Can generics "march in"?

A rarely used clause of the Bayh–Dole Act has been invoked to essentially override the patents on two drugs.

BY DAVID FILMORE

Generic drugs usually march into battle against their branded counterparts in the marketplace under the banner of "Hatch–Waxman" legislation. But if two petitions before the Department of Health and Human Services (HHS) gain traction, R&D-based pharmaceutical companies may have to look out for a new pair of senatorial names—namely Bayh and Dole.

Essential Inventions, a Washington, DC-based nonprofit organization directed by consumer activist James Love, asked HHS Secretary Tommy Thompson in January to exercise so-called march-in powers under the federal Bayh–Dole Act. Specifically, the group wants the agency to issue licenses allowing the manufacture and sale of generic versions of Norvir (ritonavir), a protease inhibitor against AIDS marketed by Abbott Laboratories, and Xalatan (latanoprost), a Pfizer glaucoma treatment. The petitions (*www.essentialinventions.org/legal*) assert that Abbott and Pfizer charge "unreasonable" prices for these drugs and that because the patents are based on National Institutes of Health-funded research, this pricing violates the law.

Essential Inventions' approach represents a new strategy for bringing generic drugs to market even before patents have expired.

"The Bayh–Dole march-in law has been on the books since 1980, but no one has ever petitioned to make a federally funded medicine more affordable for U.S. consumers," says Sean Flynn, counsel for Essential Inventions.

Bayh–Dole was enacted to promote the commercialization of inventions arising from federally funded research and to increase their public availability. The law lets universities and businesses retain patents for discoveries resulting from such research and exclusively license those patents to third parties.

However, the government can "march in" on and license such inventions to others without the patent holder's or original licensee's permission if the government finds the invention is not publicly available on "reasonable terms". For instance, according to the Act, the government should take this action "to alleviate health or safety needs that are not reasonably being satisfied by the current licensee."

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Essential Inventions contends that this and other conditions of the Bayh–Dole march-in clause are satisfied in the cases of Xalatan and Norvir.

Prices too high?

"Xalatan is being sold in the United States for between 2 and 5 times the price it is being sold for in other industrialized companies, such as Europe and Canada, despite U.S. taxpayers having originally funded the invention," Flynn says.

The petition charges that this pricing structure is unreasonable and U.S. consumers should pay a lower price than developed economies that did not invest in the drug's development. It argues that the drug's price—$50 for a 4–6-week supply—amounts to 5–8% of the total income of a single elderly individual at the poverty level.

Pfizer did not respond to a request for comment on the petition.

Essential Inventions' major complaint about Norvir relates to a substantial price increase Abbott implemented in December 2003—from $1.71 to $8.57 per 100 mg. At the same time, the price of Kaletra, an Abbott product that combines in one pill Norvir with another Abbott protease inhibitor, was unchanged.

Because Norvir is primarily used as a booster for other protease inhibitors, the effect of the price hike, Flynn says, was to raise the price of using Norvir together with competitors' drugs. Therefore, he argues, patients will be swayed to use Kaletra instead of other Norvir–protease inhibitor combinations, "even if it is not the best choice from a medical point of view."

A number of AIDS advocate groups have reiterated this general allegation of "anticompetitive" behavior. And the attorneys general of New York and Illinois are investigating Abbott for antitrust violations.

But Abbott maintains that the price change was a necessary business move and any allegations of anticompetitive behavior are false. "Abbott took this repricing step with Norvir to come to terms with economic realities, while others have addressed this through premium pricing of their new drugs," says Heather Mason, vice president of commercial operations in Abbott's Pharmaceutical Products division. The com-

pany also stresses that prior to the increase, Norvir was priced below many other protease inhibitors, but, since its unique boosting power was discovered, its "use and value have changed dramatically."

Abbott took several steps in early February after meeting with "hundreds of representatives from across the HIV community." These included freezing Norvir prices at pre-December 2003 levels for AIDS Drug Assistance Programs and for other companies testing the drug in combination with new chemical entities.

