Drug firm's wooing made whistleblower suspicious

Fort Sam doctor was early backer of medication to halt bleeding.

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Dr. Ian Black knows how far the pendulum can swing. Once a player in the world of trauma research, he became a pariah. Once a believer, he lost faith.

His journey from advocate of a drug that stopped bleeding in badly injured troops to federal whistleblower began in October 2005, around the time he attended a high-priced dinner at Emeril's restaurant in Atlanta not far from his room at the Ritz Carlton — all on the company tab, plus a $1,000 honorarium.

“You know, I was wined and dined by the companies and it was flattering, and I thought I was cutting edge and whatnot, and I guess I had a little bit of an epiphany that, ‘Oh, my God, these guys are playing me,'” he laughed.

Black is a former chief of anesthesiology at the Institute of Surgical Research, the Army organization at Fort Sam Houston that fast-tracked NovoSeven, a costly hemophilia drug, to slow bleeding in wounded GIs.

As conferences in the United States and abroad played up NovoSeven's benefits in trauma patients, his wariness grew amid mounting evidence that questioned the drug's effectiveness and potential dangers.

He resigned his active-duty commission in 2008. Fearing retaliation, Black filed a complaint with the ISR's inspector general on the day he left the Army. He later emerged as one of two whistleblowers in a Justice Department suit that alleged Danish pharmaceutical firm Novo Nordisk improperly paid military doctors to use and promote NovoSeven.

“There were multiple other people who had concerns. I mean, it wasn't just me,” said Black, 48, of Burlington, Vt. “I would also preface this by saying that if you look at 2004 and 2005, I was actually a very aggressive user of the drug. I worked at the Institute of Surgical Research, which was sort of the epicenter for both research of the drug and use of the drug, and so I was very much enamored of it.”

The lawsuit, joined by the Justice Department and settled earlier this month, said Novo Nordisk sought to woo influential military doctors and researchers in part by providing illegal incentives.

One was an ISR trial that began in August 2006 that may have violated Army regulations prohibiting clinical investigations from being conducted with funds or resources provided by for-profit businesses.

The federal lawsuit said studies and presentations made by those doctors and researchers led to NovoSeven's use in combat wounded, ultimately influencing civilian doctors and hospitals nationwide

to administer the drug as well for off-label purposes — those not specified by a Food and Drug Administration license — such as stopping bleeding in trauma and surgery.

The FDA does not forbid doctors from using drugs for off-label purposes, but they can be held liable, said Black's San Antonio attorney, Dan Hargrove.

Novo Nordisk paid the federal government, 24 states and the whistleblowers $25 million for violating the False Claims Act.

The Justice Department said the company engaged in a "fraudulent scheme to use kickbacks and off-label promotion to boost" NovoSeven sales, which rose from $250 million in 1999 to $750 million in 2004.

The company denied wrongdoing, but the settlement called events like the 2005 Atlanta dinner part of an "illegal and dangerous" scheme to expand the off-label use of NovoSeven, licensed for use in a few hundred patients. Days after the settlement was announced, the Army Medical Command said it had reopened a probe "to include a systematic review of honoraria in the medical research environment."

NovoSeven is a bioengineered version of a protein the body uses in blood clotting called Factor VIIa. It was approved in 1999 for select hemophiliacs but has since been given at up to $10,000 per dose for trauma, stroke and heart surgery patients, a total of 17,813 people in 2008 — up from 125 doses given in U.S. hospitals in 2000.

A national study of the drug's use in trauma patients, sponsored by Novo Nordisk, was halted. Two large studies published in April said there was no evidence the drug prolongs life in any of its off-label uses. In some studies of strokes and heart surgery, but not trauma, NovoSeven actually raised the risk of blood clots in the brain and heart.

Top ISR officials adopted off-label use of NovoSeven early in the Iraq war. Struggling to cope with a rising tide of wounded, the Army scrambled to stop bleeding in critically injured patients. It still uses the drug in war zones.

A chief proponent of the drug, Dr. John Holcomb, has not returned messages seeking comment. One person answering the phone at his Houston office late last week said "he is not interested."

ISR spokesman Steven Galvan also declined to comment, citing an ongoing Army investigation.

Former VA Secretary James Peake, a former Army surgeon general, praised Holcomb.

"All he cared about was doing what was right by the soldiers and stopping bleeding," Peake said, calling Holcomb "highly ethical" and a patriot.

The ISR's director until three years ago, Holcomb defended NovoSeven in a New York Times interview, saying random, controlled trials proved it was safe.

In the war zone, "you have to make a decision. It's not something you can decide to talk about. It's really yes or no," said Holcomb, a retired colonel who heads the Center for Translational Injury Research at the University of Texas Health Science Center in Houston. "You have a lot of people

bleeding to death in Iraq."

