from the appellate court. Thus, in our model, the average time from ANDA submission with PIV certification to resolution is 45.1 months for those cases that are litigated in court and 30.87 months for those that are settled on average. Further, using estimates in Table 7, we estimated that cases that result in a win for the generic litigants cost $3.5 million (inclusive of case management, discovery, motions, and claim construction, pre- and post-trial, and appeal costs) for the lead litigant and $1.05 million (50 percent of costs including case management, discovery, motions, and claims construction) for the other litigants. For cases that result in a loss, we estimated that the costs to the lead litigant would be $3.605 million (inclusive of case management, discovery, motions, and claim construction, pre- and post-trial, appeal, and mediation costs) and $1.103 million (50 percent of costs including case management, discovery, motions, claims construction, and mediation) for the other litigants. For cases that are settled out of court, we estimated the cost to the lead litigant at $2.205 million (inclusive of case management, discovery, motions, and claim construction, and mediation costs) and $0.385 million (inclusive of case management and mediation costs) for the remaining litigants.

5.7 Request for Competitive Generic Therapeutic (CGT) Designation Statement & Pre-ANDA Meeting (Stage 11)

The FDA Reauthorization Act of 2017 (FDARA) created the competitive generic therapeutic (CGT) pathway. If requested by the generic drug developer, FDARA allows FDA to designate a drug with "inadequate generic competition" as a competitive generic therapy. The Act gives FDA the flexibility to expedite the development and review of ANDAs for a CGT-designated drug. FDARA also created an alternative 180-day exclusivity for "…the first approved applicant of a drug with a CGT designation for which there were no unexpired patents or exclusivities listed in the Orange Book at the time of original submission of the ANDA…to incentivize competition for drugs that are not protected by patents or exclusivities and for which there is inadequate generic competition" (U.S. Food and Drug Administration, 2020).

Applicants can submit a request for CGT designation that includes information supporting their "inadequate generic competition" claim any time before or concurrent with submitting the ANDA. Once CGT status is granted, the applicant can also submit a request for a pre-submission meeting to "…discuss and explain the format and content of the ANDA to be submitted (e.g., the types of data that will be contained in the ANDA, the data that will support equivalence claims)" (U.S. Food and Drug Administration, 2020). "[CGT] designation has been a significant advancement in helping to bolster generic drug competition in the US," said FDA Commissioner Stephen Hahn, noting that the Agency has received more than 350 CGT requests" (Mezher, 2020). According to FDA's CGT approvals list, FDA has made determinations on 96 CGT requests as of July 29, 2021. Of these 96 CGT applications, 42 (43.8 percent) were deemed not to qualify for the CGT designation sought. Among those that qualified for the CGT designation, 9 (16.7 percent) forfeited their eligibility for exclusivity because they did not market the drug within 75 days after the date of approval of the ANDA (U.S. Food and Drug Administration, 2021).

Receipt of CGT designation can bolster financial outlook of the recipient due to 180-day exclusivity period revenues. For example, Glenmark Pharmaceuticals received a CGT designation for its hydrocortisone valerate ointment USP, 0.2%. The FDA approval of its ANDA with the CGT designation not only led to an increase in its share price (5 percent), but also contributed to an 11 percent increment in the company's US business for the financial year 2018-2019 (Mathai, 2019).

We assumed that the cost of putting together a justification was negligible, but it may take about 2 weeks (0.5 month) to get the needed information collected internally and submitted to FDA. While the likelihood of FDA approval of a CGT request is 56.2 percent (= 1 - 43.8 percent),

this does not affect the likelihood of overall ANDA approval in the model. Obtaining CGT designation could affect the revenue side as it may increase the expected revenues for the first 180-days of marketing. However, we have not identified how much, if any, revenue increase would be typical.

5.8 FDA Abbreviated New Drug Application (ANDA) Phase (Stages 12 through 15)

5.8.1 FDA ANDA Preparation and Submission (Stage 12)

FDA's final guidance titled *ANDA Submissions – Content and Format* lists the information that should be provided in each section of the common technical document (CTD) for human pharmaceutical product applications (U.S. Food and Drug Administration, 2019a). The CTD consists of five modules: Administrative Information and Prescribing Information, Summaries, Quality, Nonclinical, and Clinical. The guidance recommends that the Summaries module include (1) an overview of the chemistry, manufacturing, and controls (CMC) section of the application, (2) summary information about the drug substance (i.e., the API) and the drug product, and (3) summary data critical to the determination of BE. The Quality module needs to contain all of the CMC information necessary to support the application, including information about the drug substance, drug product, stability data, and regional information, among others. The Nonclinical module needs to include study reports and/or safety assessments conducted in support of a proposed specification only if applicable. Finally, the Clinical module should contain all of the data needed to support the application and to demonstrate that the generic drug product is bioequivalent to the RLD.

The type of information included in the Clinical module related to the demonstration of BE depends on whether the ANDA qualifies for a biowaiver. A biowaiver eliminates the need for a drug manufacturer to demonstrate in vivo BE; instead, they need only show in vitro equivalence by demonstrating certain characteristics similar to the RLD (or a previously approved generic of a higher dose that passed a BE study) (U.S. Food and Drug Administration, 2017a). There are different types of biowaivers. One typical type of biowaiver is through the Biopharmaceutical Classification System (BCS), for which FDA recommends that the applicant perform in vitro solubility, dissolution, and permeability tests (U.S. Food and Drug Administration, 2017a). Manufacturers can request a biowaiver for generic products that are immediate release, solid oral dosage forms of a drug.[17] The biowaiver package needs to include data from the proposed generic product demonstrating high solubility, high permeability, and rapid or very rapid dissolution; a description of the method of manufacture; lists of excipients in the test generic and the RLD; and, for BCS class 3 drugs, the formulation similarity of the test drug and the RLD.

The costs and time required to prepare a biowaiver submission are expected to be much lower and shorter than a typical submission involving a BE study. The biowaiver pathway is more relevant for simple drugs. If the drug product does not qualify for a biowaiver, then information on in vivo BE studies needs to be provided in the Clinical module, including their design and outcome. The submitter is also required to summarize the outcome of all in vivo studies conducted, regardless of their outcome, in a summary table.

[17] FDA may also waive in vivo testing for some topical medications, which often require a clinical study. In recent years FDA has been considering alternatives such as in vitro studies, dermatopharmacokinetic methods, dermal microdialysis, near-infrared spectroscopy, and dermal open-flow microperfusion (dOFM) as potential substitutes for in vivo testing of some topically applied drugs (Lu, et al., 2016; U.S. Food and Drug Administration, 2017)..

Upon preparing the CTD, the generic drug company then needs to submit the package (in paper or electronic form) to the FDA and pay a submission fee within 20 calendar days of ANDA filing. Table 9 depicts the various user fees assessed by the FDA from 2018 through 2021.

Table 9. Industry User Fees under Generic Drug User Fee Amendments (GDUFA) II

User Fee Type		FY 2018	FY 2019	FY 2020	FY 2021
ANDA		$171,823	$178,799	$176,237	$196,868
DMF [a]		$47,829	$55,013	$57,795	$69,921
Program [f]	Large Size	$1,590,792	$1,862,167	$1,661,684	$1,542,993
	Medium Size	$636,317	$744,867	$664,674	$617,197
	Small Size	$159,079	$186,217	$166,168	$154,299
Facility	Domestic API [b]	$45,367	$44,226	$44,400	$41,671
	Foreign API [b]	$60,367	$59,226	$59,400	$56,671
	Domestic FDF [c]	$211,087	$211,305	$195,662	$184,022
	Foreign FDF [c]	$226,087	$226,305	$210,662	$199,022
	Domestic CMO [d]	$70,362	$70,435	$65,221	$61,341
	Foreign CMO [d]	$85,362	$85,435	$80,221	$76,341
Backlog [e]		$17,434	$17,434	$17,434	$17,434

Source: (U.S. Food and Drug Administration, 2019b)
[a] DMF = Drug Master File
[b] API = Active Pharmaceutical Ingredient
[c] FDF = Finished Dosage Form
[d] CMO = Contract Manufacturing Organization
[e] This is a one-time backlog fee set in 2013.
[f] FDA assesses each company and its affiliates an annual program fee depending on the number of approved ANDAs in their portfolio. The three tiers of the program fee include:

- Large: 20 or more approved ANDAs
- Medium: between 6 and 19 approved ANDAs
- Small: 5 or fewer approved ANDAs

The generic company pays a two-part fee: a base fee for the ANDA submission and a calculated fee based on the API and facility. For example, an ANDA submitter that will be manufacturing its own API in two domestic facilities, X and Y, and its FDF in domestic facility X will be paying a total of $531,889 to the FDA in 2020 as shown in Table 10.

Table 10. 2020 GDUFA II Fees for a Hypothetical ANDA Submitter

Fee Component	Amount
ANDA Submission Fee	$176,237
DMF Submission Fee [(1 Facility X + 1 Facility Y) ×$57,795]	$115,590
Facility Fee [Facility X for API ($44,400) + Facility Y for FDF ($195,662)]	$240,062
Total	**$531,889**

For modeling purposes, we assume that the average ANDA submitter will likely be purchasing, not manufacturing, its API (which would allow for referencing the DMF of the API manufacturer) and only producing the finished dosage form (FDF) in its facility. Thus, we estimate the average GDUFA II user fee paid upon submitting an ANDA at $371,899 (= ANDA submission fee of $176,237 plus an FDF facility fee of $195,662) for a domestic and $386,899 for a foreign (= ANDA submission fee of $176,237 plus an FDF facility fee of $210,662) generic drug company. We also assume that the fee will be paid in the form of a constant stream of equal-sized payments throughout the duration of FDA review rather than a lump-sum, upfront payment in the baseline case. We further assumed that the program fee the applicant pays FDA annually will remain unchanged, i.e., if the applicant was paying $664,674. in annual program fees previously, they will

continue to pay the same amount after their new ANDA is approved by FDA. In reality, it is possible for the annual program fee to increase if the ANDA approval in question changes the program fee tier the company is in. Finally, we assumed a fixed cost of $100,000 for ANDA package preparation. We further judged that ANDA packages for those applications that qualify for a biowaiver would cost 50 percent less to prepare ($50,000).

To estimate the likelihood of FDA approval, we reviewed publicly available reports of generic drug program activities over time (Table 11).

Table 11. GDUFA Receipts and Actions, FY 2013 - FY 2020

Category	FY 2020	FY 2019	FY 2018	FY 2017	FY 2016	FY 2015	FY 2014	FY 2013	Total
GDUFA Actions									
RTR – Originals	42	52	127	142	246	236	173	150	1,168
Withdrawals - Original ANDAs	293	388	606	214	248	170	179	107	2,205
Approvals	737	935	781	763	651	492	409	440	5,208
Tentative Approvals	172	236	190	174	184	120	91	95	1,262
Complete Responses (CR)	2,010	2,310	2,648	1,603	1,725	1,180	1,254	1,251	13,981
GDUFA (Receipts) Submissions									
ANDAs [a]	865	909	1,044	1,306	852	539	1,473	968	7,956
Probability of ANDA Approval (%) [b]									**81.3%**

Source: U.S. Food and Drug Administration (2021)
RTR = Refuse to Receive
[a] ANDA Original Receipts are reported as raw receipts (versus filed receipts).
[b] The figure is computed by dividing the sum of approvals and tentative approvals across all reporting years by the number of ANDAs received, i.e.,

$$\frac{(5{,}208 \text{ Approvals} + 1{,}262 \text{ Tentative Approvals})}{7{,}956 \text{ ANDAs Received}} = 81.3 \text{ percent}$$

Some applicants withdraw their ANDAs after receiving one or more complete response letters instead of addressing the deficiencies in their ANDAs and resubmitting, whereas others do not take any action in response to a complete response letter, but do not officially withdraw their application. This coupled with the fact that timing of FDA approval of an ANDA may not coincide with the calendar year in which the ANDA was submitted, it was necessary to look across years to estimate the FDA approval probability for the model. Using the sum of ANDA approvals and tentative approvals as the numerator and the number of ANDAs received as the denominator over FY 2013 through FY 2020, we estimated the average probability of FDA approval at 81.3 percent.

We used data provided by FDA's OGD for CY 2019 to estimate the average duration for the FDA ANDA phase, from initial ANDA submission to approval (final or tentative). Table 12 presents the distribution of ANDA approvals by FDA in CY 2019 by number of cycles to approval. Overall, the average time from ANDA submission to FDA approval in CY 2019 was 28.4 months (range: 13.5 – 66.3 months). The average ANDA application required 2.47 cycles to approval. Further, about 20 percent of ANDAs received first-cycle approval, i.e., were approved without receiving a complete response letter (CRL). This figure is a significant improvement over previous reported figures; less than 1 percent before 2012 (prior to GDUFA implementation) and 12 percent for the FY 2015 – FY 2017 period (Mezher, 2019). The average approval time for first-cycle approvals was 10.6 months (range: 7.7 – 19.6 months), substantially lower than the overall average approval time. Our interviewees noted that the majority of ANDAs receive complete response letters upon initial submission and often go through multiple revisions and re-submissions. Thus, we used the overall average time from ANDA submission to FDA approval of 28.4 months as the FDA average FDA ANDA phase duration than encompasses Stages 12 and 13.

Table 12. FDA ANDA Approval Times for CY 2019, by Number of Review Cycles [a]

Cycles to Approval	Number of Applications	Percent	Average Approval Time (Months)	Minimum Approval Time (Months)	Maximum Approval Time (Months)
1	152	19.7%	10.6	7.7	19.6
2	260	33.7%	21.9	10.0	73.8
3	235	30.4%	35.3	15.8	80.8
4	100	13.0%	48.8	20.6	80.7
5	18	2.3%	57.2	30.7	83.6
6	5	0.6%	56.9	46.7	67.6
7	1	0.1%	77.2	77.2	77.2
8	1	0.1%	67.5	67.5	67.5
Total [b]	**772**	**100.0%**	**28.4**	**13.5**	**66.3**

Source: U.S. Food and Drug Administration (2020a)
CY = Calendar year
[a] The figures exclude backlog applications. Backlog applications are any ANDAs submitted to FDA that were not withdrawn, tentatively approved, or approved by October 1, 2012, when the GDUFA program began. Because pre-GDUFA review cycles were not as clearly defined as GDUFA review cycles, it is difficult to attribute a specific number of review cycles to backlog applications.
[b] The figure is the weighted average of reported approval times by review cycle where the weights are the number of applications.

5.8.2 Risk Evaluation and Mitigation Strategy (REMS) Submission (Stage 13)

FDA requires drugs that have the potential to cause serious or catastrophic adverse events if not properly prescribed, administered, or monitored to have a Risk Evaluation and Mitigation Strategy (REMS) that will "inform and/or support the safe use conditions described in the medication's FDA-approved prescribing information" (U.S. Food and Drug Administration, 2019c). If an innovator drug product is subject to REMS, the ANDA referencing that product is subject to the medication guide (MG) and Elements to Assure Safe Use (ETASU). An ANDA applicant may use a single shared system (SSS) REMS with the innovator drug for any ETASU or may develop its own different but comparable system.[18] Thus, any generic version of an RLD with a REMS must either negotiate to enter an SSS REMS with the innovator or develop and maintain its own REMS. Table 13 lays out the different components that a REMS program can have. According to FDA data, there are a total of 14 shared system REMS programs as of March 2020. Of these programs, all 14 have ETASU, 11 have implementation systems, 5 have MGs, and none have a communication plan component (U.S. Food and Drug Administration, 2020c).[19]

Table 13. Components of a REMS Program [a]

REMS Component	Description
Medication Guide (MG) or Patient Package Insert	▪ Provides FDA-approved patient-friendly labeling. ▪ Must meet requirements of 21 CFR 208: MG can be required if FDA determines one or more: – Patient labeling could help prevent serious adverse events.

[18] The revised policy is the result of the Appropriations Act 2020 (December 20, 2019) that changed section 505–1(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355–1). Along with other changes, the statement that "The Secretary may waive the requirement under the preceding sentence for a drug that is the subject of an abbreviated new drug application, and permit the applicant to use a different, comparable aspect of the elements to assure safe use…" was removed. There is no longer a requirement to form a SSS REMS and there is no longer such thing as a waiver of that requirement.
[19] As of August 24, 2020, there are 13 shared system REMS programs because the Ambrisentan PS REMS and the Ambrisentan REMS merged in April 2020. Of these programs, all 13 have ETASU, 10 have implementation systems, 5 have MGs, and none have a communication plan component.

REMS Component	Description
	– The product has serious risks that could affect patient's decision to use or continue to use. – Patient adherence to directions is crucial to product effectiveness.
Communication Plan (CP) for Healthcare Providers	FDA-approved materials used to aid sponsor's implementation of REMS and/or inform healthcare providers about risks
Elements to Assure Safe Use (ETASU)	▪ Depending on the risk, a REMS may require any or all of the following: – Certification or specialized training of HCPs who prescribe the drug. – Certification of pharmacies or other dispensers of the drug. – Dispensing/administration of drug in limited settings e.g., hospitals. – Dispensing/administration of drug only with evidence of safe-use conditions. – Each patient using the drug is subject to certain monitoring. – Enrollment of treated patients in registries.
Implementation System	▪ REMS may include an implementation system related to the following ETASU: – Certification of pharmacies and hospitals. – Healthcare settings. – Safe use conditions. ▪ May require applicant to take reasonable steps to: – Monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements. – Work to improve implementation of such elements by such persons.

Source: Lippmann (2017)
[a] Not all REMS programs have all of these components; some, for example, just consist of MG and ETASU.

In recent years, brand drug companies have used the REMS system to delay generic entry by (1) obstructing generic drug companies from getting samples of the REMS brand drug for testing (a practice which brand drug companies use to obstruct access to non-REMS products as well through exploitation of voluntarily-imposed restricted distribution programs) and (2) engaging in dilatory shared-REMS negotiations. FDA has acted to inhibit these obstructive activities.[20] In addition, Congress passed the law widely known as the CREATES Act in 2019, which established a pathway for generic and other drug developers to obtain access to needed product samples for drug development.

The cost of a shared or new REMS program is expected to vary significantly, as these programs differ in their complexity and entail both origination and maintenance costs.[21] REMS programs with an ETASU and/or implementation system appear to be the most onerous to set up and operate, and thus are likely to impose a higher burden on the generic company. However, as more companies join an SSS, the set-up and maintenance costs of the program would be shared across all participants lowering this burden on each individual participant. There are also

[20] FDA-issued guidance directs SSS negotiations to be completed within the timeframe of GDUFA II goal dates (Dabrowska, 2018).
[21] REMS may also require different BE study protocols. For instance, if REMS prevent prescribing to women that may become pregnant, a company may decide to only enroll healthy males instead.

independent contractors specializing in the design and maintenance of REMS so smaller generic companies that may not have expertise in this area are not necessarily shut out.

For the baseline model, we judged that the cost of joining an existing REMS program would be around $100,000 on average.

5.8.3 Resubmission Addressing ANDA Deficiencies (Stage 14)

Upon receipt of the ANDA application and payment of the GDUFA II fees, the generic company faces one of three outcomes:

- *A refuse-to-receive (RTR) decision* – An RTR decision indicates that the ANDA is not sufficiently complete to enable a substantive review by the FDA (U.S. Food and Drug Administration, 2016). The submitter can get 75 percent of the GDUFA II fees paid refunded if (1) the ANDA was refused for a cause other than failure to pay fees, or (2) the ANDA was withdrawn prior to receipt (Section 744B(a)(3)(D)(i) of the FD&C Act).
- *A Complete Response Letter (CRL)* – A CRL lays out FDA's review of the ANDA and the subsequent finding that it cannot approve the application in its present form under (21 CFR §314.110). A CRL describes the reasons for finding the ANDA submission inadequate and may include recommendations on how the submitter needs to address the identified deficiencies, which could be minor or major. The ANDA submitter then can amend the application and seek another full FDA review, withdraw its application, or, in some cases, not respond. Upon receipt of a resubmission, FDA reviews changes made to the ANDA in response to deficiencies identified and can either approve the application or issue another CRL.
- *A tentative or final approval* – If FDA deems that an ANDA meets the substantive requirements for approval, it issues an approval letter to the submitter. The FDA approval granted can be final or tentative; the latter is issued if the RLD is subject to unexpired patents or exclusivities.

According to a 2019 study by the U.S. Government Accountability Office (GAO), among all ANDAs reviewed by FDA over a three-year period—fiscal year (FY) 2015 through FY 2017—only about 12 percent were approved on the first cycle (Government Accountability Office, 2019). In their report, GAO identified the following factors that may have contributed to first-cycle ANDA approval (U.S. Government Accountability Office, 2019):

- **Application sufficiency.** ANDA completeness and the degree to which an applicant comprehended and fulfilled requirements influence the first-cycle approval likelihood. Applicants that are more experienced and have submitted several ANDAs are more likely to receive first-cycle approvals. In contrast, applicants that were refused previously are slightly less likely to receive first-cycle approvals.
- **Deficiencies in drug quality.** Issues related to facilities manufacturing the drug can affect drug quality and/or stability. Such problems preclude first-cycle approval.
- **Type of drug application.** Likelihood of first-cycle approval varies by several drug characteristics, including the drug's active ingredient, formulation, and route of administration. Complex drugs are less likely to receive first-cycle approval, except for topical creams (Table 14).
- **Application's priority status.** FDA may grant priority review status to certain applications, such as first generics or generics that could help address public emergencies. GAO's analysis shows that the first cycle approval rate for first generics was one-third the rate for all other priority applications and less than half the first cycle

approval rate for ANDAs without priority designation (Table 14). GAO notes that this may be due to lower quality applications from first generics as they rush to be the first to submit an application to FDA.

Table 14. First-cycle ANDA Approvals by Route of Administration and Priority Review Status, FY 2015 – FY 2017 [a]

Category	Total Applications Reviewed by FDA	Applications that Received First-cycle Approval [b]	
		Number	Percent
Route of Administration			
Topical	205	52	25%
Ophthalmic	41	0	0%
Transdermal	20	0	0%
All Other Routes of Administration	1,764	188	11%
Priority Review Status			
Applications with a first generic priority designation	516	32	6%
All other applications with priority designations	66	12	18%
Applications with no priority designation	1,448	196	14%
All Applications	**2,030**	**240**	**12%**

Source: U.S. Government Accountability Office, (2019)
[a] A first-cycle approval means an applicant receives ANDA approval from FDA without receiving a CRL.
[b] Includes both final and tentative approvals.

We acknowledge that there may be added costs to the generic applicant for a first-cycle approval in theory. For example, an applicant might take additional time and expend more resources to reverse engineer the product; to conduct more than one BE study; or expand the sample size for its BE study to improve chances for a first-cycle approval. While such costs are not accounted for in our baseline model, the user of the operational model could alter these values under the change scenario if deemed relevant for the analysis at hand.

This GAO finding is in line with what we have heard during our generic drug company interviews. Most interviewees reported receiving a CRL and having to address several deficiencies before receiving approval. As expected, this was more common for non-biological complex generics than simple generics.

As noted above, we did not delineate the costs or duration associated with this stage in the baseline model, as the values used for these parameters for Stage 12 already embody those that an average generic drug applicant would face at this stage.

5.8.4 FDA Pre-approval Inspection (PAI) (Stage 15)

When the ANDA is deemed approvable, FDA may conduct a pre-approval inspection (PAI) of the facility that will be manufacturing the FDF. The goal of a PAI is to ensure that the manufacturing establishment named in the ANDA is in fact capable of manufacturing the drug, and that the data submitted in the ANDA's CMC section are accurate and complete (DiGIulio, 2015). FDA uses a set of risk-based priority inspection criteria to determine whether to conduct a PAI. These criteria take into account several facility, product, and process risks, as shown in Table 15.

For the baseline model, we gauged that it would cost around $20,000 for a facility to prepare for and host a PAI, and that the likelihood of success would be 90 percent on average. Because these inspections are carried out before an ANDA can be approved, we did not allocate any additional time for them beyond that estimated in the baseline model for the ANDA stage overall.

Table 15. FDA Risk-Based Priority Inspection Criteria for Pre-Approval Inspections (PAIs)

Facility Risks	Product Risks	Process Risks
CGMP issues relevant to application product	New molecular entity [a]	Narrow therapeutic range (95%-105%)
Recent FARs relevant to application product	First application filed by applicant	API derivation is high risk (derived from animal tissue)
Recent recalls relevant to application product	First ANDA filed for an approved drug	PAT, NIR, QbD
Numerous applications filed at once	RLD has complaints, ADEs, stability issues	Development data are incomplete
	Patient population or for serious condition	Batch records non-specific
	Breakthrough therapy, shortage situation	Complicated process
		Substantially different process than previously covered at facility

Source: DiGIulio (2015)
PAT = Process Analytical Technology
NIR = Near-infrared spectroscopy
QbD = Quality by design
[a] Not applicable to ANDAs.

5.9 Expected Revenues

We used IQVIA NSP to estimate, by type of drug, the revenue stream that a generic drug company can reasonably anticipate upon entry into different size markets. The IQVIA NSP data set we used covered the period January 2013 through June 2021 and included the dollar and unit sales for prescription and over-the-counter (OTC) drugs sold to retail and non-retail channels by manufacturers and wholesalers in the U.S. The full list of variables we had available for the study is presented in Appendix A (Table A - 1).

To create the analysis subset, we first excluded all OTC products, identified by the Rx Status variable (i.e., RxStatus = Rx). Next, we reclassified those entries for which the Brand-Generic variable was "Branded Generic" as "Generic" if the specific market included a Brand drug and "Brand" if the specific market did not include a Brand drug. The reclassification reflects our assumption that the marketing behavior of branded generics would be similar to brand drugs in those markets where the only competition the branded generic manufacturer faces would be from other generic drug manufacturers serving the same market. These branded generic drugs include "[1] novel dosage forms of off-patent products, often in combination with another molecule, [i.e.] line extensions of off-patent products, [2] on patent with a trade name, but a molecule copy of an originator product FDA approved under an existing NDA, [3] off-patent drugs with a trade name, [or] [4] off patent [drugs] without a trade name and commonly manufactured by a single source or co-licensed from the NDA holder, [such as] sterile hospital solutions" (Berndt, et al., 2017).

We further narrowed down the subset by excluding those observations where the Combined Molecule, Brand-Generic, Sales, or NSP Extended Units variables was "Blank." Next, we converted all dollar sales into December 2020 U.S. dollars using the seasonally adjusted medical care price index for all urban consumers (Table A - 2) (U.S. Bureau of Labor Statistics, 2021).

Finally, we mapped the product formulation types provided by the Product Form 3 variable into the aggregate product form categories below and then to the different drug types we need for the model (Table A - 3):

- Oral - oral tablets, capsules, powder, liquid, etc.

