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Sued and probed, Botox maker seeks off-label relief

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The blockbuster drug Botox has just one FDA-approved cosmetic use – wrinkles between the eyebrows.

But its manufacturer, Irvine-based Allergan, rakes in an estimated \$650 million a year from the sale of Botox for treatments unapproved by the Food and Drug Administration.

The popularity of these off-label uses has brought Allergan into conflict with the federal government, which is probing whether the company illegally advertised or promoted unapproved treatments.

Off-label uses have also landed the company in court. Nine lawsuits blaming Botox for illnesses and deaths include one this spring in which the company was ordered to pay \$15 million to an Oklahoma woman who said a series of on- and off-label cosmetic Botox shots left her in pain and partially paralyzed. Allergan is appealing that verdict.

Allergan, meanwhile, has sued the FDA for the right to tell doctors more about off-label uses of Botox. The company already helps spread the word by donating hundreds of thousands of dollars each year to independent medical institutes that train doctors on how to inject Botox as a treatment for ailments not authorized by the FDA.

Allergan's lawsuit questions the FDA's control over how drug companies communicate with doctors and patients. Also at stake is the future of Botox sales, currently totaling \$1.3 billion a year. Most importantly, patients' health is at stake.

The dispute over off-label therapies highlights a gap between the American system of regulating drugs and the way the medical community prescribes them. As long as a drug is approved by the FDA for one use, doctors have the right to prescribe it for any use that they believe to be medically appropriate.

Off-label uses account for an estimated 21 percent of all prescriptions, according to researchers at Stanford University, Dartmouth Medical School and Massachusetts Institute of Technology. Common off-label therapies include treatments for cancer, HIV, psychological disorders and serious children's diseases. Among the most common is aspirin as a method of preventing a heart attack, which is not FDA-sanctioned.

As a regulator without the financial conflicts of drug companies, the FDA is best suited to decide on the merits of drugs, said Dr. Sidney Wolfe of the consumer advocate group Public Citizen. But doctors often learn about drugs from pharmaceutical companies and misleadingly small studies of off-label uses, he said.

"What is the point of having the FDA involved if a company can get a drug approved for one indication and then promote it for other ones?" he asked. "Children have died because doctors didn't know what the right dose was."

In addition to its one approved cosmetic treatment -- for wrinkles between the eyebrows -- Botox is approved by the FDA for therapeutic treatments for crossed eyes, twitching eyelids, underarm sweating and some muscle spasms in the neck, arms and hands.

Off-label uses for Botox include injections for migraines, cerebral palsy spasms, crow's feet, forehead

wrinkles and overactive bladder.

Many patients with debilitating diseases have had their symptoms relieved with off-label Botox injections. At the same time, people have been injured and some have died after off-label Botox shots. Allergan denies that any of the deaths or injuries were caused by properly administered Botox.

By filing suit against the FDA in October, Allergan became the most prominent challenger to the current system. But it is far from alone in the conflict over off-label drug therapies. The U.S. Department of Justice has recently sanctioned several drug companies for promoting off-label therapies.

In April, Johnson & Johnson pleaded guilty to a misdemeanor and agreed to pay \$81 million to settle allegations that it promoted off-label use of the Topamax epilepsy drug. That same month, AstraZeneca denied any wrongdoing but agreed to pay \$520 million related to marketing off-label uses of its anti-psychotic drug Seroquel. Last year, an off-label marketing probe ended with Pfizer agreeing to pay \$2.3 billion in fines, which included the largest criminal fine in history.

Allergan said in a Feb. 26 filing with the Securities and Exchange Commission that it expects to spend \$98 million to \$108 million by the end of this year defending against the federal probe.

Disputed deaths

Botox injections have been investigated as a possible cause for numerous deaths, according to lawsuits and reports to the FDA.

FDA researchers who examined the agency's database of medical incidents from 1989 to 2003 found 28 reported deaths among patients receiving various on- and off-label therapeutic treatments of Botox and a similar neurotoxin, Myobloc. The FDA said the causes of those deaths cannot be pinpointed, because the reports are sketchy and because the deaths might have been caused by the illnesses being treated.

In 2008, Public Citizen petitioned the FDA for stronger warning labels, citing 16 database reports of fatalities between 1997 and 2006, including 12 patients who received Botox injections and four who were treated with Myobloc. At least 10 of the 12 deaths of Botox patients occurred after off-label injections.

The agency said it could not determine what caused those and other deaths, but it did decide to strengthen the Botox warning label.

"Botox and Botox Cosmetic may cause serious side effects that can be life-threatening," the new guide warns patients. "Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with Botox or Botox Cosmetic."

Allergan remains firm in its position that Botox is safe when used as directed.

