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# Avoidance of Generic Competition by Abbott Laboratories' Fenofibrate Franchise

Nicholas S. Downing, AB; Joseph S. Ross, MD, MHS; Cynthia A. Jackevicius, PharmD, MSc; Harlan M. Krumholz, MD, SM

**T**he ongoing debate concerning the efficacy of fenofibrate has overshadowed an important aspect of the drug's history: Abbott Laboratories, the maker of branded fenofibrate, has produced several bioequivalent reformulations that dominate the market, although generic fenofibrate has been available for almost a decade. This continued use of branded formulations, which cost twice as much as generic versions of fenofibrate, imposes an annual cost of approximately \$700 million on the US health care system. Abbott Laboratories maintained its dominance of the fenofibrate market in part through a complex switching strategy involving the sequential launch of branded reformulations that had not been shown to be superior to the first-generation product and patent litigation that delayed the approval of generic formulations. The small differences in dose of the newer branded formulations prevented their substitution with generics of older-generation products. As soon as direct generic competition seemed likely at the new dose level, where substitution would be allowed, Abbott would launch another reformulation, and the cycle would repeat. Based on the fenofibrate example, our objective is to describe how current policy can allow pharmaceutical companies to maintain market share using reformulations of branded medications, without demonstrating the superiority of next-generation products.

*Arch Intern Med.*

Published online April 9, 2012.

doi:10.1001/archinternmed.2012.187

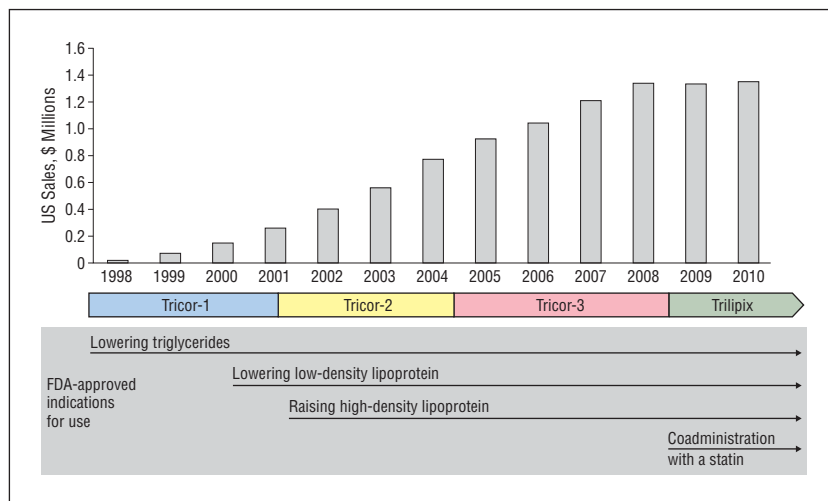
The efficacy of fenofibrate has been closely scrutinized in light of evidence suggesting that the lipid-modifying drug does little to reduce the risk of cardiovascular disease.<sup>1,2</sup> While the National Cholesterol Education Program<sup>3</sup> guidelines recommend fibrate use in conjunction with a statin for certain patients whose triglyceride level exceeds 200 mg/dL, a more recent American Heart Association<sup>4</sup> state-

ment suggests that the use of fibrates should be restricted to those with a triglyceride level above 500 mg/dL (to convert triglyceride level to millimoles per liter, multiply by 0.0113). Despite conflicting guidelines and questions about the drug's effectiveness in reducing cardiovascular risk, fenofibrate use has grown rapidly.<sup>5</sup>

**Author Affiliations:** Sections of General Internal Medicine (Dr Ross) and Cardiovascular Medicine (Dr Krumholz) and Robert Wood Johnson Clinical Scholars Program (Dr Krumholz), Department of Internal Medicine, School of Medicine, Yale–New Haven Hospital Center for Outcomes Research and Evaluation (Drs Ross and Krumholz), and Section of Health Policy and Administration, School of Public Health (Dr Krumholz), Yale University, New Haven, Connecticut; and Western University of Health Sciences, Pomona, California, and Institute for Clinical Evaluative Sciences, University of Toronto and University Health Network, Toronto, Ontario, Canada (Dr Jackevicius). Mr Downing is a medical student at Yale University School of Medicine.