- Injectable – Injectable or infusion products.
- Topical – Dermatological creams, ointments, washes, etc.
- Inhaled - Inhaled products.
- Ophthalmic – Ophthalmic products.
- Other – Other formulations such as otic drugs, suppositories, patches, etc.

For each of the markets below, we looked at the distribution of brand and generic company sales by aggregate product form category for each 12-month increment and calculated the 20th, 40th, 60th, 80th, and 100th percentile values. We used these percentile values to define market size, such that products with sales less than the 20th percentile sales estimate in a given aggregate product form category and 12-month period were considered to be in an extra-small market, those with sales greater than equal to the 20th percentile sales estimate but less than the 40th percentile sales estimate were considered to be in a small market, etc. We then evaluated the average generic and brand company sales (in dollars and units) as well as the average number of generic and brand companies with sales in each of these different-sized markets from extra small to extra large over time.

5.9.1 Paragraph IV (PIV) Generic Drug Market

We defined our Paragraph IV (PIV) market for the model by identifying those drugs with a PIV certification and market sales within 75 days of receiving their final ANDA approval from FDA during the January 2013 and June 2021 period. To identify these drugs, we relied on the *FDA Paragraph IV Certifications List*, which provides information on the date of first approval by the first applicant, date of first commercial marketing of the approved drug, the expiration date of the final brand drug patent (which pre-empts the 180-day exclusivity, if expiration occurs before the 180 days are up) along with other relevant information, such as the active ingredient name, dosage form, and strength (U.S. Food and Drug Administration, 2021). The list included a total of 1,340 entries from 2004 through July 2021 at the time it was accessed for this study.

Next, we applied the series of criteria depicted in Figure 3 to identify those drugs that received final ANDA approval from FDA and began marketing their product within 75 days of receiving that approval[22] whether alone or shared with one or more other FTF generics, between January 1, 2013 and June 30, 2021. This initially yielded a total of 49 products for our PIV market (Table A - 4), which constitute less than 1 percent of all ANDAs approved by FDA during the same time period. Examining these entries in detail, we then took the following steps:

- Three of the 49 drugs had more than one entry listed, even though the multiple entries were not materially different. Specifically, we combined the following entries into one market:

– Three entries for carvedilol phosphate—one for 10 and 20 mg ER tablets, one for 40 mg ER tablets, and a third for 80 mg ER tablets. We considered that these four strengths of the

[22] The failure to market forfeiture provision at 505(j)(5)(D)(i)(I) requires a series of later than/earlier than date analysis to come to the failure to market date, which is not always 75 days after approval. Also, FDA cannot complete this analysis unless an event under Section (bb) of the failure to market provision has also occurred. This means that the FTF does not necessarily have to begin commercial marketing within 75 days of FDA approval or risk forfeiting its exclusivity. However, we had to define a marketing time cutoff to make the analysis tractable given the time period our sales data covered. This may have resulted in a smaller than possible PIV market sample.

same form of the drug constituted one market, as they all had the same RLD and were approved and first marketed on the same days.

- Two entries for dexmethylphenidate ER capsules with strengths of 25 mg and 35 mg, also had the same RLD, approval date, and first commercial marketing date.
- We also combined two entries for doxycycline hyclate delayed release capsules of 50 mg and 200 mg. Although they did have a four-day difference in their initial marketing dates, we reasoned that this discrepancy would be innocuous, given that our sales data were on a monthly basis.
  - We dropped desonide gel (generic of Desonate, NDA 21844) from the analysis because it entered the market just 3½ weeks before the RLD's listed patent would expire.
  - Once sales data were obtained and reviewed, we found that IQVIA had recorded no sales at all for six entries during their 180-day exclusivity periods that had begun when they notified FDA that they had commenced commercial marketing. These six drugs—generics for Pristiq (NDA 21992), Canasa (21252), Istalol (21516), Entereg (21775), Aczone (207154), and Jadenu (206910)—were therefore eliminated from further analysis. [23]

This left 38 PIV generic drug markets as the subjects for this analysis of the 180-day Hatch-Waxman exclusivity (Table A - 4). We then matched the exact molecule, dosage, and formulation (e.g., oral tablet, injection) of these 38 products in the IQVIA NSP data, creating our PIV market subset.

Given the date of market entry by the FTF generic company in market *i*, the total 180-day exclusivity sales, $TS_{exclusivity}$, for any given company, *j*, in that same market can be calculated as the simple sum of that company's daily sales, *DS*, from the date of FTF generic company entry through the end of 180 days, ,. i.e.,

$$TS_{i,j,exclusivity} = DS_{i,j,1} + DS_{i,j,2} + \ldots + DS_{i,j,180} \tag{8}$$

However, it is not possible to calculate 180-day exclusivity sales in this manner because: 1) sales are reported on a monthly rather than a daily basis in the IQVIA NSP data we have available for this study, and 2) the 180-day exclusivity clock that begins on the first day of marketing by the FTF generic company to enter the market does not necessarily fall on the first day of a month.

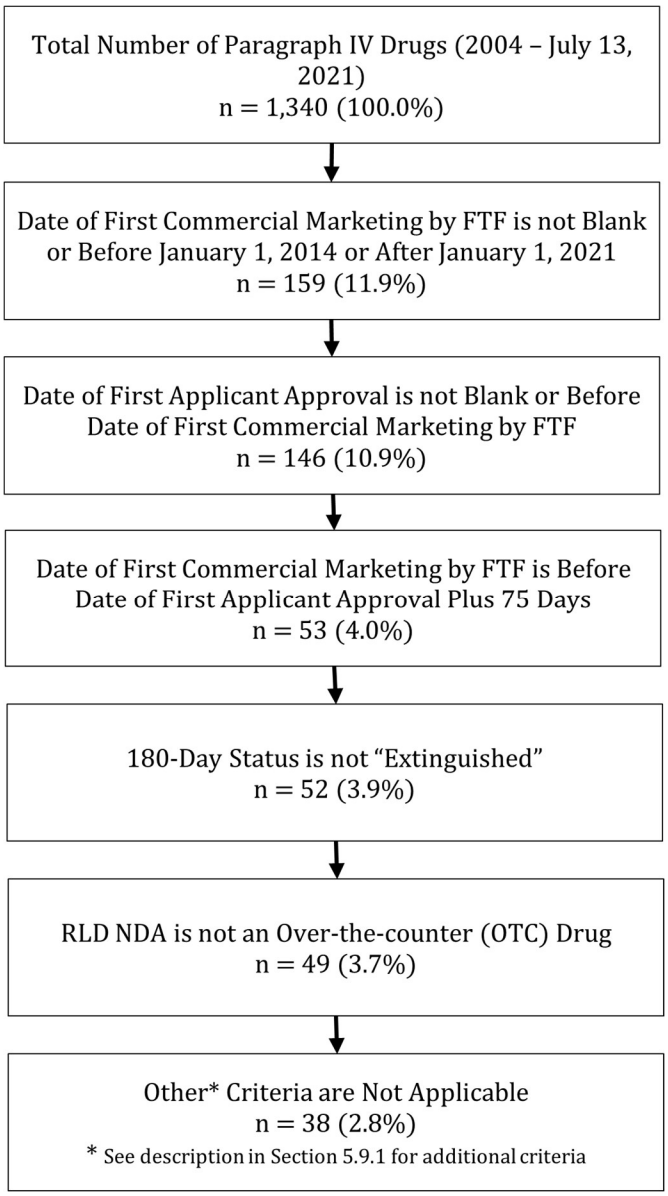
We approximated the 180-day exclusivity sales for a company *j* in market *i* by summing the monthly sales, *MS*, over a 6-month period (instead of 180 days that would correspond exactly to the 180-day exclusivity) as given in equation 2 below:

$$TS_{i,j,exclusivity} \cong MS_{i,j,1} + MS_{i,j,2} + \ldots + MS_{i,j,6} + \left(\frac{d}{30.5}\right) MS_{i,j,7} \tag{9}$$

[23] The effect of reporting the start of commercial marketing to FDA is to start the 180-day exclusivity clock for all contemporaneous and prospective PIV filers. If another company does not obtain FDA approval within the 180 days, then the exclusivity is extinguished and no longer exists as an incentive. Reasons for this unexpected finding are hypothetical, but two of the FTF drugs had, according to contemporary reports, settled their patent litigation with the RLD companies.

where *d* is the day of the month in which the FTF generic company market entry has occurred. For example, if the FTF generic company *j* entered market *i* on April 7, 2018 the exclusivity period for that market *i* lasts through October 7, 2018.

Figure 3. Identification of In-scope Paragraph IV (PIV) Drugs



Then, using equation 9 above, total exclusivity period sales for any given company *j* in that market can be calculated as:

$$TS_{i,j,exclusivity} \cong MS_{i,j,Apr18} + MS_{i,j,May18} + \ldots + MS_{i,j,Sep18} + \left(\frac{7}{30.5}\right) MS_{i,j,Oct18} \quad (10)$$

Then, we calculated the 6-month sales following the exclusivity period through the last 6-month period for which we have complete sales data for that market and company as:

$$
\begin{aligned}
TS_{i,j,1} &\cong \left(\frac{30.5-d}{30.5}\right)MS_{i,j,7} + MS_{i,j,8} + \ldots + MS_{i,j,12} + \left(\frac{d}{30.5}\right)MS_{i,j,13} \\
TS_{i,j,2} &\cong \left(\frac{30.5-d}{30.5}\right)MS_{i,j,13} + MS_{i,j,14} + \ldots + MS_{i,j,18} + \left(\frac{d}{30.5}\right)MS_{i,j,19} \\
TS_{i,j,3} &\cong \left(\frac{30.5-d}{30.5}\right)MS_{i,j,19} + \ldots
\end{aligned}
\tag{11}
$$

We used the same approach for calculating sales in dollars and units for all companies serving a given market *i* but also identified whether a company was an RLD, an AG, or a generic manufacturer. We identified the AG company in each market by using FDA's *Listing of Authorized Generics as of July 1, 2021* and the search function at authorizedgenerics.com. Out of the 38 markets noted in Table A - 4, 25 (65.8 percent) had an AG during the 180-day exclusivity period.

Next, we calculated the 12-month RLD sales prior to generic entry in a market *i* using the same approach, i.e.,:

$$
TS_{i,RLD,0} \cong \left(\frac{30.5-d}{30.5}\right)MS_{i,RLD,1} + MS_{i,RLD,2} + \ldots + MS_{i,RLD,12} + \left(\frac{d}{30.5}\right)MS_{i,RLD,13} \tag{12}
$$

Thus, in the example provided above with the FTF generic company entering a market *i* on April 7, 2018, 12-month sales for the RLD prior to entry by the FTF generic company into market *i* was calculated as:

$$
TS_{i,RLD,0} \cong \left(\frac{30.5-7}{30.5}\right)MS_{i,RLD,Apr17} + \ldots + MS_{i,RLD,Mar18} + \left(\frac{7}{30.5}\right)MS_{i,RLD,Apr18} \tag{13}
$$

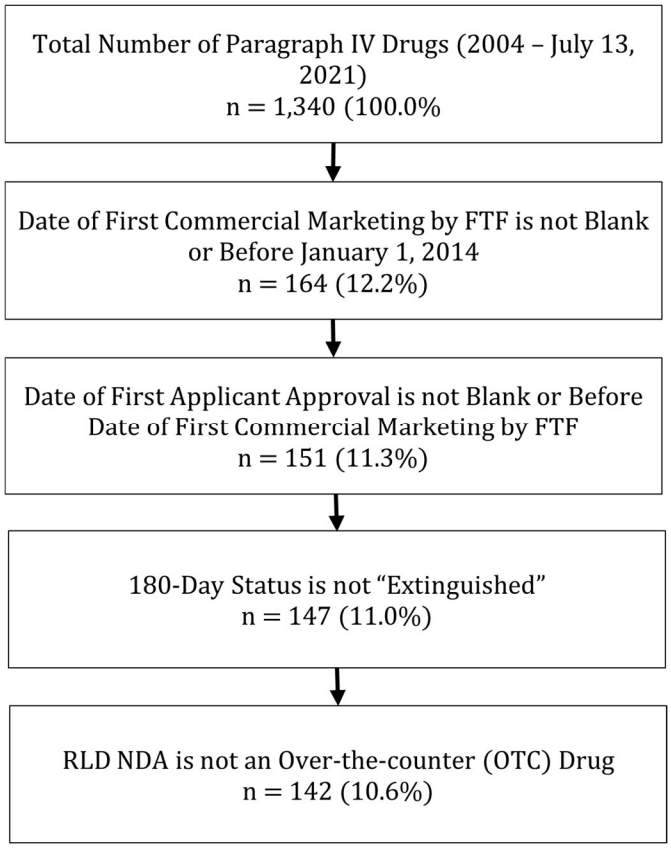
Finally, to evaluate the added value of a PIV certification to a generic company, we first created a Paragraph III (PIII) matched control group. For each of the PIV markets identified in Table A - 4, we matched the 12-month RLD sales prior to generic entry in the PIV market with that of an RLD that has the same aggregate product form category assignment (e.g., oral, injectable, etc.) and similar (+/− 8 percent) 12-month RLD sales prior to generic entry in the PIII market. Next, we calculated the difference between the average exclusivity sales for a generic company in the PIV market and the average initial 6-month sales for a generic company in the matched PIII market. This difference expressed in percentage terms represents the average value of the 180-day exclusivity for a generic company that pursues the PIV certification route in their ANDA in the model.

5.9.2 Paragraph III (PIII) Generic Drug Market

We defined a Paragraph III (PIII) market as one in which a generic company can enter via a Paragraph III certification on their ANDA. A PIII certification applies to those RLDs with an unexpired patent listed in the Orange Book that the generic drug applicant agrees to wait until the relevant patent's expiration before requesting final approval of its ANDA (U.S. Food and Drug Administration, 2020). We applied several criteria to isolate PIII markets in the IQVIA NSP data. First, it was necessary to exclude all potential PIV markets which included those identified in Section 5.9.1 plus those that could be PIV markets but were eliminated because the FTF generic

company did not begin marketing within 75 days of final FDA ANDA approval or began marketing after February 1, 2021. Figure 4 presents the criteria applied to identify potential PIV markets for exclusion. Application of the criteria in Figure 4 to the *FDA Paragraph IV Certifications List* resulted in 142 potential PIV markets which we excluded from the IQVIA NSP data (Table A - 5).

Figure 4. Identification of Potential Paragraph IV (PIV) Markets for Exclusion from Paragraph III (PIII) Markets



Next, we wanted to narrow down the data to include only those markets where we observed only brand sales for a full 12 months before any generic sales during the January 2013 – June 2021 period (i.e., 102 months of sales). For this part of the analysis, we first aggregated all strengths of the same dosage form associated with a given molecule where dosage form corresponded to the aggregate product form categories described previously. For example, if a given molecule X (e.g., value of the Combined Molecule variable in IQVIA NSP) had an oral and an injectable formulation each with multiple strengths, e.g., 5 mg, 10 mg, 25 mg for oral and 20 mg, 50 mg, and 100 mg for injectable, we defined two separate markets; a Molecule X-Oral and a Molecule X-Injectable market by aggregating the sales of all oral dosage strengths for the Molecule X-Oral market and those of all injectable dosage strengths for the Molecule X-Injectable market. The approach "… implies that different manufacturers selling the same [molecule-dosage form combination] are competing in the same product market [and] different manufacturers selling different [molecule-dosage form combinations]… used for the same or similar clinical purpose are not competing in the same product market" (Berndt, et al., 2017; Conti, RM; Berndt, ER, 2020). Then, we subset our data to include only those markets where 1) we had at least 12 months of brand sales data during which there were no generic sales and 2) generic sales were observed in month 13 or later. Then for each market, we calculated the 12-month total brand sales (in dollars

and units) pre generic entry and sales post generic entry in 12-month increments through June 2021. For example, if generic entry in a given market occurred in January 2018 in market *i*, we calculated the 12-month brand sales prior to generic entry, TS_0, as:

$$\begin{aligned} TS_{i,RLD,0} &\cong MS_{i,RLD,Jan17} + MS_{i,RLD,Fed17} + \ldots + MS_{i,RLD,Nov17} + MS_{i,RLD,Dec17} \\ TS_{i,RLD,1} &\cong MS_{i,RLD,Jan18} + MS_{i,RLD,Fed18} + \ldots + MS_{i,RLD,Nov18} + MS_{i,RLD,Dec18} \\ TS_{i,RLD,2} &\cong MS_{i,RLD,Jan19} + \ldots \end{aligned} \quad (14)$$

where *MS* represents monthly sales as before. For the same market, we also calculated the total generic 12-month sales upon entry as well as successive 12-month sales through June 2021, i.e.,

$$\begin{aligned} TS_{i,GEN,1} &\cong MS_{i,GEN,Jan18} + MS_{i,GEN,Feb18} + \ldots + MS_{i,GEN,Nov18} + MS_{i,GEN,Dec18} \\ TS_{i,GEN,2} &\cong MS_{i,GEN,Jan19} + MS_{i,GEN,Feb19} + \ldots + MS_{i,GEN,Nov19} + MS_{i,GEN,Dec19} \\ TS_{i,GEN,3} &\cong MS_{i,GEN,Jan20} + \ldots \end{aligned} \quad (15)$$

Additionally, we calculated the number of unique generic companies in the market during each 12-month time period accounting for the duration each generic company had sales. For example, if a given market had 3 generic companies with sales in a given 12-month period, with Company A having sales for 12 months, Company B having sales for 6 months, and company C having sales for only 3 months out of the 12-month period, then we calculated the total number of generic companies serving that market in that 12-month period as 1.75 (= (12+6+3]/12). Subsequently, the average revenues for a generic company in that market for the given 12-month period was calculated by dividing the total generic sales in that 12-month period by the number of generic companies serving that market.

5.9.3 Paragraph I/II (PI/II) Generic Drug Market

We defined a Paragraph I/II (PI/II) generic market as one in which a generic company is able to enter via a Paragraph I or II certification on their ANDA. A Paragraph I certification[24] applies to those RLDs that do not have any patents listed in the Orange Book and Paragraph II certification[25] applies to those whose Orange Book listed patent(s) are expired. We assumed that a market, defined as molecule-dosage form category combination as described in Section 5.9.2, becomes established after having 6-months of generic sales. Thus, to characterize the PI/II market, we subset our data to include those markets for which there was at least 6 continuous months of generic sales reported in the IQVIA NSP data. Then, we calculated 12-month generic sales in each of those markets where counted the first 12-month period starting from the 7th month of sales. For example, if the first recorded generic sales in a given market began in May 2018 and the market had generic sales through October 2018, then we calculated the initial 12-month of sales as the sum of monthly sales from November 2018 through November 2019 for that market. The 12-month sales for the subsequent periods were calculated in a similar fashion. As explained in Section 5.9.2, we

[24] Per 21 CFR 314.94(a)(12)(i)(A)(1), a generic drug applicant may submit a Paragraph I certification indicating that "…there are no patents that claim the RLD or an approved method of using the RLD" (U.S. Food and Drug Administration, 2020) to the best of their knowledge.

[25] Per 21 CFR 314.94(a)(12)(i)(A)(2), a generic drug applicant can submit a Paragraph II certification indicating that the patent(s) for the RLD is(are) expired (U.S. Food and Drug Administration, 2020).

also calculated the number of unique generic companies serving a market during each 12-month time period accounting for the duration each generic company had sales and then derived the average revenues for a generic company for each 12-month period by dividing the total generic sales in that 12-month period by the number of generic companies serving that market.

6 EXAMINATION OF COST FACTORS

Using the operational model developed, we examined the impact of several model parameters on the overall cost of development. The factors evaluated were selected based on discussions with ASPE and included: 1) change in the number of FDA ANDA review cycles, such that there are more first-cycle approvals, 2) change in FDA user fees, and 3) expansion of the ability to use biowaivers in lieu of in-vivo BE studies. The number of generic product and development pathway combinations that can be created in the operational model is quite large. Thus, we created 18 different product-pathway models shown in appendix Table A - 6 that are designed the capture a wide range of possibilities to evaluate impacts for. The models span all generic product types covered by the analytical model ranging from simple small molecule oral drugs to more complex drug-device combinations, e.g., inhalers, and those that involve complex active ingredients, e.g., glatiramoids. The models also encompass those cases where IP issues might be relevant, especially for more complex products. While the product-pathway models shown in Table A - 6 constitute a small subset of all possible combinations that can be examined by the model, they are representative of the range of models that can be created. Not all cost factors, however, are applicable to each product-pathway combination model. For example, in examining the ability to use biowaivers in lieu of in-vivo BE studies, we excluded models 1, 15, and 16 from the analysis runs as these models already use the biowaiver route to product development and approval. In contrast, we included all 18 models when examining the impact of changes in FDA user fees.

6.1 FDA ANDA Review Cycle Changes

Increasing the rate of first-cycle approvals will reduce the time to market for generic applicants of those drugs without intellectual property (IP) protections, thereby enabling significant cost savings to patients and third-party payers. While it is not feasible to examine the patient and third-party payer cost savings through lower drug prices, it is possible to evaluate the impact of an increase in the rate of first-cycle review on the ENPV for each of the 18 product-pathway models. Because the model evaluates the present value of the revenue stream a given generic drug would be expected to realize over its market lifetime at the point of launch, moving the market launch to an earlier date does not impact this calculation. In other words, we calculate the ENPV by bringing the cost up to the future value of launch compared to the revenues discounted to launch as reflected in equations 5 through 7. For example, if it takes 3 years to develop a given generic and the generic is marketed for 5 years earning revenues over that period, then we calculate the expected cost of development at the launch year (i.e., year 3) and compare that value to the present value of the 5-year revenue stream discounted to the launch year as well. This means that the delays in realizing revenues are already captured by the increase in costs. The method improves tractability by allowing us to abstract from the revenue side of the ENPV in examining the impact of a change in the rate of first-cycle reviews, focusing on the cost side instead.

To model the impact of increasing first-cycle approvals, we created three different hypothetical situations in which first-cycle approvals are higher than their current baseline rate of 19.7 percent (Table 12). In creating these scenarios (Table 16), we assumed that the rates for four-, three-, and two-cycle reviews will also decrease in varying proportions as more applications get approved in the first-cycle. For example, under Scenario 1, we assumed that the number of four-, three, and two-cycle approval applications will each decrease by 50 percent from their current levels (Table 16), e.g., 100 four-cycle approvals reduce to 50 and the remaining 50 applications get

approved in three-cycle reviews, 235 three-cycle approvals reduce to 118 and the remaining 117 applications get approved in two-cycle reviews, etc. We applied the same proportionate reductions to the remaining two scenarios.

Table 16. Hypothetical Scenarios of FDA Approval Rates by Review Cycle

Cycles to Approval	Baseline [a]		Scenario 1 [a]		Scenario 2 [a]		Scenario 3 [a]	
	Number	%	Number	%	Number	%	Number	%
1	152	19.7%	282	36.5%	406	52.6%	510	66.0%
2	260	33.7%	248	32.1%	208	26.9%	238	30.8%
3	235	30.4%	168	21.7%	134	17.3%	0	0.0%
4	100	13.0%	50	6.5%	0	0.0%	0	0.0%
5	18	2.3%	18	2.3%	18	2.3%	18	2.3%
6	5	0.7%	5	0.6%	5	0.6%	5	0.6%
7	1	0.1%	1	0.1%	1	0.1%	1	0.1%
8	1	0.1%	1	0.1%	1	0.1%	1	0.1%
Total	**772**	**100.0%**	**772**	**100.0%**	**772**	**100.0%**	**772**	**100.0%**
Average Approval Time (in Months)	**28.4**		**23.6**		**19.5**		**15.6**	

[a] Numbers may not add up to the total value due to rounding.

Table 17 shows the range of estimated impacts on the time to market, costs, and expected capitalized costs across 10 different product-pathway models. For this analysis, we excluded those product-pathway combinations that involve patent litigation because increasing the rate of first-cycle approval is not likely to impact the timeline for getting to market or expected capitalized costs due to the 30-month stay triggered by a patent challenge and the potential litigation that would ensue. As the rate of first-cycle approvals increase from its baseline level of around 20 percent to a high of 66 percent (Scenario 3), the time to market decreases by around 13 months (45 percent). Even though the development costs remain unchanged, the expected capitalized costs that incorporate the time value of money and cost of capital decrease by $3.5 million (range: -$15.1 to -$0.4 million) under Scenario 3.

Table 17. Reduction in Time to Market and Development Costs under Alternative Hypothetical Scenarios of FDA Approval Rates by Review Cycle

Parameter	Scenario 1		Scenario 2		Scenario 3	
	Number	% [a]	Number	% [a]	Number	% [a]
Change in Time to Market (in Months)	-4.8	-6.5% (-8.2% to -4.9%)	-9.0	-12.0% (-15.2% to -9.1%)	-12.8	-17.2% (-21.7% to -13.0%)
Change in Costs (in $ Million)	$0.0	0%	$0.0	0%	$0.0	0%
Change in Expected Capitalized Costs (in $ Million)	-$1.4 (-$5.8 to -$0.2)	-3.4% (-3.5% to -3.3%)	-$2.5 (-$10.7 to -$0.3)	-6.3% (-6.4% to -6.0%)	-$3.5 (-$15.1 to -$0.4)	-8.8% (-9.0% to -8.5%)

[a] The column represents percentage change from baseline figures.

6.2 Change in FDA User Fees

GDUFA user fees are negotiated between FDA and industry periodically and are used to fund "human generic drug activities," or "resources allocated for human generic drug activities" (Congressional Research Service, 2021). The fees assessed by FDA vary from year to year (Table 9) and are set by taking into account the number of ANDAs received, ANDA backlog, number of facilities to be inspected among other factors. We modeled the impact of a hypothetical 50 percent decrease in FDA ANDA submission fees on the development costs for each of the 18 product-pathway models depicted in Table A - 6. Overall, FDA ANDA submission fee constitutes 6.6 percent

(range: 0.7 to 15.3 percent) of total costs and 1.7 percent (range: 0.2 to 7.0 percent) of expected capitalized costs. The impact of a 50 percent decrease in FDA ANDA submission fees is relatively minor at -3.3 percent (range: -7.7 to -0.3 percent) and -1.2 percent (range: -4.8 to -0.1 percent) on total costs and expected capitalized costs across our 18 product-pathway combination models, respectively (Table 18). However, this assumes that the fee decreases would not affect FDA's capacity to review applications in a timely manner. A fee decrease of that magnitude could severely hamper FDA's ability to meet its congressionally mandated review timelines and would likely increase the average FDA ANDA review time estimated in the model. This could potentially countervail the cost-saving effect of FDA ANDA review fee reductions to the generic drug applicant and can even result in an increase in the overall expected capitalized development costs.