"Since its approval, over a million people have been treated with Botox Cosmetic. In its entire history, there has never been a single reported death where a causal link to Botox Cosmetic was established," said Dr. Sef Kurstjens, Allergan's chief medical officer.

The latest challenge to Allergan is a series of lawsuits claiming that Botox caused deaths and injuries. The company won the first two cases, in 2004 and this year, but it lost the third one.

In the most recent case, Sharla Helton, 44, blamed Botox for leaving her in pain, partially paralyzed and jobless after getting injections in 2006 to smooth her wrinkles.

Helton had been an active obstetrician/gynecologist, but she testified that she had to stop working because of pains and weakness she blamed on Botox. In May, a jury in Oklahoma awarded her \$15 million after deciding that Allergan was negligent in not listing all side effects on the Botox label.

Patients and their families have filed seven other complaints against Allergan that claim damages caused by Botox. Six of those involve off-label injections; three involve deaths:

- The children of Sondra Bryant of Texas allege she died in 2008 after off-label Botox injections for neck pains. That trial is scheduled for this fall in Santa Ana.

- The brother of Stanford Sody of New Jersey alleges he died after off-label Botox injections to treat his salivary glands in 2008.

- Barbara Purdon, 71, of Arizona began to suffer from difficulty in breathing, swallowing and speaking after receiving Botox injections to smooth her wrinkles in preparation for her wedding, according to her attorney and a complaint she filed against Allergan in 2008. She died before the case came to trial.

Attorney Ray Chester of Austin, Texas, is handling all three of the cases; Allergan declined to comment on the pending cases.

Off-label benefits

In Orange County, off-label therapeutic uses of Botox are offered at many prominent hospitals.

Urologists at UCI Medical Center in Orange inject Botox into the bladder as a fallback treatment for incontinence if other therapies are unsuccessful. The shots paralyze the bladder muscles, eliminating the excessive urge to urinate for six to nine months. That therapy is also offered at Orange Coast Urology, which is affiliated with Hoag Memorial Hospital Presbyterian in Newport Beach.

Allergan has applied for FDA approval for that treatment but has not yet been granted it.

Hoag doctors inject Botox into the muscles of the larynx to provide relief from vocal problems. The hospital's website calls that a "common procedure."

Miller Children's Hospital in Long Beach offers Botox injections for patients with cerebral palsy, and lists it as one of the most common treatments for those children.

"Botox can be safely and painlessly injected directly in a specific muscle to relax that muscle to temporarily stop spasms," says the hospital's website.

Cerebral palsy patient Katy Fetters, a student at Huntington Beach High School, recalls having Botox injections at age 10 to ease the pain of her contracted muscles. She wrote about the treatment on her Teen Cerebral Palsy blog, which is aimed at providing information and an online community for youths with cerebral palsy.

At Orange County Migraine and Headache Center in Irvine, Dr. Susan Hutchinson injects Botox as a treatment for migraine.

"The risks are minimal," Hutchinson says.

As for cosmetic Botox, off-label injections are standard. A typical Botox session includes shots around the eyes and in the forehead, not just between the eyebrows, which is the only FDA-approved location.

Laws about who may inject Botox vary from state to state. In California, doctors and dentists can inject, as can registered nurses and physician assistants under a doctor's supervision.

Among cosmetic doctors, the vast majority inject Botox to treat wrinkles in areas that aren't FDA-approved, said Dr. Michael Sundine of Newport Beach, president of the Orange County Society of Plastic Surgeons.

"I don't know of anyone who doesn't," he said.

Funding for training institutes

The medical community relies heavily on drug and medical device companies for financial support of doctors' continuing education. About 43 percent of all post-graduate training that doctors received in 2008 was paid for by drug or medical device manufacturers, according to a report last year.

Allergan gives hundreds of thousands of dollars a year to groups that train doctors how to inject Botox for off-label treatments. Many, but not all, of those treatments are recommended by top medical experts, who are less cautious than the FDA.

Allergan and other companies donate money in the form of "unrestricted educational grants" for purposes that

it approves, such as specific training programs. In one case, the company had a representative on the institute's advisory board until regulators cracked down. In another, the founder of a training institute landed a high-profile job with the drug company.

"We have good reason to support them," said Doug Ingram, Allergan's chief administrative officer, citing the institutes' educational programs about the latest research into the benefits and risks of Botox and other drugs.

"Are they company tools? No. Do we disseminate untrue information through them? No. That's demonstrably untrue – and insulting."

At Public Citizen, Wolfe is more skeptical.

"The FDA will have to decide if these training sessions are a violation of its regulations about advertising off-label uses," he said. "It's a problem."