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Another aspect of this story is that in the United States, in contrast to Canada, there has been a remarkable persistence in the use of branded formulations, which generate almost \$1.4 billion in sales annually, over generics.<sup>5,6</sup> Typically, a branded drug is rapidly marginalized soon



**Figure 1.** Sales, product availability, and Food and Drug Administration (FDA)-approved indications of Abbott Laboratories' fenofibrate franchise.<sup>14-18</sup>

after generics become available. For example, a recent analysis predicted that the market share of branded atorvastatin calcium (Lipitor; Pfizer, Inc) would be effectively eliminated less than 1 year after generic versions of the drug are launched.<sup>7</sup> In contrast, branded formulations account for most fenofibrate prescriptions in the United States today, although since 2002, comparable generics have been available.<sup>5</sup> This continued use of branded products causes substantially higher drug costs: if all patients taking branded formulations (ie, those who contribute to the \$1.4 billion sales figure) switched to generic fenofibrate, which is half the price of the branded drugs, our health care system could realize annual savings of approximately \$700 million.<sup>6,8,9</sup>

Abbott Laboratories' (hereafter Abbott's) commercial success can be explained in part by its complex switching strategy involving the sequential launch of branded reformulations of fenofibrate and patent litigation that delayed the approval of generics. The branded reformulations, which had no demonstrated incremental benefit on surrogate or patient outcomes (actually, none of the formulations have been shown to improve patient outcomes), obtained significant market share, while generic drugmakers sought to resolve the patent litigation with Abbott that was delaying the approval of their products. Small differences in dose prevented substitution of newer

branded reformulations with older generics. As soon as direct generic competition seemed likely with the latest formulation, where substitution would be allowed, Abbott would launch another reformulation, and the cycle would repeat.

In this article, we describe how Abbott's switching strategy fostered the continued use of branded reformulations of fenofibrate, although the company has faced generic competition for almost a decade and did not produce evidence that its reformulations were superior. This example highlights how current policy allows pharmaceutical companies to maintain market share of branded medications, without demonstrating the superiority of next-generation products.

### THE FIBRATE DRUG CLASS

Fibrates are a class of medications that target genes involved in lipid metabolism.<sup>10</sup> Since their discovery in the 1960s, several different fibrate drugs have been developed. The relevance of the earlier fibrates (clofibrate and gemfibrozil) to practice today is limited: clofibrate is no longer available in the United States, while gemfibrozil has a small market share, likely because of its association with rhabdomyolysis, manifesting potentially fatal muscle toxic effects, when given with a statin.<sup>11,12</sup>

Fenofibrate, the most commonly used medication in the class, was developed in the 1980s by

Fournier Laboratories.<sup>13</sup> The company's first new drug application (NDA) was rejected in 1984. In its review, the Food and Drug Administration (FDA)<sup>13</sup> noted that fenofibrate's efficacy, measured by observing surrogate end points, not cardiovascular outcomes, was insufficient to offset the risk of adverse events observed in trials of clofibrate. Fenofibrate was eventually approved in 1993 on the basis of its triglyceride-lowering properties. Fournier Laboratories never marketed the drug in the United States; instead, it licensed the rights to Abbott, which launched the drug, branded as Tricor, in 1998. Since then, fenofibrate has been reformulated several times at slightly different doses and has been approved for lowering low-density lipoprotein cholesterol levels and raising high-density lipoprotein cholesterol levels (**Figure 1**).<sup>14-18</sup> More recently, Abbott has launched fenofibric acid (Trilipix), a metabolite of fenofibrate, which can be used concomitantly with a statin.

