Safe at Any Cost? – Thailand's generic AIDS drug

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Thailand's generic AIDS drugs don't meet international standards and so questions about their efficacy linger.

On its face, the issue seems black and white: In issuing a compulsory license to import or produce the generic second-line HIV/AIDS drug efavirenz on November 29—two days before World AIDS Day—Thailand's military government valiantly signaled its intentions to fend off pressure from Big Pharma and supply sick patients with affordable antiretrovirals.

Who in good conscience can say that's a bad thing?

Look a bit deeper, however, and shades of gray start to emerge. In Thailand's case, these mostly surround the operations of the Government Pharmaceutical Organisation (GPO), the historically corrupt state enterprise under the Ministry of Public Health.

Under the compulsory license, the GPO has the right to import the drugs or produce them domestically until 2011. It will be able to supply no more than 200,000 Thai patients—officials say about 20,000 need the drug now—and must pay a 0.5% royalty on sales to patent holder Merck, according to a statement signed by Thawatch Soontarajarn, a Health Ministry official.

"The price of the patented efavirenz is twice of those generics produced by WHO [World Health Organization] certified GMP [Good Manufacturing Practices] factories in India," the statement says. "With this higher price, the budget allocated from the Thai Government can only cover some patients with Efavirenz, whereas the rest have to use other non-patented more toxic antiretrovirals."

The concerns expressed by Thawatch for quality drugs are certainly laudable. But the emphasis on quality disguises the fact that the GPO facilities used to manufacture first-line AIDS drugs are still not up to the WHO's standards after four years of production, even though the drugs are now also available from certified factories in India.

Moreover, it's still unclear if the GPO intends to start making efavirenz locally in the same Bangkok factory that doesn't meet WHO standards. GPO officials have already said they plan to start local production in June, at least two years before the government could complete construction on a long-discussed new production facility that meets international standards.

The question is whether the second-line drugs made in a factory that doesn't meet international standards will do more harm than good for the thousands of HIV/AIDS patients that desperately need medication. This is the ultimate gray area, since it's nearly impossible to quantify.

"Nobody would buy an airplane without wings," Dr Lembit Rago, WHO's Geneva-based coordinator for quality assurance and safety, said in a telephone interview. "Drugs should be treated the same way. But with drugs, it's difficult to understand what makes them up to a certain standard of quality

because there are so many elements involved. In certain cases, minor things are wrong, and in some, major things. Drugs that are not WHO pre-qualified may not directly kill people, but they could foster resistance to AIDS drugs."

Critics argue that is exactly what happened in Thailand with GPO-Vir, a generic triple combination of first-line ARVs Stavudine, Lamivudine, and Nevirapine. The drug was introduced with great fanfare in March 2002 as the cheapest anti-viral treatment in the world.

Resistance Developing

In 2002, the Global Fund to Fight Aids, TB and Malaria pledged $133 million to Thailand to further test and procure GPO-Vir. The fund stipulated, however, that Thailand must buy ARVs and other drugs from WHO-approved companies in three years time. That same year, the GPO resolved to make its facilities WHO-compliant in two years.

A year after that, the Thai cabinet passed a resolution approving a proposal to build a new world-class facility that met international standards. The GPO had considered upgrading its existing plant, but that would require it to close for six months.

In 2004, the International AIDS Conference rolled into Bangkok with a theme of "Access for All." Prime Minister Thaksin Shinawatra , who was deposed in a coup last September, pledged in a keynote address to supply drugs for free to HIV/AIDS patients in Thailand, Laos, Cambodia and Burma.
NGOs hailed Thaksin's commitment, and extolled GPO-Vir as a breakthrough in price and access. And indeed, it was much cheaper.

GPO-Vir, taken twice daily, costs 40 baht ($1.10) per day. Similar patented drugs cost about 252 baht ($6.90) per day. Over a year, that's a cost savings of about $2,120 per patient.

