DRUG INDUSTRY

For Mexican Antivenom Maker, U.S. Market Is a Snake Pit

When Jim Harrison was bitten on his hand last summer as he was preparing to milk a western diamondback rattlesnake for its venom, he knew what would happen if the wound went untreated. In a matter of hours, his arm would swell to several times its normal size. Blood vessels would burst, turning his skin black and blue. The excruciating pain would last for days. He could lose the arm and, if the hemorrhaging spread to his brain, suffer a stroke.

But Harrison, director of the Kentucky Reptile Zoo in Slade, had a remedy that is unavailable to most Americans. He grabbed some vials of Anavip, a pit viper antivenom made in Mexico by a firm called Instituto Bioclon, and rushed to the nearest hospital. (The pit viper family includes rattlesnakes, copperheads, and cottonmouths.) Anavip can't be sold legally in the United States; Harrison had access to it because Kentucky Reptile Zoo has a license to stock exotic antivenoms from around the world that have not been approved by the U.S. Food and Drug Administration (FDA).

Bioclon, and many snakebite experts, would like to change the status quo. But the company's January 2012 application for FDA approval to sell Anavip in the United States has led to a nasty cross-border battle. In an 11th-hour bid to block that move, BTG, the maker of CroFab, the only pit viper antivenom legally sold in the United States, filed a complaint in October with the U.S. International Trade Commission asserting that Anavip and its veterinary equivalent, ViperSTAT—made by another Mexican company, Veteria Labs—infringe its patent on antivenom compositions. BTG, based in London, has asked the trade commission to permanently ban Anavip and ViperSTAT from being imported to the United States. The trade commission launched an investigation on 29 November and later this month will set a date for its ruling.

Harrison's case suggests that BTG has good reason to see a threat to its pit viper antivenom monopoly. The herpetologist chose Anavip over CroFab because he assumed the Mexican product would have a more sustained effect, freeing him from return trips to the hospital for repeat doses of CroFab. Indeed, Harrison quickly made a full recovery. (Kentucky Reptile Zoo has sold venom to BTG and also works with Bioclon's U.S. distributor.)

Antivenom researchers contend that other snakebite victims should have the same choice Harrison did. "I want my patients to have the biggest variety of options available at the lowest cost," says Leslie Boyer, a physician and antivenom researcher at the University of Arizona in Tucson who has led company-funded clinical trials of both Anavip and CroFab. She worries that the trade commission will rule against Bioclon—or "that this is going to be such an expensive process" that Bioclon "will give up."

All antivenom recipes start out by injecting venom into a mammal. (BTG uses sheep; Bioclon opts for horses.) As doses ramp up over 6 to 9 months, antibodies against the venom develop and are harvested regularly from its blood. These immunoglobulin G (IgG) molecules are shaped like a capital Y; the two arms, called Fab fragments, bind to toxins in the venom, neutralizing it. Two of the four antivenoms approved in the United States—to treat coral snake and black widow spider bites—are composed of whole IgG molecules.

Both CroFab and Anavip try to solve a drawback of the whole-IgG approach: The stalk of the Y, called an Fc fragment, is packed with animal proteins that can trigger severe allergic reactions known as serum sickness. For half a century, the standard treatment for pit viper bites in the United States was a whole-IgG antivenom. When Boyer administered it to snakebite victims in the 1980s and 1990s, about 40% experienced "brutal" aches and pains, she says. Many were readmitted to the hospital with serum sickness about a week after being treated.

When FDA approved CroFab in 2000, "it was like a godsend," says Thomas Arnold, medical director of the Louisiana Poison Center in Shreveport. To make CroFab, BTG uses the enzyme papain to sever the IgG molecule above its middle joint, cutting loose the serum sickness–inducing Fc (which is discarded), while separating the arms of the Y into free-floating single Fab fragments. Bioclon employs a similar strategy, using the enzyme pepsin instead of papain. But pepsin makes the cut a bit lower on the Y, leaving the antigen-binding arms connected in a larger $F(ab')_2$ fragment (see diagram, next page).

In documents submitted to the trade commission, Bioclon and its distributor Laboratorios Silanes assert that leaving the arms connected gives Anavip a competitive edge. CroFab's smaller, single Fab fragments are quickly filtered out of a patient's blood, sometimes before they bind and neutralize all the venom toxins, explains Lourival Possani, a molecular biologist at the National Autonomous University of Mexico's Institute of Biotechnology in Cuernavaca, who has worked with Bioclon.

In a Bioclon-funded study published in the November issue of *Toxicon*, Boyer and colleagues reported that pit viper venom levels rebounded to as high as 25% of their pretreatment levels in the blood of four of six patients treated with CroFab; two required extra doses of the drug. Venom levels did not rebound in any of six patients treated with Anavip, and none needed additional doses.

BTG's patent, however, lays claim not just to the single Fab fragments in CroFab but also to methods for producing connected $F(ab')_2$ and whole-IgG antivenoms from horses. "We believe [Anavip] absolutely infringes our

Handle with care. When herpetologist Jim Harrison was bitten by a western diamondback rattlesnake, he opted for a Mexican-made antivenom not available for sale in the United States.

