First-Hand View of an Indian Generic Drug Company

While traveling in India, HepCBC board member and volunteer Cheryl Reitz, confronts her beliefs about generics, and shares her new-found knowledge

January 5, 2016 By Cheryl Reitz

Cheryl Reitz

Before my visit to Lupin Limited in Pune, India, on November 20, 2015:
OK, this is to prepare you for what I learned about generic drugs on November 20th. Close your eyes. What do you envision when I say: “Generic Drug Company in India”? If you’re like me, you probably have viewed these companies as inferior to companies which research and develop new drugs, rightfully hold the patents, and make the big bucks. After all, generic companies simply copy what someone else has spent years—in many cases, decades—working on, discovering the uses and analyzing the structure of unique new Active Pharmaceutical Ingredient (API) molecules. They perfect the dosage and discover side effects through clinical trials, while at the same time they’ve had to explore many research ‘dead ends’ which result in zero ‘payback’ before finally hitting on the ‘pay dirt’ of a commercially viable product.

As to the quality, while generic packaging always claims the contents to be equal to the patent version in efficacy and safety, I have commonly heard doubts about these claims, possibly because generics are often produced in countries such as India in which buyers fear quality standards may not be as strictly adhered to as in higher-income countries. Though the cheaper pricing is nice, it further adds to suspicions that generics may not be inspected as thoroughly by under-paid workers, that different standards might be applied, or that inferior APIs may have been used.

On the other hand, generic companies are often viewed more altruistically as suppliers of critical drugs to countries and peoples who simply cannot afford the patent versions. In some cases their products have resulted in saving thousands—possibly millions—of lives when the principle of “significant medical need” is deemed to overshadow the principle of “protecting intellectual property.”

Though North Americans such as myself may complain about our drug bills occasionally, we generally accept paying full price for the patented version of a prescription drug until the patent

expires. After that, doctors will still often prescribe the patent version, and patients still purchase patent versions of over-the-counter medications, even when a generic version has become available at a lower price. North Americans seldom challenge drug makers' claims that they must charge high prices during the period of the patent to recoup the significant research and development costs, assuming that once the patent expires, generic suppliers in countries with lower production costs will start selling for much less, driving down the price globally.

This system is currently being challenged by some vocal advocates in the hepatitis C world, who see the pricing of HCV drugs as one of the greatest barriers to treatment in middle and even higher income countries such as our own. So, when given the opportunity to do a little research into the generic drug industry in India in person, I jumped at it, vowing to maintain an objective stance and open mind.

The November 20th Visit and 11 Interviews

The preconceptions I've outlined above have been significantly challenged, and **I now see generic companies as important and complementary partners with patent companies, as part of the way towards the eventual eradication of this terrible virus, HCV, from the planet.** Here's what changed my mind...

While visiting my son who works in Pune, India, I was given a remarkable opportunity to meet over one full day with eleven senior members of Lupin Limited's management and research staff to interview them about the Indian generic industry. Lupin, founded in India in 1968, is now the tenth-largest generic pharmaceutical company in the world in terms of revenue, and the #6 supplier of generic drugs (in terms of prescriptions) in the USA. Lupin sells 19% of its market share to India and 45-50% to the USA. Lupin sells very little of its product line in Canada though the company recently opened an office here.

Two aspects of the company were somewhat surprising to me: First, Lupin holds numerous patents (both on drugs themselves, and on various processes they've developed to produce generic drugs). Consequently, they produce both generic and patent drugs. Second, its mission incorporates significant aspects of corporate social responsibility. Lupin was originally created to provide low cost treatment for tuberculosis in India, and continues to concentrate its new drug research and development on treatment of "unmet needs" such as rheumatoid arthritis pain management. And in 1988 the Lupin Human Welfare and Research Foundation(LHWRF) was founded; it works closely with the government to improve the lives of poor families in rural India.

While wages paid are significantly lower than in No. America, workers' living costs are proportionally lower as well. Their standard of living is comparable to ours.

I want to stress that everyone with whom I spoke at Lupin emphasized that the other large generic companies in India which sell to the No. American and European markets follow the same rules and adhere to the same high standards that Lupin does. While they provided examples from their own company, they assured me their answers were applicable to all mainstream generic drug companies in India, and, in many cases, to the industry worldwide.

