Generic Competition for Drugs Treating Rare Diseases

Health Policy Portal

Reed F. Beall, Amity E. Quinn, Aaron S. Kesselheim, Frazer A. Tessema, and Ameet Sarpatwari

About This Column

Aaron Kesselheim serves as the editor for Health Policy Portal. Dr. Kesselheim is the *JLME* editor-in-chief and director of the Program On Regulation, Therapeutics, And Law at Brigham and Women's Hospital/Harvard Medical School. This column features timely analyses and perspectives on issues at the intersection of medicine, law, and health policy that are directly relevant to patient care. If you would like to submit to this section of *JLME*, please contact Dr. Kesselheim at akesselheim@bwh.harvard.edu.

Introduction

Prescription drugs are usually very expensive until patents on the brand-name product expire, but prices of many older off-patent medicines have risen in recent years in the absence of effective generic competition.[1] In 2015, for example, Turing increased the price of pyrimethamine, a 62-year-old drug to treat toxoplasmosis, by 5000%.[2] More recently, Teva announced that it would price its generic version of trientine (Syprine), a treatment for a deficiency in copper metabolism, at $18,375 per month — 28 times the list price for the brand-name product in 2010.[3]

One common feature of these two cases is that they involve drugs indicated for rare diseases. It has been estimated that over 7,000 rare diseases affect about 10% of Americans, few with effective treatments.[4] In 1983, the Orphan Drug Act created a set of incentives for manufacturers to invest in the development of drugs for rare diseases, including a 7-year period in which the FDA cannot approve generic versions of the drug for the rare disease indication ("orphan drug exclusivity"). Since passage of the act, rare disease drugs have comprised an increasing share of new drug approvals. Between 1994 and 2004, 17% of new drugs had a rare disease indication; the following decade, 25% did.[5] However, the prices of new drugs for rare diseases are often set extremely high and may be unaffordable for patients or strain payor resources.[6] While manufacturers have justified high prices by pointing to the high cost of new drug development and the small size of rare disease markets, such prices have been tied to reduced adherence.[7]

Like patients with more common diseases, patients with rare diseases benefit from low prices associated with the introduction of generic drugs for their conditions. However, generic drugs are only inexpensive if enough market entrants spark robust price competition. Previous research has found that a single generic competitor leads to reductions in price of about 10-15%, with prices not dropping by more than 50% until there are 4 or more generic manufacturers serving a market.[8] Yet nearly one-third of eligible drugs lack sufficient generic competition and are therefore at risk for high prices.[9]

Drugs treating rare diseases may be at elevated risk of insufficient generic competition because generic manufacturers may avoid niche markets and prioritize drugs treating more prevalent conditions. To assess this hypothesis, we sought to determine the prevalence of generic availability and patent challenges — two measures of generic competition[10] — among rare disease drugs stratified by measures of market size.

Methods

Study Design and Data Sources

We assessed drugs originally approved with a rare disease indication between

Reed F. Beall, Ph.D., *is an assistant professor in health care policy in the Department of Community Health Sciences at the Cumming School of Medicine and at the O'Brien Institute for Public Health at the University of Calgary.* **Amity E. Quinn, Ph.D.,** *is a post-doctoral fellow in health economics in the Department of Community Health Sciences at the at the University of Calgary.* **Aaron S. Kesselheim, M.D., J.D, M.P.H.,** *is a professor of medicine and director of the Program On Regulation, Therapeutics, And Law (PORTAL) at Brigham and Women's Hospital and Harvard Medical School. At the time of the study,* **Frazer A. Tessema, B.A.,** *was a research assistant with PORTAL at Brigham and Women's Hospital and Harvard Medical School.* **Ameet Sarpatwari, Ph.D., J.D.,** *is an assistant professor of medicine and assistant director of PORTAL at Brigham and Women's Hospital and Harvard Medical School.*

The Journal of Law, Medicine & Ethics, 48 (2020): 789-795. © 2020 The Author(s)
DOI: 10.1177/1073110520979391

January 1983 and April 2017, the start of the most recent 6 quarters of available data (April 2017 – September 2018) in the Medicaid State Drug Utilization Database ("Medicaid Dataset"), which includes information on outpatient drug prescription fill totals. We also drew from 4 FDA databases: Drugs@FDA, the Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book"), the Orphan Drug Product Designation Database, and the Paragraph IV Certifications List. Drugs@FDA serves as a repository of names, dates of approval, and labels for FDA-approved drugs and their generic equivalents. Published annually, the Orange Book lists patents and other exclusivities for small-molecule drugs. The Orphan Drug Product Designation Database contains the dates of designation and approval for orphan-designated products and their rare disease indications. Finally, the Paragraph IV Certification List catalogues brand-name drugs for which generic manufacturers have applied for marketing approval alleging that Orange Book-listed patents covering the drugs are either irrelevant or invalid (i.e., brand-name drugs for which generic manufacturers have made a "patent challenge").

