

Cyberspace Chat

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An Examination of Brand-Name vs Generic Finasteride: A look at Active Pharmaceutical Ingredient (API), Excipients, Bioequivalence, and Other Factors Affecting Efficacy

Below are posts culled from various internet discussion forums concerning brand-name and generic finasteride:

"I'm not surprised, they might share the main ingredients, but two pills that behave very differently and affect hair on people differently as well. Ask any chemist and they will explain why certain generics aren't as affective as the original drug."

"I can safely say I'm suffering from extremely minimal side effects from 1.25mg of generic finasteride, though when I first took .50 mg as a tester I had sides [side effects] and immediately quit for a few weeks. After a few weeks went by, I took the 1.25mg dose every day since September 1st. I'm starting to get a little bit of results on the vertex and crown, but not the hairline, and the sides aren't slowing my daily life down at all. I'd say go for the full 1.25mg again for a few weeks and try to stick out the sides."

"I had originally been on Propecia for 5 years until I switched to quartered Proscar (due to the cost) this time last year and I have to say my hairline has never looked worse. It's definitely shifted up another Norwood from a steady 2 to a full on 3... looks terrible and I'm pretty sure it wasn't as bad last summer. Dunno if it was the switch that caused this or if it would have looked exactly the same if I'd remained on Propecia; guess I'll never know."

"When I first started Propecia, for the first six months things were great, hair was thickening up nicely, then switched to Proscar, not generic, 1.25mg daily, things went downhill over the next few months. I then switched back and my hair thickened again. I have spoken to a number of people who have done the same, not all have gotten the same reaction but a good number have. My conclusion, Proscar may be so unevenly distributed that it can make a difference in certain individuals."

"If you have any knowledge of how drugs are manufactured, you would know that this is not possible. How could they be sure there was 5mg in each pill if it was unevenly distributed? Pills are manufactured in bulk by machines. If the drug isn't evenly distributed in the mixture it would be impossible to manufacture pills with exactly 5mg in each."

"I know theoretically there should be no difference between Propecia and generic finasteride 1mg but there are reports on some forums stating that people noticed a difference when switching to generic. Given the big price difference I'm keen to try the generic but not if it could be less effective. Are there any accurate/genuine reports or studies about the generic being less effective?"

"I have found that if I do not cut the pills and take them whole I get much less sides."

"Just read a thread basically saying people were saying generic finasteride wasn't working for them but when they switched to Proscar or the real deal Propecia they started to see positive results."

"So if generics work for you then you might as well keep using them. If you ever find they stop working then switch to Propecia or the cheaper alternative Proscar."

I think we are all trying to figure out what type (brand or generic) and dosage of finasteride to recommend to our patients. In this vein, much has been and written. In this column, the topic was examined in 2013 by Dr. Sharon Keene who authored, "When Finasteride Suddenly Stops Working—Is It Counterfeit?" (2013; 23(6):221-222), and in 2015 Dr. John Cole and I wrote, "The Treatment of Men with Finasteride: Scientific and Anecdotal Evidence" (2015; 25(2):61-63). In that same issue, Dr. Edwin Epstein penned the lead article, "Update on Efficacy of Generic Finasteride." These articles examine many of the controversies surrounding finasteride including efficacy, side effects, dosing (including reduced dosing), counterfeits, brand name vs. generics, spitting tablets, and bioequivalence. In spite of the investigations mentioned above, the question asked most often continues to be: **Are there basic differences between brand-name and generic finasteride that lead to decreased efficacy?** Many doctors continue to have patients who complain of decreased efficacy from finasteride, manifested by hair loss, when switched from brand name to generic.

I had an interesting conversation with an acquaintance who has, for years, been employed by the international pharmaceutical industry. He spent years auditing manufacturers and is familiar with the behavior of the global industry as well as FDA monitoring activities. He had some interesting insights into the differences between brand-name and generic drugs.

My acquaintance's opinion was that there are definitely differences between brand name and generics. The biggest reason he cites is that brand-name manufacturers simply generate more money than generic manufacturers. These funds are used by brand-name makers to essentially make a better product. The API (active pharmaceutical ingredient), the machines used to process the raw materials and make the final products, as well as the excipients (inactive ingredients) used to manufacture the brand name are all of a higher quality than generics according to my "source." We were discussing brand name vs. generic in general, but I immediately saw how the information could be applied to finasteride. Although I took him for his word, I thought it prudent to research the points he made during our conversation.

