“Generic Drugs: The Same, but Not”

By Jeremy Greene from *The Atlantic*

I have a migraine. My son has strep throat. A patient presents to my clinic with signs of pneumonia. These are all common enough occurrences. When I have a migraine, a good cup of coffee and a few tablets of ibuprofen go a long way towards soothing my throbbing head and general malaise. But not all cups of coffee are equally effective against migraines. I prefer the handcrafted pour-over from my local barista to the Styrofoam cupful that’s been sitting on a warming plate at my local gas station for a few hours; I think it makes me feel better faster. Nor are all pills of ibuprofen the same. I prefer the original Advil brand to generic ibuprofen because, like a well-sourced cup of coffee, it works better at making my headaches go away. Yes, I know that both pills contain the same active pharmaceutical ingredient in the same amount, and I’m a sucker for my neighborhood café. But the particular experience of consuming Advil—its lentil shape, its candy coating—is somehow more soothing than swallowing the slightly acrid, oblong generic versions. In ibuprofen, as in coffee, the materiality of my drug of choice matters.

Migraines are irritating and potentially disabling, but not life-threatening. Untreated strep throat, on the other hand, can lead to kidney failure or cardiovascular complications. Pneumonia can lead to overwhelming sepsis, shock, and untimely death. Yet I don’t give a second thought to spooning generic amoxicillin into my son’s mouth (as long as he gets to pick the flavor), or prescribing generic levofloxacin to my patients if their lung symptoms are accompanied by a chest X-ray that suggests pneumonia. I know that over the past half century the United States Food and Drug Administration has elaborated a complex system for ensuring that the efficacy, safety, purity, and quality of generic amoxicillin and levofloxacin is equivalent to the original brand-name versions. As a patient, parent, and physician, I find myself more comfortable using generic drugs in life-or-death situations and more comfortable expressing my preferences for brand names in more trivial forms of treatment.

Generic drugs may seem humdrum, banal objects. After all, who is going to win a Nobel Prize for creating a generic drug? Yet within each of these plainly wrapped commodities lies an ideological debate that cuts to the core of modern medical practice and consumer culture. For more than 50 years, research-based pharmaceutical manufacturers have tried to convince physicians and patients that generic copies are not as good as the original brand-name drugs. On one hand, the task of differentiating one brand of products from otherwise similar competitors has been the central task of marketing for more than a century. Consider how much effort the Coca-Cola Company continues to expend on differentiating its flagship product from Pepsi (and vice versa), let alone the variety of generic colas available at local supermarkets. But even conceding that the Pepsi Challenge might count as a form of experimental evidence, neither Coke nor Pepsi ever had to fill out an application to the FDA to approve their product or submit a sequence of randomized controlled trials proving their efficacy at quenching thirst. Manufacturers of generic cola do not need to prove in advance that their cola is cola in order to market it as cola. But in order to market a new drug, a manufacturer needs to provide thousands of pages of clinical-trial data proving it to be safe and effective at doing what it claims to do. And in order to market a generic version, a pharmaceutical manufacturer needs to prove that its product is the same as the original version in terms of all important physical, chemical, and biological characteristics, including identity, purity, quality, dosage, and absorption into the bloodstream.

With these scientific proofs of similarity in hand, activists and policymakers began to argue in the 1960s—as the "miracle drugs" of the postwar years began to go off patent—that high price differences between brand-name and generic drugs were increasingly unconscionable. If generic drugs were the same thing but cheaper, they argued, all efforts by large pharmaceutical firms to claim that brand-name drugs were superior to their generic counterparts were merely attempts to extend their expiring patent monopolies into new trademark monopolies. But pharmaceutical firms were not the only entities with economic interests in the similarity and dissimilarity of generic drugs. As many physicians' organizations began to argue, policymakers and insurance companies who supported generic substitution could also be accused of having an equal and opposite economic interest: the incentive to spend less money whether the quality of care was the same or not. These two mutually suspicious positions, pro-generic and anti-generic, hardened into fairly stable ideologies by the close of the 20th century.

Viewed from a single moment in time, this debate can appear intractable, whether it concerns the pros and cons of generic steroids in 1961 or generic epilepsy medications in 2014. Viewed over time, however, conflicts over generic drugs form a shifting historical dialectic of similarity and difference. Consider the case of Parke-Davis' blockbuster drug Chloromycetin, which in 1966 was one of the first broad-spectrum antibiotics to go off patent and face generic competition. To a host of consumer advocates and policymakers in the federal government, the chemically equivalent generic versions offered a remarkable opportunity to rein in the increasing amount of taxpayer dollars that, since the passage of Medicare and Medicaid two years earlier, were now being spent on brand-name drugs. To executives at Parke-Davis, generic competition meant the potentially disastrous loss of market share for their flagship product.