Table 18. Reduction in Development Costs from a Hypothetical 50 Percent Decrease in the Average FDA ANDA Submission Fee Paid

Parameter	Scenario	
	$	Percent
Change in Average FDA ANDA Submission Fee	-$185,950	50%
Change in Time to Market	0.0 months	0%
Change in Costs	-$185,950	-3.3% (-7.7% to -0.3%)
Change in Expected Capitalized Costs	-$0.27 million (-$0.25 to -$0.29 million)	-1.2% (-4.8% to -0.1%)

6.3 Use of Biowaivers in Lieu of In-vivo Bioequivalence (BE) Studies

As discussed in Section 5.8.1, a biowaiver eliminates the need for a generic drug manufacturer to conduct in vivo BE studies, a significant development cost component. Further, the costs and time required to prepare a biowaiver submission to FDA are also much lower and shorter than a typical submission involving a BE study. We examined the impact of expanding the use of biowaivers on time to market as well as total development costs for 15 of 18 product-pathway models shown in Table A - 6 which included BE study requirement. Elimination of the need to conduct a BE study saves money and time. On average, the time to market reduces by 10.6 months (range: 4.9 to 20.3 months) across our 15 product-pathway models (Table 19). While the reduction in time to market is only 11.8 percent (range: 4.9 to 23.4 percent), the impact on expected capitalized costs is much higher at 66.9 percent (range: 43.3 to 92.3 percent).

Table 19. Reduction in Time to Market and Development Costs from Biowaivers

Parameter	Scenario	
	$	Percent
Change in Time to Market	-10.6 months (-20.3 to -4.9 months)	-11.8% (-23.4% to -4.9%)
Change in Costs	-$11.0 million (-$48.7 to -$0.2 million)	-37.2% (-93.4% to -5.9%)
Change in Expected Capitalized Costs	-$50.7 million (-$186.8 to -$4.2 million)	-66.9% (-92.3% to -43.3%)

7 EXAMINATION OF BARRIERS

Barriers to generic drug development and approval can be broadly categorized into those that are related to IP protections, i.e., IP barriers, and others that are not, i.e., non-IP barriers. Both types of barriers increase generic drug development costs and/or impede market entry. We examine these barriers in detail in the sections below.

7.1 Intellectual Property (IP) Barriers

In the U.S., patents and FDA-granted exclusivities protect innovator (aka brand-name) drugs from generic competition for an extended period after regulatory approval of the brand drug. Patents are granted by the U.S. Patent and Trademark Office (USPTO) for 20 years. Recognizing the several years of patent exclusivity consumed during clinical trials and the NDA approval process, FDA generally will not accept an ANDA until five years after approval of an NCE's NDA. FDA also may grant other regulatory exclusivity periods for specific purposes that range from 3 to 7 years (Table 20). "Some drugs have both patent and exclusivity protection while others have just one or neither. [Further] patents and exclusivity may or may not run concurrently and may or may not cover the same aspects of the drug product" (U.S. Food and Drug Administration, 2020).

Table 20. Regulatory Exclusivities Available to Brand Drugs in the U.S. from FDA

Type of Regulatory Exclusivity	Exclusivity Period Granted	Explanation
New Chemical Entity (NCE) Exclusivity	5 years	NCE exclusivity is available for drugs that contain an active moiety that has not previously been approved by FDA. The exclusivity means that no generic can submit an ANDA until 5 years after the NCE drug's NDA approval. If the ANDA includes a PIV challenge, it can be submitted 4 years after the NDA was approved.
Orphan Drug Exclusivity (ODE)	7 years	Granted to a drug that is indicated for a disease or condition that affects fewer than 200,000 people in the U.S., or that affects more people, but for which the drug company can demonstrate that it will not be able, practically, to recover the costs of development and manufacture. Exclusivity is limited to the first sponsor that obtains approval for a drug that targets a rare disease. FDA does not grant this exclusivity to a drug if it has previously approved the same drug for the same disease.†
New Clinical Investigation (NCI) Exclusivity	3 years	Granted to a brand drug with an active ingredient that has been approved before if the company provides new clinical studies in humans to show, for example: ▪ A new way of delivering the active ingredient, or ▪ A different disease or condition that the drug can treat.
Generating Antibiotic Incentives Now (GAIN) Exclusivity	5 years additional	Granted to certain brand-name antibiotic drugs that are designated as a Qualified Infectious Disease Product (QIDP)
Pediatric Exclusivity (PED)	6 months additional	Granted to a brand-name drug upon completion of pediatric studies by the sponsor in response to a written request from FDA. PED runs for 6 months after any other exclusivities have expired.

Source: U.S. Food and Drug Administration (2020)
† This is meant to avoid serial exclusivity (Hong, et al., 2019).

Combined, these protections provide brand-name drugs in the United States protected access to their markets for 12.5 years, on average (IQR: 8.5-14.8) (Grabowski, et al., 2017; Wang, et al., 2015; Hemphill & Sampat, 2012; Kesselheim, et al., 2017). However, the effective market exclusivity period (i.e., the time during which the brand drug has patent protection plus any periods of market exclusivity prescribed by regulatory policy) varies by such factors as therapeutic area the

drug is in, degree of innovativeness, developmental designation status, review status, and company size (Table 21).

Table 21. Effective Market Exclusivity Periods of Top-Selling Prescription Drugs That Experienced Generic Competition, 2000-2012, As Reported in Wang, et al. (2015)

Pharmaceutical Agent Classification	Sample Size (n)	Years of Effective Market Exclusivity, Median (IQR)
All agents	175	12.5 (8.5 – 14.8)
Chemical type		
New molecular entity	102	13.8 (10.8 – 14.8)
New formulation	73	10.0 (6.9 – 13.9)
Therapeutic area		
Dermatology	10	14.8 (9.0 – 16.3)
Cardiovascular disease	33	14.5 (11.5 – 15.0)
Infectious disease	28	14.4 (11.6 – 16.0)
Antibiotics and antifungals	21	14.0 (10.4 – 16.0)
Antivirals	7	14.8 (13.5 – 16.3)
Hematology and oncology	5	14.3 (8.0 – 16.0)
Gastroenterology	11	13.8 (10.5 – 14.9)
Allergy and pulmonology	16	11.6 (8.0 – 13.3)
Neuropsychiatry	36	11.4 (8.9 – 14.0)
Rheumatology	4	10.8 (8.1 – 13.0)
Genitourinary	5	10.0 (6.3 – 13.6)
Endocrinology	7	9.8 (4.0 – 11.5)
Analgesics	11	8.0 (5.8 – 10.0)
Other [a]	9	14.3 (7.9 – 15.6)
Review status		
Priority review	39	14.5 (11.8 – 15.3)
Standard review	136	12.0 (8.3 – 14.5)
Special developmental designations		
Orphan drug, accelerated approval, or fast track [b]	13	14.8 (13.0 – 16.0)
No special developmental designations	162	12.5 (8.5 – 14.8)
New molecular entity innovativeness [c]		
First in class	22	14.5 (13.3 – 15.8)
Advance in class	19	14.3 (11.8 – 15.0)
Addition to class	56	12.9 (9.8 – 14.8)
New molecular entity manufacturer size [c]		
Large company [d]	72	13.8 (11.1 – 14.8)
Small company	25	13.5 (7.3 – 15.6)

Source: Wang, et al. (2015)
IQR = Interquartile range
[a] Includes musculoskeletal drugs (n = 2), ophthalmologic drugs (n = 4), and transplantation medicine (n = 3).
[b] Includes 5 drugs granted orphan drug status, 6 granted accelerated approval, and 8 granted fast-track designation (6 drugs granted more than 1 designation).
[c] For innovativeness and manufacturer size, the study authors used an FDA framework to categorize all new molecular entities with the exception of 5 drugs.
[d] Large company defined as top 25 in the marketplace by sales revenue in drug's year of approval.

During its effective marketing exclusivity period, the brand-name drug reaps monopoly rents due to lack of generic competition. While patients, government, and private insurers bear the cost of high drug prices during this period, innovator companies assert that these economic rents

encourage them to make substantial investments in research, development, and production facilities. The precise levels of R&D investment by innovator companies—and hence the level of revenue necessary to sustain R&D investment at its current levels—is a matter of debate (Light & Warburton, 2011; Morgan, et al., 2011; Prasad & Mailankody, 2017). Nevertheless, the current protections afforded brand companies, theoretically at least, align with the primary objective of market protections afforded by patent law and regulatory exclusivities, i.e., to reward innovation, thereby incentivizing continuous investment in new drug development. Once these protections expire, lower-priced generic versions of the brand-name drug enter the market, significantly eroding the economic rents of the innovator. Grabowski, et al. (2016) found that the market share of a brand-name drug falls from 100 percent to 12 percent within the first year of generic entry, on average, and for those brand-name drugs with annual sales exceeding $250 million, the authors report that market share is reduced to 7 percent of its pre-generic level within the first year.[26] Given the significant negative impact of generic entry on revenues, brand-name companies employ several strategies to deter and/or delay generic entry.

7.1.1 Strategic Accumulation of Patents

Accumulation of patents is one strategy by which the brand drug aims to extend its presence in the market free of generic competition. The innovator company seeks to acquire 'secondary' or 'subsidiary' patents to cover different aspects of their brand-name drug, such as its formulation, composition, method of use, method of manufacture, and dosages, thereby creating several layers of defense – aka patent "walls," "forests," "thickets," or "estates" – around the base patent on its API. Aside from the merit of any specific patents, patent accumulation may deter challengers by its sheer mass. Moreover, the innovator company may also increase the number of patent applications "by dividing out from a parent patent application one or several (narrower) applications, which … then have a procedural life of their own" (Gurgula, 2017). Even if such divisions are unlikely to extend the effective market protection period, they increase uncertainty for the generic companies, complicating their market entry decision-making process (Gurgula, 2017). Finally, these patent walls may also complicate generic entry even after the drug substance, formulation, or method of use patents expire or are invalidated. It may be difficult for a generic company to develop its product without infringing on one or more of these secondary patents.

Drug companies must submit information to FDA regarding "drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents" within 30 days of patent issuance (21 C.F.R. § 314.53(b)(1)). Using publicly available data reported in FDA's Orange Book, Feldman (2018) examined patent and exclusivity accumulation behavior of innovator companies from 2005 – 2015 and found that about 40 percent of all drugs marketed in the U.S. had patents and exclusivities added to them. Not unexpectedly, the practice was more prevalent among blockbuster drugs, with more than 70 percent having had their market protection periods extended at least once, and around 50 percent more than once.

According to a 2018 report by the Initiative for Medicines, Access & Knowledge (I-MAK), an organization whose mission is to increase global access to affordable, lifesaving medicines, more than half of the top twelve drugs in the U.S. have applied for or received more than 100 patents per drug. These patent protection attempts sought to increase marketing protections by 38 years on average – almost twice the length of protection intended under U.S. patent law (I-MAK, 2018).

[26] The reported estimates cover the 2013-2014 period. Comparable estimates of brand-name market share within first year of generic entry for earlier years are higher: around 50 percent for 1999-2000; 35 percent for 2001-2002; 28 percent for 2003-2004; 26 percent for 2005-2006 and 2009-2010; 20 percent for 2007-2008 and 2011-2012 (Grabowski, et al., 2016).

Table 22 summarizes I-MAK's data and main findings. As can be observed from the table, strategic accumulation of patents appears to be more prevalent for large molecule drugs (i.e., biologics), possibly because the complex molecular structure and manufacturing processes for biologics provide more patentable elements. Nevertheless, four out of the twelve drugs with the highest global sales volume in 2017 included in I-MAK's list are small molecule drugs: Revlimid, Eliquis, Xarelto, and Lyrica. The numbers of patent applications (including patents applied for but not abandoned and active patents) among these four drugs are also sizable, ranging from 48 (Eliquis) to 118 (Lyrica). Moreover, the potential total years of marketing exclusivity sought by these patents range from 31 (Xarelto) to 40 years (Revlimid) from approval.

Table 22. Marketing Exclusivity Protection Attempts for the Top Twelve Drugs (by 2017 Sales Volume) in the U.S. as Reported in I-MAK (2018)

Type of Drug	Name	Indication(s)	Company	Number of Patent Applications [a]	First Year Marketed in the U.S.	Potential Total Years of Exclusivity [a]	Price Change, 2012-2017
Small Molecule	Revlimid	Multiple Myeloma	Celgene	106	2005	40	79%
	Eliquis	Stroke/ Embolism	Pfizer/Bristol Myers Squibb	48	2012	34	69%
	Xarelto	Blood Clots	Johnson & Johnson	49	2011	31	87%
	Lyrica	Chronic Pain	Pfizer	118	2004	32	163%
Large Molecule	Humira	Arthritis	Abbvie	247	2002	39	144%
	Rituxan	Cancer	Biogen/Genentech	204	1997	47	25%
	Enbrel	Arthritis	Amgen	57	1998	39	155%
	Herceptin	Cancer	Roche/Genentech	186	1998	48	-58%
	Remicade	Arthritis	Johnson & Johnson	123	1998	32	18%
	Avastin	Cancer	Roche	219	2004	43	16%
	Eylea	Macular Degeneration	Bayer/Regeneron	67	2011	34	6%
	Lantus	Diabetes	Sanofi	74	2000	37	114%

Source: I-MAK, (2018)
[a] Includes granted and active patent applications.

When we examined patents and exclusivities in the 2021 Orange Book, however, we found that only a fraction of these applications has been listed for these drugs (Table 23).[27]

[27] Currently, not all patents associated with a brand-name drug need to be listed in the FDA Orange Book. Under 21 C.F.R. § 314.53(b)(1), those patents whose information "must" be submitted include drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents.

Table 23. 2021 FDA Orange Book Information on Four Top-selling (by 2017 Sales Volume) Small Molecule Drugs in the U.S.

Drug Name	Formulation	Number of Patent Applications	Number of Orange Book Patents	Number of Orange Book Exclusivities	First Year Marketed in the U.S.	End Date of Market Protection, from Orange Book	Potential Total Years of Effective Market Exclusivity
Revlimid	Capsule	106	15	6	2005	2027	22
Eliquis	Tablet	48	2	0	2012	2031	19
Xarelto	Tablet	49	3	2	2011	2039	28
Lyrica	Capsule	118	0	4	2004	2022	18
	Solution		0	4	2010	2022	12
	Extended-release (XR) Tablet		6	1	2017	2027	10

Source: U.S. Food and Drug Administration (2021); I-MAK, (2018)

Further examination of the markets for these four drugs indicates that generic market entry is not necessarily as remote as suggested by I-MAK:

- *Revlimid* – Latest Orange Book patent expiration—2027. Celgene, a subsidiary of Bristol Myers Squibb, the owner of the Revlimid patents, entered into a settlement with Cipla, a large generic company, in 2020 that allows Cipla "to manufacture and sell certain volume-limited amounts of generic lenalidomide in the U.S. beginning on a confidential date that is some time after March 2022." (Levy, 2020). Further, Cipla would be able to commence unlimited generic production in 2026.
- *Eliquis* – Latest Orange Book patent expiration—2031. In 2017, 25 companies filed PIV certifications for generic versions of Eliquis. Bristol Myers Squibb and Pfizer, who share the brand name drug's revenue, have settled with some, but not all litigants. Currently, two generic companies (Accord Healthcare Inc. and Indoco Remedies Ltd.) are listed in the Orange Book with active ANDAs and three (Micro Labs Limited, Mylan Pharmaceuticals Inc., and BionPharma Inc.) with discontinued ANDAs. Micro Labs Limited and Mylan Pharmaceuticals Inc. will be able to enter the market sometime after 2025 under their settlement agreements.
- *Xarelto* – Latest Orange Book patent expiration—2039. Janssen Pharmaceuticals Inc., which markets Xarelto, has two patents expiring in 2021 and 2022, and a method-of-use patent that stretches out to 2039. However, method-of-use patents are often worked around by generics, for instance by using a labeling carve-out of the patented use(s). The 2039 patent is only for a very specific medical use of Xarelto, and does not apply to its major uses, i.e., treating pulmonary edema or deep vein thrombosis.
- *Lyrica* – Latest Orange Book patent expiration—2027. In a major setback to Pfizer, the UK Supreme Court ruled its new use patents for Lyrica invalid in 2015, prompting damages suits by generic competitors in this complex case (Hirschler, 2015). There are now 18 manufacturers of generic Lyrica (pregabalin) in capsule form listed in the Orange Book. However, Pfizer has introduced additional formulations of the drug (solution and XR) to extend its effective market protection, a strategy known as product hopping (see Section 7.1.2).

7.1.2 Product Hopping

Product hopping is another strategy used by innovator companies to extend the effective marketing exclusivity period for their branded drugs. It is the process by which a brand company, using its market position, forces a "hop" from its existing drug, whose patent is expiring (or facing a negative court ruling), to a newer reformulated version that has patent protection (Congressional Research Service, 2020; Klusty, 2015). When the brand company leaves the original drug on the market, this is considered a "soft switch"; a "hard switch" occurs when the brand company removes the original product from the market (Carrier & Shadowen, 2017; Congressional Research Service, 2020). The practice is generally viewed as anticompetitive because it allows the innovator company "to maintain its dominant market position (and higher prices) without substantial benefits for consumers" (Congressional Research Service, 2020). Despite the drug product selection laws enacted in all states that require pharmacists to fill prescriptions written for brand-name drugs with their "AB-rated" generic versions, the length of time and expense to obtain the AB-rating may preclude or delay generic entry, extending the effective exclusivity period of brand name drugs.[28]

Brand companies can use one of three types of product reformulation. The first involves developing a new form of the drug, e.g., switching from a capsule to an XR tablet, a strategy Pfizer employed for its blockbuster chronic pain drug Lyrica (Table 23). The second type of reformulation involves changing the moieties of a drug by adding or removing compounds. For example, "a manufacturer can switch from a chemical compound that is an equal mixture of each enantiomer, only one of which contains the active ingredient, to a compound that includes only the enantiomer that contains the active ingredient" (Carrier & Shadowen, 2017). The third reformulation category involves combining two or more drugs that have been sold separately before, such as the high-blood-pressure medications: Azor, which combines Norvasc and Benicar; Caduet, which combines Norvasc and Lipitor; and Exforge, which combines Norvasc and Diovan (Carrier & Shadowen, 2017).

Currently, there are no laws that prohibit product hopping practices of brand name companies. The strategy has been challenged in court as being anticompetitive several times in the past and such challenges are likely to continue in the foreseeable future. Some of the notable court cases that have shaped the criteria applied in evaluating whether a particular product hopping case constitutes a violation of antitrust laws includes the following:

- *Abbott Laboratories v. Teva Pharmaceuticals USA, Inc. (TriCor)* 432 F. Supp. 2d 408 (D. Del. 2006) – Abbott made a series of changes to its blockbuster cholesterol and triglycerides drug, TriCor. These changes were also accompanied by a hard switch, i.e., Abbott removed older versions of the drug from the market. Even though the case was ultimately settled before trial, the court opined that "[Abbott Laboratories] prevented a choice between products by removing the old formulations from the market while introducing new formulations… [and that] total foreclosure of the market is not required for an antitrust violation" (American Conference Institute, 2014).
- *Walgreen Co. v. AstraZeneca Pharmaceuticals L.P. (Walgreens)* 534 F. Supp. 2d 146 (D.D.C. 2008) – AstraZeneca converted its high selling heartburn drug Prilosec to

[28] Drugs listed in the FDA Orange Book are rated as A (substitutable) or B (non-interchangeable). Drugs with "A" rating include those for which: (1) there are no (known or suspected) BE problems.; (U.S. Food and Drug Administration, 2021b); or (2) BE problems (actual or potential) have been resolved with adequate in vivo and/or in vitro evidence. These drugs are designated as AB. (U.S. Food and Drug Administration, 2021b).

Nexium by slightly altering its chemical makeup.[29] Even though AstraZeneca did not remove Prilosec from the market, they engaged in a soft switch strategy by ceasing Prilosec marketing and increasing Nexium promotions to healthcare professionals and patients. Walgreens sued AstraZeneca alleging that they "engaged in exclusionary conduct in violation of Section 2 of the Sherman Act" (American Conference Institute, 2014). The court did not agree with the plaintiffs' allegation that AstraZeneca's actions reduced consumer choice and granted AstraZeneca's motion to dismiss.

- *In re: Suboxone (Buprenorphine Hydrochlorine and Naloxone) Antitrust Litigation* 64 F. Supp. 3d 665 (E.D. Pa. 2014) – Purchasers of Suboxone tablets, a prescription drug used to treat opioid addiction, filed a lawsuit alleging that Reckitt violated Section 2 of the Sherman Act by engaging in an effort to coerce prescribers to substitute the sublingual film version of the drug with its original tablet version. Further, Reckitt discontinued the tablet version of the drug employing a hard switch strategy. The court sided with the plaintiffs and noted that "the facts presented sufficiently allege that the disparagement of Suboxone tablets took place alongside 'coercive' measures as the threatened removal of the tablets from the market in conjunction with the alleged fabricated safety concerns could plausibly coerce patients and doctors to switch from tablet to film" (Carrier & Shadowen, 2017).
- *Mylan Pharmaceuticals v. Warner Chilcott (Doryx)* No. 15-2236, 2016 WL 5403626 (3d Cir. Sept. 28, 2016) – Similar to the practices used buy Abbott Laboratories in the TriCor case described above, Warner Chilcott made a series of formulation changes to its acne drug, Doryx. Moreover, Warner Chilcott removed the earlier version of the drug from the market, even buying back wholesaler inventory. Mylan filed a suit alleging that Warner Chilcott's sequential product improvements to its acne drug Doryx coupled with their hard switch strategy violated the Sherman Act. The court ruled that there was insufficient evidence for Warner Chilcott's monopoly power or anticompetitive conduct based on the evidence put forth by Mylan.
- *New York ex rel. Schneiderman v. Actavis PLC (Namenda)* 787 F.3d 638, 656 (2d Cir. 2015) – Actavis introduced an XR version of its Alzheimer's disease drug, Namenda when the patent term on its instant release (IR) version was running out. Similar to the behavior observed in earlier cases of product hopping described above, Actavis aggressively marketed its XR version to get patients to switch away from its IR version. While Actavis kept the IR version of Namenda available in the market initially, they later discontinued it completely after realizing that their soft switch strategy was only marginally successful (Congressional Research Service, 2020). As a result, the State of New York brought an antitrust action lawsuit against Actavis in 2015. The court found that "neither product withdrawal nor product improvement alone is anticompetitive [but], when a monopolist combines product withdrawal with some other conduct, the overall effect of which is to coerce consumers rather than persuade them on the merits and to impede competition, its actions are anticompetitive under the Sherman Act" (Carrier & Shadowen, 2017). Actavis was subsequently required to keep Namenda IR on the market by the court.

Studies have shown that successful "product hopping" can reduce the market share of a generic by patenting new versions of the brand drug with enhanced features—such as timed release or faster release into the bloodstream—thereby offering features that the newly approved

[29] Prilosec contains two isomers of the active ingredient omeprazole, while Nexium only contains one. The two drugs are composed of the same building blocks arranged differently (Morris, 2020).

generic version of the "old" brand drug does not have. This tactic can blunt the market share of a generic, potentially until the expiration of the patents for the newly-enhanced brand drug (Klusty, 2015). According to a recent study that examined product hopping for five brand drugs—Prilosec, TriCor, Suboxone, Doryx, and Namenda—the strategy cost the U.S. healthcare system $4.7 billion annually (Brill, 2020).

Drug-device combination products comprise some of the largest brand drug markets in the United States, including drug-devices for treating widespread conditions such as asthma, chronic obstructive pulmonary disease (COPD), diabetes, and severe allergic reactions. Classes of drug-device combinations include pre-filled syringes; pen injectors and auto-injectors; inhalation products; aerosol delivery systems; transdermal delivery systems; and kits that contain drugs along with devices to administer them (Chan, undated). Because patents are normally obtained for both the brand drug and its associated device, additional opportunities for patent accumulation and/or product hopping—sometimes called "divergent innovation"—can be present.

Manufacturers of brand-name drug-device combination products can time their device patent applications to lengthen their protection against generic competition. Beall et al. (2016) analyzed 235 patents associated with 49 drug-device products and found that device patents provided a median extension of 4.7 years beyond the expiration of the patents on their associated drugs. Fourteen of the 49 drug-device combinations they studied were protected only by device patents. By sequentially patenting different elements of a drug-device delivery system, a company can extend its patent protection by many years.[30] By patenting minimal changes in the features of a drug delivery system, for instance, or, a brand drug-device manufacturer can bolster its sales while competing against market entrants that are basing their delivery system on the brand's "old" system.[31] Research (Beall & Kesselheim, 2018) has revealed that taking out multiple tertiary patents (i.e., patents by drug-device manufacturers on their drug delivery systems) has expanded over the past 15 to 20 years. In 2000 there were 42 drug-device combinations with 85 patents, of which 29 were tertiary patents. In 2016, the authors found 127 drug-device products associated with 844 patents, 478 of which were tertiary patents (Beall & Kesselheim, 2018). Price (2020) points out that drug-device markets under the current patent system are prone to "negative divergent innovation." Price uses as examples the markets for insulin self-injection kits and epinephrine auto-injectors (manufactured by Medtronic and Mylan/Pfizer, respectively).[32] Although these two major manufacturers applied different strategies to protect their market positions—Mylan has thus far not changed its EpiPen delivery design—the result in both instances has been a profusion of different and non-interchangeable delivery technologies from potential competitors. These technologies are devised not to enhance patient safety or to make drug delivery

[30] Beall and Kesselheim (2018) point out that the EpiPen has four device patents that expire in 2024, fully 37 years after the EpiPen was first marketed. While competitors have brought similar products with different delivery systems to market, these have not been notably successful in achieving patient or physician acceptance.

[31] Although FDA emphasizes that generic drug-device combination products need not be identical in all respects to the RLD, the generic version should be useable, without retraining, by patients formerly prescribed the brand product. As with NBCDs, generic drug-device sponsors are encouraged to schedule pre-ANDA meetings with FDA early in their process.

[32] Neither insulin nor epinephrine have been protected by patents for some time. Medtronic has been the largest manufacturer of insulin pumps, all of which used the same system to connect to insulin sets, which are manufactured by Medtronic and several other companies. In 2001, Medtronic responded to a serious challenge to its insulin pump market predominance by patenting a new connection system for a new line of pumps. Some manufacturers of insulin sets left the market; others started to market their own proprietary pumps and connection systems, a process Price (2020) considered negative divergent innovation.

more efficacious, but simply to avoid infringing on existing patents when entering the market (Price, 2020).