Profits

It does appear that more money is generated from the sale of brand-name medications. Branded drugs are priced higher than the generic drugs. Therefore, the sales commission is much higher for everyone in the supply chain. Since the generics are priced considerably lower, the revenue earned by everyone in the supply chain is lower. Cost differences can be substantial between brand-name medications and generic medications with the same active ingredients in identical amounts. Generic drugs see price reductions in three phases. When the first generic medication is introduced following the patent expiration of a brand-name medication, typically the cost is reduced only slightly due to its 6-month marketing exclusivity. The second reduction, after these 6 months, when production is limited to a few generic manufacturers, is approximately half the brand-name cost. The third phase is seen if a large number of generic manufacturers are attracted to market and introduce competing generic medications. The average cost may fall to 20% of the branded cost, and sometimes lower.¹

Of course, there are reasons for the initial high prices for brand-name medications. First, the estimated cost of taking a medication to market is \$1 billion. This figure is self-reported by the pharmaceutical industry and may be exaggerated. The approval process (the time from identification of a promising chemical to FDA approval) ranges from 8 to 12 years. This means that half of the 20-year patent period has passed by the time the medication reaches the market, and the time to recoup developmental costs and make a profit is short. Second, the pharmaceutical companies spend very large amounts on marketing their patent-protected medications. Advertising expenditures typically exceed those invested in research and development. Third, a main objective of any pharmaceutical company is to generate profit for its shareholders. Over the past decade, this industry has been among the most profitable of all industries. High medication costs are required to produce high profits and to keep stock prices from falling. Fourth, pharmaceutical manufacturers set a high price for their new drugs because they can; a patent protected, brand-name drug is a monopoly.¹

Medications, especially brand-name medications, are more expensive in the United States than in any other country in the world. There are many explanations for this. The United States is the only country that has so-called “open pricing,” which means pharmaceutical companies can set any price for their new drugs. Other countries establish a reimbursement price for every new medication, based on its health effects, the availability of treatment alternatives, and other factors. In the United States, companies can increase the price of their products at any time without any justification, which is why costs increase more on an annual basis than the inflation rate.¹ While it is difficult to discern the profits made by actual manufacturers of the various raw materials as well as the finished products, I would say that my “source” is correct in saying that brand-name manufacturers simply make more money.

Active Pharmaceutical Ingredient: API

The purpose of APIs according to the FDA is to cause “pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the human body.” Any drug or medication is composed of two components. The first is the API, which

is the central ingredient. The second is known as the excipient, which is the inactive substance that serves as the vehicle for the API itself. If the drug is in a syrup form, then the excipient is the liquid that has been used to make it as such.² APIs are commonly referred to as “bulk pharmaceuticals” and are in fact usually made in places at quite a distance to where tablets, suspensions, and liquids are manufactured. Today, the greatest concentrations of API manufacturers are located around Asia, specifically in India and China. This has led more and more companies to outsource API manufacturing to such places, which has the main benefit of eliminating the need to invest in highly expensive equipment and infrastructure—which on top of everything can also be complicated to install and maintain.² Brand-name manufacturers spend much more on equipment used to process drugs. For example, a U.S. company may spend \$800,000 on a German-made dryer or separator while a generic manufacturer in India or China may spend as little as \$80,000 on a machine used for the same purpose. This contributes to a lower-quality product. Brand makers have processing lines exclusively dedicated to one product for many years with resultant consistently high quality and low variance. Generic makers switch drugs on the same line according to my source. He noted contamination of one drug with an unrelated drug when both were run on the same line one after the other.

Major API manufacturers such as Merck, AstraZeneca, and GlaxoSmithKline are also moving away from multifunctional plants and instead opting for specific activities at specific sites. In this way, there are serious concerns as to how any centralized control could function, as after all, an API manufactured by one company, in one country, with the excipient manufactured in another by a different company, then packaged and distributed by another company altogether makes the route rather difficult to monitor or control.² My source was adamant in saying that even though the requisite bioequivalence studies show that the API is identical in brand and generics, there are certainly differences in the final product. The brand-name manufacturer gets the (more expensive) API as a white fluffy powder while the generic company may get the API in a solid brick that needs to be crushed. There are more impurities and contamination. In the end, the product just isn't as good even though it's the same chemical.