Among the Allergan-supported groups is Aesthetic Advancements Inc. of Buford, Ga., which trains doctors and nurses in off-label Botox shots throughout the lower face and neck and around the eyes, nose, eyelids and mouth. One of the institute's trainers was the nurse who injected Sharla Helton, the Oklahoma woman who won \$15 million in damages, according to testimony and institute officials. The nurse was named in the original lawsuit but was subsequently dropped as a defendant.

President Jill Jones said the institute is a respectable educational company that's independent of Allergan. It gets about a quarter of its revenue from corporations, including Allergan, with the rest coming from the doctors and nurses it trains, she said.

An Allergan employee who is listed on the institute's website as a member of the advisory board has been removed from that post because of new regulations aimed at limiting corporate influence on continuing education, Jones said.

We Move, a nonprofit based in New York, was founded in 1991 by Dr. Mitchell Brin, who became Allergan's vice president for Botox/neurology in 2001. Its off-label training includes Botox shots for treatment of spasticity, pediatric movement disorders, whiplash pain, jaw disorders, drooling and writer's cramp.

According to public filings, We Move had income of \$1.3 million and assets of \$481,000 in fiscal year 2008; funding comes from nonprofit patient foundations and drug companies such as Allergan, Ipsen and Merz.

Online information provided by We Move describes injections of up to 8 units of Botox per kilogram of body weight as a treatment for cerebral palsy. The executive director did not return calls requesting further information.

The Neurotoxin Institute of New York provides off-label training for Botox and other injectables for treatment of headaches, pain syndromes and urinary problems.

The institute, which is run by for-profit Scientiae LLC, is entirely supported by drug companies, according to President Lisa Gottlieb. This year's funding, she said, probably will be contributed evenly by Allergan, Ipsen (manufacturer of the neurotoxin Dysport) and Merz Pharmaceuticals (maker of injectable filler Belotero Balance). Allergan has contributed "south of \$500,000" for training programs and website redesign, she said.

Doctors in the training programs have "no direct relationships" at all with Allergan, said Dr. Mark Hallett, chairman of the institute's steering committee.

"Lots of people have substantially benefited" from having their doctors trained in off-label uses of neurotoxins, he said. "The FDA process is very limited."

Allergan vs. Uncle Sam

In early 2008, Allergan disclosed that it received a subpoena from the U.S. Department of Justice requesting documents detailing the marketing of Botox.

"The subpoena broadly requests documents regarding promotional, educational and other activities relating to Botox. Allergan's current understanding is that the inquiry involves questions regarding alleged off-label promotion relating to the use of Botox for the treatment of headache," the company said.

Investigators also demanded documents relating to Allergan's speakers bureau, through which the company pays experts who discuss Allergan products, the company said.

Allergan executive Ingram said doctors need to understand both the risks and benefits of medications, but the FDA makes that difficult. The FDA only allows drug companies to discuss the risks, not the benefits, of off-label uses, he said.

In October 2009, Allergan struck back with a lawsuit that says the FDA's limits on discussion of off-label uses violate the company's "First Amendment rights, while also impairing public health and safety."

The company cited the federal probe as a reason why it fears "criminal prosecution and severe civil penalties" if it proceeds with "truthful, non-misleading scientific speech to physicians about the use of Botox" beyond what the FDA has authorized.

Allergan said, for example, that it had proposed sending a warning to doctors that Botox shots for cerebral palsy patients – a widely prescribed off-label treatment – have not been adequately studied at doses greater than 8 units of Botox per kilogram of body weight. According to Allergan, the FDA rejected that proposal, saying it would imply that lower doses of Botox are safe, which the agency has not determined.

In its response to the lawsuit, the Department of Justice called the complaint "a sweeping assault on FDA's authority ... to require manufacturers to show that a drug is both safe and effective for each of its uses before the manufacturer promotes the product for such use."

If Allergan wins the suit, the company could promote the sale of its drugs "for unsafe or ineffective uses, placing the public health in ongoing jeopardy," the brief said.

Public Citizen filed an amicus brief in support of the FDA, saying that the restrictions challenged by Allergan are crucial for protecting patient health.

A victory by Allergan would "return the nation to the days of snake-oil salesmen, when products were regularly promoted with unproved, exaggerated or fraudulent health claims," Public Citizen argued.

"There couldn't be a better example than Botox," Wolfe said. "The number of different 'diseases' it treats is enormous. Name a part of the body with nerves – someone is doing a study of poisoning it with Botox to benefit a patient."

If the company wins, it would not have the right to distribute falsehoods, according to an Allergan ally, the **Washington Legal Foundation**, which fights for First Amendment rights for businesses.

"It's a matter of public health," said Richard Samp, the group's chief counsel. "It is always in the public interest to allow free flow of truthful information. ... If a doctor wants to use Botox for a particular condition, Allergan should be allowed to say, 'Here is the information we have about proper dosing.' Who better than Allergan to know that?"

No trial date for the lawsuit has yet been set.

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