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 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). BTG’s patent, however, lays claim not just to the single Fab fragments in CroFab but also to methods for producing connected Fab fragments (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 Fab fragments (see diagram, next page). Bioclon employs a similar strategy, using the enzyme pepsin instead of papain. But papain 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).
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