





BRAND-NAME vs. Generic Drugs

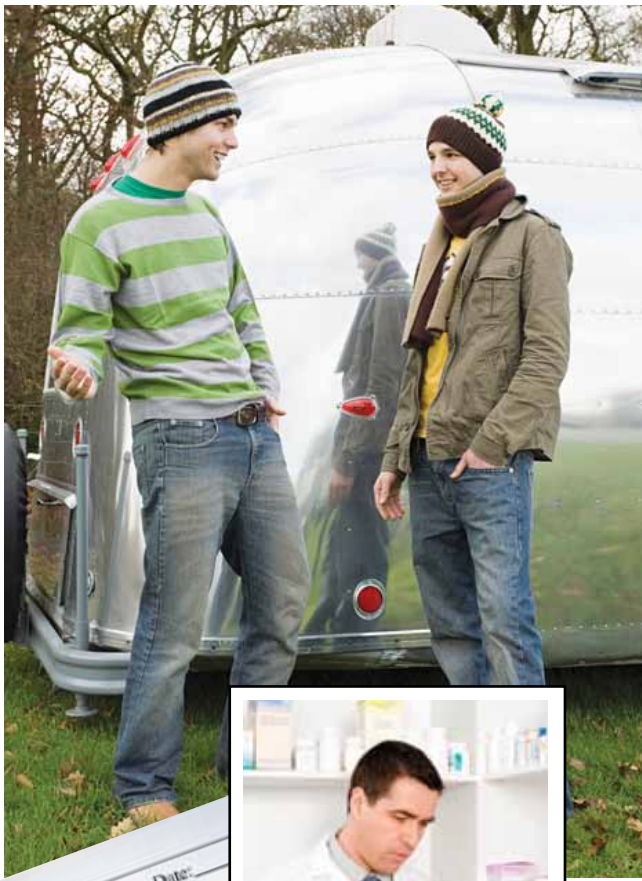
What's the Difference?

By Cynthia Washam

Jason and Derek are good friends. In March 2012, Derek was diagnosed with epilepsy, as was his friend Jason, who had been diagnosed with epilepsy five years earlier. They noticed that their doctors had prescribed the same drug, but, surprisingly, one week after Derek started taking his medication, he had a seizure.

Derek's parents called the family doctor, who explained that the antiseizure drug taken by Derek was a generic substitute for a brand-name drug. He suggested that Derek switch to the brand-name drug. He added that any generic drug available on a drugstore shelf has the approval of the U.S. Food and Drug Administration (FDA) but that sometimes patients react better to either the generic or the brand-name drug. Sure enough, Derek has not had any seizures since he switched to the brand-name medication.

But why do patients react so differently to either type of medication? The FDA requires that generic drugs have the same active ingredients as the brand-name drug, but are they really the same?



Active versus inactive ingredients

By law, brand-name and generic drugs must have the same active ingredients. These are the ingredients that cause the drug's effect, such as pain relief or antinausea. But the generic manufacturer does not have the brand company's list of ingredients. For that reason, inactive ingredients, such as pigments, flavoring, and binders holding the tablet together, often differ.



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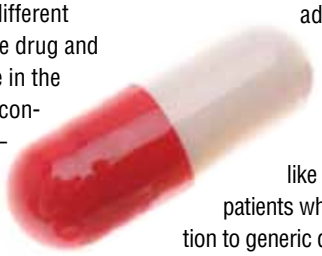




These inactive ingredients can affect the way a drug dissolves in the stomach and small intestine. In the stomach, molecules binding to the drug break apart in the acidic environment of the stomach, allowing the drug to pass through the stomach wall into the bloodstream. Other drugs do not dissolve easily in the stomach and instead are carried into the small intestine, where they dissolve in its alkaline environment before being carried into the bloodstream.

Temperature also affects solubility. Pharmaceutical companies design their drugs to dissolve at body temperature. The effect of temperature on solubility is easy to demonstrate by stirring a teaspoon of sugar into a cup of boiling water, then trying it with a glass of cold water. Hot solvents dissolve solids faster because their molecules move faster than cold ones. Increased molecular motion competes with the attraction between the molecules in the solute and tends to make them come apart more easily. Increased molecular motion also causes more solvent molecules to interact with solute molecules and pull on them with more force, which makes them dissolve more.