Fibrate use in the United States doubled in the 7-year period ending December 31, 2009.<sup>5</sup> Sales of Abbott's fibrate franchise follow a similar upward pattern that tracks its expanding number of approved indications (Figure 1). The publication of a large outcomes trial in 2005 showing that fenofibrate had little effect on cardiovascular outcomes did not slow sales growth.<sup>5</sup> Sales of Abbott's fibrate franchise eclipsed \$1 billion in 2006 and were expected to reach almost \$1.4 billion in 2011, according to Morgan Stanley Research North America.<sup>6,15</sup>

### PROTECTING FENOFIBRATE'S MARKET EXCLUSIVITY

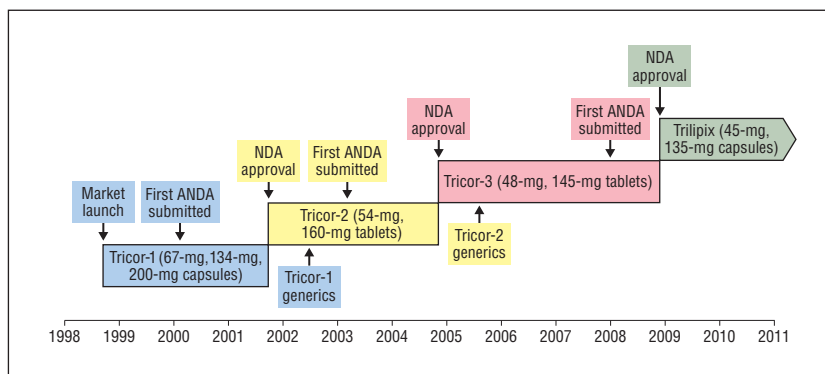
#### Market Exclusivity Concepts and the Generic Drug Approval Process

Branded drugs are usually protected from competition for several years after approval, allowing their prices to be set at almost any level, to reward drugmakers for their investment in the research and development process. Patent protection and data exclusivity work together to do this, as detailed in eAp-

pendix 1 (<http://www.archinternmed.com>). Novel drugs are typically granted a data exclusivity period, which prevents others from using the clinical data generated by the drug's originator, precluding generic applications. Once the data exclusivity period expires, generic drugmakers can submit an abbreviated NDA (ANDA) that relies on the original data, so long as these applications do not infringe on the branded drugmaker's patents. Alternatively, generic drugmakers can challenge remaining patents by including a special certification in their ANDAs (eAppendix 1). In this case, a branded drugmaker typically responds by filing lawsuits that assert that the ANDAs infringe on its intellectual property. By law, this action requires the FDA to delay approval of the ANDAs by up to 30 months to give the legal system an opportunity to resolve the dispute, meaning that the branded drugmaker remains protected from generic competition during this time. If litigation is still ongoing after 30 months, the FDA approves the ANDA by default. This allows generics to be launched "at risk": generic drugmakers can sell generics but risk paying substantial damages if they are found in violation of the branded drugmaker's patents.

### Generic Drugmakers Sought to Copy Tricor-1 Soon After Launch

The original formulation of fenofibrate (Tricor-1) became susceptible to generic applications soon after its launch because most of its data exclusivity period was consumed by the delay between its approval (in 1993) and its launch (in 1998). By February 2000, Novopharm, a generic drugmaker, had filed an ANDA challenging a patent used in the manufacture of Tricor-1. Abbott rapidly responded by filing a patent infringement suit, which legally delayed the approval of this ANDA by 30 months or until the litigation was resolved, protecting Tricor-1 from competition (eAppendix 2). Eighteen months later, Abbott won approval for a new formulation (Tricor-2), while its litigation with Novopharm, which had been acquired by Teva Pharmaceu-



**Figure 2.** Evolution of Abbott Laboratories' fenofibrate franchise relative to generic competition. ANDA indicates abbreviated NDA; NDA, new drug application.

**Table. Summary of the Formulations of Fenofibrate<sup>13,19-21</sup>**

Brand Name (Active Ingredient)	Dosing and Formulation	Basis of Food and Drug Administration Approval	Notable Outcomes Trials
Tricor-1 (fenofibrate)	67-mg, 134-mg, 200-mg Capsules	Clinical trials demonstrating the drug's effect on triglycerides and low-density lipoprotein cholesterol levels	Keech et al, <sup>1</sup> 2005 (fenofibrate did not reduce the rate of coronary events)
Tricor-2 (fenofibrate)	54-mg, 160-mg Tablets	Bioequivalence studies showing that Tricor-2 is equivalent to Tricor-1 Analysis of old Tricor-1 data to support inclusion of high-density lipoprotein cholesterol-lowering claims in the label (no clinical trials)	Ginsberg et al, <sup>2</sup> 2010 (fenofibrate in combination with simvastatin did not reduce the rate of cardiovascular events)
Tricor-3 (fenofibrate)	48-mg, 145-mg Tablets	Bioequivalence studies showing that Tricor-3 is equivalent to Tricor-1 (no clinical trials)	None
Trilipix (fenofibric acid)	45-mg, 135-mg "Delayed-release" capsules	Bioequivalence studies showing that Trilipix is equivalent to Tricor-1 Clinical trials to support the combination therapy indication	None