Drug Selection

We used Drugs@FDA and the Orphan Drug Product Designation Database to identify all new small-molecule drugs approved with a rare disease indication approved prior between January 1983 and March 2017 ("study drugs"). We excluded biologic drugs because only sponsors of small-molecule drugs were historically required to report patent information to the FDA for listing in the Orange Book.

Drug-Specific Data Collection

We recorded each study drug's rare disease indication(s) using the Orphan Drug Product Designation Database and last-expiring patent using the Orange Book (1983-2018). We then gathered data for 2 measures of generic competition: whether any prescription fills for a generic equivalent had been reported in the Medicaid Dataset, and whether a patent challenge was listed for the brand-name product in the Paragraph IV Certification List (reflecting the interest of generic manufacturers entering the market promptly). We also collected the total number of fills per drug (brand-name or generic), which served as a measure of market size. We used fills rather than expenditures to avoid misclassification owing to undisclosed rebates that affect Medicaid expenditures and possible decreases in expenditure following generic entry.

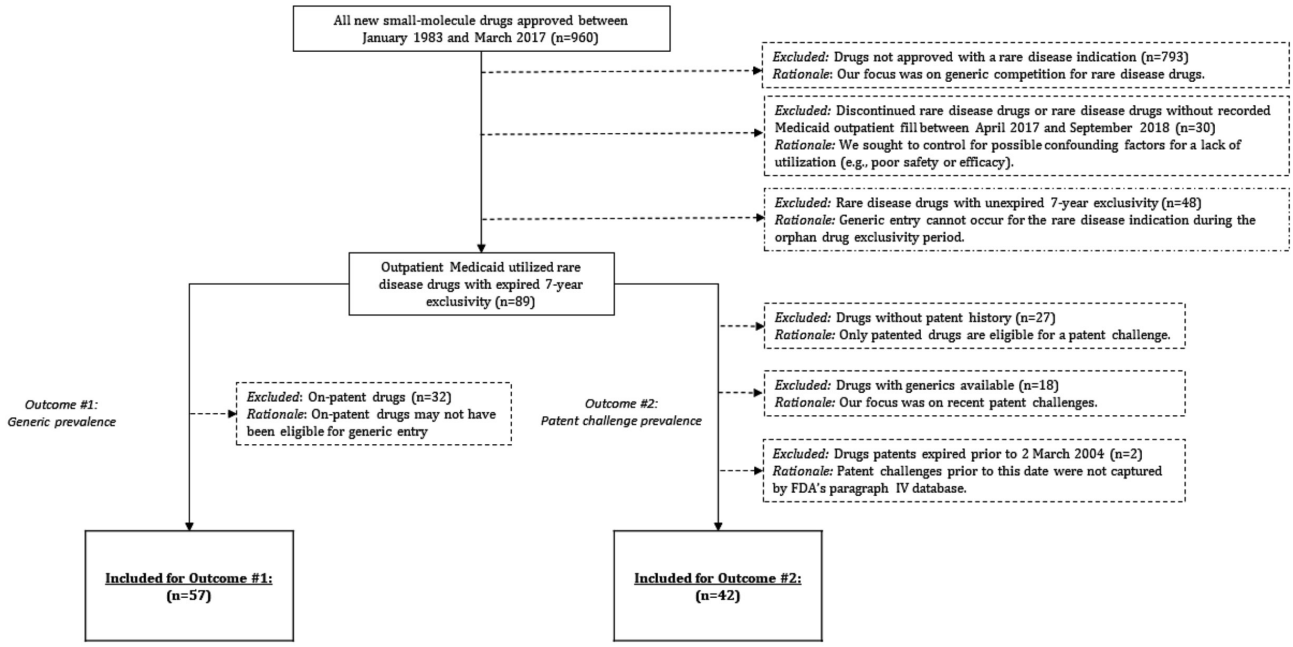
Analysis

PREVALENCE OF GENERIC AVAILABILITY

To estimate generic availability, we calculated the proportion of "generic-

Figure

Approach to assessing market size, generic competition, and patent challenges



Sources: Authors' study design and analysis of data of drugs approval for rare diseases based upon four FDA databases (Drugs@FDA, the Approved Drug Products with Therapeutic Equivalence Evaluations ["Orange Book"], the Orphan Drug Product Designation Database, and the Paragraph IV Certifications List) and the Medicaid State Drug Utilization database (second quarter of 2017 — third quarter of 2018).