The current growth in new medical technologies is spurring the demand for APIs worldwide today, especially with the increased importation of raw pharmaceutical ingredients from emerging markets. According to Boehringer Ingelheim, countries such as India and China, which now supply over 40% of APIs used in the United States will double that figure to a whopping 80% in just the next 10 years.²

Food and Drug Administration (FDA)

Regardless of where the active pharmaceutical ingredient is made, companies must adhere to strict safety and quality standards set by the country where it will be used. So those APIs manufactured in China or India for use in the United States must still be inspected and licensed by the FDA. Similarly, if the API is intended for use in Europe, they would need to meet regulations set by the European Medicines Agency. Regular inspection outside the country of use however can prove difficult with counterfeiting and contamination being high on the list of various agencies' concerns.² The Food and Drug Administration is cracking down on drug makers selling products in the United

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States (mostly generic drugs) that were made at certain plants in India.³ The agency also says that import bans affect only a fraction of the drugs made in India for the U.S. market. The FDA banned U.S. imports of some generic drugs whose companies have a manufacturing presence in India presumably to keep costs low. These sanctions raise concerns about the quality of the drugs the U.S. imports from India and from other parts of the world. Inspectors from the United States and India have increased their efforts to make sure facilities in India that export drugs to the U.S. adhere to strict manufacturing standards and regulations required by the FDA. The FDA, with the approval of the Indian government, has increased the number of inspectors working in India. In the past too few inspectors were spread too thin. Congress requires the FDA to inspect foreign facilities that make drugs sold in the U.S. as often as domestic facilities.³

The problems encountered by FDA investigators are not limited to India. The FDA has also sent warning letters about manufacturing or packaging violations to companies operating plants in Australia, Austria, Canada, China, Germany, Japan, Ireland, and Spain. Common issues include inadequate testing and quality checks, inconsistencies in data collection, and contaminated products.³ Drug imports from China increased fivefold from 2007 to 2013 making it difficult for the FDA to keep up. The FDA has sanctioned China about as much as India in the last five years and plans on increasing the number of inspectors in China.³

My source did note that with the increase in drugs being produced outside the United States in recent years, the FDA is hiring more inspectors and inspecting foreign facilities more often. His opinion is that generic drugs are becoming safer. However, he mentioned there are significant problems with language barriers encountered by American inspectors working in foreign countries, especially in India and China. In addition, inspectors can get distracted when traveling to exotic locations.

Widespread manufacturing irregularities at generic drug factories around the world are endangering America's health and costing consumers a bundle, according to Dr. Chauncey Crandall, chief of the cardiac transplant program at Palm Beach Cardiovascular Clinic in Palm Beach Gardens, Florida.⁴ In October 2015, an Indian company recalled more than 216,000 bottles of drugs after trace elements of the chemical benzophenone were found in the medications. That recall included 187,106 bottles of felodipine (Plendil), a blood pressure medication, and 29,660 bottles of the antidepressant imipramine (Tofranil). Dr. Crandall contends that generic drug companies are taking advantage of the global economy and that in countries like India, Taiwan, and China, large companies farm out their contracts to "mom and pop" operations that may be making drugs over coal-fired stoves in unsanitary conditions. "This is leading to a tremendous problem. No one knows what kind of impurities are getting into these drugs, no one knows what kinds of fillers are being used," states Dr. Crandall.⁴

Bioequivalence

When a generic drug is used to substitute for a brand-name drug, studies are required to determine bioequivalence. The two drugs must have very similar blood concentrations. Bioequivalence is a mathematical calculation based on a graph of blood

concentration versus time, and it correlates well with total drug exposure. The mathematics are complicated but essentially it is a logarithmic calculation. A 90% confidence interval equates to 80-125% range. There is a common misperception that generic drug concentrations can be 80% to 125% of the brand-name formulation; in other words, that the variance may be up to 45%. This is not true. When there is a 90% confidence interval, in an 85-125% range, the variance is only 5%, which is internationally accepted as bioequivalence for all medications including anti-coagulants, anticonvulsants, and anti-arrhythmic medications. Even though bioequivalence has been established for generic substitutes, there still remains marked differences for the reasons described above and below. When the original application for a generic is filed, bioequivalence must be established for all ingredients. But subsequently, not every batch or every tablet is similarly analyzed.