Among our 38 PIV drug markets, we identified several examples of probable and potential product hopping for closer examination. These include the following:

- *Pennsaid (diclofenac sodium 1.5% topical solution).* In January 2013, brand manufacturer Nuvo Research and its U.S. distributor Mallinckrodt reached a settlement with FTF ANDA applicant Apotex that called for Apotex to begin commercial marketing of its generic of Pennsaid 1.5% solution no earlier than 45 days after Mallinckrodt's newer version of the drug, Pennsaid 2.0% (provided in a measured dose pump container) was approved and entered the market (Nuvo Research, Inc., 2013). The sales volume of Pennsaid 1.5% during the 6 months before generic entry was 6.2 million units (at a price of $1.89 per unit). During the 6 months after Apotex entered the market on May 27, 2014, the brand's volume Pennsaid 1.5% sank to 955,000 and continued to decline after the brand stopped marketing Pennsaid 1.5% on January 1, 2015. Residual supplies were sold until 3 years after first generic entry, amounting to just 1,084 units during the entire third year. However, the generic versions of the 1.5% solution were selling at volumes comparable to the brand's volume before generic entry (6.2 million units). Because of the competition among generics, the price per unit fell from $1.41 for the FTF during the 180-day exclusivity to an average of $0.49 among 6 generics 2.5 years after generic entry. During the seventh year after generic entry, the six generics sold an average of just over a million units per month—about the same as the market volume before generic entry, but at an average price per unit of just under $0.20. Meanwhile, Horizon Pharma, which had purchased the U.S. rights to Pennsaid 2.0% from Nuvo, reported sales of $72 million in just one quarter (ending June 30, 2016). Although Nuvo stopped supplying Pennsaid 1.5% in 2015, several generics continue to supply it as a low-cost alternative to Pennsaid 2.0%.
- *Doryx (doxycycline hyclate, 50 mg and 200 mg DR tablets).* The FTF generic of Doryx, approved in two strengths by FDA in May 2016, are themselves generics of a "hopped-to" brand drug. Mayne, which holds the rights to the brand drug, attempted to deflect generic infiltration of its market by withdrawing all Doryx capsules from the market, to be replaced by Doryx XR tablets. Several lawsuits by stakeholders ensued and were settled in 2014 (Koenig, 2014). After Mylan (Viatris) entered the market with its FTF generic versions of the 50 mg and 200 mg tablets, Mayne's share of the units sold plummeted from 41 percent during Mylan's exclusivity to 7.1 percent, 2.9 percent, and 1.2 percent at the end of the first, second, and third years after generic entry. Additionally, Mayne licensed its AG to Alvogen, which sold the AG at $0.33 per unit, compared to $19.11 and $22.25 per unit for the FTF and brand, respectively. The AG captured the majority (67 percent) of the total unit volume by the second 6-month sales period and sold over 70 percent of the unit volume in every 6-month period until the end of the third year after generic entry. The FTF did not attempt to compete with the AG's price but dropped its price from $19.11 in period 1 to $9.71 at the end of the third year (period 6) after it entered the market. Despite competition from other generics and the AG, the FTF accounted for 15.0 to 18.6 percent of the total unit volume sold in each of the 6-month periods 3, 4, and 5. In period 6, its unit volume dropped to 0.5 percent and went to zero the following period. The abandonment of this market by the AG and the brand may have been due to the market entry of Doryx MPC 60 mg and 120 mg tablets, a version of Doryx with a denser coating that extends release of the drug longer than Doryx DR. FDA lists a PIV ANDA submission for a generic of Doryx MPC

dated 9/28/2017 on their PIV Certification List, but no other milestone for that PIV submission is listed.

- *Copaxone (glatiramer acetate).* In 2014, just as Teva's last patent on its 20 mg injectable multiple sclerosis drug was about to expire, it introduced a pre-filled 40 mg syringe with a patent expiration in 2030. This caused potential generic competitors, primarily Mylan, to submit a new PIV ANDA with the newly patented version of Copaxone as the RLD, a two-year delay that, according to one analysis, caused "excess U.S. spending of $4.3 billion to $6.5 billion" (Smyth, 2020). Ultimately, Mylan (Viatris) sued Teva in 2021 for anti-competitive practices, including "misleading doctors about the efficacy of Copaxone generics, shifting the market to a higher-dose formulation and forging deals with specialty pharmacies and PBMs to keep Copaxone generics off prescribing lists" (Kansteiner, 2021). Despite a unit price that has been close to or less than a third of the unit price for brand Copaxone for the past 2.5 years, Mylan's FTF generic was able to capture only 38 percent of total sales.

While it is difficult to generalize from the above case studies, product hopping by the brand company could reduce the size of the market (in terms of units sold) for the FTF and other generic entrants by 29 percent on average (range: 8 to 69 percent) within the first year after generic entry and more in subsequent years (Figure 5). As a consequence, this reduction in the volume of units sold over time results in declining revenues for all generics in the market including the FTF from one year to the next until they reach a level that cannot be sustained (Figure 6). It is challenging to quantify the impact of product hopping on the market share (in terms of dollar sales) of a generic entrant even for the cases discussed above because the counterfactual for each is unknown (i.e., the share of the market that could have been captured in the absence of product hopping). In our PIII market sample, the average market share of generic sales in dollar terms is around 50 percent overall. In the above case study for Copaxone, Mylan reportedly captured only 38 percent of the total sales, which is 12 percent lower than the average market share for a generic entrant. This directly translates to a 12 percent reduction in the lifetime sales of a generic applicant across all product-pathway combination models in Table A - 6.

7.1.3 Settlements and Pay-for-delay

Hatch-Waxman Act's PIV certification route is intended to offset the market protection strategies of innovator companies described above. Under 21 CFR 314.94(a)(12)(i)(A)(4), an ANDA applicant can submit a PIV certification that asserts that a patent listed in the FDA Orange Book held by the RLD holder (i.e., the brand drug, or RLD, holder) "is invalid or will not be infringed by the manufacture, use, or sale" of the generic product, which is a legal act of infringement. The applicant must inform the patent holder of this technical infringement upon filing the certification with FDA. If the patent holder takes legal action against the applicant's "infringement" within 45 days, FDA is required to delay the approval of the applicant's ANDA for 30 months or until the litigation is resolved, whichever happens first. If the "infringement" is not challenged by the patent holder within the 45-day period, FDA may approve the application when it meets the scientific approval requirements. As discussed previously, the first applicant(s) to submit a substantially complete ANDA containing a PIV certification to at least one patent at least one of the patents listed in the Orange Book generally is eligible for the exclusive right to market the generic drug for 180 days.[33]

[33] Some observers have looked askance at the PIV certification route as "an artificial act of infringement … essentially a no-risk way for a generic to provoke a challenge, putting the patent at issue," (Bernard, 2014), or even as an instance of government-authorized infringement of pharmaceutical patents (Ropes and Gray LLP, 2020).

Figure 5. Percentage Change in Total Units Sold After Generic Entry Compared to Before Generic Entry for Three Drugs Over Time in 6-Month Increments

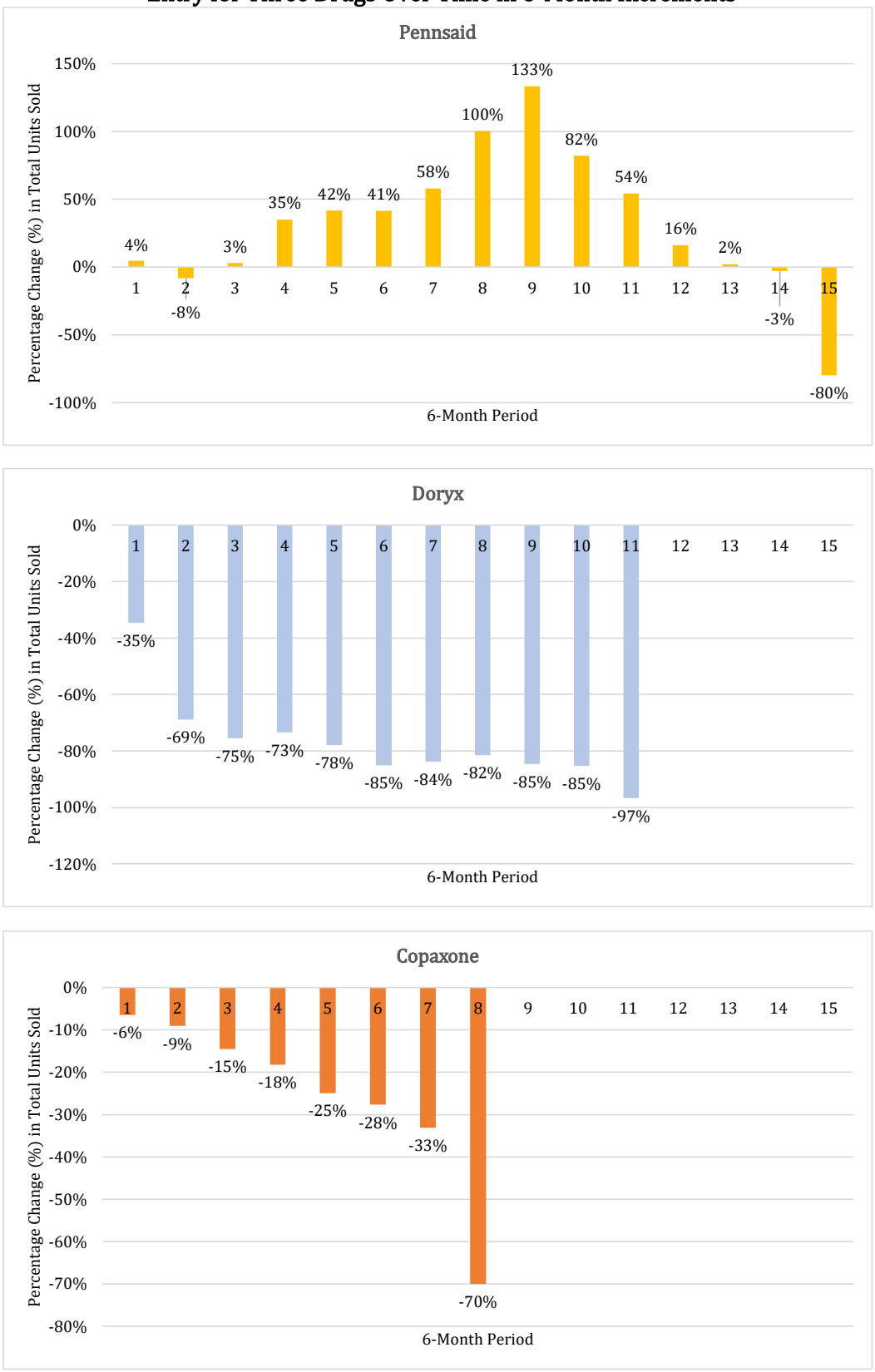
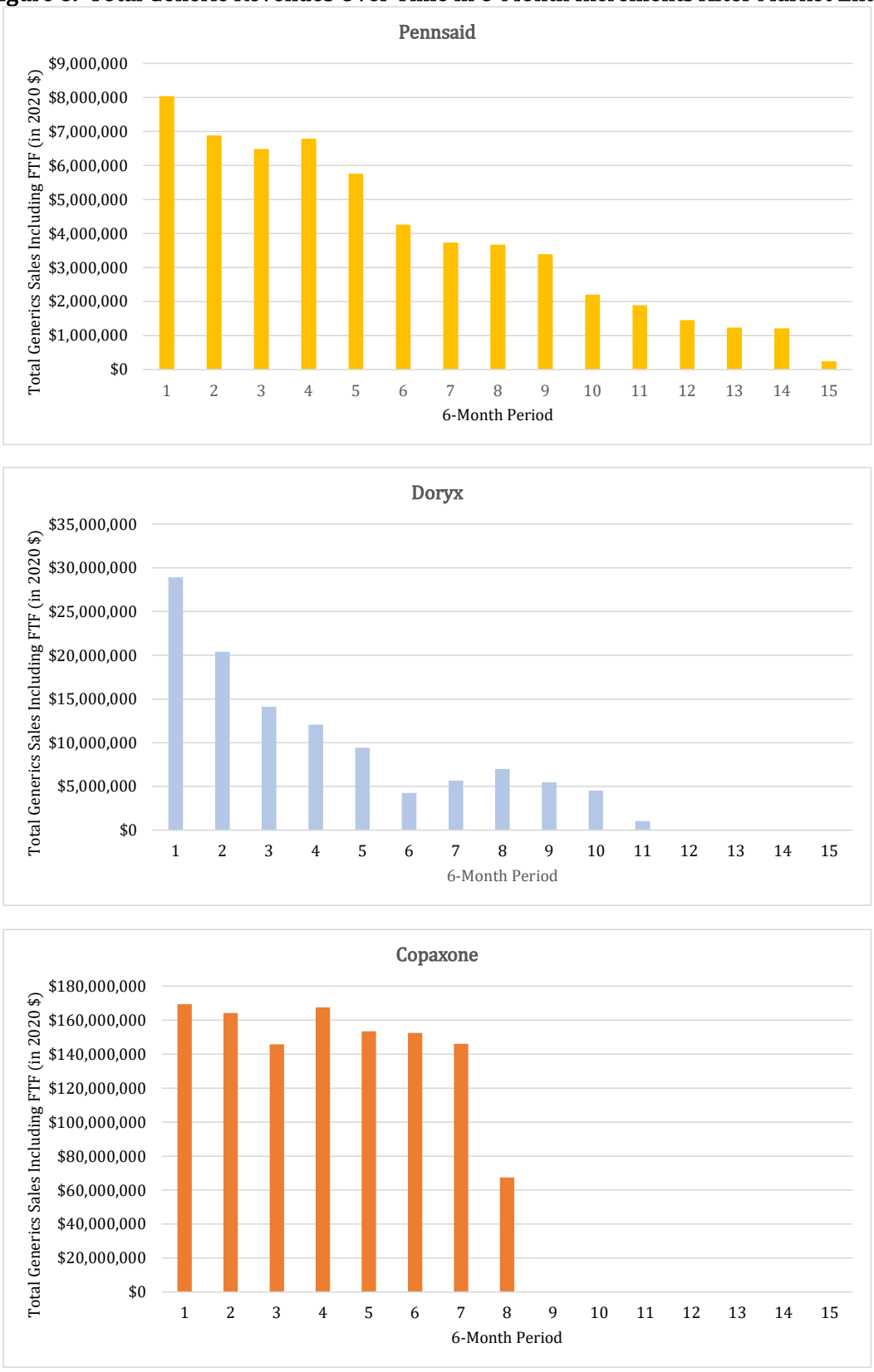


Figure 6. Total Generic Revenues Over Time in 6-Month Increments After Market Entry



While a 180-day period of exclusivity is valuable to a generic company, especially if the market for the drug is sizable, patent litigation is costly (see Table 7) and a win for the generic company is not guaranteed, although neither is an infringement suit against them. An early study by the FTC (Federal Trade Commission, 2002), found that 29 of 104 brand drugs notified of a PIV certification did not bring action within the 45-day limit (which would have triggered an automatic 30 month delay in approving the generics' ANDA).[34] Furthermore, the possibility of sharing exclusivity with other generic companies reduces the value of 180-day exclusivity to a given ANDA applicant.[35] Thus, settling out of court becomes an attractive option as it reduces legal costs and eliminates uncertainty for both parties.

However, PIV patent litigation settlements (often called reverse payment settlements)[36] also create perverse incentives from a societal perspective; they incentivize ANDA applicants to file a PIV certification but disincentivize them to carry the case on to a final court decision. As a result, market entry of lower-cost generic drugs is delayed which burdens the healthcare system. According to a study by the FTC, such settlements cost patients and payers $3.5 billion annually from 2001 to 2008 (Federal Trade Commission, 2010). Another more recent study by Dave, et al. (2020) estimated the excess cost to Medicaid programs of generic drug entry delays from patent litigation at $761 million over seven years ($109 million annually) using data on a cohort of drugs whose patents have expired between 2010 and 2015. Among the 69 brand-name drugs in the study cohort, they found that generic drug entry was delayed by more than one quarter[37] for 31 brand-name drugs (45 percent) or did not occur at all. In contrast, a newer analysis using six different estimation methods by Feldman (Feldman, 2021a) finds that the average annual cost to consumers of pay-for-delay settlements between 2006 and 2017 ranged between $6.4 billion per year and $36 billion per year.

Given their potentially anticompetitive effects, i.e., preservation of some weak patents "unlikely to withstand reexamination" (Lemus & Temnyalov, 2020), Hatch-Waxman litigation settlements have been scrutinized closely by the courts and FTC since the Act's enactment in 1985. Two key court decisions are important to highlight:

- *Schering Plough, Inc. v. FTC*, 2005.
- *FTC v. Actavis, Inc. et al.*, 2013.

In *Schering Plough, Inc. v. FTC* , the 11th Circuit Court of Appeals ruled that reverse payments were not *per se* violative of antitrust laws, and that the proper method to determine if a

[34] FTC noted that the median net sales of the 29 brand drugs that did not sue for infringement within 45 days was under $100 million, while for the 75 brand drugs that did sue, the median was $190 million.

[35] All applicants submitting ANDAs containing PIV certifications for a particular drug product received on the same day are eligible for exclusivity if no other ANDA with a PIV certification for the drug product has been previously filed. In this case, FDA considers all such applicants as first applicants.

[36] In virtually all patent infringement settlements outside of the Hatch-Waxman PIV framework, the alleged infringer typically compensates the patent holder (to varying degrees) for royalties or profits lost due to the alleged infringement. In settlements of PIV litigation, however, the roles are reversed—the patent holder is in the position of trying to compensate the alleged infringer for ending their legal effort to enter the market early. For this reason, PIV settlements began to be called "reverse payment" settlements. "Pay-for-delay" settlements comprise a subset of PIV settlements in which the patent holder pays the alleged infringer to postpone the latter's early entry into the market in case of a court decision of non-infringement or patent invalidity.

[37] The authors defined "market entry" as the first appearance of a generic in the Medicaid State Drug Utilization files. As these files are updated quarterly, if a generic version of a brand drug appeared in the files within one quarter of the brand drug's expected patent expiration date, this was considered timely market entry.

settlement is anticompetitive is to consider: "(1) the scope of the exclusionary potential of the patent; (2) the extent to which the agreements exceed that scope; and (3) the resulting anticompetitive effects."[38] (The Supreme Court refused to review.) While the 11th Circuit's ruling did not eliminate ambiguity regarding Hatch-Waxman settlements, its rejection of FTC's position that reverse payments were *per se* anticompetitive widened the field for Hatch-Waxman settlements. The 11th Circuit's opinion in *Schering-Plough* contrasted with that of the 6th Circuit in 2003 in another case, which "found a reverse payment to be a *per se* violation of the antitrust laws"[39] (Axinn, Veltrop & Harkrider LLP, 2005). In at least two cases[40] district courts tended to agree, "stating that *per se* treatment of reverse payments may be appropriate" (Axinn, Veltrop & Harkrider LLP, 2005).

The Supreme Court addressed the conflicting appellate court opinions in their decision in *FTC v. Actavis, Inc. et al.*, 570 U.S. 136 (2013). In 2013, FTC filed suit, alleging that Actavis Inc. and Paddock "violated Section 5 of the FTC Act by unlawfully agreeing to abandon their patent challenges, to refrain from launching their low-cost generic drugs, and to share in Solvay's [RLD patent holder] monopoly profits." In its decision, the Supreme Court affirmed that compensated settlements were not *per se* anticompetitive, but also directed that a traditional "rule of reason" framework could be applied to assess if aspects of a settlement transgressed antitrust laws. The Supreme Court left it to lower courts to determine the structural details that should be applied to Hatch-Waxman settlements under a rule-of-reason rubric, although they pointed out that antitrust laws prohibit monetary payments that are "large and unjustified." The Court did say that reasonable monetary compensation for litigation costs should not be considered anticompetitive.

Table 24 presents the annual frequency of Hatch-Waxman litigation settlements overall, as well as the number of settlements incorporating two potentially anticompetitive features, viz., restricted generic entry and compensation over $7 million (Federal Trade Commission, 2020).[41] The data show substantial and steady increases in the frequency of settlements and settlements with compensation during the 2005-2013 period, i.e., the years between the Schering-Plough and Actavis decisions.

[38] The original PIV certification for a generic version of Schering's patented K-Dur 20 potassium supplement was filed in 1995 by Upshur-Smith and ESI Lederle. Schering settled with the two filers in 1997 and 1998, respectively. The patent expired in 2006; the settlement allowed Upshur to enter the market in 2001, ESI in 2004. The largest payment involved was for a "side deal" of $60 million to Upshur for a license allowing Schering to market one of Upshur's drugs.

[39] In re Cardizem CD Antitrust Litig., 332 F.3d 896 (6th Cir. 2003), cert. denied, 125 S. Ct. 308 (Oct. 12, 2004).

[40] In re K-Dur Antitrust Litigation, 338 F. Supp. 2d 517 (D.N.J. 2004); In re Ciprofloxacin Hydrochloride Antitrust Litig., 261 F. Supp. 2d 188, 251 (E.D.N.Y. 2003).

[41] The rationale for the $7 million limit on compensation for past and potential litigation costs was questioned at an FTC press conference on May 28, 2015, announcing FTC's $1.2 billion anti-trust settlement with Cephalon regarding the latter's anticompetitive actions to keep generic Provigil out of the market. Asked "how you came up with the cap on litigation expenses of $7 million in future pay-for-delay deals," FTC Chair Ramirez responded that, "generally speaking, it was based on publicly available information." Asked by another journalist, "to what extent does this [injunction] form a template in terms of the $7 million litigation expenses…for other cases," Chairperson Ramirez replied that "…it does convey an important message about what we believe to be anti-competitive conduct… but it's not an attempt to define everything that could be problematic industrywide in connection with these types of arrangements" (Federal Trade Commission, 2015).

Table 24. Disposition of Hatch-Waxman Litigation Settlements, 2004-2020

Fiscal Year	Number of Final Settlements	Number of Restricted Generic Entry and Compensation Settlements	Number of Restricted Generic Entry and Compensation Settlements (Excluding Solely Litigation Fees < $7 Million)	Number of Restricted Generic Entry and Compensation Settlements Involving First Filers
2004	14	0	0	0
2005 [a]	11	3	3	2
2006	28	14	13	9
2007	33	14	14	11
2008	66	16	15	13
2009	68	19	11	15
2010	113	31	17	26
2011	156	28	25	18
2012	140	40	33	23
2013 [b]	145	29	15	13
2014	160	21	11	11
2015	170	14	5	7
2016	232	30	1	16
2017	226	20	3	6
2018	NA	NA	NA	NA
2019 [c]	146	NA	NA	NA
2020 [c]	185	NA	NA	NA

Sources: Federal Trade Commission (2020); (Hovden, et al., 2019) (Hovden, et al., 2020)
NA = Not available
[a] *Schering-Plough Corp. v. FTC,* 402 F.3d 1056 (11th Cir. 2005) March 8.
[b] *FTC v. Actavis, Inc.*, decision issued by Supreme Court June 2013.
[c] When this report was written, FTC had not yet published its analysis of Hatch-Waxman settlements finalized after 2017. The reported figures are from (Hovden, et al., 2019) and (Hovden, et al., 2020).

The impact of *Actavis* is evident (Table 24) in the diminishing number of settlements that involved payments over $7 million—FTC having determined that $7 million was about the maximum reasonable compensation that brand companies could offer to generics for the costs of litigation and still avoid antitrust scrutiny.

An operational definition of "large and unjustified" in this legal context has proven to be nearly as problematic for the lower courts as defining "payment." Brand companies devised more creative non-monetary compensation to offer generics in settlement. In FTC's summary of Hatch-Waxman settlements submitted to it in 2017, the Commission reported an array of settlement features that it considers evidently or potentially anticompetitive compensation for restricted generic entry, including: (1) assigning the generic company several patents unrelated to the litigated product at no cost; (2) buying "intellectual property related to the litigated product from the generic litigant"; (3) committing not to contract a third party to distribute an AG "for a period of time, such as during first-filer exclusivity"; (4) providing a supply of AGs to a non-first-filer ANDA holder during the first-filer's exclusivity period (which would enable the non-first-filer ANDA holder to enter the market 6 months earlier than otherwise) (Federal Trade Commission, 2020).

Of the 226 final settlements submitted to FTC in 2017, "169 [75 percent] restrict the generic manufacturer's ability to market its product but contain no explicit or possible compensation" and 29 final settlements (12.8 percent) that "contain no restrictions on generic entry." (Federal Trade Commission, 2020). Three settlements included "explicit" compensation beyond litigation costs,

and FTC considered eight others to include "potential" compensation.[42] The comparable figures for 2015 were: 170 final settlements, of which 126 (74 percent) "restrict the generic manufacturer's ability to market its product but contain no explicit or possible compensation" and 20 (11.8%) that "contain no restrictions on generic entry." Four settlements involved restrictions of generic marketing and compensation in the form of an agreement not to market an AG for some period of time. Ten other settlements were considered by FTC to include "potential compensation."

While there have been some differences in judicial opinions about what "large and unjustified payments" comprise, Hatch-Waxman litigants are apparently increasingly reluctant to risk having to defend antitrust actions and their concomitant potential for triple damages. Virtually every aspect of a settlement can be evaluated for its dollar value to the generic company, including every month in advance of patent expiration that the brand company enables the generic to be in the market. Widening the definition of anticompetitive compensation is intended to pressure brand companies seeking settlement to offer the generic more and more time in the market in advance of patent expiration. Earlier market entry of more generic competitors is, after all, the primary strategy advanced by Hatch-Waxman to achieve its goal of lower drug prices through competition.

Bills to eliminate or severely restrict settlement of Hatch-Waxman have been introduced—and re-introduced—in the House and Senate in 2007, 2009, and 2019.[43] None have been voted on by a full chamber. Only S. 369, the Preserve Access to Affordable Generics Act (2009), has been reported out of committee. California, however, has enacted a law (CA Health & Safety Code § 134002 (2019)) that forbids brand companies from providing "anything of value" to a generic company in settlement of Hatch-Waxman litigation. The law went into effect in January 2020 and exposes violators to civil litigation and penalties of at least $20 million, up to three times the dollar value of the "anything of value" offered by the brand company,[44] though enumerating several inducements that the brand company could offer that would not be considered "of value" under the statute, including market entry before the RLD patent expiration, compensation for legal costs, and up to five percent of the generic drug's forecast profits over its first three years in the market.

It is yet unclear how or if the potential enforcement of this law may have affected settlements since its enactment. Its effects seem unlikely to be bounded by the state's borders. Aside from the difficulty of negotiating settlements under two sets of criteria—FTC's and California's—"nothing in the Act limits its application to settlements that were negotiated, completed or entered into in California or by California companies." (Hale, 2020). Thus, if a drug is marketed in California, any PIV settlement involving that drug may be liable to the considerable potential damages the law provides.

While settlements involving compensation in excess of $7 million in litigation costs have become less frequent since the 2013 Supreme Court decision, "they now often involve complex marketing agreements intended to obscure payment" (Vokinger, et al., 2017). Such agreements may include licensing or distribution arrangements unrelated to the patent(s) at issue and which

[42] FTC has stated that "…the two most pernicious and common forms of reverse payments [are]: (1) a side deal, in which the generic company receives compensation in the form of a business transaction entered at the same time as the patent litigation settlement; and (2) a no-AG [authorized generic] commitment, in which a brand company agrees not to compete with an AG version of a drug for a period of time." (Federal Trade Commission, 2019)

[43] Preserve Access to Affordable Generics Act, S. 316 (2007); Preserve Access to Affordable Generics Act S. 369, (2009); Protecting Consumer Access to Generic Drugs Act of 2009, H.R. 1706; Protecting Consumer Access to Generic Drugs Act of 2019, H.R. 1499.

