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“For Me There Is No Substitute”—Authenticity, Uniqueness, and the Lessons of Lipitor

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Analysts of the pharmaceutical industry have questioned what will happen in 2011 when Lipitor—Pfizer’s sales leader for more than a decade and the world’s best-selling prescription drug, ever—loses its patent exclusivity and faces generic competition [1]. When it was first approved for marketing by the U.S. Food and Drug Administration (FDA) in January 1997, Lipitor (atorvastatin) was a “me-too” drug, the fifth entry into the therapeutic class of HMG-CoA-reductase inhibitors, or statins. Entering this already-crowded field alongside Merck’s Mevacor (lovastatin) and Zocor (simvastatin), Novartis’ Lescol (fluvastatin) and Bristol-Myers Squibb’s Pravachol (pravastatin), Lipitor stood out for its claims of superior cholesterol-lowering ability, which—along with a massive marketing campaign—led to its swift and lasting dominance of the statin market, even as other agents became available in generic forms at far lower prices. Indeed, for most of the past decade, Pfizer’s promotion of Lipitor has centered on convincing consumers (and their physicians) that no generic could compare to Lipitor.

The phrase “I take Lipitor instead of a generic” was embedded in the public consciousness through an advertising campaign that featured Robert Jarvik, the medical investigator-cum-entrepreneur credited with the invention of the Jarvik artificial heart. The Jarvik Lipitor campaign, first aired in early 2006, coincided with the market entry of generic simvastatin. Many readers will remember images of his silver-haired visage on bus-stops and billboards, and video sequences of a calm, confident Dr. Jarvik rowing across a mountain lake while discussing the central role of Lipitor in the maintenance of his own cardiovascular vigor. These advertisements taught patients to be wary of pharmacists, insurers, or physicians who might try to substitute a generic statin for Lipitor. “For me,” Dr. Jarvik voiced, looking straight into the camera, “there is no substitute.”

The campaign revolved around authenticity and the perils of imitation. Dr. Jarvik, as many would soon point out, was not an actor playing a doctor, but a “real” doctor—the first well-known case of a physician serving as a celebrity sponsor for pharmaceutical promotion. By analogy, Lipitor was the authentic center of cholesterol therapy—the market leader and strongest statin available (until the launch of Astra-Zeneca’s Crestor [rosuvastatin] and now Kowa’s Livalo [pitavastatin]). While the forces of cost containment might attempt to foist cheap generic “substitutes” upon patients and prescribers, the ads seemed to imply, none of these could boast the same results as Lipitor.

These claims of superior efficacy were based partly on pharmacological principles of potency—milligram per milligram, Lipitor reduced the biomarker of low-density lipoprotein (LDL)-cholesterol more than any generic statin, an abstract concept cleverly rendered graphic in the form of the curve traced by Jarvik’s boat. Beyond biomarkers, by the time of the Jarvik ad campaign Pfizer could point to more than 400 trials of Lipitor, involving over 80,000 patients, which allowed for claims of clinical efficacy simply not studied in other statins. For example, one year into the Jarvik campaign, Lipitor became the first cholesterol-reducing drug approved by the FDA to lower the risk of hospitalization in patients with heart failure [2]. In other, select cases, Lipitor had been compared to the now-generically available statins in, for example, the PROVE-IT trial, which revealed better cardiovascular outcomes for patients treated with Lipitor at high doses than for those treated with pravastatin at conventional doses following myocardial infarction [3]. The implication was clear: what other drug could claim to be the same as Lipitor?

Pfizer’s narrative of authenticity would soon backfire. In a popular and political environment increasingly skeptical of direct-to-consumer (DTC) pharmaceutical advertising, this broadly visible campaign was a lightning rod for criticism. Katie Watson, a bioethicist at Northwestern University, claimed that it was an ethical lapse for someone who appeared to be a practicing physician—who had direct responsibilities to patients—to accept funds to promote a prescription pharmaceutical [4]. As Jarvik became a topic of conversation for pharmaceutical industry bloggers both sympathetic to and critical of DTC advertising, publicly available sources of information were scoured to flesh out the story of this controversial spokesperson.