GPO-Vir certainly seemed like a godsend. After the AIDS conference, even the US said it wanted to buy the generic drug for its $15 billion program to provide relief to HIV patients in 14 African countries and Vietnam.
But though the commitments and pledges made for good headlines when the global AIDS spotlight shined brightly on Bangkok, GPO-Vir quickly lost some luster. The Global Fund quietly said it wouldn't support Thaksin's plans to distribute the drug to neighboring countries since it had not received WHO approval. And just last August, the fund withdrew support for GPO-Vir altogether because the GPO still had not brought its factory up to international standards. In addition, the US Food and Drug Administration still has not approved the drug for safety, making it ineligible for President George W Bush's $15 billion AIDS relief program.

The drug's efficacy started to be questioned in 2005, when a study by Mahidol University's faculty of medicine found that resistance to GPO-Vir had grown dramatically in the previous few years. In a survey of 300 patients using the drug, researchers found that 49 percent were resistant to Lamivudine, 39.6 percent to Stavudine and 58 percent to Nevirapine.
Increased rates of resistance meant that more people had to switch to more expensive, patented second-line treatments such as efavirenz. Merck says it supplies that drug for "no profit" at 1,400 baht for a month's supply. The GPO says it can cut that in half with generics, saving the government millions of baht.

Compulsory Licensing

To be clear, the quality of Thai-produced generic drugs should not be confused with the issue of drug access. The Thai government was well within its legal rights in issuing the compulsory license

for efavirenz without prior negotiations with Merck.

The World Trade Organization's agreement on Trade Related Aspects of Intellectual Property Rights, commonly known as TRIPS, gives countries the right to issue compulsory licenses for drugs essential to public health if they pay a royalty. And, in what AIDS activists see as the ultimate hypocrisy, the US has issued compulsory licenses routinely for other forms of intellectual property like satellite carriers, Internet access and file sharing.

Although Thailand has issued the compulsory license for efavirenz, it has yet to implement it. Indeed, the threat of a compulsory license may simply be a bargaining chip to prompt Merck to lower prices. Brazil has threatened compulsory licenses no less than three times on AIDS drugs, and each time reached a deal with Big Pharma.

To that end Merck said it would seek talks with health officials to propose discounts or a so-called "voluntary" license for the GPO to produce a generic version of efavirenz, which goes by the brand name Stocrin. These talks are apparently ongoing, as Thailand has yet to import generics from India two months after saying it would do so. NGOs are pushing for Thailand to implement the compulsory license to set a precedent for other governments.

The theoretical debate over intellectual property is hard to quantify because it contains many hypothetical questions. Certainly HIV patients in developing countries that need treatment now would see no harm in breaking patents to be able to afford the drugs that could extend and improve their lives. Major pharmaceutical companies retort that without guaranteed patent protection, they will have no incentive to research and develop new drugs—and, maybe one day, find a cure for AIDS. Whether that is an empty threat remains to be seen.

The debates over intellectual property typically play out at the WTO and on a bilateral level. In the stalled trade talks between Thailand and the US, for instance, access to the data used to make patented HIV/AIDS drugs proved a key issue in mobilizing resistance to a potential agreement.

But while AIDS activists tend to see big pharmaceutical companies as the enemy, they seldom lash out at companies in developing nations that provide generic drugs. Thailand's GPO is a case in point. It nearly always receives plaudits for breaking patents, but gets little grief over the quality of its production facilities. Its medicines are also not required to receive national Food and Drug Administration approval.

"In some countries, the government is given some kind of immunity from regulators," Dr Lembit said. "It's like some people believe that everything that comes from the government must be good."

Murky

Indeed, a cursory look at the GPO reveals a murky, corrupt state enterprise that looks like anything but David fighting Goliath.

In 2002, Auditor-General Jaruvan Maintaka issued a report saying the GPO sold about 60% of its medical products to government agencies at above market prices. In some cases, products were marked up 1,000 percent.
"The purchase of drugs through GPO still has many defects and gives officials the chance to reap personal benefits," Jaruvan, Thailand's top graft-buster who is now leading investigations against Thaksin, said at the time. "The drug purchasing process becomes intransparent, inefficient and wastes money."