Notes: Flow diagram of inclusion criteria that was used to arrive at the final analysis tables for the 2 outcome vriables.

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eligible" study drugs that had an approved generic equivalent with prescription fills in the Medicaid Dataset as of April 2018. We excluded study drugs that had been discontinued or that did not have any prescription fills (brand-name or generic) in the Medicaid Dataset (Figure). We also excluded study drugs still covered by orphan drug exclusivity or with active patent protection.

We tested for differences in fills between generic-eligible study drugs with and without generics using the Mann-Whitney rank sum test. We then divided fills into quartiles and performed logistic regression modeling, testing for trend using Pearson's correlation coefficient. All tests were performed using Stata version 14 (StataCorp, College Station, TX).

PREVALENCE OF PATENT CHALLENGES

Next, we calculated the proportion of "challenge-eligible" study drugs with a recorded patent challenge as of April 2018. As with our analysis of generic availability, we excluded study drugs that had been discontinued or that did not have any prescription fills (brand-name or generic) in the Medicaid Dataset (Figure) and study drugs still covered by orphan drug exclusivity. We also excluded study drugs without a record of patents in the Orange Book. To focus on more recent patent challenges and reduce the effect of changes in market size due to generic entry, we further excluded study drugs with a generic equivalent. Finally, we excluded drugs that were off-patent prior to the start of the FDA's Paragraph IV Certifications List in March 2004. We then repeated the analyses performed for generic availability to assess the relationship between market size and patent challenges.

Results

Among 960 new small-molecule drugs approved between 1983 and the first quarter of 2017, 17% (n=167) had at least one rare disease indication, of which 17% (n=28) had record of prescription fills for a generic equivalent. These 28 drugs spanned several therapeutic classes, of which the two largest were cancer and immunotherapy (12/28, 43%) (Appendix).

Table

Prevalence of generic competition by Medicaid outpatient prescription fill quartiles

Outcome #1: Prevalence of generic availability		
Quartile	**Range of prescription fill counts**	**Observed generic availability**
1	0†-270	2/14 (14%)
2	271-1,576	6/14 (43%)
3	1,577-5,016	6/14 (43%)
4	5,017-201,319‡	9/15 (67%)
Overall	0†-201,319‡	24/57 (42%)
Outcome #2: Prevalence of patent challenges		
Quartile	**Range of prescription fill counts**	**Observed patent challenge prevalence**
1	0†-654	4/11 (36%)
2	655-2,769	2/10 (20%)
3	2,770-23,655	6/10 (60%)
4	23,655-285,193‡	9/11 (82%)
Overall	0†-285,193‡	21/42 (50%)

Sources: Authors' study design and analysis of data of drugs approval for rare diseases based upon four FDA databases (Drugs@FDA, the Approved Drug Products with Therapeutic Equivalence Evaluations ["Orange Book"], the Orphan Drug Product Designation Database, and the Paragraph IV Certifications List) and Medicaid State Drug Utilization database (second quarter of 2017 — third quarter of 2018).

Notes: The prevalence of generic competition declines with market size quartile, both in terms of the availability of generic equivalents and of the prevalence of patent challenges.
†Medicaid records with zero fills were only included if censoring was indicated (meaning the product was in active use)
‡Some drugs had multiple indications and/or may be used off-label, which may explain higher numbers of prescription fills than may be anticipated for rare disease drugs.

Prevalence of Generic Availability

Fifty-seven study drugs were off-patent and had been approved before April 2010. Of these generic-eligible study drugs, 42% (n=24) had a generic with a recorded fill in the Medicaid Dataset (Table). The median number of fills was higher for off-patent study drugs with generics than for off-patent drugs without generics: 3,874 (interquartile range [IQR]: 649-12,243) vs. 1,273 (IQR: 114-2,920) (Mann-Whitney: p=0.014). Logistic regression modeling revealed an association between generic availability and fill quartiles, with generic availability increasing from 14% in the first (i.e., lowest) quartile, to 43% in the second and third quartiles, to 67% in the fourth quartile (trend: p=0.006).

Prevalence of Patent Challenges

Forty-two (47%) study drugs lacked generic availability and had been approved with at least one Orange Book-listed patent (Figure). Of these challenge-eligible study drugs, 21 (50%) had a recorded challenge (Table). The number of fills for challenged study drugs was higher than for unchallenged study drugs: 21,068 (IQR: 1,474-30,067) vs. 1,286 (IQR: 194-2,994) (p=0.010). Logistic regression modeling revealed an association between patent challenges and prescription fill quartiles, with patent challenges increasing from 36% and 20% in the first and second quartiles, respectively; to 60% in the

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third quartile; to 82% in the fourth quartile (trend; p=0.004).