The Justice Department saw things differently. It said in the settlement that Novo Nordisk "sought out influential Army physicians," including Holcomb, who it said "was eventually responsible for drafting clinical practice guidelines for use in the military theater that promoted broad use of Factor VIIa for off-label purposes." The firm earmarked $19,500 to support presentations by Holcomb and another doctor at a 2005 symposium.

Black emerged as the sole ISR whistleblower, yet he insisted others worked within channels to curb NovoSeven's use. But Holcomb, he said, wielded tremendous power.

"The ISR is unique in that the person who was in charge of the trauma database, the commander of the institute who is in charge of research and the person who is in charge of clinical practice guidelines, was all the same person. And the person who was the commander and was responsible for evaluations was all the same person," Black said.

"So I don't want to impugn Dr. Holcomb by saying he had bad motives, because he had served honorably in Somalia, he served honorably in Iraq, but certainly if you have one person as the focal point and that person has an opinion on something, it's harder to have that spirited debate.

"Did the spirited debate happen? I don't think so."

The Justice Department alleged the company conducted a campaign to manipulate experts in and out of the Army. Just before a May 2005 seminar at the ISR on NovoSeven in trauma patients, Novo Nordisk sent its U.S. sales representatives and medical sciences liaisons on the Queen Elizabeth II from London to Denmark. The Justice Department called the European cruise a "plan of attack meeting."

Novo Nordisk funded more than 25 ISR research projects. The settlement said the company gave ISR officials speaking engagements, positions on advisory boards, unrestricted research grants "and other kickbacks" to promote the drug's use. The firm sponsored three conferences from 2005 to 2007, paying honoraria to physicians for speaking in favor of NovoSeven.

One meeting was the one at the Ritz Carlton in Atlanta, but there were others. Holcomb made two presentations at a symposium in Germany.

Black's evolution from a supporter of NovoSeven to skeptic was a process of sorts. He was puzzled by Army's early, aggressive use of the drug. But his doubts grew in the more than two years following the Atlanta conference.

The thought that Novo Nordisk representatives were stroking his ego, and that of other doctors, was a factor in his conversion, but so, too, was a series of critical studies. Most, he said, were poorly done. A study on the safety and efficacy of Factor VIIa for off-label use found just 16 of 64 reports were based on random, controlled trials. The rest were observational studies.

That was in 2005. The next year, in Iraq, Black was stunned by how often NovoSeven was used in combat hospitals. It was often given, including to those not bleeding badly, said Black, whose doubts

grew after two patients had embolisms.

Tales of NovoSeven's popularity and suspected side effects were well-known to medical personnel in Iraq. One, surgeon Dr. Sudip Bose, said NovoSeven had a “miraculous” impact on some troops, while others developed blood clots in their legs after taking the drug. Many presumed NovoSeven was the cause.

Things came to a head when Black was ordered to do a study of clinical practice guidelines after arriving at Baghdad's 28th Combat Support Hospital in fall 2006.

He was troubled at the lack of serious studies into NovoSeven's impact on trauma patients. The one high-quality study he found was for patients who had cerebral hemorrhage.

But in 2006, five FDA physicians reported 185 thromboembolic events, such as blot clots, were linked to NovoSeven. Drugs reporting 10 or 20 events often were taken off the market, Black said, adding, “It didn't mean for sure it caused it, but it certainly gave me pause.”

After researching NovoSeven's use at the 28th Combat Support Hospital, Black issued guidelines recommending a drastic curtailment of the drug. His guidelines went up the chain of command, but never were adopted.

Still, doctors dramatically cut back their use of NovoSeven. Black said the survival rate for the hospital, which saw one of its busiest periods as violence spiked, remained the same. Back home, one ISR researcher's PowerPoint presentation in September 2007 called Factor VIIa “an unproven tool” being “used on blind faith.”

Black said his relationship with Holcomb changed after he submitted his guidelines. In a phone conversation while Black still was in Baghdad, he said, Holcomb was miffed over not seeing the guidelines before they were sent to commanders.

Black said he told Holcomb the proper thing to do was run the guidelines through his chain of command at the hospital. Black also offered to take a job outside of the ISR on returning to San Antonio.

Holcomb agreed.

An Army Reserve major due to return to Iraq this fall, Black worries his next promotion will be spiked out of revenge. Still, he believes that he's kept faith with the troops — and his conscience.

“For me, the story was sort of we promised these soldiers, sailors, Marines that we're going to take the best care of them,” said Black, who went to work at Brooke Army Medical Center when his tour ended in spring 2007. “I think a lot of times the Army health care providers and the public translate that into doing the most expensive drug, the newest procedures, the newest technology, but if you look at most of the civilian literature now, good health care institutions are very disciplined and systematic in how they adapt innovation and how they review that innovation.

“And I think that's sort of where the system failed a little bit. And I don't think that's a very sexy story.

I mean, nobody wants to talk about that, that maybe more soldiers would be saved just by having system changes than giving some life-saving drug or life-saving bandage. People want to hear those feel-good stories."

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