The report said that the GPO, dubbed the "skimming profits" agency by cynical Thai observers,

pilfered about 486 million baht, or about $13.3 million, from government coffers each year from 1998 to 2002. When confronted with the report four years ago, the GPO immediately lowered drug prices across the board. In its defense, Managing Director Thongchai Thawichachat told reporters that the GPO sent 200 million baht annually to government coffers, and claimed its generic production of antiretrovirals saved the government 10 billion baht per year—a claim that certainly raised the ire of Western pharmaceutical firms in light of the corruption allegations.
In 2003, the GPO made a net profit of 624.2 million baht on revenues of 3.7 billion baht. A year later, revenues topped 4 billion baht, and rose to five billion in 2005. Profits for the GPO topped one billion baht in 2005, according to Anuthin Charnveerakul, the deputy public health minister under Thaksin, who also scolded the state enterprise for spending a mere 19 million baht—just two percent of net profit—on research and development.

Now the GPO plans to double revenue to 10 billion baht by 2010. Those plans include a new factory to produce generics that will comply with WHO standards. The plant itself would bring the GPO more than four billion baht every year, with 900 million baht in profits, according to Monkol Jivasantikarn, GPO's managing director.

But for reasons that most attribute to corruption, bidding for the plant has been delayed for more than four years. Frustration mounted last year as Anuthin urged the GPO to build the factory before the Global Fund pulled funding for GPO-Vir in August. It still remains unclear when the factory will be built.

"When Thailand changed governments in September, they set up a new board, which wants some time to evaluate every new project," said a GPO official, speaking on condition of anonymity. "I don't know how long it will be before the factory is built."

AIDS activists have also been frustrated by the delay, but appeared reluctant to criticize the GPO.

"I think a lot of the delay is to do with purchasing a large area of land and building a large production facility," said Paul Cawthorne, head of the Thailand office for Medecins Sans Frontieres. "Since it's a government department, the GPO can't just build like a commercial company would. They need to go through the nightmare bureaucracy of the Thai government. And of course in any big government program, there is a lot of room for corruption. I know they are trying hard, but the whole thing takes 20 times longer than it normally would."

MSF, also known as Doctors Without Borders, loudly applauded the government's decision to issue a compulsory license for efavirenz, and urged it to do the same for other AIDS drugs, like the combination of lopinavir/ritonavir, which costs about 7,000 baht per month in Thailand. The GPO plans to do just that. When announcing the compulsory license, Mongkol said the state enterprise would start making generic versions of patented antiretrovirals Indinavir, Saquinavir, didanosine and Lopinavir within two years.

Can the drugs be trusted?

With all this new production, can poor Thai patients be sure they are getting drugs of the highest quality? MSF and other activist groups say yes, as they vouch for the safety of GPO-Vir even though it has not met international standards. MSF has distributed the drug to nearly 100,000 people in Thailand, Burma and Cambodia.

"I think the drugs [produced by the GPO] are fine to be quite honest," Cawthorne said. "We've had our own pharmacist check out the production site because we needed to see that the way the drugs are produced is up to a standard we felt happy with. So in fact for MSF we have no big concerns on

the GPO's antiretrovirals."

Cawthorne dismisses allegations that GPO-Vir has caused increased resistance. The resistance has mainly grown, he and other AIDS activists say, because more drugs are being distributed, and more people are using them incorrectly.

"We think there are very little problems with resistance to first-line drugs, and when we've seen resistance, we've always been able to determine the reason why someone is resistant," he said. "Perhaps someone has not taken the medicine correctly, or they'd been in surgery. There's always been some other reason besides the drugs themselves.

"You can have the best drugs in the world, and if people don't take them properly, you'll have problems," he added. "It takes a lot of patient education."

GPO officials say the same thing. They claim that GPO-Vir poses no risk. They also downplay concerns that the WHO has not yet approved the drug.
"The approval of the facility is not related to the quality of the drug," Achara Akesangsri, the GPO's deputy chief of research and development, said in an interview. "We can ensure that our product has the same quality as those approved by the WHO."

