The Role of Topical Generic Drugs: Clinical Considerations

Experts weigh in on the state of the generic drugs in the specialty and their broader influence over the practice of medicine.

By Ted Pigeon, Senior Associate Editor

With prominence in all medical practices and specialties, generic drugs have become a staple of the American healthcare system. Containing the same active ingredients as the corresponding innovator formulations preceding them, generic drugs are known for providing cost-efficient alternatives for patients and their prescription plans. Many insurance plans are designed to allow greater access to generic drugs, while pharmacies are also incentivized with drug formularies favoring generics. In addition, most states allow pharmacists to substitute prescriptions written for brand-name drugs with generic versions.

While media representations often frame generic drugs in a positive manner and questions loom about the implications of their extensive use across all medical specialties. In dermatology, the issue of bioequivalence has become a significant area of controversy, particularly with topical formulations. In addition to concerns over bioequivalence and bioavailability, the topic of generic drugs also prompts questions about socioeconomic aspects of medicine. Clinicians and patients must ascertain a proper role for generics in medical care.

Determining a Standard of Bioequivalence

Although generic drugs have been part of medicine since the early 20th century, they were not subject to strict regulation until 1962, when the FDA dramatically altered its regulation and oversight of drug approvals to ensure safety and efficacy. Generic drugs were then subject to the same trials as innovator drugs, thus dwindling their influence. But in 1984, legislation was passed that has since become the standard for generic drug approval. It stated that generic drug companies merely had to prove that their formulations contained the same

Take-Home Tips. As the issue of generics becomes increasingly complex, clinicians should be prepared to discuss therapeutic options with patients. Strategies to help patients understand which therapy is best for them—and ensure they receive the prescription you wrote—include understanding the patient’s perception of generic costs; taking time to educate patients about available formulations; putting the decision in context, so patients understand the overall goals of therapy; addressing long-term costs, including office co-pays; and offering samples so patients will recognize the formulation.
active ingredient as the innovator formulation and show that it performs in the body the same way. Since then, the FDA has maintained consistent bioequivalence standards requiring all generic drugs to be between 80 percent and 125 percent of that of the innovator drugs.

The extent to which generic drugs mimic their brand-name counterparts may vary, however, based on the mode of delivery. While the ingredients of a drug may be largely the same, how those ingredients are formulated and delivered may affect clinical outcomes. In dermatology, topical formulations for application to the skin are perhaps the most common delivery system. However, some controversy exists regarding bioequivalence and vehicle.

“Bioequivalence is measured by the stability of the active ingredient rather than how well the vehicle is tolerated,” says Neal Bhatia, MD, Associate Clinical Professor at the University of Wisconsin Medical School. He further notes that a generic formulation meeting the FDA standard of bioequivalence may be poorly tolerated by the skin, resulting in a greater likelihood of adverse events and compromised efficacy. Given the importance of the vehicle to both the safety and efficacy of a drug, the specialty of dermatology appears to be at a disadvantage when it comes to generic formulations due to the high proportion of topical treatments in its drug repertoire.

According to Dennis P. West, PhD, Vincent F. Foglia Family Research Professor of Dermatology at Northwestern University, the FDA does not have a concrete set of bioequivalence standards for drugs delivered to the skin. “The current 80 to 125 percent bioequivalence standard for other dosage forms generally does not apply to tissue interaction with topical medications applied to the skin, and thus many generic topical formulations may not have pharmacokinetic properties or bioavailability equivalent to the innovator drug,” observes Dr. West. Importantly, uniform release of the agent from the vehicle is perhaps one of the most essential aspects of topical drug delivery, according to Dr. West. “The stability monitoring profile, temperature conditions, and variability in the human skin barrier all contribute to drug diffusion characteristics,” he notes. And since the current FDA standards do not directly address human skin diffusion (i.e. rate and extent of absorption through the skin), according to Dr. West, they do not translate well to drug behavior in the tissue. “Typically, generic drug companies will perform smaller studies with volunteer panels to ensure that a given generic formulation performs similarly to its innovator counterpart in regards to irritation and allergy, but the FDA does not require a company to provide bioavailability data specific to a given product, nor does it examine whether a given formulation performs adequately on human skin or whether it is cosmetically acceptable,” says Dr. West. “The FDA does require companies to meet a ‘batch-to-batch’ diffusion uniformity standard utilizing synthetic markers most often.” However, he notes that the presence of the active ingredient in the formulation does not guarantee that it’s being delivered adequately to the target tissue.