Federal funding factor

The patents on latanoprost and ritonavir are vulnerable to a march-in by HHS, Flynn says, because of the federal funding involved in the drugs' development. Essential Inventions' petitions stress that taxpayer support during early development reduced the investment the company had to make to bring the products to market.

Latanoprost was identified at Columbia University through research funded by the National Eye Institute, and the school's patents for the drug were licensed to Pharmacia, now owned by Pfizer, in the 1980s.

Ritonavir was initially developed at Abbott, but the National Institute of Allergy and Infectious Diseases funded the research in the 1980s and 1990s to encourage private development at a time when AIDS therapies weren't considered a substantial pharmaceutical market. In an affidavit submitted in January, John Erickson, who directed Abbott's protease inhibitor R&D from 1987 to 1991, wrote that the ritonavir research "would probably not have been brought to a successful outcome without the involvement of the federal government and its funding."

Essential Inventions asserts that the march-in clause expressly intends considering price as a factor in assessing whether contractors are exercising licenses under "reasonable terms". In its petitions, the group cites the Bayh–Dole legislative record and a survey of case law to support this claim.

The Xalatan and Norvir cases "are precisely the type of abusive pricing problems the march-in clauses were meant to remedy," Flynn says.

But Marjorie Powell, senior assistant general counsel at the Pharmaceutical Research and Manufacturers of America, says there is a great distinction between what a company receives from a government license and a marketable product.

As a general rule, she explains, companies "invest an enormous amount of money into continuing basic R&D, which includes all of the safety and toxicity testing as well as the clinical trials." Any march-in powers the government has, she believes, should be for the original research, but "not for the drug as finally approved by the FDA."

HHS has received only one other march-in petition, in which CellPro, a now defunct biotechnology company, asked the agency to open up the licenses for a Johns Hopkins University discovery for isolating stem cells that was licensed to Baxter Healthcare. HHS denied the petition in 1997 on the basis of the merits of the case, which did not involve the issue of price.

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A more telling precedent might be a short-lived NIH policy initiated in 1989 in response to concerns about taxpayers receiving appropriate return on their investments in biomedical research. The rule required "a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public," and that pricing be a factor in Bayh–Dole licensing negotiations with industry.

However, many companies swiftly withdrew from pursuing licenses for federally funded inventions because of the new stipulation. In 1995, based on limited growth in such licensing agreements, the NIH decided the "reasonable pricing" policy actually posed a barrier to commercializing these discoveries and using them for the public good. The policy, it determined, was in conflict with the Bayh–Dole Act's purpose and subsequently revoked.

Since then, companies making royalty payments to the government have been the primary means for a financial return on these investments.

Powell says companies much prefer this option because there are established industry mechanisms for these types of agreements. And the government can use this money however it chooses, she points out. "They could decide to use the royalty payments to make drugs accessible to people who, for example, don't have insurance coverage for drugs."

The R&D question

Abbott contends that supporting its own ability to conduct R&D was the primary goal of the Norvir price increase. The pharmaceutical industry often cites the high risk of performing drug R&D as justification for drug pricing.

Flynn acknowledges the negative effect a march-in action might have on a company's incentives to pursue R&D. To counteract this consequence, Essential Inventions proposes in its petitions that generic manufacturers of latanoprost and ritonavir be required to contribute a percentage of sales to an "R&D fund" targeting eye disease and HIV/AIDS treatments, respectively. It also offers suggestions on amounts and how the fund might be managed, but essentially leaves these issues up to HHS.

"The point is to create a fund so that licensing of the patent does not decrease the overall R&D in that area of medicine," Flynn says. "This fund would give a transparent, exact number that would only go for R&D and not into marketing or other things on which sales are traditionally spent."

The petitions also propose that the patent holders receive royalty payments based on sales of the generic versions.

Whether these suggestions will influence HHS's ruling on the petitions—which are under review at the NIH—remains to be seen. Already, Flynn says, several companies are interested in supplying generic versions of these drugs. He expects a decision from HHS by the end of July.

Powell warns, however, that if HHS were to show an inclination toward exercising march-in powers, "it would make anyone looking at licensing a government technology nervous." ■