[44] When this report was written, the Association for Affordable Medicines (AAM), having lost its initial suit against California's attorney general (AAM v. Xavier Becerra, 20-cv-01708-TLN-DB, E.D. Cal.), had filed a second action seeking to stop or slow enforcement.

may be difficult for antitrust analysts to evaluate, particularly if both parties have an interest in minimizing the value of the arrangement to the generic litigant(s).

Most PIV settlements include acceleration clauses, the term given to a settlement provision guaranteeing that each generic litigant will get the same best deal agreed to by any co-litigant. More recently, the acceleration provisions in Hatch-Waxman settlements have been receiving closer scrutiny from FTC and the courts. There are two types of acceleration provisions in these settlements: most favored entry (MFE) and most favored entry plus (MFEP). Many RLD patent cases are joined by several generic litigants. To facilitate settlements with individual litigants, a brand company's settlement offer usually guarantees the generic company that if an earlier market entry date is settled upon in a subsequent negotiation, that date will apply to all other settlements for that drug. The MFEP is a variation that guarantees any company with 6-month FTF exclusivity that no other settlement will violate their exclusivity.

It is apparent that such clauses are all but essential in most settlements; without them, a generic firm could be seriously disadvantaged by other generic companies bargaining for earlier market entry dates. Court decisions have varied on the anticompetitive or procompetitive qualities of acceleration provisions, depending on specific circumstances surrounding each case. Hence, some observers (Fernandez & Keeley, 2020) consider that such provisions may be structured and used in ways that diminish the risk of being ruled anticompetitive. This seems highly probable, as can be inferred from the fact that FTC has in recent reports found it difficult to discern where and if some settlements have crossed the line FTC and the courts have thus far drawn. Both brand and generic companies have responded ingeniously to the increasingly constricted settlement environment.[45]

Acceleration provisions are not expressly prohibited by the California statute. However, analysts expect important court decisions in 2021 that will affect Hatch-Waxman settlement ground rules (Ginsberg, et al., 2021), including decisions on licensing AGs; the nature and admissibility of expert witness testimony regarding the probable outcome of the patent litigation under settlement; and decisions on the legality and enforceability of California's anti-pay-for-delay law (CA Health & Safety Code § 134002 (2019)). Other observers (Feldman & Misra, 2019), warn that "camouflaged pay-for-delay" settlements will become more subtle and difficult for courts and regulators to discern and evaluate. Feldman has suggested that a legal presumption that Hatch-Waxman settlements are anticompetitive would pressure the litigants to demonstrate that their deal was in fact not anticompetitive, thereby making transparent settlement details that are now still closely held. Increased transparency, Feldman suggested, would go a long way to promote settlements that were reasonable and less costly to consumers than at present (Feldman, 2021a).

Overall, Hatch-Waxman patent settlements continue to be "one of the most intensely litigated issues at the intersection of patent and antitrust law" (Fernandez & Keeley, 2020). From an economic perspective, however, the ability to settle expands the options for generic companies, reduces their risk, and makes generic drug development more profitable. Settlements redistribute producer surplus from the brand company to the generic company, but patients do not benefit. In this sense, settlements can be viewed as a barrier to lowering generic drug prices but not necessarily a barrier to generic drug development.

[45] In its most recent summary of settlements (Federal Trade Commission, 2020), FTC identified eight settlements as providing "possible compensation" because "it is not clear from the face of each agreement whether certain provisions act as compensation to the generic patent challenger. Analysis of whether there is compensation requires inquiry into specific marketplace circumstances…"

7.2 Other Non-IP Barriers

7.2.1 Formulary Tier Manipulation and Brand Drug Rebates

Formulary tiers are groupings of drugs by price that, for insured individuals, determine what their copay will be. Drugs on a higher formulary tier cost the insured individual a higher copay than one on a lower tier. PBMs, in addition to receiving rebates from manufacturers, also determine which of five tiers the manufacturer's drug product will go on. "Uptiering" is a serious concern to first-time generic market entrants.

PBMs have drawn investigative attention from legislative committees, state attorneys general, and U.S. attorneys for several apparently questionable strategies, such as extracting hundreds of millions in excessive reimbursements from state Medicaid plans (Rowland, 2020; Pifer, 2021; Burns, 2019); and cutting reimbursements to independent pharmacies for months to weaken their finances before trying to purchase them (Mitchell & Freed, 2021). It is the PBMs' role in establishing drug formularies for insurers, coupled with their negotiation of rebates from brand drug companies, that has drawn disapproving attention from generic manufacturers, insurers, and investigators over the past several years.

Representatives of several generic manufacturers interviewed for this study emphasized that "uptiering" of generic drug products in PBM-designed formularies—or simply excluding a generic version of a brand drug from a formulary— was a more immediate concern than "yesterday's battles" (i.e., recognized barriers such as evergreening, REMS manipulation, etc., that had gotten attention from FDA and legislators). Ultimately, the goal of a brand manufacturer is to maintain as much market share for as long as possible, especially for its most profitable products. If generic competitors do enter a market, either through a successful PIV process or by waiting until patents expire, brand manufacturers have still been able to limit their incursion owing to a labyrinthine and opaque system of pricing, distribution, secret rebates, and cost reimbursements. The nexus of this system is occupied by PBMs, which negotiate rebates from brand drug manufacturers, manage prescription benefit programs and formularies for public and private health insurers, and manage distribution of drug products to retail pharmacies.

For generic drug manufacturers, the key function of PBMs is their construction of formularies for insurers (i.e., the drugs that the insurer will cover for their clients) and assigning formulary drugs to an appropriate cost-sharing tier. Several representatives of generic drug companies interviewed mentioned adverse formulary positioning as a potential stumbling block in marketing a newly-approved generic drug product. One very large manufacturer described entering a first generic into a market after a 9-year effort (including patent litigation). The generic drug's price was set at 70 percent of the brand drug's price, yet their product's market share was just 25 percent, whereas "historically" they would have expected to achieve 90 percent market share.

Formulary manipulation can simply be excluding a generic drug from the formulary or assigning a generic, particularly a specialty generic, to the same or even a higher formulary tier than its RLD. This influences patients (and doctors) to use the brand drug, as the copays for the brand drug would be either the same or lower than the copay for the generic (depending on the tier). This benefit to brand manufacturers could be used by PBMs to negotiate higher rebates, which translate to higher profits for PBMs. Stripped of detail, PBMs keep a percentage of the rebates they negotiate off the list prices of brand drugs. This system also encourages brand manufacturers to raise the list price of a drug rather than increasing the rebate—a simple, no-cost (to them) way of increasing the PBM's profit in exchange for protecting the brand drug on PBM formularies. Unfortunately, higher list prices impact those who must pay them, including patients with plans requiring them to pay full

price until a deductible is met, Medicare beneficiaries in the "donut hole," and patients without prescription drug insurance (Feldman, 2019a).

A spur to uptiering generic drugs occurred in 2016, when the Centers for Medicare and Medicaid Services (CMS), in response to enquiries from PBMs and Part D insurers, said that for plan year 2017, the "nonpreferred brand" tier (tier 4) could be renamed "nonpreferred drugs," depending on whether brands or generics comprised the majority of drugs on that tier. After this, several studies demonstrated the accelerating trend among Part D formularies in assigning generics to the higher tier. Table 25 and Table 26, below, present cost sharing data and the distribution of listed drugs by tier from the formularies of two regional health care companies: (1) HealthPartners of Bloomington, Minnesota, a nonprofit health insurer and care company, which offers several insurance plans and operates eight hospitals and 55 clinics; and (2) Health Partners Medicare Prime, an HMO in eastern Pennsylvania.

Table 25. Cost Sharing Levels by Plan and Drug Tier, HealthPartners 2021

Tier	Plan P	Plan S	Plan D	Plan S	R. B.	R. M.	Listed Drugs by Tier N= 1,958	
1—Preferred Generic	$8	$6	$5	$4	$2	$2	161	8.2%
2—Generic	$14	$12	S10	S10	$9	$9	346	17.7%
3—Preferred Brand	$47	$47	$47	S47	$47	$47	500	25.6%
3—Select Insulin Drugs	$35	$35	$35	$35	$35	$35		
4—Nonpreferred Drug	35%	40%	40%	40%	$100	$100	477	24.3%
5—Specialty	27%	27%	27%	27%	29%	29%	474	24.2%

Source: HealthPartners (2021)

Table 26. Health Partners Medicare Prime: Cost sharing for Each Tier in the 2021 Formulary and Distribution of Listed Drugs by Tier

Tier	Retail Cost-Sharing (30-day supply)	Mail-Order Cost-Sharing (90-day supply)	Listed drugs by tier N=2,133	
			Number	% of Total
1—Preferred Generic	$0	$0	767	36.0%
2—Generic	$10	$20	534	25.0%
3—Preferred Brand	$47	$94	243	11.4%
4—Nonpreferred Drug	$100	$200	161	7.5%
5—Specialty	33%	Not offered	428	20.1%

Source: Health Partners Medicare Prime (2020)

Table 27 presents data from four publications showing the percentages of generic drugs distributed among Part D formulary tiers from 2010 to 2020. The trend toward assigning generic drugs to non-generic tiers (mainly tiers 3 and 4) is apparent in the table.

It is unclear to what extent PBMs' manipulation of generics across formulary tiers and the rebate system affect the decision of a generic firm to enter a market, the costs of entering a market, or even the revenue model of entering a generic market. In the latter case, some representatives of generic manufacturers interviewed for this report have commented on the decline in anticipated market share for first or early entrants to a market. However, none was able to quantify this impact with any degree of certainty.

The more publicized issue surrounding manufacturers' rebates has been that patients at the point of sale see so little benefit from them. The PBMs usually pass along most of the savings to the insurers, while keeping a portion for their own services. PBMs and insurers have responded to such criticism by pointing out that consumers benefit from lower (or less steeply rising) premiums. Manufacturers point out that they have separate coupon programs that make brand drugs more

affordable for consumers— and often drop brand drug copays and coinsurance below those of generic competitors. When this is the case, brand drug coupons tend to have a similar effect as uptiering generics, i.e., encouraging consumers to purchase the brand drug rather than the generic. Some states have enacted legislation prohibiting retail brand drug coupons if a generic version of the drug is available. In the absence of Congressional action, numerous states have enacted various statutes and regulations aimed at ameliorating a variety of PBM practices that have come to be seen as having high abuse potential: gag clauses, secret rebates, secrecy of other contract terms, spread pricing, claw-backs, etc.

Table 27. Distribution of Generic Drugs on Part D Formulary Tiers, As Reported in 4 Studies

Tier	2010 [a]	2011 [b]	2015 [b]	2016 [c]	2017 [c]	2018 [c]	2019 [c]	2020 [d]
1—Preferred Generic		71%	19%	14%	14%	14%	14%	10%
1—Preferred Generic	73%	→	→	→	28%			
2—Generic		22%	46%	61%	44%	41%	39%	37%
3—Preferred Brand		4%	19%	15%	16%	17%	18%	19%
4—Non-preferred Brand *or* 4—Non-preferred Drug [e]		2%	15%	18%	23%	28%	26%	28%
5—Specialty		0%	1%	3%	3%	3%	3%	6%

[a] From Feldman (2019a)
[b] From Avalere Health (2018)
[c] From Avalere Health (2019)
[d] From Fix, et al., (2021)
[e] The "nonpreferred drug" label for tier 4 became available in plan year 2017.

In September 2021, HHS unveiled its comprehensive plan to address high drug prices in response to the Executive Order on Competition in the American Economy (Office of the Assistant Secretary for Planning and Evaluation, 2021). The plan includes requiring issuers of Affordable Care Act (ACA) "marketplace plans or their PBMs to provide drug, rebate, and spread pricing information" to HHS through its data collection portal starting in 2022.

Through this plan, HHS hopes to shift PBMs away from the opaque complexity of the current rebate system, which it recognizes as being anti-competitive. The plan has the potential to inhibit PBMs from formulary manipulations that benefit brand manufacturers by inhibiting the manufacturers' current quid pro quo, i.e., rebates paid to PBMs, supported at least partly by price increases. As for the effect of brand drug price increases, in its 2020 Report, the Medicare Payment Advisory Commission observed that: "Although brand-name drugs accounted for only about 13 percent of prescriptions in 2018, brand-name drugs made up 80 percent of all Part D spending. As a result, price increases for brand-name drugs overwhelmed the effects of using lower priced generics." (Medicare Payment Advisory Commission, 2020)

Socal and colleagues (2019) looked at 57 unique drug formularies offered across all 750 Medicare Part D stand-alone prescription drug plans in November 2016. First, they found that, out of 935 multi-source drugs (i.e., drugs with both generic and brand versions available), 120 (12.8 percent) did not have a generic version covered in any of the 57 formularies. Of 222 multi-source drugs that had both generic and brand versions represented in at least one formulary, 5 percent had the generic version in a higher tier than the brand version. The authors noted that "favorable formulary placement of branded drugs encourages the use of more expensive products and can lead to higher costs for Medicare beneficiaries and higher expenditures for the Part D program" (Socal, et al., 2019).

Avalere's studies on this issue in Part D formularies (Avalere Health, 2018; Avalere Health, 2019) show that uptiering of generics has caused the percentage of generics assigned to the lowest cost tier (tier 1) has declined from 71 percent in 2011 to 19 percent in 2015, and 14 percent in

2019. In the 2019 plan year, 46 percent of generic drugs were placed on non-generic—i.e., higher cost—tiers.

Others taking an opposing view claim that uptiering is a "utilization management strategy" (along with step therapy and "benefit exclusion") that helps control costs by incentivizing patients to move from higher cost specialty generics to less expensive, "comparable" treatments (Blum, 2019).

7.2.2 RLD Labeling Changes Near Patent and/or Exclusivity Expiry

With an important exception discussed below in Section 8.3, FDA requires that the label of a generic drug be identical to that of the brand drug (RLD). Some industry representatives claim that brand drug companies may try to delay generic market entry by submitting changes to the label of the RLD, timing their submission in a way that forestalls final ANDA approval and/or market entry (i.e., near or at patent expiry and/or exclusivity). The generic company must then update its label to conform to the revised RLD label. It is unclear from the literature review and interviews with industry personnel how long changes in the RLD label are likely to delay a generic's market entry. That said, even one extra month of an RLD monopoly can be worth tens or hundreds of million dollars to the brand company.

The exception to FDA's directive that a generic drug's label must be the same as that of the RLD occurs when a generic applicant submits a statement to FDA under 21 U.S.C. § 355(j)(2)(A)(viii))—a "section viii" statement—that the generic drug's label will omit ("carve out") patent protected uses or indications of the RLD.[46] The section viii statement and the carved-out label (or "skinny label") allow FDA to approve the ANDA after determining that the skinny label does not trespass on any of the RLD's Orange Book use codes.[47]

In 2013, FDA proposed the Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products rule, which was meant to allow generic manufacturers to update safety information on their labels as new adverse event or other safety-related data emerged. Previously, only FDA could initiate changes to generic drug labels. The rule was opposed by generic companies because it was likely to increase their exposure to safety-related failure-to-warn tort litigation. In fact, a 2011 decision by the Supreme Court (Pliva v. Mensing) held that FDA's total control over generic labeling meant that generic companies could not be responsible for any failure-to-warn issues that arose from omissions in RLD labeling.

Ultimately, FDA withdrew the proposed rule in 2018. However, FDA's estimate of the rule's burden to industry suggests a basic cost to a generic firm of making a label change: 15 hours—12 hours for preparing the FDA submission and 3 hours for the notice to the NDA holder (Federal Register, 2013; 78 FR 67985).

The real cost to the generic firm, beyond the 15 hours of labor, would be represented by the delay in marketing their product, a delay potentially caused by a late RLD label change. The

[46] The section viii carve-out is available only if the RLD's live patents are for methods of use only.

[47] Currently, the skinny label route to market is under severe judicial pressure. In October 2020, a three-judge panel of the U.S. Appeals Court for the Federal District upheld a jury decision in favor of GlaxoSmithKline (GSK), manufacturer of Coreg (the RLD), against Teva. GSK had alleged that the skinny label on Teva's generic had "induced infringement" of Coreg's patent by implicitly encouraging physicians to prescribe the generic for the carved-out use. The panel re-heard the case in February 2021 and on August 5, 2021, upheld the $235 million award to GSK in a 2-1 vote. The impact may be to limit generic drug makers' options in bringing a generic to market before all RLD patents expire. The dissenting judge commented that the ruling "creates confusion for generics, leaving them in the dark about what might expose them to liability." (Brittain, 2021)

importance of this timing will vary widely. A generic company with shared exclusivity could lose valuable weeks of exclusivity in the market if another FTF company can adjust their label sooner. Contracts with wholesalers or distributors may have to be modified to account for a delay. However, neither the expense nor the potential delay caused by an RLD label change were considered serious barriers by manufacturing representatives interviewed for this study.

7.2.3 Authorized Generics (AGs)

AGs are identical to brand drugs in every way except the packaging or printing on the pill or capsule. Because they are identical to the brand product, they need not go through ANDA approval. They are manufactured either by the brand company itself or its licensee. AGs emerged in 2003 as a tactic to stake out a larger market share prior to the entry of independent generics and to undermine the value of the 180-day exclusivity period for the FTF and first to market generic. By 2005, at least two dozen AGs had been launched (Understahl, 2006). Currently, FDA lists 1,214 AGs (U.S. Food and Drug Administration, 2019). A little more than half are different strengths or dosage forms of the same drug; there are about 539 different drugs named on the list. FDA notes that these data are not submitted to them but result from their research into drug companies' annual reports and other documentation.

In 2005, FDA decided against generic manufacturers' petitions to prohibit the marketing of AGs during the 180-day exclusivity period, which is the reward to true generic manufacturers for developing the generic and challenging the brand's patent(s). FDA's position was upheld by the District Court in *Teva Pharmaceuticals Industries, Ltd, v. FDA,* 355 F. Supp. 2d 111 (D.D.C. 2004).

Although FDA argued that an AG in a market results in a lower drug price sooner to many patients, this may not always be the case. One report (Advisory Board, 2019) quoted an anonymous PBM employee who said that rebates off the list price of one brand drug—Humalog, listed at $275—lowered the brand's actual cost to $137, equal to the price set for Humalog's AG when it hit the market.

The advantages to the brand manufacturer of the AG are several. In addition to staking out a share of the generic market, the AG gains the advantage in markets where insurers insist that a generic be provided to the patient unless the prescribing physician provides medical reasons for use of the brand. Physicians who might have a hard time "selling" a generic to a patient—about one-third of patients do not believe that generics are as safe or effective as the brand (Shrank, et al., 2009)—can try explaining that the AG is in every physical way identical to the brand.

Recent research by Feldman focuses on how AGs (called "captive generics" by the author) function to inhibit market penetration by true generic drugs, bolster brand sales, and limit the number of true generic competitors in a market (Feldman, 2021b). Analyzing Medicare Part D sales data from 2006-2018, Feldman examined 134 generic drug markets in which there was competition between an AG, a brand drug, and true generics; and 239 markets in which only the brand drug and one or more true generics were present. The net effect on generic market share was that "across the drug markets in [her] analysis, the presence of a captive generic reduced the market share of true generics by about 22 percent over the first three years following the entry of the first true generic. " (Feldman, 2021b) Feldman did not report data on the effect of an AG on the market share of an FTF generic during the latter's 180-day exclusivity. Data from the ERG analysis of drug sales by PIV generics during their exclusivity period are presented below and address this issue.

Aside from their very important impacts on drug markets, AGs, being identical to the brand drug but identified as a generic, have been useful as controls in research on patient acceptance of and attitudes toward generic drugs. One recent publication (Gagne, et al., 2019) used AGs to

demonstrate that a nocebo effect[48] impacts patients' reports of the effectiveness of some generic drugs versus brand drugs. When researchers compared patient descriptions of treatment outcomes across generic, AG, and brand versions of numerous drugs, both real generics and AGs were judged equally inferior to the brand drug with the same frequency, even though the AG and the brand drug are identical. With similar results across numerous drugs, physicians and patients may become persuadable that many brand drugs—at the very least, those whose AGs have exhibited a nocebo effect—really do not offer an advantage over their generic competitors.

We used our PIV market sample to examine the impact of an AG on an FTF generic's market performance during the latter's 180-day exclusivity period. Of the 38 products that comprised our PIV market sample, 25 (66 percent) had an AG with which the FTF had to compete against during its 180-day exclusivity period. Among those 25 PIV drug markets with AGs present, just one, the AG for ProAir HFA (albuterol sulfate), had sales recorded in the six months before generic entry. Another AG, for Seroquel (quetiapine fumarate), entered the market on the first day after the FTF's 180-day exclusivity.[49] Other than these two instances, AGs entered the markets in our sample during the FTF's 180-day exclusivity period. We compared the average share of total sales an FTF generic was able to capture during its 180-day exclusivity in markets where there were AGs to those where no AGs were present. From Table 28, we observe that the average market share in terms of dollar sales of an FTF generic is 7 percent higher if there are no AGs during its 180-day exclusivity period. Similarly, the brand company can expect to lose around 7 percent of market share during the same 180-days on average if they decide not to market an AG. Given that in general an FTF generic earns 60 to 80 percent of its profit in its 180-day exclusivity period (Coughlin & Dede, 2006), we can assume that the first-year revenues of the FTF could be roughly 5 percent higher in the absence of an AG. This translates to an average increase of 10.9 percent (range: 0.05 to 65.4 percent) in the ENPV of an FTF generic company that prevails in its PIV challenge and markets its product without facing competition from an AG during its 180-day exclusivity period *ceteris paribus* across the applicable product-pathway models depicted in Table A - 6.

Table 28. Share of Total 180-day Sales (%) After First Generic Entry, by Company Type and in Markets with and Without AGs

Company Type	Market with AG (n = 25)			Market without AG (n = 13)			Difference [a]	
	Mean	Median	Stdev	Mean	Median	Stdev	Mean	Median
FTF	28.2%	27.3%	12.1%	35.2%	36.4%	20.8%	7.0%	9.1%
Real Generics (excluding FTF)	0.1%	0.0%	0.6%	0.1%	0.0%	0.1%	-0.1%	0.0%
Real Generics (including FTF)	28.3%	27.3%	12.1%	35.2%	36.4%	20.8%	6.9%	9.1%
AG	21.2%	19.5%	14.5%	NA	NA	NA	NA	NA
Brand	50.5%	49.6%	16.0%	64.8%	63.6%	20.8%	14.3%	14.0%
Brand plus AG	71.7%	72.7%	12.1%				-6.9%	-9.1%

NA = Not applicable

[a] Given small sample sizes and relatively large variances, none of the differences is significant at the 95 percent confidence level.

[48] The nocebo effect occurs when a negative health outcome or adverse event occurs in a patient due to their negative expectations regarding the effects of treatment. A simple example comprises adverse events that occur in clinical trial subjects who received a placebo (and thus had no physiological basis to experience any effects at all from the "drug").

[49] A settlement agreement called for the FTF manufacturer to delay their market entry until six months before the brand's patent expired and for the brand manufacturer to delay entering an AG until after the FTF's period of exclusivity.

8 EXAMINATION OF INCENTIVES

8.1 180-Day Exclusivity Modifications

The primary incentive that Hatch-Waxman established for generic drug companies to attempt market entry before a brand drug's patent(s) expired was the 180-day period of exclusive presence in the market that the FTF generic applicant would enjoy upon entering the commercial market. As mentioned in previous sections, the value of this incentive is thought to have been diminished by the possibility of having to share some of the period of exclusivity with other FTF generic candidates, as well as the various tactics that brand drug companies have available to preserve as much market share as possible, including distributing AGs, obscuring price points through rebates to PBMs, and introducing "new and improved" versions of their RLD that could reclaim some of the market lost to the generic.

These pressures on the 180-day exclusivity incentive have prompted consideration of modifications to the structure of the incentive to further encourage PIV certifications. In order to assess the baseline status of the incentive, we first undertook a case study analysis where we examined the current status of several successful PIV generics and the value they have derived from entering their markets with 180-day exclusivity. Next we conducted a case-matched control study as described in Section 5.9.1 to compare the average exclusivity sales for a PIV generic to that of a comparable PIII generic.

FDA provides, and frequently updates, a list of PIV ANDAs, i.e., ANDAs that were accompanied by the generic's certification that their product did not infringe upon one or more of the active patents of the RLD. That list comprises drug/dosage combinations for which an ANDA and a PIV certification had been submitted, from 2004 through April 2021. The July 13, 2021 list we used for our analysis had 1,340 entries for which several milestones are reported for each item, including ANDA submission date, ANDA approval date, date of first commercial marketing—which marks day 1 of the 180-day market exclusivity period—and the expiration date of the final brand drug patent (which pre-empts the 180-day exclusivity, if expiration occurs before the 180 days are up). We used this list to select a proper sample of drug/dosage combinations that had entered the generic market with PIV exclusivity, whether alone or shared with one or more other FTF generics, between January 1, 2014 and June 30, 2021 using the steps listed in Figure 3 in Section 5.9.1.

We then used IQVIA NSP data from October 1, 2014 through June 30, 2021 to generate sales for 6-month periods, including the 6 full months before generic entry, 6 months after first generic entry (to cover the exclusivity period), and every 6 full months thereafter for the next 30 months. We also compiled information on the brand drug sales (and the AG if one was present) in the dosage form and strengths that were listed by FDA for the generic applicant for one year before generic entry.[50] We identified AG companies in each selected market by reviewing FDA's *Listing of Authorized Generics as of July 1, 2021,* the search function at authorizedgenerics.com, examining available FDA documentation, and contemporary news reports and press releases.

Table 29 compares overall units sold for 15 PIV generics during the 6 months before generic entry with overall units sold during months 25 through 30 after generic entry. One observation at this early stage of the analysis is the apparent emergence of an aspect of the generic competition paradox, namely that the overall volume of a drug market declines after the market

[50] If 12 months of sales data before generic entry were not available, market size was determined either by extrapolating from available before-generic-entry sales data or from annual sales reports in online sources.

opens to generic competition.[51] From the table, three of the 15 drugs had higher unit sales during the 25-30 months after generic entry than during the last 6 months before generic entry. Two of these increases were quite modest (generics of Saphris and Tikosyn, 5.8 percent and 2.6 percent, respectively). In contrast, 12 markets declined, five of them by nearly 50 percent. The average decline was 33.2 percent, and the median was 30.9 percent. As the footnotes indicate, four of the drugs experienced generic entry too recently to record 30 months of sales data; for those four, the table reports unit sales from the last full 6-month period included the last full 6-month period of sales after generic entry.