tical Industries (hereafter Teva), remained unresolved. Consequently, Tricor-2 did not face generic competition at launch (**Figure 2**). The approval of Tricor-2, a branded reformulation of Tricor-1, was based solely on bioequivalence evidence showing that the new 54-mg and 160-mg tablets had the same pharmacological properties as the origi-

nal formulation of 67-mg, 134-mg, and 200-mg capsules (**Table**). No clinical trials involving Tricor-2 were submitted in this NDA.<sup>19</sup>

### Tricor-2 Rapidly Replaced Tricor-1

Six months after approval, Tricor-2 accounted for 97% of fenofibrate

prescriptions.<sup>9</sup> Although it is not entirely clear how this switch was facilitated, antitrust lawsuits alleged that Abbott stopped detailing Tricor-1 and destroyed part of its inventory of the drug (eAppendix 2). In addition, other pricing, marketing, and promotional actions may have had a role. Nevertheless, a switch to a next-generation drug was accomplished before a generic of the first generation was approved. Soon, a judge granted summary judgment in favor of Teva, paving the way for generic Tricor-1. However, this generic was unable to challenge Tricor-2's dominance; Tricor-2 could not be substituted for generic Tricor-1 because of differences in dose between the formulations, although FDA approval of Tricor-2 was largely based on its bioequivalence data with Tricor-1. Unlike branded drugmakers, generic drugmakers do not have extensive sales forces. Instead, they rely on pharmacists, as well as physicians and payers, to switch patients from more expensive branded drugs to their generics. Most states have laws that require pharmacists to inform patients filling prescriptions for branded drugs when a generic is available and to ask their consent to dispense the generic.<sup>22,23</sup> In some states, this switching process is mandatory unless the prescriber specifically requests the branded drug. However, the minor dose difference between Tricor-2 and generic Tricor-1 meant that generic drugmakers were unable to benefit from these regulations because pharmacists are not permitted to change the dose when substituting a generic for a branded drug.<sup>22</sup>

#### Generic Tricor-2 and the Development of a Third Formulation

Because Tricor-2 was approved on the basis of bioequivalence studies only, it was ineligible for data exclusivity, meaning that generic drugmakers could immediately attempt to launch generic versions by challenging Abbott's patents. Teva, undeterred by its earlier experience, as well as Impax Laboratories, submitted ANDAs for generic Tricor-2 in late 2002. Abbott rapidly filed patent

infringement complaints, postponing the approval of these ANDAs for as long as 30 months or until the litigation was resolved. Later in 2003, Abbott sued another generic drugmaker, Ranbaxy Pharmaceuticals, Inc, in response to another ANDA seeking to produce generic Tricor-2. Meanwhile, Abbott continued to develop a new formulation of fenofibrate (Tricor-3) at slightly different doses than earlier versions (Table). Again, Abbott used bioequivalence data that linked its new formulation back to clinical trials of Tricor-1 as the basis of its NDA. This new formulation had a small convenience claim: it could be taken anytime, while Tricor-1 and Tricor-2 were supposed to be taken with food. However, this claim was based on Tricor-3 meeting specific bioavailability criteria in pharmacodynamic investigations of patients taking the drug in the fasting state.<sup>20</sup> Abbott did not submit any comparative studies demonstrating the superiority of Tricor-3 over its earlier formulations for this claim.