When generic Chloromycetin capsules emerged on the market, however, one of these newer and cheaper products did not dissolve in water. Further testing in human subjects (euphemistically labeled volunteers) at a series of military bases and prisons showed that some of these capsules passed through the human digestive tract completely unabsorbed. Even though these products had proven to be the same according to a series of stringent tests of chemical equivalence, they were not the same in their effects on the human body. In response, the FDA pulled the generic versions from the market and instituted a new proof of biological equivalence, requiring any generic version of this drug to demonstrate that it would be absorbed into the bloodstream of patients. A year later, a newer, bioequivalent generic version of Chloromycetin was approved by the FDA, and bioequivalence has since worked its way into the matrix of proofs required to sell all generic drugs in the United States.

Generic drugs are not marketed as identical to the brand but as the same in all the ways that matter. They are allowed to be different from the brand name versions in some respects—in their price, color, size, shape, place of manufacture, the specific dyes used to create them, the filling agents that they contain, the chemical binders that hold their active components together, or the lacquered coatings that they employ—but key to their approval and marketing is the claim that the differences are trivial and the similarities are substantial. As the case of Chloromycetin reminds us, however, our understanding of what is trivial and what is significant in medical sciences is a moving target, a contested form of knowledge that emerges at the interface of interested claims to similarity and difference.

To speak of the chemistry or the biology of equivalence is to name only two of the many possible metrics of similarity and difference that emerge in contests over generic drugs. New sciences of similarity and difference continue to proliferate, and have only become more urgent as generic drugs have grown from roughly 10 percent of all drugs prescribed in 1960 to more than 80 percent of all drugs prescribed in 2010. The FDA has recently expanded funding for new regulatory sciences of generic similarity, with the understanding that new forms of potential difference continue to emerge, requiring new proofs of similarity.

Should a different standard of proof be used to prove the similarity of high-stakes drugs (such as immunosuppressants and anti-seizure medications) for populations (such as transplant recipients and persons living with epilepsy) for whom a single botched dosage could entail loss of livelihood or life? What new proofs can provide confidence that copies of large and complex biotech drugs are the same as the original versions when the precise molecular structure of the original drugs is not fully knowable?

In these contests of similarity and difference, almost anything can matter, even things that are not technically active ingredients. When we swallow a tablet of ibuprofen we tend to think of it as simply the molecule ibuprofen in swallowable form. But a tablet contains more than ibuprofen: it is also ionized to a salt; suspended in a milieu of fixatives, binders, and fillers; and covered in a proprietary lacquer. All of these inactive ingredients represent trade secrets and several of the material aspects—such as pill size, shape, and color—are protected by trademark law. And yet clinical research going back to the 1950s has demonstrated that the vehicle of medication (especially for dermatological preparations) can be just as important to its efficacy as the content. Whether understood in terms of the placebo effect or the complex series of variables that influence whether people successfully adhere to the onerous requirements of chronic pharmaceuticals, an increasing body of evidence has begun to suggest that the changing appearance of generic drugs is associated with failure to adhere to medical regimens, even among patients who have just suffered a heart attack.

Perhaps, at some point in time, enough evidence will build to support a measure ensuring that all generic versions of a medication copy the size, shape, and color of the original brand. The current interpretation of FDA approval pathways and U.S. trademark law, however, still considers things like the lentil shape and candy coating of my Advils to be unimportant to the overall efficacy of ibuprofen and, therefore, these attributes remain proprietary features that continue to distinguish the brand from its generic competitors in ways that many consumers (myself included) can still find compelling. Taste and appearance is probably a trivial thing when it comes to whether my patients will swallow their levofloxacin in the face of a potentially life-threatening case of pneumonia. It matters a bit more to whether my 5-year old son will swallow his strawberry-flavored amoxicillin for his strep throat. And for reasons I still cannot claim to understand, it matters to me when I have a migraine.

Each generic drug can be considered a case study in understanding what is at stake when we take two things to be the same. As students of classification—from Claude Levi-Strauss to Jorge Luis Borges—have noted, the way we organize things rarely carves nature at the joint: we create our classification systems based on what matters to us. Which forms of difference are truly significant? The answer to this question does not reside in the natural world; it is a product of social and technological moments. Two cartons of eggs that would have been marketed as equivalent in the 1980s are now marketed differently if one is derived from cage-free birds and the other comes from caged hens. Raspberries are newly differentiated between organic and not, coffee and chocolate is newly separated into fair trade and non-fair trade, tomatoes are branded GMO or non-GMO (at least in Europe). The distinctions of similarity and difference that we impose on the world of goods are fickle and highly mobile. So too with generic drugs. Is the generic drug the same or not the same? It is both, all at once.

Citation:

Greene, Jeremy. “Generic Drugs: The Same, but Not.” The Atlantic, 30 March 2015, https://www.theatlantic.com/health/archive/2015/03/generic-drugs-the-same-but- not/388592/.