Table 29. Change in Total Units Sold in PIV Markets, Before and After Generic Entry

Generic Drug Name	Brand Drug Name	Total Units Sold, 6 months Before Generic Entry	Total Units Sold, 25-30 Months After Generic Entry	Change in Total Units Sold (Brand + Generics) from 6 Months Before Generic Entry to 25-30 Months After Generic Entry
Clofarabine	Clolar	198,920	85,160	-57.2%
Abacavir Sulfate and Lamivudine	Epzicom	5,337,720	2,397,480	-55.1%
Abiraterone Acetate	Zytiga	9,396,840	11,718,360	+24.7%
Aliskiren Hemifurate	Tekturna	3,420,240	1,718,580	-49.7%
Alvimopan [a]	Entereg	282,960	243,278	-14.0%
Asenapine Maleate [b]	Saphris	5,508,130	5,828,030	+5.8%
Dimethyl Fumarate [c]	Tecfidera	15,015,668	13,142,880	-12.5%
Dofetilide	Tikosyn	19,761,112	20,274,370	+2.6%
Efavirenz	Sustiva	212,670	103,170	-51.5%
Febuxostat [d]	Uloric	27,187,560	18,717,480	-31.2%
Imatinib	Gleevec	5,836,410	5,746,030	-1.5%
Lanthanum	Fosrenol	5,094,720	3,544,135	-30.5%
Lapatinib [e]	Tykerb	494,100	389,850	-21.1%
Lopinavir and Ritonavir	Kaletra	941,440	482,880	-48.7%
Tavaborole	Kerydin	277,578	206,738	-25.5%

[a] Represents unit sales in third 6-month period after generic entry. No data available after June 30, 2021.
[b] Represents unit sales in first 6-month period after generic entry, which ended June 10, 2021
[c] Represents unit sales in first 6-month period after generic entry, which ended Feb. 18, 2021.
[d] Represents unit sales in 4th 6-month period after generic entry, ending June 30, 2021.
[e] Represents unit sales in first 6-month period after generic entry, ending March 28, 2021.

There are several potential reasons for a decline in total units sold in a market after generic entry: less promotion by the brand drug; effects of product hopping; a product recall or warning by FDA; or competition from a newer competitor brand drug treating the same condition. Whether this trend predominates throughout the PIV entries may become evident with further analysis.

As an indicator of the value of the 180-day exclusivity period for the successful FTF generic company, we began with an analysis comparing 13 PIV drugs to PIII drugs that entered markets of similar size. As described in Section 5.9.1, we first looked at the sales for the brand/RLD drugs for one year before generic entry, for both PIV drugs and PIII drugs. The full year of brand sales data before PIV generic entry were matched to one or more PIII molecules that had brand sales +/- 8

[51] Huckfeldt and Knitter (2011) reported that the size of the market (i.e., units sold) began declining two years before first generic entry (and continued thereafter). We did not look for this pre-generic entry effect, as our focus was limited to one year before generic entry, mainly to determine market size, and six months before generic entry to facilitate comparisons with data from the 180-day exclusivity period and later.

percent of the PIV brand sales. This resulted in a one-to-many match of market size. Based on several data limitations, our case – matched control group only included 11 PIV drugs. If more than one PIII drug matched the PIV case drug, we used the average sales across those companies for those matched control drugs. We then looked at the generic sales for each company for the first year after generic entry in each of those markets and compared the cases to the matched controls. The results appear in Table 30 and Figure 7 below.

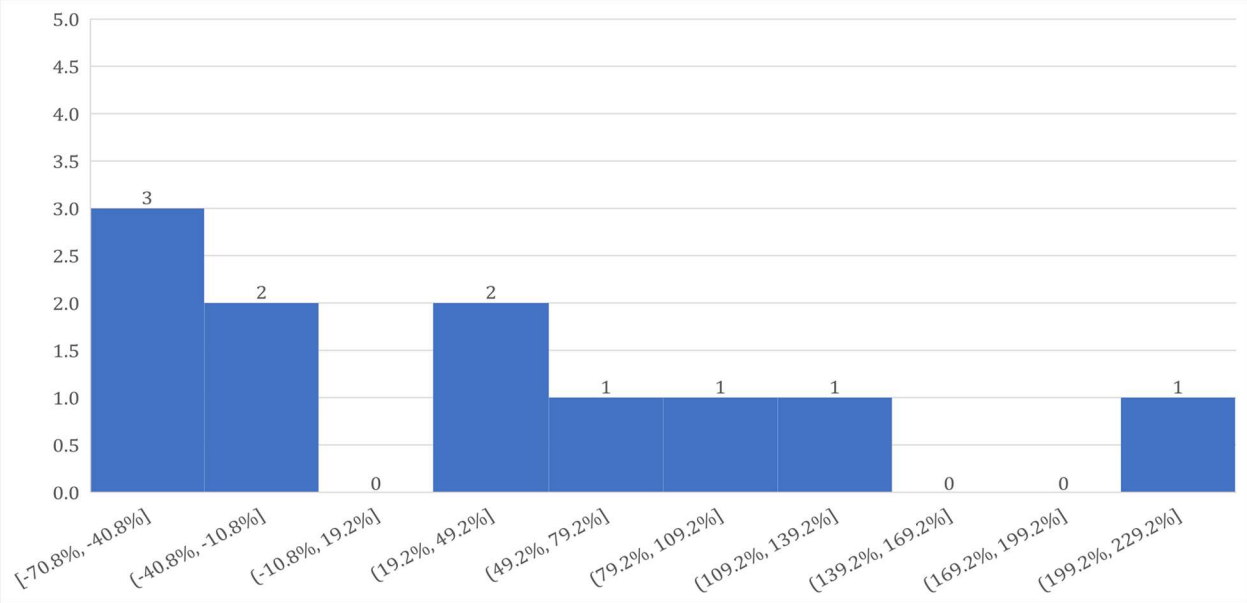
Among this limited set of matched PIV and PIII generic drugs, five PIVs had first year in-market sales lower than their matched PIII generic counterparts. The average shortfall was –$23.38 million, with a median of –$11.6 million. The PIV generics that exceeded the revenues of their matched PIIIs did so by an average of $24.3 million, with a median of $9.4 million. The 5 PIV generics that underperformed their matched PIII counterparts did so by an average of –48 percent; whereas the six that outperformed the PIIIs did so by an average of 92.7 percent. The total average revenues for the PIV generics in the first year after entry was $404 million; for the PIIIs, $376 million. For all 11 matched drugs, the average revenue per company was $2.56 million and the median was $0.30 million. Despite the limited sample, these preliminary results suggest that the 180-day exclusivity period, in the overall market, may not, on average, provide a consistently substantial revenue advantage over non-exclusive generic entrants into markets of comparable size, however, further analysis is needed with an expanded sample size.

Table 30. Comparative Revenues for 11 PIV Generics (with 180-Day Exclusivity) and PIII Generics Matched by Before-Generic-Entry Brand Market Size

PIV Generic Drug	RLD Brand Name	AG, First Year in Market [a]	Average First-year Revenues per Generic Company ($ million)		Difference between PIV Case and Average of PIII Matched Control(s) ($ million)		Number of Matched Control Molecules
			PIV Case	PIII Matched Controls	$	%	
Clofarabine	Clolar	0.67	$4.8	$16.4	-$11.6	-70.8%	2
Abacavir Sulfate and Lamivudine	Epzicom	1.00	$19.1	$8.8	$10.3	116.1%	3
Abiraterone Acetate	Zytiga	0.00	$34.3	$100.4	-$66.1	-65.8%	2
Aliskiren Hemifurate	Tekturna	1.00	$10.4	$7.1	$3.2	45.3%	4
Alvimopan	Entereg	0.00	$19.8	$11.4	$8.4	73.6%	3
Dofetilide	Tikosyn	1.00	$28.8	$32.9	-$4.1	-12.6%	2
Efavirenz	Sustiva	0.00	$1.4	$2.2	-$0.8	-34.9%	2
Febuxostat	Uloric	0.00	$25.4	$60.2	-$34.8	-57.8%	4
Imatinib	Gleevec	0.00	$227.3	$125.3	$101.9	81.3%	2
Lanthanum	Fosrenol	1.00	$31.3	$9.8	$21.5	220.1%	3
Lopinavir and Ritonavir	Kaletra	0.00	$1.6	$1.3	$0.3	19.9%	1

[a] 0.00 = No AG in market in first year; 1.00 = One AG in market for entire year; 0.67 = AG in market for 8 months.

Figure 7. Frequency Distribution of Difference in Average Per-company Generic Revenues Between PIV (Case) and PIII (Matched Control) Generics



We conducted a supplementary analysis to evaluate the value of 180-day market exclusivity to an FTF generic drug by comparing the performance of FTF generic drugs with the performance of other generics entering the market without exclusivity. To characterize the incentive value of changes to the length of the exclusivity period for the FTF, we examined the sales of our sample of FTF generics during their last month of exclusivity and the first month after their exclusivity ended. Table A - 7 in the appendix presents the FTF revenues for our PIV drug sample for months 6 and 7 after market entry, i.e., the sales for the last month of exclusivity and sales for the first month the market was open to competition.[52] In 25 (67.6 percent) out of the 37 PIV drug markets[53] in our sample, the FTF generic company experienced a reduction in sales from month 6 to month 7 (Table 31).

Table 31. Average Change in FTF Sales from Month 6 (Last Month of 180-Exclusivity) to Month 7 by Type of PIV Drug Market

Type	Market with AG		Market without AG		Total	
	n	Average Change from Month 6 to Month 7	n	Average Change from Month 6 to Month 7	n	Average Change from Month 6 to Month 7
Sales from Month 6 to Month 7 Declined	15	(38.4%)	10	(15.0%)	25	(29.0%)
Sales from Month 6 to Month 7 Increased	9	22.8%	3	13.6%	12	20.5%
Overall	24	(15.4%)	12	(8.4%)	37	(13.0%)

The overall average decline in sales from month 6 to month 7 was 13.0 percent. Among the 25 PIV drug markets in which the FTF experienced a decline in sales, the average decrease was 29.0 percent. Of these 25 PIV markets 15 had an AG that the FTF generic had to compete with and the

[52] By "competitors" in this context we mean other generic drugs; both the brand and an authorized generic are free to compete during the 180-day exclusivity period.

[53] For this analysis, we also excluded Saphris (NDA 22117) because it did not have a full month of sales data after its 180-day exclusivity period ended in mid-June, 2021.

remaining 10 did not. The decline in sales for the FTF generic from month 6 to month 7 was 38.4 percent when the market had an AG and 15.0 percent when no AG was present. Among the remaining 12 PIV drug markets in which the FTF experienced an increase in sales, the average gain was 20.5 percent. There may be several reasons why FTF generic sales may increase from month 6 to month 7 including no new competition entering the market, a more effective sales force, the observation of potential customers that the FTF generic performed well medically with minimal side effects, an even lower price per unit, etc. As for the FTF generics whose sales declined from month 6 to month 7, the most intuitive reason would be the entry of new generic competitors into the market. While it is tempting to infer that, for the FTF generics in our sample, the average effect of adding a seventh month of market exclusivity is an average increase in sales of 13.0 percent over realized sales in month 7, it would be fallacious. We would expect that an extra month of exclusivity will not actually harm or undermine the sales of those 12 FTF generics in our sample that managed to increase their sales in month 7. Therefore, it is not appropriate to include their percentage change in sales in calculating the average value of an extra month of exclusivity. Rather, it makes sense to infer that an extra month of exclusivity for those FTF generics would have enabled even larger increases in sales than observed. Based on this analysis, we estimate that the potential value of an additional month of exclusivity to an FTF generic at 29.0 percent of the FTF generic's month 6 sales.

8.2 Additional FDA Product Specific Guidances (PSGs)

As part of its effort to facilitate generic drug market entry, FDA has accelerated its production of product-specific guidances (PSGs). These documents present the recommended methods and standards for demonstrating BE for numerous specific drug products with approved NDAs. FDA's most recently updated number of published PSGs is 1,949 as of December 2021 and it has been averaging 111 new PSGs per year from FY 2016 to FY 2020. FDA also issues revisions to some PSGs, and these revisions have been increasing in number; FY2019 and FY2020 were the first years in which revised PSGs exceeded new PSGs.

The value of PSGs for prospective ANDAs of non-biological complex drugs (NBCDs) is substantial and has been mentioned in a previous section. Although there was some caviling by one interviewee about FDA "changing its standards" by revising a PSG while the company's generic product was in mid-development, this seems like a low probability event. The most recent disposition of planned PSG revisions for complex generic drug products on the FDA site (updated May 19, 2021) listed 86 PSGs for revision; just three of the revisions were classified as "major," 81 were "minor," and 69 "editorial." In fact, many of the minor and editorial revisions were apparently related to FDA's move toward using in vitro release tests and in vitro permeation tests instead of in vivo studies for topically applied generics (Dandamudi, 2017). This change has been expected to lower costs and accelerate completion of successful BE testing for dermal and transdermal ANDA applicants (Drummond, 2019).

Regarding new PSGs, FDA's May 19, 2021, list of *Planned New PSGs for Complex Generic Drug Products* has 57 entries, including 12 topically applied products. FDA's commitment under GDUFA is to issue PSGs for "90% of non-complex New Chemical Entities…at least 2 years prior to the earliest allowable ANDA submission date" and "issue PSGs for complex products as soon as scientific recommendations are available."

While the industry representatives interviewed for the study were unable to quantify the impact of FDA PSGs on development costs, they indicated that the existence of a PSG can save "several years" of development, especially for complex generic drugs and potentially reduce early development as well as BE study costs. To model the hypothetical impact of this incentive, we assumed that a PSG could potentially reduce Stage 1 and Stage 2 durations and BE study costs

(Stages 5, 7, and 9) by up to 50 percent. Table 32 below summarizes the average impacts on time to market, development costs, and ENPV we estimated across 10 product-pathway combination models depicted in Table A - 6. Under the modeled scenario, a PSG reduces time to market by 18.3 months (range: 13.3 to 21.7 months) and improves the ENPV of the generic drug applicant by $25.9 million (range: $2.5 to 77.2 million) on average. As can be observed from the table, the estimated increase in ENPV is identical to the reduction in expected capitalized costs as expected because having a PSG does not affect revenue expectations of the generic drug applicant.

Table 32. Potential Impact of Having an FDA Product-specific Guidance (PSG) on the Time to Market, Development Costs, and ENPV of a Generic Drug Applicant

Parameter	Scenario	
	Number	Percent
Change in Time to Market	-18.3 months (-21.7 to -13.3 months)	-19.9% (-26.1% to -14.3%)
Change in Costs	$8.0 million (-$24.3 to -$0.4 million)	-23.8% (-46.7% to -4.3%)
Change in Expected Capitalized Costs	-$25.9 million (-$77.2 to -$2.5 million)	-22.3% (-39.7% to -11.3%)
Change in ENPV	$25.9 million ($2.5 to $77.2 million)	30.6% (2.9% to 70.0%)

8.3 RLD Full Ingredient List Disclosure Requirements

There has been some discussion regarding the incentive value of having brand drugs fully disclose all active ingredients and excipients in their drug products. This would seem to be particularly advantageous for complex generic drug applicants, some of whom FDA requires to have the same API and excipients in the same proportion as the RLD.

In response to queries on this matter, FDA has pointed out that 21 CFR 201.100(b) requires that the active ingredient and, if the drug is for other than oral use, the names of all inactive ingredients (except flavorings, perfumes, color additives, and trace amounts of harmless substances added for identification) be disclosed on the label of prescription drugs intended for human use. The regulations require the quantity or proportion of each active ingredient to be disclosed. For parenteral products, the regulations also require applicants to disclose the quantity or proportion of all inactive ingredients, other than pH adjusters, isotonicity agents, or water for injection. While the regulations outline the requirements for what must be listed on the drug label, FDA considers only the active and inactive ingredient information actually disclosed on the prescription drug label or other publicly available website or document to be public information, so if the RLD manufacturer fails to disclose any of the required information, a generic manufacturer cannot otherwise access it from FDA.

By regulation, generic drugs that are intended for parenteral, otic, or ophthalmic use are required to "contain the same inactive ingredients and in the same concentration as the reference listed drug" with certain limited exceptions described in 21 CFR 314.94(a)(9)(iii) and (iv). Aside from parenteral, otic, and ophthalmic drugs, no other dosage forms, including topicals, are required to have the same inactive ingredients in the same concentrations as the RLD. FDA estimates that approximately 28 percent of all ANDAs received in FY 2020 (233/830) fell into the three categories required to have the same APIs and excipients as the RLD, and in the same proportion. FDA also pointed out that, consistent with 21 CFR 314.99(b), they have waived the requirement for inactive ingredient sameness where applicants have been able to demonstrate that any qualitative or quantitative differences in the formulation compared to the RLD do not impact the safety or efficacy of the drug product.

Based on the information provided by FDA, full disclosure of all excipients and their relative volumes in a brand drug would most substantially benefit manufacturers of generic otic and ophthalmic products. Parenteral RLDs must already disclose these data, with the exceptions outlined above for pH adjusters, isotonicity agents, or water for injection, but the lack of full information about these excipients does disadvantage manufacturers of generics parenteral products as well. Other than parenteral, otic, and ophthalmic products, no other types of generic drugs are required to have the same excipients in the same proportion. It is true that having this information could save the generic entrant a relatively small amount of time and effort involved in reverse engineering the RLD during initial R&D.

FDA adds that, generally, they encourage applicants to submit a controlled correspondence, prior to submission of an ANDA, with a request for a qualitative and/or quantitative sameness assessment so that applicants can develop the correct formulation prior to initiating any required studies for approval. However, if an applicant does reformulate, the question of whether studies need to be repeated depends on the circumstances of each application. For some drug products, the requirement for in vivo BE testing may be waived, so the new formulation would not require studies to be repeated (see 21 CFR 320.22). However, the applicant would still need to manufacture new batches for certain in vitro requirements, such as stability and release testing. To the extent that BE studies are required and not waivable, there may be multiple studies that have to be repeated to establish BE of the new formulation.

To model the hypothetical impact of this incentive, we assumed that an RLD full ingredient list disclosure could potentially reduce Stage 1 costs by up to 10 percent. Table 33 below summarizes the average impacts on time to market, development costs, and ENPV we estimated across the applicable product-pathway combination models depicted in Table A - 6. Under the modeled scenario, the full ingredient list disclosure requirement for the RLD reduces development costs by $3.35 million (range: $3.2 to $3.6 million) on average. Similar to Section 8.2, the estimated dollar increase in ENPV is identical to the reduction in expected capitalized costs as expected.

Table 33. Potential Impact of RLD Full Ingredient List Disclosure Requirement on the Time to Market, Development Costs, and ENPV of a Generic Drug Applicant [a]

Parameter	Scenario	
	Number	Percent
Change in Time to Market	0.0 months	0.0%
Change in Costs	$0.15 million	-0.3%
Change in Expected Capitalized Costs	-$3.35 million (-$3.56 to -$3.15 million)	-1.9% (-1.9% to -1.8%)
Change in ENPV	$3.35 million ($3.15 to $3.56 million)	2.1% (2.1% to 2.2%)

[a] The incentive is only applicable to 2 out of 18 product-pathway combination models in Table A - 6. Hence, the reported range for the average change in expected capitalized costs is very narrow.

9 CONCLUSIONS

In this study, we developed an analytical framework for examining the expected net present value (ENPV) (i.e., the difference between the present value of expected revenues over product life and cost of product development and approval) to a generic drug developer in different size drug markets. The framework formed the basis for an accompanying operational model that enables the user to specify numerous details of a generic drug development project and estimate its associated costs, revenues, and ENPV. Moreover, the developed model allows the user to easily alter model parameters to evaluate special cases, specific generic drug markets, as well as the impact of different types of policies on generic drug developer returns. The operational model, which is

based on the framework presented in Figure 1, accounts for the following technical factors, development stages, and activities associated with generic drug development and approval:

- **Characteristics or type of drug**—Costs, timelines, and phase transition success probabilities can vary widely depending on the complexity of the generic drug project at issue. The model allows the user to examine different types of generic drugs ranging from simple oral tablets to solutions, emulsions, topicals, injectable solutions, narrow-therapeutic index (NTI) drugs, and ophthalmic drugs.
- **Opportunity cost of capital**—This is the annual return (net of inflation) a drug developer could expect from the capital should they not invest in the generic drug project; estimated at 8.82 percent for this model, which represents the average across five studies and information provided by industry representatives interviewed for the study (see Table 5). The model user has the ability to alter this value if desired.
- **Fifteen development stages**—Detailed in Sections 5.3 through 5.8, these development stages include such activities as reverse engineering an RLD; testing the equivalence of the API and the formulation; demonstrating BE and stability; IP challenge and litigation; and preparing and submitting an ANDA to the FDA. Each of these development stages involves a range of activities that the generic drug company spends resources to conduct and spans several months. The stages applicable to any given generic drug project, referred to as "pathway," vary by drug type, whether the RLD is subject to any patents/exclusivities, among other factors, all of which can be specified by the model user.[54]
- **Revenue expectations—**Using IQVIA NSP data on sales, the model provides estimates of average lifetime expected revenues (years 1 through 5) by type of drug in five different sized markets (extra small, small, medium, large, and extra-large) where market size was defined as the average generic drug revenues corresponding to 20th, 40th, 60th, 80th, and 100th percentile of the market.

To estimate model parameters, we synthesized available information from published studies (e.g., peer reviewed and gray literature; FDA guidances, white papers, and presentations), structured interviews with industry representatives, and IQVIA NSP data on monthly drug sales from January 2013 through June 2021. We also worked with a subject matter expert to extrapolate missing values from the available data.

Using the model, we then examined the impact of different types of cost factors, barriers to generic drug development and market entry and a range of incentives designed to mitigate these barriers on the ENPV of the generic drug developer. These included:

- **Cost factors**
  - *FDA ANDA review cycle changes*—Increasing the rate of first-cycle approvals will reduce the time to market for generic applicants of those drugs without IP protections, thereby enabling significant cost savings to patients and third-party payers.
  - *Change in FDA user fees*—GDUFA user fees are negotiated between FDA and industry periodically and are used to fund human generic drug activities. These fees

[54] For example, development stages 5 through 8, 10, 13, and 15 in Figure 1 are not relevant for an off-patent off patent, simple immediate-release oral generic drug that is eligible to have in vivo testing waived by FDA in favor of successful in vitro tests, and for which FDA does not require a REMS submission or a PAI.

vary from year to year and are set by taking into account the number of ANDAs received, ANDA backlog, number of facilities to be inspected among other factors.

- *Use of biowaivers in lieu of in-vivo BE studies*—A biowaiver eliminates the need for a generic drug applicant to conduct in vivo BE studies, a significant development cost component. Further, the costs and time required to prepare a biowaiver submission to FDA are also much lower and shorter than a typical submission involving a BE study.

- IP barriers
  - *Strategic accumulation of patents*—Patents granted by the USPTO and FDA-granted exclusivities protect brand-name drugs from generic competition for an extended period after regulatory approval of the brand drug. Accumulation of patents is one strategy by which the brand drug companies aim to extend their presence in the market free of generic competition. The brand drug companies seek to acquire 'secondary' or 'subsidiary' patents to cover different aspects of their brand-name drugs, such as its formulation, composition, method of use, method of manufacture, and dosages, thereby creating several layers of defense – aka patent "walls," "forests," "thickets," or "estates" – around the base patent on their APIs.
  - *Product hopping*—This refers to the case when a brand drug company, in the face of imminent generic competition, brings a "new and improved" variant—often a slight variant—of their brand drug to market, thereby disadvantaging the generic version(s) of the now "old" or "obsolete" drug.
  - *Settlements and pay-for-delay*—PIV patent litigation settlements (often called reverse payment settlements) between the brand drug company and the generic company that has filed a PIV certification incentivize ANDA applicants to file a PIV certification but disincentivize them to carry the case on to a final court decision. As a result, market entry of lower-cost generic drugs is delayed which burdens the healthcare system. However, settlements redistribute producer surplus from the brand company to the generic company and improve the ENPV of the generic drug developer. In this sense, settlements can be viewed as a barrier to lowering generic drug prices but not necessarily a barrier to generic drug development.

- Other non-IP barriers
  - *Formulary tier manipulation and brand drug rebates*—Formulary tiers are groupings of drugs by price that, for insured individuals, determine what their copay will be. Drugs on a higher formulary tier cost the insured individual a higher copay than one on a lower tier. Formulary manipulation can simply be excluding a generic drug from the formulary or assigning a generic, particularly a specialty generic, to the same or even a higher formulary tier than its RLD. This influences patients (and doctors) to use the brand drug, as the copays for the brand drug would be either the same or lower than the copay for the generic (depending on the tier). This benefit to brand manufacturers could be used by PBMs to negotiate higher rebates, which translate to higher profits for PBMs
  - *RLD labeling changes near patent and/or exclusivity expiry*—FDA requires that the label of a generic drug be identical to that of the RLD. According to several industry observers, brand drug companies may try to delay generic market entry by submitting changes to the label of the RLD, timing their submission in a way that forestalls final ANDA approval and/or market entry (i.e., near or at patent expiry

and/or exclusivity). The generic company must then update its label to conform to the revised RLD label which may delay market entry.

- *Authorized generics (AGs)*—AGs are identical to brand drugs in every way except the packaging or printing on the pill or capsule. Because they are identical to the brand product, they need not go through ANDA approval. Since 2003, brand companies have started marketing AGs to improve their market position prior to generic entry and to undermine the value of the 180-day exclusivity period for the FTF and first to market generic.

- Incentives
  - *180-day exclusivity modifications*—The value of the 180-day exclusivity gained via a successful PIV challenge is thought to have been diminished due to (1) the possibility of having to share some of the period of exclusivity with other FTF generic candidates, (2) the various strategies that brand drug companies employ to maintain their market dominance, such as distributing AGs, obscuring price points through rebates to PBMs, and introducing "new and improved" versions of their RLD that could reclaim some of the market lost to the generic. These pressures have prompted consideration of modifications to the structure of the incentive to further encourage PIV certifications.
  - *Additional FDA product-specific guidances (PSGs)*—FDA PSGs present the recommended methods and standards for demonstrating BE for numerous specific drug products with approved NDAs. The value of PSGs for prospective ANDA applicants, especially those applicants of NBCDs is substantial.
  - *RLD full ingredient list disclosure requirements*—Generic drugs that are intended for parenteral, otic, or ophthalmic use are required to "contain the same inactive ingredients and in the same concentration as the reference listed drug" with certain limited exceptions as per 21 CFR 314.94(a)(9)(iii) and (iv). While 21 CFR 201.100(b) outlines the requirements for what must be listed on the drug label, FDA considers only the active and inactive ingredient information actually disclosed on the prescription drug label or other publicly available website or document to be public information, so if the RLD manufacturer fails to disclose any of the required information, a generic manufacturer cannot otherwise access it.