#### Tricor-3 Quickly Replaced Tricor-2

Generic Tricor-2 was not available when Tricor-3 was approved in November 2004 because the patent infringement litigation had not been resolved.<sup>20</sup> Patients were rapidly switched to Tricor-3; antitrust lawsuits alleged that Abbott used tactics similar to the earlier switch to drive uptake of its new reformulation (eAppendix 2). By whatever means it occurred, the end result was that less than 70 days after Tricor-3's approval, Abbott reported that 70% of patients had been switched, and by the time generic versions of Tricor-2 were eventually approved (in May 2005), 96% of fenofibrate prescriptions were written for the Tricor-3 reformulation.<sup>9,16</sup> The new doses of Tricor-3 would again prevent pharmacists from switching patients to Tricor-1 or Tricor-2 generics, presumably explaining why at the end of 2006, generics accounted for only 2.2% of all fenofibrate prescriptions.<sup>9</sup>

#### The Launch of Trilipix Extended Fenofibrate's Market Exclusivity Through 2011

In December 2007, just before Teva filed an ANDA for generic Tricor-3, Abbott submitted an NDA for its fourth formulation, which it branded as Trilipix.<sup>21</sup> Aside from changing the dosing and switching back to a capsule formulation, Abbott changed the active ingredient from fenofibrate to fenofibric acid, a metabolite of fenofibrate. Trilipix's NDA demonstrates the similarity between these 2 drugs by presenting bioequivalence data comparing Trilipix with Tricor-1.<sup>21</sup> Abbott also performed clinical trials measuring surrogate markers, such as high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, to demonstrate Trilipix's efficacy when combined with a statin.<sup>21</sup> According to FDA statutory requirements, Trilipix was granted a 3-year period of data exclusivity, which lasted until December 2011, despite similarities with earlier formulations and limited outcomes data supporting fibrate use.<sup>24</sup> Meanwhile, Abbott's litigation with Teva continued. Although the lawsuit was ultimately resolved in November 2009, a year after Trilipix was approved, Teva has not launched a generic version of Tricor-3 to date (Lupin Pharmaceuticals, Inc received approval for such a generic in late December 2011).<sup>11</sup> Other companies' efforts to disrupt Abbott's fibrate franchise by launching various fenofibrate generics and branded generics have had limited success. In December 2009, Abbott's fibrate franchise accounted for 77% of all fenofibrate prescriptions and 58% of the fibric acid derivatives market.<sup>9</sup>

#### IMPLICATIONS OF FENOFIBRATE'S PROLONGED EXCLUSIVITY

##### Cost Consequences

There is no evidence that Abbott's successive reformulations of fenofibrate have improved patient outcomes. Abbott's NDAs presented bioequivalence evidence, not comparative data, that demonstrated the

benefit of its next-generation products. However, these reformulations have imposed a substantial cost on our health care system by slowing the uptake of cheaper generics. The annual cost savings from switching all branded fenofibrate users to generic formulations could exceed \$700 million.<sup>6,8,9</sup>

### Legal Fallout

Abbott's strategy did not go entirely unnoticed. In May 2005, the Louisiana Wholesale Drug Company filed a class action lawsuit against Abbott, on behalf of all pharmacies and wholesalers that purchased Tricor, alleging the company's "unlawful exclusion of competition from the market for fenofibrate" (eAppendix 2). Abbott was the subject of a similar antitrust complaint brought by various patients taking Tricor. Both lawsuits cite the same sequence of events described herein as evidence that Abbott violated the Sherman Antitrust Act (15 USC §1-7 [1890]), which outlaws monopolies and any effort to establish such market position. Abbott was sued again in 2008 by 19 different states, which made allegations similar to those of the plaintiffs in the earlier lawsuits but also highlighted their view that Abbott had broken various state antitrust laws. Ultimately, Abbott settled each of these lawsuits at a combined cost to the company of more than \$300 million, which amounts to less than 4% of total sales to date of Abbott's fibrate franchise (eAppendix 2).

### POLICY IMPLICATIONS

We believe that various stakeholders, namely, payers, physicians, pharmacists, patients, and lawmakers, can act to ensure that market exclusivity and premium prices are reserved for real innovations that improve patient outcomes. Because the pharmaceutical industry may be influenced by its investors' focus on profitability and because this strategy contributed to Abbott's profits, external encouragement may help focus industry's research and development efforts on innovations that improve patient care rather than on reformulations lacking demonstrated

benefits over original drugs. In this section, we discuss how various stakeholders could reduce the attractiveness of similar switching strategies, thereby challenging industry to demonstrate the value of its next-generation products over the prior generation or be forced to face generic competition.