Discussion

In our study, 42% of generic-eligible rare disease drugs had generic equivalents in active use. Market size, based on Medicaid prescription fills, was associated with both generic availability and patent challenges, suggesting that generic manufacturers are less likely to enter "ultra-rare"[11] disease markets, even if unprotected by patents.

Our results complement existing studies in the peer-review medical literature. A previous investigation reported that 55% of generic-eligible rare disease drugs had an approved generic equivalent compared to 88% of generic-eligible non-rare disease drugs.[12] Our estimate, based on a larger sample and a more stringent requirement for of a recorded fill within Medicaid, was lower. Another study found that 77% of top-selling, patented drugs faced patent challenges,[13] considerably higher than the 36% we found among challenge-eligible study drugs in the lowest fill quartile but comparable to the 82% observed in the highest fill quartile.

The substantial heterogeneity in generic competition we observed suggests that proposed incentives to bolster generic competition may reinforce existing patterns more than boosting the number of drugs with first-time generic approvals.[14] Instead, effective policy proposals will have to account for the possibility that ultra-rare diseases markets may be too small to sustain the number of generic suppliers necessary to realize major price reductions. One option may be to introduce new insurance schemes for affected patients lacking adequate health coverage. Other ideas include promoting long-term purchasing contracts to stabilize demand after expiration of market exclusivity[15] and government-sponsored or non-profit manufacturing facilities.[16] Designing such systems are critical given an ongoing movement toward drug development for increasingly specific patient populations (i.e., precision and personalized medicine),[17] which will further increase the number of ultra-rare disease drugs available to patients.

In our study, 42% of generic-eligible rare disease drugs had generic equivalents in active use. Market size, based on Medicaid prescription fills, was associated with both generic availability and patent challenges, suggesting that generic manufacturers are less likely to enter "ultra-rare" disease markets, even if unprotected by patents.

Some limitations of our study warrant discussion. First, the design of our investigation limits causal inference. For example, it is possible that generic entry prompted an increase in the number of prescription fills (not vice-versa). However, as the Medicaid population is insured, there may not have been substantially more prescription fills attributable to lower prices from competition. Second, our focus on utilization data from a single national payor (i.e., Medicaid) and small-molecule drugs may limit the generalizability of our results.

Third, our study sought to estimate the prevalence of generic availability among rare disease drugs, rather than to quantify the number of suppliers of a particular drug for treating a particular rare condition. Such a future investigation may reveal even lower levels of competition in rare disease markets relative to drugs for more common diseases. It may also explore the extent to which the inverse association between the number of suppliers and drug prices holds true for rare disease drugs. This study would ideally take into account the sustainability of having multiple manufacturers supplying the same rare disease drug for such small patient populations.

Conclusion

The prevalence of generic competition among ultra-rare disease drugs is low. While generic competition has been an important policy tool for lowering prices and increasing accessibility, it may not be effective for such drugs. Absent new policies specific to these markets, high drug prices will likely persist for a growing number of drugs far beyond patent expiration, increasing the burden on patients, their families, and the health care system.

Note

This work was funded by Arnold Ventures. Dr. Kesselheim and Dr. Sarpatwari also receive support from the Harvard-MIT Center for Regulatory Science and the Engelberg Foundation. Dr. Quinn reports grants from Canadian Institutes of Health Research. All authors declare that they have no competing interests or conflicts of interest for this work.

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https://doi.org/10.1177/1073110520979391 Published online by Cambridge University Press

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Appendix

Table

Rare disease drugs with utilization of generic equivalents in Medicaid

Ingredient (Brand Name)	ACT Class	Orphan Indications
Anagrelide (Agrylin)	Antineoplastic and Immunomodulating Agents	Treatment of patients with essential thrombocythemia to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms.
Atovaquone (Mepron)	Antiparasitic	(i) For the acute oral treatment of mild to moderate Pneumocystis carinii pneumonia in patients who are intolerant to trimethoprim-sulfamethoxazole; (ii) Prevention of Pneumocystis carinii pneumonia (PCP) in high-risk, HIV-infected patients defined by a history of one or more episodes of PCP and/or a peripheral CD4+ (T4 helper/inducer) lymphocyte count less than or equal to 200/mm3.
Azacitidine (Vidaza)	Antineoplastic and Immunomodulating Agents	Treatment of myelodysplastic syndromes.
Bexarotene (Targretin)	Antineoplastic and Immunomodulating Agents	Treatment of cutaneous T-cell lymphoma.
Cladribine (Leustatin)	Antineoplastic and Immunomodulating Agents	Treatment of hairy cell leukemia.
Clofarabine (Clolar)	Antineoplastic and Immunomodulating Agents	Treatment of acute lymphoblastic leukemia
Decitabine (Dacogen)	Antineoplastic and Immunomodulating Agents	Treatment of myelodysplastic syndromes.