According to Achara, the WHO is in the process of auditing the firm that conducted bioequivalency studies for the GPO on the first-line generic drug. Those ensure that the drugs are essentially the same.

"The guidelines for the WHO are upgraded every year," she said. "Some studies we did before the new guidelines of the WHO, so we need to update them."

But although the GPO may claim GPO-Vir is bioequivalent to the brand-name drugs, the WHO says those statements need proof to back them up.

"A company will often say a drug is of good quality," the WHO's Dr Lembit said. "Well, why should we believe you when there are no studies to prove it?"

"Manufacturers, including those run by governments, are in business," he added. "If they can sell drugs with less questions being asked, they will certainly do that. And if they can apply political pressure to stop people from asking questions, they will certainly do that as well."

Lembit cites a recent case in Panama as an example of what can go wrong when governments don't adhere to international standards in making drugs. In October, a cough syrup made in a government-run laboratory was found to contain diethylene glycol, a toxic chemical used in antifreeze and paint. About 30 Panamanians died as a result, and others were hospitalized.
"The Panama case is a good example of what bad drugs can cost people," he said. "The disease was not deadly, but now these people are dead because of the drugs."

Lembit declined to discuss why GPO-Vir has not received WHO approval, as the organization has a policy of only publicizing positive news. But when asked about Thailand, he said: "We've given a lot of technical assistance, but things have moved very, very slowly. This is a disappointment. There are a lot of ARVs moving around the world that are of a much lower quality."
(In a later email, Lembit wrote: "In the case of Thailand, I want to say that I have a great respect for them and I would not like to offend them in any way. They have made certain progress and I hope they can speed up to make even more. We have been willing to help and we will continue to be willing to help all those who want to improve.")

Although four years have gone by without GPO-Vir meeting international standards, Lembit says the process takes about three months if all the paperwork is in place. If something is not right, such as proper documentation for claims of bioequivalency, then the WHO tells the company and waits for new studies to be done or data to be compiled.

“The ball is mostly in the manufacturer’s court,” Lembit said. “If something is left out, we cannot continue with the process.

“We want to help the manufacturers,” he added. “We want the generic drugs to pass inspection. But manufacturers need to do their part as well.”
The WHO has approved 34 generic drugs or drug combinations for HIV/AIDS produced in 11 countries. Most are made in India, though others are made in South Africa, Spain and Puerto Rico. No Thai produced drugs have been prequalified.

The GPO may be forgiven for still producing GPO-Vir at its factories even though they could import a better quality generic version from India, as those drugs weren’t around when the state-run firm started production four years ago.

But efavirenz is a different story. Buying the drug from WHO certified factories in India would cost the same as drugs the GPO would produce locally. Moreover, since the drugs have WHO approval, the government could use Global Fund money to buy them. Therefore, the government would get higher quality drugs for HIV patients without having to pay for them out of government coffers. GPO’s generic efavirenz would not be certified by the WHO, and Thai taxpayers would have to foot the bill.

So why produce them locally?

“If we produce locally, we can ensure about the stock,” Achara said. “The drugs should be the same price as those in India.”

Irregular supply was one of the key reasons cited by MSF in its support of the GPO’s move to issue a compulsory license for efavirenz. But the NGO did not see supply as a reason for the GPO to produce efavirenz locally instead of importing the drug from India.

“I think the GPO will wait until the new factory is built before producing efavirenz locally,” MSF’s Cawthorne said. “The site they have at moment is already working at full capacity. They’re not going to be able to make efavirenz in the current site, because they can’t expand the site. It’s quite urgent to get the new facility built.”

The GPO “might” start building the perennially delayed new factory later this year, Achara said. It would take two years to build, meaning the earliest Thai HIV patients are likely to get WHO-approved generic drugs—aside from a brief window in which the government may import them from India—will be late 2009.

“The new factory is a priority for the GPO,” Achara said. “But we have to go step by step.”

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