The FDA requires manufacturers of generic drugs to demonstrate that their products not only have the same active ingredients as the brand-name drug but also act essentially the same way in the body as the brand-name drug. But because it can take a different amount of time for a brand-name drug and its generic equivalent to dissolve in the body—even though both drugs contain the same active ingredient—it may take longer for one of the drugs to take effect.



The FDA allows limited leeway in absorption rates. The time it takes either a generic drug to reach its highest concentration in the bloodstream can vary by up to 20% from the brand-name drug. This can be represented by a curve showing the rise and fall of a drug's blood levels over a period of 24 hours.

This curve, called the concentration-time graph, results from measuring the concentration of a drug in the bloodstream at various times (Fig. 1). These measurements are made at regular time intervals—say, every 30 minutes—and the point measurements are connected, resulting in a smooth curve. At first, the drug is absorbed quickly, so its concentration increases, and then the drug starts to be eliminated from the blood—by the liver and the kidneys—which explains its steady decrease.

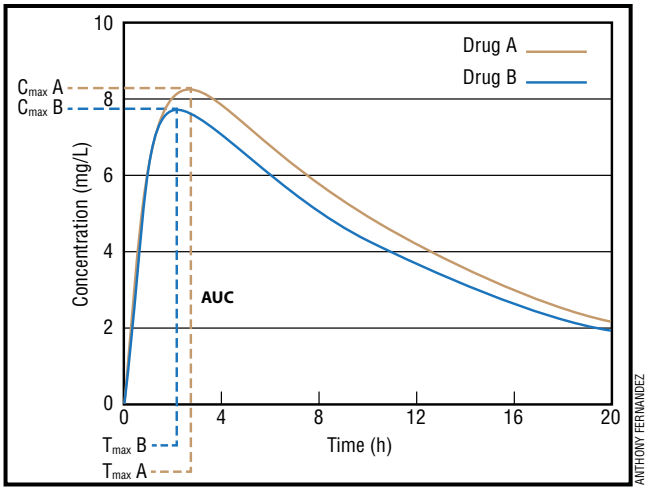


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For a few drugs, even a 20% variation in concentration between generic and brand-name drugs can have a big effect. Antiepileptic drugs, also called anticonvulsants, are among them.

Gregory Krauss, a professor of neurology at the Johns Hopkins Hospital, Baltimore, Md., estimates 5% to 10% of epilepsy patients do not react well to medication changes, although he and others admit that it is difficult to establish whether a medication is responsible for causing a seizure.

In the case of Derek, it seems like he is one of the 5% to 10% of patients who experience an adverse reaction to generic drugs.



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Figure 1. Concentration-time graph for two drug products

Switching between two generics

In September 2012, Jason noticed that the refill pills had a different color. His mother checked with the pharmacist, who said the pharmacy had replaced the generic brand Jason had been taking with another one. "The drug and dose are the same, so there should be no problem," the pharmacist said.





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But as it turned out, this was not the case. Shortly after taking the new generic, Jason had a seizure. "Switching from one generic to another can actually be riskier than switching from a brand-name to a generic drug," said Brien Smith, an epilepsy specialist in Michigan and chairman of the national Epilepsy Foundation, a non-profit U.S. foundation dedicated to the well-being of people with epilepsy and seizure disorders.

Here is why. The 20% acceptable variation between blood-concentration levels of brand-name drugs and their generic equivalents may be at the high or low end. So when a patient switches from a generic drug that is near the low end of the limit to one that is near the high end, the difference between the two generic drugs can be as much as 40%.

"The question is: Should the 20% range be tightened?" Smith said.

Several years ago, the FDA reduced the allowable blood-concentration range for the syn-

thetic hormone levothyroxine sodium when it became clear that patients were highly sensitive to variations. The blood-concentration curves of the generic and brand-name versions of the drug, which is used to treat hypothyroidism, now must be within 5% of each other. Hypothyroidism is a condition in which the thyroid gland does not make enough thyroid hormone, which regulates metabolism.