Given these conditions, the variability in safety and efficacy in generic formulations can be much greater and the results more unpredictable. For example, according to Dr. Bhatia, a generic version of imiquimod has in his experience been associated with patients experiencing greater discomfort and burning of the skin due to changes in the vehicle from the brand. Other drugs, primarily inherently irritating agents, such as tretinoin, can also have a variable incidence of adverse events. “Topical generic formulations can therefore have a significant impact on compliance, because patients are much less likely to adhere to therapy if it is unpredictably painful or uncomfortable,” notes Dr. Bhatia. Thus, a poorly engineered and perhaps unstable vehicle can trigger a chain of events that leads to diminished compliance and reduced efficacy on a broader scale.

Some dermatologists prescribe brand name agents whenever possible to ensure that patients receive a drug that has been formulated carefully and has been adequately tested. According to Joseph B. Bikowski, MD, Clinical Assistant Director of the Hyperpigmentation Unit at Skokie, Ill., some pre-existing skin conditions may be a deciding factor when choosing whether to use a generic or brand name version of a medication. “Each patient is different,” he says. “Some are more concerned about the cost of the medication, while others prioritize the absence of side effects. Ultimately, it is up to the doctor and patient to determine the best course of action.”
Professor of Dermatology at Ohio State University, a physician’s decision on what to prescribe should be purely clinical. “Physicians should always prescribe the medication that has the best chance to help the patient’s condition, with the smallest likelihood of causing unwanted side effects,” notes Dr. Bikowski. Given the unpredictable nature of the vehicle in many generic topical formulations, Dr. Bikowski endorses prescribing brand-name medications whenever possible for the purposes of reliability. “Regarding topical medications, the vehicle is as important as the active ingredient in achieving successful outcomes, therefore it is not a reasonable risk to take if we cannot be certain that the vehicle has been formulated for maximum safety and efficacy for delivery into the skin,” he observes. “Our job as clinicians is to steer the patient in the best direction with our clinical evaluations and judgments,” he explains.

The Decision-Making Process
Although the issue of cost should not weigh on the individual’s decision on which medication to prescribe, it is an inevitable area of conflict.

Understand the patient’s perception. For patients, the least costly option is often perceived as the best one. Dr. Bhatia illustrates this with what he calls the “supermarket” analogy. “When individuals go to the supermarket, the generic products are often right next to the brand name products, and they can see exactly how much they would save if they opted to buy the generic product,” says Dr. Bhatia. “However, most individuals would likely select the brand name product because the perception of the generic product is that it is not equivalent. In other words, to employ the cliché, ‘you get what you pay for’, Dr. Bhatia explains. However, with drugs, patients may not have those same perceptions. “Patients often think that generic drugs are cheaper versions of the same drug,” he says. One of the reasons for this might be due to the fact that most patients see drugs as already being expensive, so they might be willing to compromise more easily given the high costs of medical expenses.

Take time to educate. Since patients may be attracted to generic drugs for economic reasons, Dr. Bikowski suggests making time during a patient’s visit to discuss the risk/benefit profile of a given drug and, in cases in which you believe a brand-name topical agent is more reliable, explain why it will likely result in greater efficacy and fewer adverse events compared to alternatives. “Informing patients about your concerns related to the efficacy of a topical generic agent may help them understand that brand name topical agents may be more cost-efficient in the long-term,” Dr. Bikowski notes. But, in the end, Dr. Bikowski observes that patients should be responsible for decisions regarding cost.

Put it in context. Placing a disease in context can be another helpful strategy, according to Dr. Bhatia. “Asking how their disease state affects them allows patients to understand the importance of effective treatment,” Dr. Bhatia says. “You could prescribe generic betamethasone ointment for a patient with hand eczema, but this will likely start a cycle that never sees the condition as best addressed as it should be,” says Dr. Bhatia. “In a case like that, explain the importance of barrier protection and a quality formulation so that they learn about the importance of skin care in addition to being treated with the best available product,” he continues.