Given the hundreds of different product-pathway combinations that can be specified in the model, we created 18 different product-pathway combination models (see Table A - 6) that are designed to capture a wide range of possibilities to evaluate impacts for. These 18 models spanned all generic product types ranging from simple small molecule oral drugs to more complex drug-device combinations, e.g., inhalers, and those that involve complex active ingredients, e.g., glatiramoids. The models also encompassed those cases where IP issues might be relevant, especially for more complex products. Even though the 18 product-pathway models constituted a small subset of all possible combinations that can be examined by the operational model, they are representative of the range of models that could be created.

The key findings from our analysis of cost factors, barriers, and incentives included the following:

- Increasing the rate of FDA first-cycle approvals from its current baseline level of around 20 percent to a high of 66 percent reduces the time to market for the generic drug developer by around 13 months (45 percent) resulting in a $3.5 million decline in expected capitalized costs to the generic applicant across all types of ANDAs.

- The effect of a 50 percent decrease in FDA ANDA submission fees is relatively minor at -1.2 percent expected capitalized costs.
- In-vivo BE studies constitute a major portion of overall development costs. Thus, expanding the use of biowaivers in lieu of BE studies, where possible, saves money and time. On average, the time to market reduces by 10.6 months (11.8 percent) and expected capitalized costs could decline by as much as 66.9 percent.
- Based on three case studies (Pennsaid [diclofenac sodium 1.5% topical solution], Doryx [doxycycline hyclate, 50 mg and 200 mg DR tablets], and Copaxone [glatiramer acetate]) and IQVIA NSP sales data, product hopping by the brand company (i.e., the introduction of a newly patented version of the brand drug, such as an extended-release [XR] version) could reduce the size of the market (in terms of units sold) for the FTF generic and other generic entrants by up to 29 percent on average within the first year after generic entry and more in subsequent years. Subsequently, this reduction in the volume of units sold over time results in declining revenues for all generics in the market including the FTF from one year to the next until they reach a level that cannot be sustained.
- The extent to which PBMs' placement of generics across formulary tiers and the rebate system affect the decision of a generic firm to enter a market, the costs of entering a market, or even the revenue model of entering a generic market is indeterminate. Some generic manufacturer representatives interviewed for this study commented on the decline in anticipated market share for first or early entrants to a market. However, none was able to quantify this impact with any degree of certainty.
- RLD labeling changes by the brand drug company near patent and/or exclusivity expiry can potentially delay market entry of a generic drug. However, the importance of this timing varies widely. A generic company with shared exclusivity could lose valuable weeks of exclusivity in the market if another FTF generic can adjust their label sooner. Contracts with wholesalers or distributors may have to be modified to account for a delay. However, neither the expense nor the potential delay caused by an RLD label change were considered serious barriers by manufacturing representatives interviewed for this study.
- The average market share in terms of dollar sales of an FTF generic is 7 percent higher on average if there are no AGs during its 180-day exclusivity period. Consequently, the first-year revenues of the FTF generic could be roughly 5 percent higher in the absence of an AG which translates to an average increase of 10.9 percent in the ENPV of an FTF generic company that prevails in its PIV challenge and markets its product without facing competition from an AG during its 180-day exclusivity period.
- The 180-day exclusivity period may not, on average, provide a consistently substantial revenue advantage in the first year after entry over non-exclusive generic entrants into markets of comparable size, however, further analysis is needed with an expanded sample of PIV drugs. We find some evidence that the potential value of an additional month of exclusivity to an FTF generic could be as much as 29.0 percent of the FTF generic's month 6 sales, but it is not clear whether this would translate to an overall gain for the first year.
- Existence of an FDA PSG can save "several years" of development, especially for complex generic drugs and potentially reduce early development as well as BE study costs. We estimate that these savings could reduce the expected capitalized costs of a generic drug

developer by 22.3 percent ($25.9 million) on average. Under GDUFA, FDA is committed to issuing PSGs for complex products as soon as scientific recommendations are available. FDA's list of *Planned New PSGs for Complex Generic Drug Products* contained 57 entries as of May 19, 2021 and has 69 entries as of November 8, 2021.

- The full ingredient list disclosure requirement for the RLD could reduce development costs by $3.35 million on average for otic and ophthalmic generic drugs if the expected reduction in Stage 1—R&D to Establish Equivalence for API—costs due to the disclosure requirement is 10 percent. By regulation, drugs that are intended for parenteral, otic, or ophthalmic use are required to "contain the same inactive ingredients and in the same concentration as the reference listed drug" with certain limited exceptions described in 21 CFR 314.94(a)(9)(iii) and (iv). In FY 2020, these types of drugs accounted for approximately one quarter of all ANDAs received (233 out of 830).

Our analysis has several limitations. First, most of our model parameter estimates are based on information from interviews we conducted with industry representatives. In accordance with Paperwork Reduction Act (PRA) requirements, the number of interviews involving the same set of questions were limited to fewer than 10 entities. Further, it was often difficult for interviewees to provide the type of information requested, e.g., reduction in duration attributable to the presence of an FDA PSG by development stage, during the course of an interview. Second, the data available for the PIV market analysis and assessment of the value of 180-day exclusivity were limited precluding the use of more robust statistical methods. For example, our PIV market comprised of 38 drugs and only 11 of these drugs had the data coverage needed for the matched case control study. Third, for tractability, our operational model parameters reflect averages for aggregate categories of generic drug types, e.g., small molecule, topical, NTI, etc. We recognize that there likely is significant variation within a generic drug type category; for example, to establish pharmaceutical equivalence for most true solutions is typically much shorter than for emulsions even though both are classified in the same generic drug category in the operational model. Fourth, our analysis did not encompass biosimilars even though they constitute an increasingly important part of the generic drug landscape. Finally, reported impacts are applicable to the 18 product-pathway combination models we selected. While we aimed to make the models representative, a different selection of pathways would naturally result in different estimate ranges for the impacts considered.

Despite its limitations, the model developed under this study fills an important gap for policymakers on generic drug development and approval costs for whom information on this issue has been sparse to date. The previous estimates of generic drug development and approval costs, with figures ranging from as low as $250,000 to as high as $25 million reported in three earlier studies (Morton & Fiona, 1999; Reiffen & Ward, 2005; Federal Trade Commission, 2009) are out of date and do not provide sufficient detail to craft targeted policies to encourage generic drug development and market entry. As described in this study, the cost of development is not uniform among companies or products and potential barriers may keep applicants from seeking approval for certain types of generic drug products with high development costs and/or small markets. The analytical model and the accompanying operational model that allows for an examination of barriers and potential incentives designed to alleviate them presented herein provide more comprehensive information that can help policymakers to effectively target efforts to increase generic competition.

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APPENDIX A: SUPPLEMENTARY TABLES

Table A - 1. IQVIA NSP Data Elements Available for Analysis

IQVIA NSP Variable Name	Explanation
Product	For branded and branded generics, trademark name by which the drug is called and registered with the FDA; for generic drugs, the molecule name of the main active ingredient
NDC	FDA-assigned 10-digit, 3-segment national drug code (NDC) number that identifies the labeler, the product, and the package for the product
Delivery System 2 [a]	ADD-Vantage™ vials
	Ampoules
	Bottles/bags, large volume
	Cartridges
	N/A (delivery system not applicable)
	Injectable, unspecified
	Kits
	Minibags, premix
	Multi-dose vials
	Piggyback vials
	Single-dose vials
	Syringes, prefill
	Blank
Corporation	Name of the parent corporation that manufactures the product
Manufacturer	Name of the company that manufactures or markets the product
Combined Molecule	Unique combination of molecules comprising the product
Product Form 3	Physical dosage form of the product at the most detailed level
Strength	Product strength (e.g., 250 mg tablet, 500 mg tablet)
Brand-Generic	Brand = Drug with a patent and/or exclusivity sold by one company
	Generic = Drug with no patent and/or exclusivity sold by one or more companies
	Branded Generic = Drug with no patent and/or exclusivity but sold under a name other than the chemical name by a generic manufacturer or by the brand manufacturer after patent/exclusivity expiration
	Other = Applies to OTC products
	Blank
Rx Status	OTC = Over the counter
	OTC Insulin = Over the counter insulin product that falls under USC3 39100 Diabetes Therapy
	Rx = Prescription
	N/A = Not available
	Blank
Repackage	Original manufacturer
	Repackager
Month	Calendar month
Sales	Total dollar sales to retail and non-retail channels from manufacturers and drug wholesalers
Units	Total number of packages sold of the product
Eaches	Total number of single items, e.g., vials, syringes, bottles, or packet of pills
NSP Extended Units	Number of tablets, capsules, mL, etc. calculated by multiplying the vial volume or bottle size reported for the Eaches variable

[a] Delivery system description applicable to injectable products only

Table A - 2. Consumer Price Index for All Urban Consumers: Medical Care in U.S. City Average, Index 1982-1984=100, Monthly, Seasonally Adjusted [CPIMEDSL], January 2013 – December 2020

Observation Date	CPIMEDSL	Sales Adjustment Factor [a]
2013-01-01	421.114	1.234
2013-02-01	421.601	1.233
2013-03-01	423.089	1.228
2013-04-01	423.025	1.228
2013-05-01	422.316	1.231
2013-06-01	424.286	1.225
2013-07-01	425.008	1.223
2013-08-01	427.168	1.217
2013-09-01	428.290	1.213
2013-10-01	428.586	1.213
2013-11-01	428.485	1.213
2013-12-01	428.622	1.212
2014-01-01	429.989	1.209
2014-02-01	431.137	1.205
2014-03-01	432.211	1.202
2014-04-01	433.260	1.199
2014-05-01	434.262	1.197
2014-06-01	435.187	1.194
2014-07-01	435.864	1.192
2014-08-01	436.041	1.192
2014-09-01	437.091	1.189
2014-10-01	437.758	1.187
2014-11-01	439.408	1.183
2014-12-01	441.464	1.177
2015-01-01	441.351	1.177
2015-02-01	441.101	1.178
2015-03-01	442.943	1.173
2015-04-01	445.822	1.166
2015-05-01	446.743	1.163
2015-06-01	446.330	1.164
2015-07-01	446.953	1.163
2015-08-01	446.612	1.164
2015-09-01	447.648	1.161
2015-10-01	450.681	1.153
2015-11-01	452.225	1.149
2015-12-01	452.732	1.148
2016-01-01	454.194	1.144
2016-02-01	456.922	1.137
2016-03-01	457.723	1.135
2016-04-01	459.245	1.132
2016-05-01	460.487	1.129
2016-06-01	462.090	1.125
2016-07-01	464.439	1.119
2016-08-01	469.020	1.108
2016-09-01	469.816	1.106
2016-10-01	469.749	1.106
2016-11-01	469.914	1.106
2016-12-01	470.539	1.104
2017-01-01	471.544	1.102

Observation Date	CPIMEDSL	Sales Adjustment Factor [a]
2017-02-01	473.177	1.098
2017-03-01	473.660	1.097
2017-04-01	472.923	1.099
2017-05-01	472.892	1.099
2017-06-01	474.435	1.095
2017-07-01	476.386	1.091
2017-08-01	477.450	1.088
2017-09-01	477.153	1.089
2017-10-01	477.653	1.088
2017-11-01	477.727	1.088
2017-12-01	478.799	1.085
2018-01-01	480.771	1.081
2018-02-01	481.574	1.079
2018-03-01	483.043	1.076
2018-04-01	483.441	1.075
2018-05-01	484.380	1.073
2018-06-01	486.124	1.069
2018-07-01	485.455	1.070
2018-08-01	484.676	1.072
2018-09-01	485.374	1.071
2018-10-01	485.800	1.070
2018-11-01	487.419	1.066
2018-12-01	488.381	1.064
2019-01-01	489.815	1.061
2019-02-01	490.006	1.061
2019-03-01	491.327	1.058
2019-04-01	492.783	1.055
2019-05-01	494.576	1.051
2019-06-01	495.650	1.048
2019-07-01	497.916	1.044
2019-08-01	501.371	1.036
2019-09-01	502.145	1.035
2019-10-01	506.711	1.026
2019-11-01	508.102	1.023
2019-12-01	510.605	1.018
2020-01-01	511.681	1.016
2020-02-01	512.730	1.014
2020-03-01	514.565	1.010
2020-04-01	516.484	1.006
2020-05-01	518.877	1.002
2020-06-01	520.802	0.998
2020-07-01	522.898	0.994
2020-08-01	523.770	0.992
2020-09-01	523.289	0.993
2020-10-01	521.370	0.997
2020-11-01	520.401	0.999
2020-12-01	519.664	1.000

Source: U.S. Bureau of Labor Statistics (2021)
[a] Calculated by dividing the difference between CPIMEDSL value for 2020-12-01 (i.e., 519.664) and CPIMEDSL value for the given date by CPIMEDSL for 2020-12-01.

Table A - 3. Mapping of IQVIA NSP Product Form Categories onto Drug Types in Model

Product Form 3	Aggregate Product Form Category	Drug Type in Model
LNS LUNG SOLUTS FOR INHA	Inhaled	Inhalers
LNP LUNG POWDER FOR INHA		
HHS INHALANTS,SOLUTION		
HHA INHALANTS,PRESS AERO		
HHP INHALANTS,POWDER		
IAC INJECT,IV REG	Injectable	Liposomes, Dendrimers, Polymeric Micelles
IAK INJECT,INFUSION REG		
IAN INJECT,OPHTH REG		
IAA INJECT,IM REG		
IAG INJECT,MULT ADM REG		
IAE INJECT,SUBCUT REG		Iron Carbohydrate Complexes
IAX INJECT,OTHER REG		
IVR INJECT,IV PIGBACK		
IAB INJECT,IM L.A		
IAZ INJECT,OTHER L.A		
IAH INJECT,MULT ADM L.A		Glatiramoids
IAL INJECT,INFUSION L.A		
IAI INJECT,INT-ARTIC REG		
IAF INJECT,SUBCUT L.A		
IAJ INJECT,INT-ARTIC L.A		
PPL OPHTHALMICS,LIQUID	Ophthalmic	Ophthalmic Emulsions
PPO OPHTHALMICS,OINTMENT		
PPI OPHTHALMICS,INSERT		
OSR ORALS,SOL,TAB/CAP RE	Oral	Small Molecule Drugs
OLL ORALS,LIQ,NON-SPEC L		
OLE ORALS,LIQ,ELIXIR		
OLR ORALS,LIQ,READY-MDE		
OSE ORALS,SOL,EFFERVESCE		
OLS ORALS,LIQ,SYRUP		
OSO ORALS,SOL,TAB/CAP OT		
OLP ORALS,LIQ,POW/GRN X		
OSC ORALS,SOL,CHEWABLE		Narrow Therapeutic Index (NTI) Drugs
OSZ ORALS,SOL,OTHER		
OSP ORALS,SOL,POW/GRAN		
OSB ORALS,SOL,BUCCL/SUBL		
OSY ORALS,SOL,WAF/LOZ/ET		
OLZ ORALS,LIQ,OTHER		
OSA ORALS,SOL,SOLUBLE		
OLD ORALS,LIQ,DROPS		
OSF ORALS,SOL,CAP/SPRINK		
YAZ ALL OTHERS	Other	Not mapped
EAR OTICS		
SAZ OTHER SYSTEMICS		
SNA OTH SYS NASAL SPRAY		
NOS NASAL,SPRAY/AEROSOL		
URI UROLOGICALS,IRRIGANT		
RRS RECTALS SYST,SUPPOST		
MND MOUTH & THROAT,DNTL		
DDD DERM,DRSSNG/BNDG/PLS		
JWT INSRT/IMPLANT,TRANSD		

Product Form 3	Aggregate Product Form Category	Drug Type in Model
MNL MOUTH & THROAT,LIQUI		
VAC VAGINALS,CREAM/OINTM		
VAI VAGINALS,INSERT		
MNZ MOUTH & THROAT,OTHER		
NOL NASAL,LIQUID		
SNB OTH SYS NASAL SOLN		
VAZ VAGINALS,OTHER		
JWZ INSRT/IMPLANT,TRANS		
MNS MOUTH & THROAT,SP/SW		
ANS RECTALS,TOP,SUPPOSIT		
ANO RECTALS,TOP,OINT/CRE		
ANE RECTALS,TOP,ENEMA		
ANZ RECTALS,TOP,OTHER		
NOZ NASAL,OTHER		
DDO DERM,OINTMENT		
DDC DERM,CREAM		
DDG DERM,GEL		
DDL DERM,LIQUID/LOTION		
TOZ OTHER TOPICALS	Topical	Topical Drugs
DDS DERM,SPRAY/AEROSOL		
DDF DERM,FOAM		
DDW DERM,WASH		
DDZ DERM,OTHER		

Table A - 4. List of In-scope Paragraph IV (PIV) Drugs Included in Paragraph IV Market Analysis

Drug Name	Dosage From	Strength	RLD / NDA Number	Date of First Applicant Approval	Date of First Commercial Marketing by the First-to-file (FTF) Applicant	End of 180-Day Exclusivity Period [a]
Abacavir Sulfate and Lamivudine	Tablets	600 mg/300 mg	Epzicom / 21652	9/29/2016	9/29/2016	3/28/2017
Abiraterone Acetate	Tablets	250 mg	Zytiga / 202379	10/31/2018	11/21/2018	5/20/2019
Albuterol Sulfate	Inhalation Aerosol	0.09 mg base per actuation	Pro-Air HFA / 21457	2/24/2020	2/26/2020	8/24/2020
Aliskiren Hemifumarate	Tablets	150 mg and 300 mg	Tekturna / 21985	3/22/2019	3/25/2019	9/21/2019
Alosetron Hydrochloride	Tablets	0.5 mg and 1 mg	Lotronex / 21107	5/4/2015	5/21/2015	11/17/2015
Asenapine Maleate	Sublingual Tablets	5 mg and 10 mg	Saphris / 22117	12/10/2020	12/10/2020	6/8/2021
Budesonide	Extended-release (XR) Tablets	9 mg	Uceris / 203634	7/3/2018	7/5/2018	1/1/2019
Carvedilol Phosphate	Extended-release (XR)Capsules	10 mg and 20 mg	Coreg CR / 22012	10/25/2017	11/8/2017	5/7/2018
		40 mg				
		80 mg				
Clofarabine	Injection	1 mg/mL, 20 mL vial	Clolar / 21673	5/9/2017	5/9/2017	11/5/2017
Dexmethylphenidate	Extended-release (XR)Capsules	35 mg	Focalin XR / 21802	11/30/2016	1/5/2017	7/4/2017
		25 mg				
Diclofenac Sodium	Topical Solution	1.5%	Pennsaid / 20947	5/27/2014	5/27/2014	11/23/2014
Dimethyl Fumarate	Delayed-release Capsules	120 mg and 240 mg	Tecfidera / 204063	8/17/2020	8/18/2020	2/14/2021
Dofetilide	Capsules	0.125 mg, 0.25 mg, and 0.5 mg	Tikosyn / 20931	6/6/2016	6/7/2016	12/4/2016
Doxycycline Hyclate	Delayed-release Tablets	200 mg	Doryx / 50795	5/19/2016	5/19/2016	11/15/2016
		50 mg		5/23/2016	5/23/2016	11/19/2016
Drospirenone and Ethinyl; Estradiol and Levomefolate; Calcium and Levomefolate Calcium	Tablets	3 mg, 0.02 mg, 0.451 mg, and 0.451 mg	Beyaz / 22532	10/11/2016	10/11/2016	4/9/2017
Efavirenz	Capsules	50 mg, 100 mg, and 200 mg	Sustiva / 20972	12/15/2017	12/21/2017	6/19/2018
Entecavir	Tablets	0.5 mg and 1 mg	Baraclude / 21797	8/26/2014	9/4/2014	3/3/2015
Epoprostenol Sodium	Injection	0. 5m/vial and 1.5 mg/vial	Veletri / 22260	1/15/2021	1/27/2021	7/26/2021
Febuxostat	Tablets	40 mg and 80 mg	Uloric / 21856	7/1/2019	7/1/2019	12/28/2019
Fluocinonide	Cream	0.1%	Vanos / 21758	1/14/2014	1/14/2014	7/13/2014
Glatiramer Acetate	Injection	40 mg/mL, 1 mL pre- filled syringe	Copaxone / 20622	10/3/2017	10/4/2017	4/2/2018
Imatinib Mesylate	Tablets	100 mg and 400 mg	Gleevec / 21588	12/3/2015	2/1/2016	7/30/2016
Ivermectin	Cream	1%	Soolantra / 206255	9/13/2019	10/14/2019	4/11/2020
Lanthanum Carbonate	Chewable Tablet	500 mg, 750 mg, and 1000 mg	Fosrenol / 21468	8/11/2017	8/30/2017	2/26/2018
Lapatinib Ditosylate	Tablets	250 mg	Tykerb / 22059	9/29/2020	9/29/2020	3/28/2021
Lopinavir and Ritonavir	Oral Solution	80 mg/20 mg per mL	Kaletra / 21251	12/27/2016	1/23/2017	7/22/2017

Drug Name	Dosage From	Strength	RLD / NDA Number	Date of First Applicant Approval	Date of First Commercial Marketing by the First-to-file (FTF) Applicant	End of 180-Day Exclusivity Period [a]
Mesalamine	Delayed-release Tablets	1.2 g	Lialda / 22000	6/5/2017	7/18/2017	1/14/2018
Pantoprazole Sodium	Delayed-release Oral Suspension	40 mg	Protonix / 22020	6/30/2020	8/13/2020	2/9/2021
Quetiapine Fumarate	Extended-release (XR) Tablets	400 mg	Seroquel XR / 22047	11/1/2016	11/1/2016	4/30/2017
Ribavirin	Inhalation Solution	6 gm/vial	Virazole / 18859	10/6/2016	12/15/2016	6/13/2017
Risedronate Sodium	Delayed-release Tablets	35 mg	Atelvia / 22560	5/18/2015	5/18/2015	11/14/2015
Rivastigmine	Transdermal System Extended-release (XR)	13.3 mg/24 hr	Exelon / 22083	8/31/2015	9/2/2015	2/29/2016
Ropivacaine Hydrochloride	Injection	2 mg/mL, 100 mL	Naropin / 20533	7/13/2016	9/15/2016	3/14/2017
Rosuvastatin Calcium	Tablets	5 mg, 10 mg, 20 mg, and 40 mg	Crestor / 21366	4/29/2016	5/2/2016	10/29/2016
Sirolimus	Tablets	0.5 mg	Rapamune / 21110	1/8/2014	1/16/2014	7/15/2014
Tadalafil	Tablets	20 mg	Adcirca / 22332	8/3/2018	8/8/2018	2/4/2019
Tavaborole	Topical Solution	5%	Kerydin / 204427	10/13/2020	10/19/2020	4/17/2021
Telmisartan	Tablets	20 mg, 40 mg, and 80 mg	Micardis / 20850	1/8/2014	1/8/2014	7/7/2014
Valsartan	Tablets	40 mg, 80 mg, 160 mg, and 320 mg	Diovan / 21283	6/26/2014	7/7/2014	1/3/2015

[a] Calculated by adding 180 days to the date of first commercial marketing by the FTF.