The FDA may consider narrowing the range for anticonvulsants, too, depending on the results of a pair of studies. The agency recently funded the studies in response to reports of complications from generic antiseizure drugs. If the studies show that patients are sensitive to variations in different versions of the drug, the FDA will consider narrowing the acceptable variation between blood-concentration levels of brand-name drugs and their generic equivalents.

Blood thinners and antidepressants also have drawn concerns. Those concerns led to the FDA's action against a generic substitute for the antidepressant Wellbutrin. On October 3, 2012, the agency withdrew its approval of the generic version when studies showed it released the antidepressant at a different rate and level from the brand-name equivalent.

But overall, troublesome generics are rare. Millions of Americans take generics every day with no unusual side effects. Sidney Wolfe, director of the influential Public Citizen's Health Research Group, contends that most drugs pulled off the market over safety concerns have been brand names. That typically happens during the drug's first years on the market, when it is still under patent. So, by the time the patent expires—usually after seven years—and generics become available, the drug has been tried and proven to be safe.

Jason's and Derek's doctors could not say for sure that the generic drug caused their seizures. Attributing a seizure to medication in an individual patient would be unscientific. It's only through large population studies that researchers have proven some epilepsy patients are sensitive to subtle variations between different versions of the same drug.

The FDA expects to answer questions about the anticonvulsant lamotrigine with two major population studies, which are currently under way. If the studies show patients are sensitive to variations in different versions of the drug, the FDA may consider narrowing the acceptable range for blood concentration in the generic equivalents of antiseizure medications. If that happens, then maybe Derek will be able to use the cheaper, generic substitute for the brand-name drug he is currently using. *CM*

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Cynthia Washam is a science writer in Jensen Beach, Fla. Her latest *ChemMatters* article "Unwrapping the Mystery of Mummies," appeared in the February 2012 issue.

Activity: Dissolving rates of pain relievers

This activity is intended for high school students under the supervision of an adult. During the activity, students must wear latex gloves, safety goggles, and an apron.

By dissolving pain relievers in an acidic solution, you can simulate how quickly they dissolve in the stomach. Experimenting with several brands and types of pain relievers shows how quickly they work.

Materials

- 3 transparent glasses or plastic cups
- 2 Motrin tablets
- 2 Aleve tablets
- 2 Tylenol tablets
- 2 plain aspirin tablets
- 2 buffered aspirin tablets
- 2 enteric-coated aspirin tablets
- Stopwatch
- 6 cups of white vinegar
- 6 cups of water

What to do

- Pour 1/2 cup of water into each of the three cups. Label the cups "Motrin," "Aleve," and "Tylenol," and simultaneously drop a tablet of each type of pain reliever into the corresponding cup. Start the stopwatch. Check each tablet every 30 seconds and note changes. Continue until the changes stop. How quickly did the tablets dissolve? Was there a difference among "Motrin," "Aleve," and "Tylenol"?
- Empty and wash the cups. Refill each with 1/2 cup of white vinegar, which is close to the pH of stomach acid (between 1.5 and 3.5). Repeat the experiment with "Motrin," "Aleve," and "Tylenol." Does the dissolving time change? Note that most pain relievers are highly soluble, so they can act quickly. Water starts the dissolving, but acid speeds it up.
- Empty and wash the cups again. This time, fill each with 1/2 cup of water and repeat the experiment with the three types of aspirin. How do they compare to Motrin, Aleve, and Tylenol and to each other?
- Empty and wash, then fill each with 1/2 cup white vinegar again. Repeat the experiment with the three types of aspirin. How does acid affect their dissolving time? What variation do you see among the products? Note that buffered aspirin is aspirin mixed with a combination of chemicals that reduces acidity. Buffered aspirin is recommended for people who have an upset stomach when they take aspirin.
- People who need to take aspirin every day—for example, those who suffer from arthritis—usually take enteric-coated aspirin. This type of aspirin is coated with a substance that resists the acid juices of the stomach but dissolves quickly in the basic environment of the intestine (pH of about 8). These tablets eliminate stomach irritation but work only after moving from the stomach to the small intestine, which can take up to three hours.
- To simulate the basic environment of the intestine, repeat the experiment more by replacing the water or vinegar with a solution containing 1 ½ teaspoon of baking soda ($NaHCO_3$) and 1/2 cup of water. One of the tablets—now you know which one—will dissolve, but not the others.

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