Another tool to determine bioequivalence and ensure interchangeability is *in vitro* dissolution behavior. The pharmacological activity of a drug can be evaluated by assessing its dissolution behavior. Dissolution is the amount of substance that goes into solution per unit time under standardized conditions of liquid/solid interface, solvent composition, and temperature.⁶ In a study performed to compare the differences in dissolution behavior of solid forms between brand names and their generic counterparts, many generic medicines showed significant differences from their branded counterparts during the dissolution tests. Some generics showed incomplete dissolution and others showed that they dissolve slower or faster than their branded counterparts. Significant differences in dissolution rate were also shown in batch-to-batch comparison.⁶ Factors that could explain the differences include manufacturer, surface area of the drug, storage, dosage form, and the amount and type of excipients. In the literature, it is reported that there are variable clinical responses to the same dosage form of a drug product supplied by different manufacturers. For example, a study compared 19 different generic formulations of simvastatin tablets and capsules obtained from international manufacturers to the U.S. brand-name product regarding pharmaceutical quality. It revealed that manufacturing standards for the international generics were not equivalent in quality aspects with the U.S. brand-name drug. Significant variability was also found among foreign-made tablets themselves.⁷ Therefore, the interchangeability of these drugs is questioned.

Excipients

Pharmaceutical excipients are substances that are included in a pharmaceutical dosage form not for their direct therapeutic action, but to aid the manufacturing process; to protect, support, or enhance stability; or for bioavailability or patient acceptability. They may also assist in product identification and enhance the overall safety or function of the product during storage or use. Excipients make up, on average, about 90% of each product. Thousands of different excipients are used in medicines.⁵ Practically all marketed drugs contain excipients. Pharmaceutical regulations and standards require that all ingredients in drugs, as well as their chemical decomposition products, be identified and shown to be safe.

Differences in dissolution rates between the branded and their generic counterpart drugs can also be related to the composition of excipients. This can mainly influence the side-effects profile of the generic drugs. Results in this study,⁷ like others in the litera-

ture, suggest that when performing generic substitution, switching among generics and/or switching from one form to another for the same medicine, patient monitoring should be essential, especially for the side effects. In many cases, the performance of a drug can greatly depend on the quality of excipients used in manufacturing and on the quality of the process.

In addition to the deficiencies found in generic formulations described above, lower quality basic materials, cheaper machines, and lack of foreign inspectors can lead to decreased absorption and contamination, bacterial (increased bacterial load) and non-bacterial.

Splitting

If one was to accept the argument that generics can have less active ingredient, one would have to believe that a higher dose would be more effective. If a 1mg generic tablet of finasteride had 80% of the active ingredient (0.8mg), the patient may experience shedding. If a generic 5mg tablet was similarly 80% effective, ¼ of a tablet (1.25mg) would contain 1mg of finasteride. My source did make the point that the lower the mg amount in a dose, the more magnified the problem of decreased efficacy. Of course, we don't know which prescription we write may have fewer mg and be less effective. I think there is a general consensus that patients who switch to 1mg generic finasteride have the greatest chance of shedding. Prescribing 1.25mg per day (split 5mg) puts the patient at risk for side effects if each tablet does contain 5mg. I know of a physician who is facing legal action for that reason, prescribing 1.25mg/day to a patient who claims he has persistent finasteride side effects. As always, with each patient informed consent should be given and clinical correlation considered.

Conclusion

We are in a position to visually observe the variance of effects of a medication given to our patients, finasteride. The effect, increased volume of hair, and loss of effect, less hair volume, are noted by our patients and can be followed by photographs. With

most other medications, this is not the case. Medications that vary in efficacy, such as anti-hypertensives, cholesterol lowering, antibiotics, and many others, will have no observable change with a variance in efficacy. Many of our patients have reported and we have observed the loss of effect when changed from brand-name to generic finasteride. I have presented evidence that generic medications can be less effective than brand-name medications. Of course, one can always find written evidence to support his or her hypothesis. If we follow our patients closely, we should have some indication of which form and dose of finasteride is effective.

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