### FDA and Federal Lawmakers Could Eliminate the Moral Hazard of the 30-Month Stay

The 30-month stay of ANDA approvals, triggered by Abbott's patent infringement lawsuits, created a critical delay between the launch of Abbott's new formulations and the approval of generics of older fenofibrate formulations. This delay facilitated uptake of Abbott's branded reformulations because they faced no generic competition. The FDA could require that all drugmakers seeking approval for NDAs involving a new formulation or dose of a previously approved molecule must resolve any outstanding patent infringement lawsuits concerning the original drug before their application is approved. Such a law would allow the FDA to approve these NDAs at the same time as ANDAs involving older formulations. (Decisions about these generic applications are now delayed by the 30-month stay.) Establishing a mechanism that approves branded reformulations and generics simultaneously would allow drugmakers to compete for patients on a level playing field. If the formulations are equivalent, then the price will determine the choice. If a new formulation offers a demonstrated advantage, then it may justify a higher price. In this approach, branded drugmakers are protected from invalid challenges to their intellectual property because the original formulation's exclusivity is preserved until the litigation has been resolved and the new branded drug is approved. Judges have the authority to reduce the length of the 30-month stay, limiting the risk that branded drugmakers will attempt to obstruct the legal process.

### FDA and Federal Lawmakers Could Alert Other Stakeholders of Reformulations

Abbott's subtle reformulations were somewhat obscured by the company's ability to retain the Tricor brand name for its first 3 formulations of fenofibrate. In contrast, Abbott changed its Canadian brand name with each reformulation, clearly signaling to other stakeholders that the drug had been modified. The FDA could help raise awareness of reformulations if the law required that branded drugmakers must market their reformulations under different brand names.

### Patients and Payers Could Demand Cost-effective Treatments

The commercial success of fenofibrate is even more remarkable given that only Trilipix, and to a lesser extent Tricor-1, enjoyed data exclusivity, which provides complete protection from generic competition. The strength of Abbott's fibrate franchise in the absence of such protection suggests that regulatory changes could be of modest benefit. Although there is little that patients and payers could have done to promote generic competition for fenofibrate, these stakeholders were well positioned, as the pharmaceutical industry's customers, to challenge the high price of Abbott's drugs. In a similar drug class, payers have used the availability of generics to extract discounts from branded drugmakers: Express Scripts, Inc, a large pharmacy benefit manager, removed atorvastatin, the world's best-selling drug, from its formulary for several months in 2006 because of a price dispute when generic versions of simvastatin, a related low-density lipoprotein cholesterol-lowering drug, became available.<sup>25</sup> Eventually, Express Scripts, Inc, won concessions from Pfizer, Inc, highlighting the increasing influence of payers and pharmacy benefit managers in determining drug costs. Although many generics are available, Tricor-3 continues to command a premium price, suggesting that such cost-effectiveness calculations are not used systematically.<sup>8</sup>

The French approach to setting prices for new drugs provides a notable case study. It incorporates an assessment of a drug's innovation and incremental benefit, which is directly linked to the drugmakers' ability to name their own price.<sup>26,27</sup> Although our health care system has avoided price regulation, payers could consider a similar approach when negotiating drug prices. This would inform formulary position and translate into changes in copayment level, empowering patients and physicians to determine if a drug's demonstrated benefits are worth additional cost. Payers could mitigate concerns about rationing by applying this value-based calculus to reformulated drugs only. Few payers seem to have adopted this strategy: Trilipix has a low copayment level in several leading formularies.<sup>28</sup>

#### Pharmacists and State Lawmakers Could Facilitate Generic Switching at Bioequivalent Doses

The inability of pharmacists to switch patients with prescriptions for the new reformulations to generics prevented meaningful uptake of these less expensive drugs. Although Abbott conducted bioequivalence trials showing that its reformulations had the same effects as Tricor-L, pharmacists were unable to switch patients because of dose differences between each of the Tricor formulations. Revising the language of generic substitution statutes to allow switching between bioequivalent drug formulations (including those at different doses) could prevent the recurrence of similar switching strategies. Such an approach would require careful consideration of bioequivalence criteria, which mandate that the pharmacokinetic properties of a generic drug must fall within a certain range relative to those of the original drug. Drugs that have large therapeutic windows, such as fenofibrate, can be safely substituted with bioequivalent formulations. However, the substitution of other drugs, such as warfarin sodium, with bioequivalent preparations could compromise patient safety because there is a much smaller difference between effective and toxic doses. Consequently, any

attempt to promote switching between different yet bioequivalent formulations of the same drug must carefully balance potential safety risks. The challenge of setting appropriate bioequivalence criteria has been highlighted by current efforts to formalize the approval process for "biosimilars" (generic versions of biologic drugs). Also, generic substitution laws are set by the states, so such an approach would require substantial legislative efforts at the state level.