Do you use the exact same formulation and standards for the same product being sold in China or Nigeria as you do for that sold in Canada?
No. We carefully customize product formulation and packaging according to the rules and standards of the country in which they will be sold. No batch will be sold to more than one country, except in the rare case they go by absolutely the same standards. While the international generic name must be included on all products, each country and company may have its own unique brand name for the same product. In some cases, a US and Canadian product may share the same generic brand name from the same company, but frequently they are different. In India, the pharma standards branch has been working closely with the USA's standards branch, the US Pharmacopeia (USP), with the goal of reaching equity, eventually. At present India has regional variations in standards. The Indian standard does not in any way affect the country-specific international standards used by India's generic companies.

How do you ensure that the active pharmaceutical ingredients (API) are as efficacious and of the same formulation as the original?
To quote Dr. Makarand K. Avachat, Senior Vice President of Lupin's Pharma Research and Development in Pune: "When doing generic product development, the sole aim is to make a product which is as pure and consistent as possible a copy of the original molecule, on a commercial scale." The generic company must submit to the government a very detailed plan of how they will ensure this; this plan, which must include the medical information insert and even the packaging materials, must be approved prior to starting commercial production.

Companies working under the auspices of the original manufacturer generally are able to make this plan quickly, getting the generic version to market much sooner as they are able to quickly access the original molecule(s') formulae, APIs and production processes for this. However, typically a company must independently develop its own version of the molecule and how to produce it. These must be evaluated through Bio-equivalency Studies (BES), which take 2-3 years or more of research. The BES may involve clinical trials; sometimes these are required by the Indian or other government regulatory agencies. The need for BES helps explain why Lupin, like many other generics, spends at least 9% of its revenue on research, which can frequently result in development of production processes which are patentable.

Lupin produces approximately 60% of its own APIs, and the rest come primarily from China or elsewhere in India. Lupin communicates its high standards to each supplier, visits the supplier in person, and measures the purity, both in visits and delivery spot checks. If the APIs submitted to Lupin fail to meet the standard, defective batches are destroyed and another supplier, found. The US Food and Drug Administration (FDA) has inspectors in India who inspect APIs and generic products going to the USA; the European Medicines Agency (EMA) similarly inspects APIs ending up in European medications.

How do you ensure safety by removing dangerous impurities?
This question was answered by Dr. Pritesh R. Upadhyay, Lupin's Senior Vice President of Analytical Research. The first question Lupin researchers ask about a new product is, "What is the 'total impurity' of this product?" If over 0.10%, the researchers must determine if any of those impurities

are genotoxic, carcinogenic, or mutagenic. Lupin uses an Indonesian software program called DEREK to look for and analyze these particular impurities; about 80% of impurities are found to be benign or safe. If dangerous impurities are found, Lupin researchers develop a test that will cross-check the confirmation predicted by DEREK. Then they inform the company that a particular impurity is toxic, and that it must improve the process to remove the toxic substance below a certain (safe) limit. Once production starts, the inspection process will include stringent monitoring for any toxic impurities."

How does India's generic drug industry respect international Intellectual Property laws?

Generic drugs are produced following the expiry of the patent, or in a cooperative sub-contract with the patent-owner, or in a patent-superseding agreement with an official body such as the government of India, Medicines Patent Pool, UNAIDS, or the World Health Organization. There is also a precedent for superseding patents in India through granting an Indian generic company a Voluntary License (VL). In these cases, the price of a vital drug in India is thought to be unaffordable to India's citizens, so the patent holder is first asked to lower its price, or to share its Intellectual Property license with the generic company and mutually negotiate royalties. At this point, if the patent holder agrees to the proposal, a VL is issued to the generic company. If the patent holder refuses, the generic company can then ask the government for a Compulsory License (CL). The likelihood of the CL being approved depends on the severity of the disease, the drug's benefit to the public health, and the price. In all cases, these VL and CL drugs cannot be exported to countries which have granted sole market to the patent holder; however, patients from any country may come to India and be treated by Indian doctors with the drug through recognized procedures developed by India's Dept. of Medical Tourism.

That's it! With the understanding gained through this experience, I have much more confidence in the quality of generic drugs, and tons more respect for this industry and the people who work in it. I hope you will join me in gratitude to these eleven researchers who so willingly shared their extensive knowledge and experience with this non-medical Canadian grandmother, and that you have enjoyed and learned something new during this armchair journey with me.

Cheryl Reitz taught English in Canada and Asia for many years. Diagnosed as HCV+ in 1992, she failed her first treatment in 2009. In 2011, Cheryl joined a 24-week trial with the new DAAs which worked very well and had no side-effects; she walked a half marathon in the middle of treatment. She is a grandmother of three, retired, and rapidly recovering from cirrhosis. Cheryl now volunteers for HepCBC and is a former vice-chair of Action Hepatitis Canada.

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