Jarvik had received poor grades as an undergraduate at Syracuse University. He had difficulty getting into medical school and had ultimately received his MD from an offshore medical school, after having been rejected for admission by American schools. Then came the most surprising detail: not only had Jarvik attended a suspect school—he was not a cardiologist [5]. Not only was he not a cardiologist, he was not currently licensed to practice medicine. Not only was he not currently licensed, but he had never had a license to prescribe drugs in the United States. Indeed, through the work of a loose collective of bloggers, it soon became apparent that Robert Jarvik—though an accomplished researcher who had received a full undergraduate medical education—had never completed a residency or internship and had no clinical experience in internal medicine beyond the few months afforded by his undergraduate clerkships. As the story grew, competitors in the field of cardiovascular engineering came forward and announced that Jarvik had falsely claimed credit for inventing the artificial heart, arguing that the concept and technique had predated his own work.

These critiques of Jarvik as professional were soon joined by critiques of Jarvik as patient. By mid-2006, a middle-aged rower in Seattle named Dennis Williams, whose receding silver hairline bore close similarity to Jarvik’s own, announced that he had served as a body double for Jarvik’s solo-rowing craft during a 3-day commercial shoot at Lake Crescent, Washington [6]. Jarvik, who had rowed when

younger but had not been an active rower for several years, was filmed with oars in hand on a rowing platform by the side of the lake, and the frames had been superimposed to give the appearance that Jarvik himself was navigating the mountain waters. A subsequent admission by Jarvik that his own use of Lipitor did not begin until after he had been hired as a Pfizer spokesperson rendered the implied depiction of Lipitor as responsible for Jarvik's cardiovascular health still more troubling [7].

Jarvik's authenticity as both physician and patient spokesperson was visibly frayed. Taken claim by claim, the Jarvik Lipitor advertisements contained no outright lies, but constituted an assemblage of partial truths that, taken together, gave viewers the wrong impression. For a marketing campaign based on the importance of authenticity, these revelations of dissimulation were intensely damaging. The rowing ad was replaced by an ad showing a person unequivocally identifiable as Jarvik jogging with his son. But substituting one form of cardiovascular performance (jogging) for another (rowing) was not sufficient to quell the growing unrest over the campaign. By late 2007, it had been taken up by Congressman John Dingell's (D-MI) Committee on Energy and Commerce as a signature example of duplicity in DTC marketing. Pfizer received letters of investigation and a subpoena in January of 2008, and a Pfizer executive appeared in congressional hearings to testify about the campaign in May of 2008 [8]. Concerns about Jarvik's authenticity as clinician, prescriber, patient, and athlete seemed to threaten Lipitor's authenticity as a singular form of therapy. The portrayal of Jarvik as spokesperson and the positioning of Lipitor as superior to generic statins were explicitly linked in the congressional cross-examination of Pfizer's representative. If, for Jarvik, there clearly *was* a substitute (Dennis Williams), then quite possibly there was a substitute for Lipitor as well (generic simvastatin).

By the time of the congressional hearings, Pfizer had already announced the termination of the Jarvik ads. The executive responsible for marketing Lipitor, James Sage, apologized and said that, while Pfizer regretted that "the way in which we presented Dr. Jarvik in these ads has, unfortunately, led to mis-impressions and distractions" [9], Pfizer and Jarvik could nonetheless maintain that every individual statement made in these advertisements was based in a defensible claim. Real physicians and patients were left to wonder how much of Lipitor's reputation was likewise based on a string of facts each of which may have been technically correct, but which taken together may have created an impression that was misleading. After the Congressional hearings, the matter was soon forgotten: no fines or penalties were issued, no aspect of DTC advertising regulations was changed, and Pfizer moved on to another, less controversial Lipitor campaign involving "everyman" patients in place of experts.