Table A - 5. List of Potential Paragraph IV (PIV) Drugs Excluded from Paragraph III (PIII) Market Analysis

Drug Name	Dosage From	Strength	RLD / NDA Number	Date of First Applicant Approval	Date of First Commercial Marketing by the First-to-file (FTF) Applicant	End of 180-Day Exclusivity Period [a]
Abacavir	Oral Solution	20 mg/mL	Ziagen / 20978	9/26/2016	9/15/2017	3/14/2018
Abacavir Sulfate and Lamivudine	Tablets	600 mg/300 mg	Epzicom / 21652	9/29/2016	9/29/2016	3/28/2017
Abiraterone Acetate	Tablets	250 mg	Zytiga / 202379	10/31/2018	11/21/2018	5/20/2019
Adapalene	Topical Gel	0.30%	Differin / 21753	6/14/2012	4/28/2014	10/25/2014
Adapalene and Benzoyl Peroxide	Gel	0.1%/2.5%	Epiduo / 22320	9/30/2015	7/27/2017	1/23/2018
Albuterol Sulfate	Inhalation Aerosol	0.09 mg base per actuation	Pro-Air HFA / 21457	2/24/2020	2/26/2020	8/24/2020
Aliskiren Hemifumarate	Tablets	150 mg and 300 mg	Tekturna / 21985	3/22/2019	3/25/2019	9/21/2019
Alosetron Hydrochloride	Tablets	0.5 mg and 1 mg	Lotronex / 21107	5/4/2015	5/21/2015	11/17/2015
Alvimopan	Capsules	12 mg	Entereg / 21775	12/19/2019	12/19/2019	6/16/2020
Amlodipine Besylate and Valsartan	Tablets	5 mg/160 mg	Exforge / 21990	3/28/2013	9/30/2014	3/29/2015
Amlodipine Besylate and Valsartan	Tablets	5 mg/320 mg	Exforge / 21990	3/28/2013	9/30/2014	3/29/2015
Amlodipine Besylate and Valsartan	Tablets	10 mg/160 mg	Exforge / 21990	3/28/2013	9/30/2014	3/29/2015
Amlodipine Besylate and Valsartan	Tablets	10 mg/320 mg	Exforge / 21990	3/28/2013	9/30/2014	3/29/2015
Amlodipine, Hydrochlorothiazide and Valsartan	Tablets	5 mg/12.5 mg/160 mg, 5 mg/25 mg/160 mg, 10 mg/25 mg/160 mg and 10 mg/25 mg/320 mg	Exforge HCT / 22314	9/25/2012	12/1/2014	5/30/2015
Amlodipine, Hydrochlorothiazide and Valsartan	Tablets	10 mg/12.5 mg/160 mg	Exforge HCT / 22314	9/25/2012	12/1/2014	5/30/2015
Aprepitant	Capsule	40 mg, 80 mg and 125 mg	Emend / 21549	9/24/2012	12/27/2016	6/25/2017
Armodafinil	Tablets	50 mg, 150 mg, and 250 mg	Nuvigil / 21875	6/1/2012	6/1/2016	11/28/2016
Asenapine Maleate	Sublingual Tablets	5 mg and 10 mg	Saphris / 22117	12/10/2020	12/10/2020	6/8/2021
Aspirin and Dipyridamole	Extended-release (XR) Capsules	25 mg and 200 mg	Aggrenox / 20884	8/14/2009	7/1/2015	12/28/2015
Atazanavir Sulfate	Capsules	100 mg and 150 mg	Reyataz / 21567	4/22/2014	12/27/2017	6/25/2018
Atazanavir Sulfate	Capsules	200 mg	Reyataz / 21567	4/22/2014	12/27/2017	6/25/2018
Atazanavir Sulfate	Capsules	300 mg	Reyataz / 21567	4/22/2014	12/27/2017	6/25/2018
Azelastine Hydrochloride and Fluticasone Propionate	Nasal Spray	137 mcg/50 mcg per spray	Dymista / 202236	4/28/2017	3/2/2020	8/29/2020
Bexarotene	Capsules	75 mg	Targretin / 20155	8/12/2014	7/9/2015	1/5/2016
Budesonide	Inhalation Suspension	1 mg/2 mL	Pulmicort Respules / 20929	9/27/2013	7/27/2015	1/23/2016
Budesonide	Extended-release (XR) Tablets	9 mg	Uceris / 203634	7/3/2018	7/5/2018	1/1/2019
Calcipotriene and Betamethasone Dipropionate	Ointment	0.005%/0.064%	Taclonex / 21852	1/14/2013	3/31/2014	9/27/2014
Carvedilol Phosphate	Extended-release (XR) Capsules	10 mg and 20 mg	Coreg CR / 22012	10/25/2017	11/8/2017	5/7/2018
Carvedilol Phosphate	Extended-release (XR) Capsules	40 mg	Coreg CR / 22012	10/25/2017	11/8/2017	5/7/2018

Drug Name	Dosage From	Strength	RLD / NDA Number	Date of First Applicant Approval	Date of First Commercial Marketing by the First-to-file (FTF) Applicant	End of 180-Day Exclusivity Period [a]
Carvedilol Phosphate	Extended-release (XR) Capsules	80 mg	Coreg CR / 22012	10/25/2017	11/8/2017	5/7/2018
Clindamycin Phosphate and Benzoyl Peroxide	Gel	1.2%/2.5%	Acanya / 50819	6/19/2015	2/19/2019	8/18/2019
Clindamycin Phosphate and Tretinoin	Gel	1.2%/0.025%	Ziana / 50802	6/12/2015	7/5/2016	1/1/2017
Clobetasol Propionate	Spray	0.05%	Clobex / 21835	6/16/2011	1/1/2015	6/30/2015
Clofarabine	Injection	1 mg/mL, 20 mL vial	Clolar / 21673	5/9/2017	5/9/2017	11/5/2017
Dalfampridine	Extended-release (XR) Tablets	10 mg	Ampyra / 22250	1/23/2017	9/10/2018	3/9/2019
Dapsone	Gel	7.5%	Aczone / 207154	6/26/2019	6/26/2019	12/23/2019
Darifenacin Hydrobromide	Extended-release (XR) Tablets	7.5 mg and 15 mg	Enablex / 21513	3/13/2015	3/15/2016	9/11/2016
Deferasirox	Tablets for Suspension	125 mg, 250 mg, and 500 mg	Exjade / 21882	1/26/2016	3/22/2019	9/18/2019
Deferasirox	Tablets	180 mg	Jadenu / 206910	12/13/2019	12/17/2019	6/14/2020
Deferiprone	Tablets	500 mg	Ferriprox / 21825	2/8/2019	9/28/2020	3/27/2021
Desonide	Gel	0.05%	Desonate / 21844	5/11/2020	7/9/2020	1/5/2021
Desvenlafaxine Succinate	Extended-release (XR) Tablets	50 mg and 100 mg	Pristiq / 21992	6/29/2015	2/28/2017	8/27/2017
Desvenlafaxine Succinate	Extended-release (XR) Tablets	25 mg	Pristiq / 21992	7/29/2016	7/29/2016	1/25/2017
Dexmedetomidine	Injection	4 mcg/mL, 20 mL vials	Precedex / 21038	11/29/2018	6/3/2019	11/30/2019
Dexmethylphenidate	Extended-release (XR) Capsules	35 mg	Focalin XR / 21802	11/30/2016	1/5/2017	7/4/2017
Dexmethylphenidate	Extended-release (XR) Capsules	25 mg	Focalin XR / 21802	11/30/2016	1/5/2017	7/4/2017
Dexmethylphenidate Hydrochloride	Extended-release (XR) Capsules	5 mg, 10 mg, and 20 mg	Focalin XR / 21802	11/19/2013	11/10/2014	5/9/2015
Diclofenac Sodium	Topical Solution	1.5%	Pennsaid / 20947	5/27/2014	5/27/2014	11/23/2014
Dimethyl Fumarate	Delayed-release Capsules	120 mg and 240 mg	Tecfidera / 204063	8/17/2020	8/18/2020	2/14/2021
Dofetilide	Capsules	0.125 mg, 0.25 mg, and 0.5 mg	Tikosyn / 20931	6/6/2016	6/7/2016	12/4/2016
Doxycycline Hyclate	Delayed-release Tablets	200 mg	Doryx / 50795	5/19/2016	5/19/2016	11/15/2016
Doxycycline Hyclate	Delayed-release Tablets	50 mg	Doryx / 50795	5/23/2016	5/23/2016	11/19/2016
Drospirenone and Ethinyl Estradiol	Tablets	3 mg/0.02 mg	Yaz / 21676	3/30/2009	6/1/2020	11/28/2020
Drospirenone and Ethinyl Estradiol and Levomefolate Calcium and Levomefolate Calcium	Tablets	3 mg/0.02 mg/0.451 mg and 0.451 mg	Beyaz / 22532	10/11/2016	10/11/2016	4/9/2017
Duloxetine Hydrochloride	Delayed-release Capsules	40 mg	Cymbalta / 21427	12/11/2013	7/15/2015	1/11/2016
Dutasteride	Capsules	0.5 mg	Avodart / 21319	12/21/2010	10/9/2015	4/6/2016
Dutasteride and Tamsulosin Hydrochloride	Capsules	0.5 mg/0.4 mg	Jalyn / 22460	2/26/2014	11/18/2015	5/16/2016
Efavirenz	Tablets	600 mg	Sustiva / 21360	2/17/2016	1/30/2018	7/29/2018
Efavirenz	Capsules	50 mg, 100 mg and 200 mg	Sustiva / 20972	12/15/2017	12/21/2017	6/19/2018
Emtricitabine	Capsules	200 mg	Emtriva / 21500	7/2/2018	8/31/2020	2/27/2021

Drug Name	Dosage From	Strength	RLD / NDA Number	Date of First Applicant Approval	Date of First Commercial Marketing by the First-to-file (FTF) Applicant	End of 180-Day Exclusivity Period [a]
Emtricitabine and Tenofovir Disoproxil Fumarate	Tablets	100 mg/150 mg, 133 mg/200 mg, 167 mg/250 mg	Truvada / 21752	8/22/2018	1/18/2021	7/17/2021
Entecavir	Tablets	0.5 mg and 1 mg	Baraclude / 21797	8/26/2014	9/4/2014	3/3/2015
Epinephrine	Injection (Auto- injector)	0.15 mg/0.3 mL and 0.3 mg/0.3 mL	Epipen and Epipen Jr. / 19430	8/16/2018	8/19/2019	2/15/2020
Epoprostenol Sodium	Injection	0. 5m/vial and 1.5 mg/vial	Veletri / 22260	1/15/2021	1/27/2021	7/26/2021
Eptifibatide	Injection	0.75 mg/mL, 100 mL vial	Integrilin / 21437	6/5/2015	12/14/2015	6/11/2016
Erlotinib Hydrochloride	Tablets	100 mg and 150 mg	Tarceva / 21743	6/11/2014	5/9/2019	11/5/2019
Erlotinib Hydrochloride	Tablets	25 mg	Tarceva / 21743	6/11/2014	5/9/2019	11/5/2019
Esomeprazole Sodium	For Injection	20 mg/vial and 40 mg/vial	Nexium IV / 21689	3/18/2013	1/15/2014	7/14/2014
Estradiol	Vaginal Tablets	10 mcg	Vagifem / 20908	5/29/2015	10/17/2016	4/15/2017
Estradiol	Transdermal System	0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, 0.1 mg/day	Minivelle / 203752	8/15/2018	11/1/2018	4/30/2019
Estradiol	Transdermal System	0.025 mg/day	Minivelle / 203752	8/15/2018	11/1/2018	4/30/2019
Eszopiclone	Tablets	1 mg, 2 mg, and 3 mg	Lunesta / 21476	5/23/2011	4/15/2014	10/12/2014
Ezetimibe	Tablets	10 mg	Zetia / 21445	6/26/2015	12/12/2016	6/10/2017
Febuxostat	Tablets	40 mg and 80 mg	Uloric / 21856	7/1/2019	7/1/2019	12/28/2019
Fluocinonide	Cream	0.1%	Vanos / 21758	1/14/2014	1/14/2014	7/13/2014
Frovatriptan Succinate	Tablets	2.5 mg	Frova / 21006	7/8/2014	4/29/2016	10/26/2016
Glatiramer Acetate	Injection	40 mg/mL, 1 mL pre- filled syringe	Copaxone / 20622	10/3/2017	10/4/2017	4/2/2018
Glycopyrrolate	Tablets	2 mg	Robinul Forte / 12827	2/3/2014	12/21/2015	6/18/2016
Guanfacine Hydrochloride	Extended-release (XR) Tablets	1 mg, 2 mg, 3 mg, and 4 mg	Intuniv / 22037	10/5/2012	12/1/2014	5/30/2015
Hydrocodone Bitartrate	Extended-release (XR) Tablets	20 mg, 60 mg, and 120 mg	Hysingla ER / 206627	3/1/2021	3/1/2021	8/28/2021
Hydrocodone Bitartrate	Extended-release (XR) Tablets	30 mg, 40 mg, 80 mg, and 100 mg	Hysingla ER / 206627	3/1/2021	3/1/2021	8/28/2021
Hydrocortisone Butyrate	Lotion	0.10%	Locoid / 22076	11/21/2017	2/12/2018	8/11/2018
Icosapent Ethyl	Capsules	1 g	Vascepa / 202057	5/21/2020	11/4/2020	5/3/2021
Imatinib Mesylate	Tablets	100 mg and 400 mg	Gleevec / 21588	12/3/2015	2/1/2016	7/30/2016
Itraconazole	Oral Solution	10 mg/mL	Sporanox / 20657	10/30/2015	9/18/2018	3/17/2019
Ivermectin	Lotion	0.50%	Sklice / 202736	5/6/2020	11/30/2020	5/29/2021
Ivermectin	Cream	1%	Soolantra / 206255	9/13/2019	10/14/2019	4/11/2020
Lamivudine	Oral Solution	10 mg/mL	Epivir	10/31/2014	3/5/2015	9/1/2015
Lanthanum Carbonate	Chewable Tablet	500 mg, 750 mg, and 1000 mg	Fosrenol / 21468	8/11/2017	8/30/2017	2/26/2018

Drug Name	Dosage From	Strength	RLD / NDA Number	Date of First Applicant Approval	Date of First Commercial Marketing by the First-to-file (FTF) Applicant	End of 180-Day Exclusivity Period [a]
Lapatinib Ditosylate	Tablets	250 mg	Tykerb / 22059	9/29/2020	9/29/2020	3/28/2021
Levothyroxine Sodium	Injection	100 mcg/vial and 500 mcg/vial	Levothyroxine Sodium / 202231	6/29/2016	4/2/2018	9/29/2018
Levothyroxine Sodium	Injection	200 mcg/vial	Levothyroxine Sodium / 202231	12/7/2015	7/5/2016	1/1/2017
Lopinavir and Ritonavir	Oral Solution	80 mg/20 mg per mL	Kaletra / 21251	12/27/2016	1/23/2017	7/22/2017
Mesalamine	Delayed-release Tablets	1.2 g	Lialda / 22000	6/5/2017	7/18/2017	1/14/2018
Mesalamine	Suppository	1000 mg	Canasa / 21252	11/24/2015	11/24/2015	5/22/2016
Metformin Hydrochloride	Extended-release (XR) Tablets	500 mg and 1000 mg	Glumetza / 21748	7/19/2013	2/1/2016	7/30/2016
Methylphenidate Hydrochloride	Extended-release (XR) Capsules	60 mg	Aptensio XR / 205831	12/13/2018	9/25/2020	3/24/2021
Methylphenidate Hydrochloride	Extended-release (XR) Capsules	10 mg	Aptensio XR / 205831	12/13/2018	9/25/2020	3/24/2021
Methylphenidate Hydrochloride	Extended-release (XR) Capsules	15 mg, 20 mg, 40 mg and 50 mg	Aptensio XR / 205831	12/13/2018	9/25/2020	3/24/2021
Methylphenidate Hydrochloride	Extended-release (XR) Capsules	30 mg	Aptensio XR / 205831	12/13/2018	9/25/2020	3/24/2021
Micafungin Sodium	For Injection	50 mg/vial and 100 mg/vial	Mycamine / 21506	5/17/2019	5/8/2020	11/4/2020
Moxifloxacin Hydrochloride	Injection	1.6 mg/mL	Avelox in Sodium Chloride 0.8% in plastic container / 21277	5/5/2017	10/3/2017	4/1/2018
Nitric Oxide	for Inhalation	100 ppm and 800 ppm	INomax / 20845	10/2/2018	4/1/2019	9/28/2019
Norethindrone Acetate and Ethinyl Estradiol and Ferrous Fumarate	Chewable Tablets	1 mg/0.02 mg and 75 mg	Minastrin 24 Fe / 203667	5/24/2016	3/15/2017	9/11/2017
Olopatadine Hydrochloride	Ophthalmic Solution	0.2%	Pataday / 21545	7/13/2015	6/8/2017	12/5/2017
Pantoprazole Sodium	for Delayed-release Oral Suspension	40 mg	Protonix / 22020	6/30/2020	8/13/2020	2/9/2021
Polyethylene Glycol 3350, Sodium Sulfate, Sodium Chloride, Potassium Chloride, Sodium Ascorbate and Ascorbic Acid	For Oral Solution	100 g, 7.5 g, 2.691 g, 1.015 g, 5.9 g and 4.7 g per pouch	Moviprep / 21881	1/25/2012	8/31/2020	2/27/2021
Prednisolone Sodium Phosphate	Orally Disintegrating Tablets	10 mg, 15 mg, and 30 mg	Orapred / 21959	4/10/2013	12/8/2014	6/6/2015
Quetiapine Fumarate	Extended-release (XR) Tablets	400 mg	Seroquel XR / 22047	11/1/2016	11/1/2016	4/30/2017
Ramelteon	Tablets	8 mg	Rozerem / 21782	7/26/2013	7/22/2019	1/18/2020
Ranolazine	Extended-release (XR)	500 mg and 1000 mg	Renexa / 21526	7/29/2013	1/27/2019	7/26/2019
Rasagiline Mesylate	Tablets	0.5 mg and 1 mg	Azilect / 21461	9/12/2013	1/2/2017	7/1/2017
Ribavirin	for Inhalation Solution	6 gm/vial	Virazole / 18859	10/6/2016	12/15/2016	6/13/2017
Risedronate Sodium	Tablets	5 mg, 30 mg and 35 mg	Actonel / 20835	10/5/2007	6/1/2015	11/28/2015
Risedronate Sodium	Delayed-release Tablets	35 mg	Atelvia / 22560	5/18/2015	5/18/2015	11/14/2015
Ritonavir	Tablets	100 mg	Norvir / 22417	1/15/2015	3/20/2018	9/16/2018

Drug Name	Dosage From	Strength	RLD / NDA Number	Date of First Applicant Approval	Date of First Commercial Marketing by the First-to-file (FTF) Applicant	End of 180-Day Exclusivity Period [a]
Rivastigmine	Transdermal System Extended-release (XR)	13.3 mg/24 hr	Exelon / 22083	8/31/2015	9/2/2015	2/29/2016
Ropivacaine Hydrochloride	Injection	2 mg/mL, 100 mL	Naropin / 20533	7/13/2016	9/15/2016	3/14/2017
Rosuvastatin Calcium	Tablets	5 mg, 10 mg, 20 mg, and 40 mg	Crestor / 21366	4/29/2016	5/2/2016	10/29/2016
Rufinamide	Tablets	100 mg, 200 mg, and 400 mg	Banzel / 21911	5/16/2016	6/1/2021	11/28/2021
Sapropterin Dihydrochloride	Tablets	100 mg	Kuvan / 22181	5/10/2019	10/1/2020	3/30/2021
Sapropterin Dihydrochloride	Powder for Oral Solution	100 mg per packet	Kuvan / 205065	8/20/2019	10/1/2020	3/30/2021
Sapropterin Dihydrochloride	Powder for Oral Solution	500 mg per packet	Kuvan / 205065	8/20/2019	10/1/2020	3/30/2021
Sildenafil Citrate	Tablets	25 mg and 50 mg	Viagra / 20895	3/9/2016	12/11/2017	6/9/2018
Sildenafil Citrate	Tablets	100 mg	Viagra / 20895	3/9/2016	12/11/2017	6/9/2018
Sirolimus	Tablets	0.5 mg	Rapamune / 21110	1/8/2014	1/16/2014	7/15/2014
Tadalafil	Tablets	2.5 mg	Cialis / 21368	5/22/2018	9/27/2018	3/26/2019
Tadalafil	Tablets	5 mg, 10 mg and 20 mg	Cialis / 21368	5/22/2018	9/27/2018	3/26/2019
Tadalafil	Tablets	20 mg	Adcirca / 22332	8/3/2018	8/8/2018	2/4/2019
Tavaborole	Topical Solution	5%	Kerydin / 204427	10/13/2020	10/19/2020	4/17/2021
Telmisartan	Tablets	20 mg, 40 mg and 80 mg	Micardis / 20850	1/8/2014	1/8/2014	7/7/2014
Tenofovir Disoproxil Fumarate	Tablets	300 mg	Viread / 21356	3/18/2015	12/15/2017	6/13/2018
Testosterone	Gel	1.62% (pump)	Androgel	8/4/2015	10/12/2018	4/10/2019
Timolol Maleate	Ophthalmic Solution	0.5%	Istalol / 21516	4/17/2015	4/17/2015	10/14/2015
Treprostinil Sodium	Injection	10 mg/mL, 20 mL vial	Remodulin / 21272	11/30/2017	3/25/2019	9/21/2019
Treprostinil Sodium	Injection	1 mg/mL, 2.5 mg/mL, and 5 mg/mL, 20 mL vial	Remodulin / 21272	11/30/2017	3/25/2019	9/21/2019
Valsartan	Tablets	40 mg, 80 mg, 160 mg, and 320 mg	Diovan / 21283	6/26/2014	7/7/2014	1/3/2015
Vardenafil Hydrochloride	Tablets	2.5 mg	Levitra / 21400	5/3/2012	10/3/2018	4/1/2019
Vardenafil Hydrochloride	Tablets	5 mg and 10 mg	Levitra / 21400	5/3/2012	10/3/2018	4/1/2019
Vardenafil Hydrochloride	Tablets	20 mg	Levitra / 21400	5/3/2012	10/3/2018	4/1/2019
Zolpidem Tartrate	Extended-release (XR) Tablets	12.5 mg	Ambien CR / 21774	12/3/2010	12/6/2020	6/4/2021
Zolpidem Tartrate	Sublingual Tablets	1.75 mg and 3.5 mg	Intermezzo / 22328	6/3/2015	3/23/2016	9/19/2016

[a] Calculated by adding 180 days to the date of first commercial marketing by the FTF.

Table A - 6. Product-Pathway Combination Models for Analysis of Cost Factors, Barriers, and Incentives

Type of Drug			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
			Small Molecule Drugs	Small Molecule Drugs	Topical Drugs	Topical Drugs	Narrow Therapeutic Index (NTI) Drugs	Narrow Therapeutic Index (NTI) Drugs	Inhalers	Inhalers	Liposomes, Dendrimers, Polymeric Micelles	Liposomes, Dendrimers, Polymeric Micelles	Iron Carbohydrate Complexes	Iron Carbohydrate Complexes	Ophthalmic Emulsions	Ophthalmic Emulsions	Glatiramoids	Glatiramoids	Glatiramoids	Glatiramoids
In vivo Bioequivalence (BE) Study Needed?			No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Type of Bioequivalence (BE) Study				HV	P	P&CE	HV	HV	HV	HV	P	P&CE	HV	HV	P&CE	P&CE			HV	P&CE
BE Study Location				US	US	US	US	US	US	US	US	US	US	US	US	US			US	US
Is a Bridging Study Needed Based on Stability Testing Results?			No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
RLD Subject to Intellectual Property (IP) Protection?			No	No	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
PIV Challenge Applicable?						Yes		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Type of PIV Challenge						PI/N		PI/N		PI/N		PI/N		PI/N		PI/N		PI/N		PI/N
Type of Patent Challenge						F/C		F/C		F/C		F/C		F/C		F/C		F/C		F/C
Litigation Strategy						Lead		Lead		Lead		Lead		Lead		Lead		Lead		Lead
Competitive Generic Therapeutic (CGT) Designation Sought?			No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
RLD Subject to REMS?			No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Finished Dosage Form (FDF) Facility Location?			D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	D
Pre-approval Inspection (PAI) Needed?			No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Market Size			Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med	Med
Expected Years in Market			5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Applicable Cost Factors, IP-Barriers, Non-IP Barriers, and Incentives																				
Cost Factors	Increase in first-cycle approvals	Scenario 1	✓	✓	✓		✓		✓		✓		✓		✓		✓		✓	
		Scenario 2	✓	✓	✓		✓		✓		✓		✓		✓		✓		✓	
		Scenario 3	✓	✓	✓		✓		✓		✓		✓		✓		✓		✓	
	Change in FDA User Fees		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Use of Biowaivers in Lieu of In-vivo BE Studies			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓
IP Barriers	Strategic Accumulation of Patents		Examined Separately																	
	Product Hopping		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Settlements and Pay-for-delay		Examined Separately																	

Type of Drug		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
		Small Molecule Drugs	Small Molecule Drugs	Topical Drugs	Topical Drugs	Narrow Therapeutic Index (NTI) Drugs	Narrow Therapeutic Index (NTI) Drugs	Inhalers	Inhalers	Liposomes, Dendrimers, Polymeric Micelles	Liposomes, Dendrimers, Polymeric Micelles	Iron Carbohydrate Complexes	Iron Carbohydrate Complexes	Ophthalmic Emulsions	Ophthalmic Emulsions	Glatiramoids	Glatiramoids	Glatiramoids	Glatiramoids
Non-IP Barriers	Formulary Tier Manipulation and RLD Rebates	Examined Separately																	
	RLD Labeling Changes Near Patent Expiry	Not Modeled – Impacts Negligible [a]																	
	Authorized Generics				✓		✓		✓		✓		✓		✓		✓		✓
Incentives	180-day Exclusivity Modifications	Examined Separately																	
	FDA Product-specific Guidances (PSGs)			✓	✓			✓	✓			✓	✓	✓	✓			✓	✓
	RLD Full Ingredient List Disclosures													✓	✓				

HV = Healthy Volunteers
P = Patients
P&CE = Patients and Clinical Endpoint
PI/N = Patent Invalidity/Noninfringement
F/C = Formulation/Composition
D = Domestic
Med = Medium
[a] Neither the expense nor the potential delay caused by an RLD label change were considered serious barriers by manufacturing representatives interviewed for this study as described in Section 7.2.2.

Table A - 7. FTF Sales of PIV Market Sample Drugs for Months 6 and 7

RLD Brand Name	Market has AG (Yes/No)?	FTF Sales (in 2020 $)		Change in FTF Sales from Month 6 to Month 7	
		Month 6	Month 7	$ (in 2020 $)	Percentage
Adcirca	No	$18,077,414	$13,246,794	($4,830,620)	(26.7%)
Atelvia	Yes	$2,093,852	$1,975,948	($117,904)	(5.6%)
Baraclude	Yes	$6,474,581	$9,418,458	$2,943,876	45.5%
Beyaz	Yes	$934,950	$648,421	($286,529)	(30.6%)
Clolar	Yes	$1,142,743	$1,526,637	$383,894	33.6%
Copaxone	No	$38,909,245	$32,943,267	($5,965,977)	(15.3%)
Coreg CR	Yes	$4,643,834	$4,801,037	$157,203	3.4%
Crestor	No	$18,349,273	$16,083,839	($2,265,434)	(12.3%)
Diovan	Yes	$36,847,405	$14,943,067	($21,904,338)	(59.4%)
Doryx 50795	Yes	$4,387,053	$4,742,167	$355,114	8.1%
Epzicom	Yes	$6,225,266	$3,299,027	($2,926,239)	(47.0%)
Exelon	Yes	$2,328,832	$2,711,948	$383,116	16.5%
Focalin XR	Yes	$1,232,025	$749,659	($482,367)	(39.2%)
Fosrenol	Yes	$2,456,621	$2,992,302	$535,681	21.8%
Gleevec	No	$66,766,447	$57,836,828	($8,929,620)	(13.4%)
Kaletra	No	$140,828	$135,630	($5,198)	(3.7%)
Kerydin	No	$772,667	$601,318	($171,349)	(22.2%)
Lialda	Yes	$33,572,828	$29,327,974	($4,244,855)	(12.6%)
Lotronex	Yes	$1,135,241	$1,386,044	$250,803	22.1%
Micardis	Yes	$6,248,879	$2,823,599	($3,425,280)	(54.8%)
Naropin	No	$47,756	$46,738	($1,018)	(2.1%)
Pennsaid	No	$1,233,734	$1,181,421	($52,313)	(4.2%)
Pro-Air HFA	Yes	$15,825,194	$8,583,615	($7,241,579)	(45.8%)
Protonix	No	$2,597,574	$2,852,064	$254,490	9.8%
Rapamune	Yes	$364,639	$291,101	($73,539)	(20.2%)
Seroquel	Yes	$10,669,703	$3,064,108	($7,605,595)	(71.3%)
Soolantra	Yes	$3,481,909	$779,351	($2,702,558)	(77.6%)
Sustiva	No	$144,759	$149,197	$4,438	3.1%
Tecfidera	Yes	$10,471,770	$13,181,144	$2,709,374	25.9%
Tekturna	Yes	$1,123,173	$905,702	($217,471)	(19.4%)
Tikosyn	Yes	$6,083,303	$7,812,505	$1,729,202	28.4%
Tykerb	No	$1,510,593	$1,213,420	($297,173)	(19.7%)
Uceris	Yes	$5,518,394	$3,868,884	($1,649,510)	(29.9%)
Uloric	No	$1,965,005	$1,371,861	($593,144)	(30.2%)
Vanos	Yes	$2,165,898	$1,214,167	($951,731)	(43.9%)
Virazole	No	$751,378	$961,278	$209,900	27.9%
Zytiga	Yes	$11,116,225	$9,120,129	($1,996,097)	(18.0%)
Total	**NA**	**$327,810,991**	**$258,790,647**	**($69,020,344)**	**(13.0%)**

NA = Not applicable

[a] Out of the 38 drugs in our PIV market sample, we did not have month 7 sales for one drug, Saphris, because the exclusivity period for the drug ended in mid-June, 2021 and our IQVIA NSP data period ended in June 2021. Thus, we excluded Saphris from this assessment.