Address long-term costs. While patients appear to focus most on upfront costs, Dr. Bhatia recommends discussing the long-term angle. “If a medication is working, that means fewer visits to the dermatologist and fewer co-pays,” he notes. “For example, one of my patients with chronic inflammation and dermatitis was being treated with fluocinonide cream and had to come in to the office three or four times a year. I switched him to a branded steroid (Vanos Cream) and explained the importance of routine moisturization and now I only see him once a year,” Dr. Bhatia explains. In addition, patients should also consider the costs incurred for negative outcomes of therapy. If they experience flaring or irritation, they will have to visit the office and be prescribed another medica-
tion to deal with the side effects, in addition to the primary condition itself, observes Dr. Bhatia.

**Offer samples.** Unfortunately, however, the decision for a patient to receive a brand-name or generic medication may not be the patient’s or the physician’s to make. “Many pharmacists are incentivized to provide generic formulations over brand-name drugs often because the profit margins are greater,” says Dr. Bhatia. It can be especially frustrating for dermatologists when substitutions are made for topical formulations when pharmacists and patients are not usually adequately informed as to the importance of a particular vehicle. That’s why Dr. Bhatia urges use of samples. “Samples allow patients to know exactly what it is they should be receiving because they can take a sample to the pharmacy and re-iterate to the pharmacist that this particular drug was prescribed to ensure that it is not substituted,” Dr. Bhatia observes.

Dr. West reiterates this by describing how pharmacists are often powerless over generic substitutions. “Most often, prescribers, patients, and pharmacists have little choice in determining a generic versus brand name medication,” he explains. “Insurance plans essentially dictate with multiple tier systems what patients receive, and the choice will usually be the product that is most cost-effective for the insurance plan,” notes Dr. West. Most insurance plans are designed not to easily allow physicians, patients, or pharmacists to truly make a choice, according to Dr. West. “It can be a great burden for physicians to convince pharmacies and insurance companies to allow a patient to receive the brand-name medication, because they often need to show that a patient doesn’t tolerate the generic formulation or a particular ingredient in the generic formulation,” Dr. West observes. As a result, some physicians may commonly write a generic prescription as the path of least resistance. “Physicians may follow-up with pharmacies and insurance companies and insist that the patient receive the specific product prescribed, but this often takes a great deal of their time and staff time,” Dr. West explains.

### A Broader Perspective

The controversy regarding non-bio-equivalent topical dermatological formulations underlines a broader struggle in contemporary medicine with social and financial implications. With continued prominence of formulations with ill-defined bioequivalence, dermatologists express concern about the future of the specialty and the development of new agents. “We currently have fewer new drugs on the market and fewer in the pipeline, which, at least in part, is related to limited funds for research,” says Dr. Bikowski. Moreover, according to Dr. Bhatia, pharmaceutical companies have less incentive to fund research and investigate new agents because the return on investment is typically somewhat lower with generic drugs. Nevertheless, insurance companies, Federal and state governments, and even patients largely advocate generic drugs, signaling that generic drugs will continually play a significant role in healthcare.

One course of action that pharmaceutical companies have taken, according to Dr. West, is to create generic versions of their own innovator drugs and to market their generic version as a “branded” generic product. This approach brings some degree of bioequivalence to the generic marketplace that did not exist before.

Given the difficulties that face physicians, pharmacists, and patients regarding control over the decision to prescribe/dispense/receive generic or brand-name medications, Dr. West stresses the importance of recognizing these conflicts and taking action to ensure bioequivalence standards for all drugs. “Certainly dermatologists understand this from their specialized training, but physicians in general may be up against a brick wall, with therapeutic substitution by insurance plans, but they should always keep in mind that vehicles do matter for topical dermatological formulations,” notes Dr. West.

For more information on the science and practical implications of topical drug formulations, read *Vehicles Matter, Parts I and II* available online at www.vehiclesmatter.com.