The artful negotiation of similarity and difference continues, however, to be central to Lipitor's marketing success as the company girds for the imminent appearance of generic atorvastatin products. This is perhaps most explicit in the current Lipitor campaign, which claims with deliberate (and, for now, easy to defend) tautology that

“only Lipitor is Lipitor” [10]. Absent Jarvik, the underlying promotional message of inimitableness is still in place. Also in place is a delicate fabric of implication in which individually verifiable claims are woven together to suggest a broader untruth: that *for most patients* Lipitor is a drug incommensurate with all other statins.

Although Lipitor is more potent than generically available statins, the utility of taking a more potent drug at a higher price —when equivalent LDL-lowering capacity for most patients can simply be found at a higher dosage of the generic— remains irrelevant for most statin consumers other than those with stubbornly high initial LDL levels, or patients who require extreme lipid lowering. While clinical trials support claims of Lipitor’s superior efficacy in preventing coronary events in specific sub-populations (i.e., those who have just had a myocardial infarction or been diagnosed with heart failure), these populations do not represent the lion’s share of Lipitor consumers, many of whom take it at low doses, at which it is basically interchangeable with other statins.

For the majority of Lipitor consumers—who take Lipitor for primary prevention— there is no clear evidence that the higher potency of this statin translates into more favorable outcomes. There is, however, evidence that patients who take brand-name drugs are significantly *less* likely to be consistently adherent with their treatment regimens than those who take generic drugs [11], and high cost is a clear predictor of poorer adherence—a very real cause of adverse clinical outcomes. Moreover, while it is true in late 2010 that there is no generic equivalent of Lipitor, this will no longer be true in 6 months. The concept that “only Lipitor is Lipitor” seems intended to last long after atorvastatin is generically available.

Conclusion

As pharmaceutical scandals go, the Jarvik/Lipitor story was a minor affair. But the importance of scandals lies not so much in the extraordinary circumstances that give rise to their publicity, but in the vantage they provide on the political, economic, and moral structures governing ordinary activity. For decades the substitution of brand-name drugs with chemically equivalent generic versions—which provide vital cost savings for the increasingly unaffordable American health system—has been undercut by the marketing efforts of brand-name pharmaceutical manufacturers.

Although suspicion of therapeutic equivalence is occasionally grounded by specific demonstrations of well-demarcated, clinically important differences between putative equivalents (as in the case of high-dose Lipitor’s superiority over moderate-dose pravastatin in post-MI patients), the history of generic drugs is a chronicle of the repeated magnification of small and specific differences into widespread popular and professional skepticism of generic drugs as a category [12]. Indeed, only in recent years has a consensus emerged that generic drugs—at least within the field of cardiovascular medicine—can be equivalent and cost-effective replacements for brand-name versions [13]. Within other fields of medicine, such as neurology, antigeneric sentiment continues apace and has led to efforts in recent years to undo state laws governing generic substitution [14]. As the economic crisis of American

health care continues to intensify, the need to reconcile our aversion to substitution in medicine has only become more urgent.

For the practicing physician, the ethics of therapeutic substitution must navigate between two comparable potential harms. On the one hand, to substitute a drug that is therapeutically different—under the pretext of assumed similarity—risks harming the patient through adverse effects, allergic responses, or decreased efficacy. On the other hand, to prescribe an expensive, brand-name drug when an inexpensive generic form is therapeutically equivalent is to cause another form of harm to the individual patient's chances for long-term therapeutic adherence—not to mention his or her pocketbook.

More perilous still is the paucity of data available to distinguish between these two risks. Indeed, the continued promotion of Lipitor's singularity in the face of impending generic competition reminds us how heavily our system for generating, circulating, and acting on medical knowledge relies upon industry-funded and industry-promoted studies meant to differentiate products rather than to provide meaningful clinical comparisons of therapies. Recent enhanced federal support for the field of comparative effectiveness research and the founding of a new Patient-Centered Outcomes Research Institute under the Patient Protection and Affordable Care Act of 2010 offer some promise for patching up these gaps in our collective knowledge base. For the present, however, resolving the everyday yet urgent problems of therapeutic equivalence—or knowing when a medicine is good enough—remains elusive for real and imitation doctors alike.

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