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https://doi.org/10.1177/1073110520979391 Published online by Cambridge University Press

Table (continued)

Rare disease drugs with utilization of generic equivalents in Medicaid

Ingredient (Brand Name)	ACT Class	Orphan Indications
Dexrazoxane (Zinecard)	Various – Detoxifying agents for antineoplastic treatments	Cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative dose of 300mg/m2.
Epirubicin (Ellence)	Antineoplastic and Immunomodulating Agents	Treatment of breast cancer.
Epoprostenol (Flolan)	Blood and Blood Forming Organs	(i) Long-term intravenous treatment of primary pulmonary hypertension in NYHA Class III and Class IV patients; (ii) Treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity.
Felbamate (Felbatol)	Nervous System	As adjunctive therapy in the treatment of partial and generalized seizures associated with the Lennox-Gastaut syndrome in children.
Fludarabine (Fludara)	Antineoplastic and Immunomodulating Agents	Treatment of chronic lymphocytic leukemia (CLL), including refractory CLL.
Fomepizole (Antizol)	Various – Antidotes	(i) As an antidote to ethylene glycol (antifreeze) poisoning, or for use in suspected ethylene glycol ingestion; (ii) Use for suspected or confirmed methanol poisoning, either alone or in combination with hemodialysis.
Fosphenytoin (Cerebyx)	Nervous System	For the control of generalized convulsive status epilepticus.
Glatiramer (Copaxone)	Antineoplastic and Immunomodulating Agents	For reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis.
Ifosfamide (Ifex)	Antineoplastic and Immunomodulating Agents	Treatment of juvenile rheumatoid arthritis.
Levocarnitine (Carnitor)	Alimentary Tract and Metabolism	(i) Treatment of genetic carnitine deficiency; (ii) Treatment of primary and secondary carnitine deficiency of genetic origin; (iii) Treatment of manifestations of carnitine deficiency in patients with end stage renal disease who require dialysis.
Mesna (Mesnex)	Respiratory System	For use as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis.
Miglustat (Zavesca)	Alimentary Tract and Metabolism	Treatment of Gaucher disease.
Mitoxantrone (Novantrone)	Antineoplastic and Immunomodulating Agents	(i) In combination with other approved drug(s) is indicated in the initial therapy of acute nonlymphocytic leukemia (ANLL) in adults; (ii) In combination with corticosteroids as initial chemotherapy for the treatment of patients with pain related to advanced hormone-refractory prostate cancer; (iii) Treatment of secondary-progressive multiple sclerosis. Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses); (iv) Treatment of progressive-relapsing multiple sclerosis. Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e., patients whose neurologic status is significantly abnormal between relapses).
Rifabutin (Mycobutin)	Anti-infectives for Systemic Use	Prevention of disseminated Mycobacterium avium complex disease in patients with advanced HIV infections.
Selegiline (Eldepryl)	Nervous System	As an adjuvant to levodopa and carbidopa treatment of idiopathic Parkinson's disease (paralysis agitans), postencephalitic Parkinsonism, and symptomatic Parkinsonism.

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Ingredient (Brand Name)	ACT Class	Orphan Indications
Temozolomide (Temodar)	Antineoplastic and Immunomodulating Agents	(i) Treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine; (ii) Treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.
Tranexamic acid (Cyklokapron)	Blood and Blood Forming Organs	Treatment of patients with hemophilia for short term use (2 to 8 days) before and after tooth extraction to reduce or prevent hemorrhage and reduce the need for replacement therapy.
Trientine (Syprine)	Alimentary Tract and Metabolism	Treatment of patients with Wilson's disease who are intolerant, or inadequately responsive to penicillamine.
Vigabatrin (Sabril)	Nervous System	Treatment of infantile spasms.
Zidovudine (Retrovir)	Anti-infectives for Systemic Use	Management of certain adult patients with symptomatic HIV infection (AIDS and advanced ARC) who have a history of cytologically confirmed Pneumocytis carinii pneumonia (PCP) or an absolute CD4 (T4 helper/inducer) lymphocyte count of less than 200/mm in the peripheral blood before therapy is begun.
Zoledronic acid (Zometa)	Musculoskeletal System	Treatment of tumor induced hypercalcemia.

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