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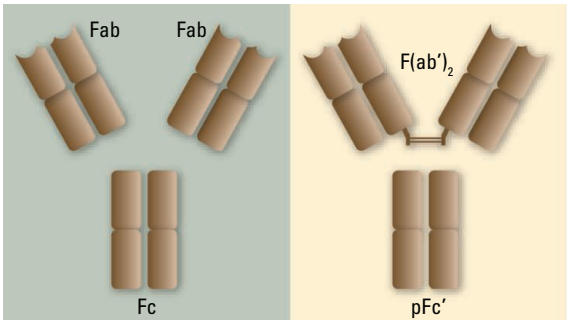
Published by AAAS

patent" and has "piggybacked off our ideas," says Andy Burrows, BTG's director of investor relations. In their submission to the trade commission, Bioclon and Laboratorios Silanes stress the difference between Fab and $F(ab')_2$ antivenoms and state that they haven't yet sold Anavip on the open market in the United States.

Access to a small but lucrative market hinges on the outcome of the trade commission's investigation. In the United States, about 5500 people are bitten each year by a pit viper of some kind, according to Burrows. Depending on a victim's body size and the amount of venom injected, a typical bite requires 20 to 25 vials of CroFab, which BTG says it sells to hospitals and distributors at $2000 per vial. After hospital markups on CroFab and intensive care charges, Boyer says, "it's very common for the actual bill that a person receives to be greater than $100,000."

In Mexico, Anavip and Bioclon's antivenoms against coral snakes, scorpions, and black widow spiders sell for less than $100 a vial. Possani says the price reflects the lower costs of drug approval in Mexico and higher demand. Scorpion stings and snakebites are serious public health issues in Mexico, and the country is the world's largest antivenom producer, Possani says.



Fab prize fight. In the left corner, a pit viper antivenom with free-floating Fab fragments. The challenger's antigen-binding arms remain connected (*right*).

In 2011, Bioclon's scorpion antivenom, Anascorp, became the first Mexican drug to win FDA approval. The experience was demoralizing, says a Mexican scientist who works with Bioclon and requested anonymity. Bioclon funded 12 years of clinical trials before applying, forcing its U.S. distributor, Rare Disease Therapeutics Inc., to price Anascorp so high—$3500 per vial—that it is worth the cost only for the most severe, potentially life-threatening scorpion stings, according to a recent study in *Toxicon*. And that high price comes even after Bioclon passed off a portion of the costs of pursuing FDA approval to consumers back home; Anascorp's price quintupled in Mexico since the clinical trials began, says the Mexican scientist. "It's just tragic" that Mexican scorpion sting patients, who are often poor and live in rural areas, "are subsidizing the U.S. market," Boyer says.

The Mexican scientist assails the FDA approval process as "too expensive, in both money and effort." He hopes that BTG's complaint will inspire Bioclon to abandon the U.S. market and focus on developing antivenoms for Central and South America, the Middle East, and especially Africa, where Bioclon is already working with the World Health Organization. "My job is to continue making antivenoms," he says. "If they can't be used in the U.S., fine. That's not my problem." Snakebite victims this side of the border might not agree.

–LIZZIE WADE

AGRICULTURE

Global Research Network Raises $1 Billion for Its Centers

Internal reforms and rising public interest in food security have helped an international network of agricultural research centers achieve an ambitious goal of doubling its budget in 5 years, boosting efforts to help farmers and improve crops.

After playing a central role in the Green Revolution, the Consultative Group on International Agricultural Research (CGIAR) system fell into decline during the 1980s and 1990s. Like many national agricultural research centers, the budget for CGIAR's 15 centers flattened as infrastructure deteriorated and top scientists left. "We lost ground in the work to provide farmers with the tools they need," says Sara Boettiger of the University of California, Berkeley, who retired this past April as chair of CGIAR's International Maize and Wheat Improvement Center in Mexico.

But recent years have seen a remarkable turnaround, and on 17 December CGIAR announced that it had reached its $1 billion target. The money came from outside sources, mainly development agencies in industrialized countries and private philanthropies. "It's great news," says economist Prabhu Pingali of Cornell University, who led the agricultural development program at the Bill & Melinda Gates Foundation until May 2013. The increased funds have already allowed the 15 centers to scale up work aimed at helping small farmers.

CGIAR's recovery was aided by the food price crisis in 2008 and by a 2006 initiative in agricultural development by the Gates Foundation. In 2010, CGIAR streamlined its management structure to better coordinate the research strategies of its centers. "That resonated with donors," says Jonathan Wadsworth, executive secretary of the CGIAR Fund, which was created to disperse funds to centers. "We've been able to show them the research plans, show them the priorities, what [the centers] aim to achieve with added resources."

The increased funding has also allowed centers to focus on coping with climate change and improving nutrition and health. One new project involves breeding a sweet potato enriched with a vitamin A precursor. Another effort uses satellite imagery to help make crop insurance programs more effective. New policy research is looking at whether raising the price of electricity for irrigation in the Punjab will save energy and water. CGIAR scientists are also now working to boost the photosynthetic efficiency of rice by changing metabolic pathways in the plant.

The centers must work around spending restrictions imposed by donors. And there's little money available for new infrastructure or initiatives such as upgrading information technology systems to provide greater public access to the centers' databases.

To address those problems, a few centers have been doing their own fundraising. In February, the maize and wheat institute cut the ribbon for 5500 square meters of research labs and greenhouses built with $25 million from the Gates Foundation and the Carlos Slim Foundation.

Wadsworth says an upcoming independent review will look at whether the group's budget needs to grow further. Some say any additional money for agricultural research should go to national centers, which often partner with CGIAR centers to adapt crops to local conditions. "The missing gap here," Pingali says, "is the capacity of the national systems to absorb the knowledge coming out of the [CGIAR]."

–ERIK STOKSTAD

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Published by AAAS