#### Physicians Could Take Responsibility for Cost-effective Care

The fenofibrate example is also a cautionary tale for physicians, who must accept some responsibility for the continued use of branded fenofibrate. Despite the availability of many fenofibrate generics during the past 9 years, physicians have continued to prescribe Abbott's more expensive formulations, which in December 2009 accounted for more than 75% of all fenofibrate prescriptions.<sup>5,9</sup> Physicians should be prepared to question minor dosing changes to branded drugs. In this example, physicians could have asked for data demonstrating what the benefit of each reformulation was or why fenofibrate's dosing was repeatedly changed. Admittedly, Abbott's switching strategy left them little choice until the generic versions were approved. Improvements in information systems, such as electronic medical records and drug databases, could be used to highlight the availability of comparable or bioequivalent generic drugs. Even if such improvements are made, physicians make the ultimate prescribing decision and must take responsibility for providing the highest quality of care, at a reasonable cost, for patients.

#### CONCLUSIONS

While we have used Abbott's handling of fenofibrate as an illustrative example of a branded drugmaker's maintaining a dominant market share years after generic competition was permitted, it is only one example. There are instances of similar strategies. AstraZeneca's efforts

to switch patients from omeprazole (Prilosec) to the active enantiomer of the old drug, esomeprazole magnesium (Nexium), in 2001 is well documented.<sup>29</sup> Such strategies are particularly worrying given concerns about the unsustainable growth of health care costs. Fortunately, this is a solvable problem because small changes to the current regulations and structure of our health care system have the potential to foster appropriate generic competition and to ensure that drugmakers demonstrate the value of their next-generation products.

**Accepted for Publication:** January 9, 2012.

**Published Online:** April 9, 2012.  
doi:10.1001/archinternmed.2012.187

**Correspondence:** Harlan M. Krumholz, MD, SM, Section of Cardiovascular Medicine, Department of Internal Medicine, School of Medicine, Yale University, 1 Church St, Ste 200, New Haven, CT 06510 (harlan.krumholz@yale.edu).

**Author Contributions:** *Study concept and design:* Downing, Ross, and Krumholz. *Acquisition of data:* Downing and Jackevicius. *Analysis and interpretation of data:* Downing, Ross, Jackevicius, and Krumholz. *Drafting of the manuscript:* Downing. *Critical revision of the manuscript for important intellectual content:* Ross, Jackevicius, and Krumholz. *Statistical analysis:* Jackevicius. *Obtained funding:* Krumholz. *Administrative, technical, and material support:* Downing and Krumholz.

**Financial Disclosure:** Dr Ross serves on a scientific advisory board for FAIR Health, Inc and is a recipient of a research grant from Medtronic, Inc through Yale University. Dr Krumholz chairs a cardiac scientific advisory board for United-Health Group and is a recipient of a research grant from Medtronic, Inc through Yale University.

**Funding/Support:** Mr Downing is supported by the Richard A. Moggio, MD, Student Research Fellowship, Yale University. Dr Ross is supported by grant K08 AG032886 from the National Institute on Aging and by the American Federation for Aging Research through the Paul B.

Beeson Career Development Award Program. Dr Jackevicius is supported by the College of Pharmacy of Western University of Health Sciences. Dr Krumholz is supported by grant U01-HL105270-02 (to the Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute.

**Role of the Sponsors:** The sources of support had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

**Disclaimer:** The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities and are based in part on data obtained under license from the National Prescription Audit (2002-2009).

**Online-Only Material:** The eAppendixes are available at <http://www.archinternmed.com>.

**Additional Contributions:** IMS Health Incorporated provided the data required for the analyses from the National Prescription Audit.

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