

Bad to the bone: A medical horror story

September 18, 2012: 5:00 AM ET

When medical device company Synthes decided to illegally test a bone cement on people, the results were disastrous. A disturbing tale of corporate crime and punishment.

By Mina Kimes, writer

FORTUNE -- On Nov. 16, 2011, Georgia Baddley, a 70-year-old woman living near Salt Lake City, received a shocking call from a special agent at the U.S. Department of Health and Human Services. The agent told her that the government had come across new information about her mother's death.

Baddley was speechless. Eight years before, her 83-year-old mother, Barbara Marcelino, had unexpectedly died during spine surgery. At the time, Baddley didn't question what had happened; surgery was always risky for a woman of that age. She was horrified when the agent told her that the surgeon had injected bone cement into her mother's spine and that the product -- which was not approved for that use -- may have played a role in her death.

The agent explained that the government had filed criminal charges against the maker of the cement, a company called Synthes, and four of its executives. After hanging up the phone, Baddley sat in stunned silence. "I was taken aback," she says. "I had no idea that anything like that had happened."

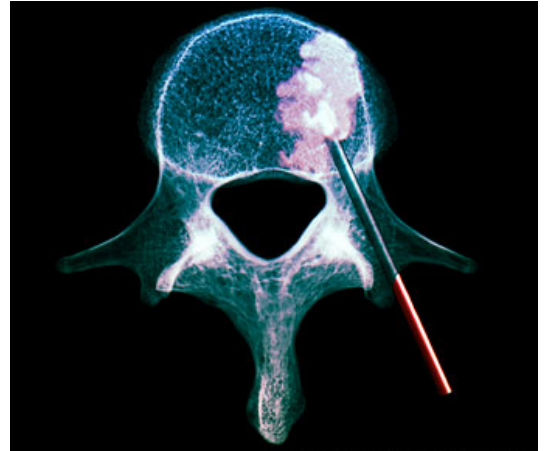
Most people have never heard of Synthes, a medical device maker headquartered in West Chester, Pa. But the company became part of one of the most recognizable names in health care in June when Johnson & Johnson (**JNJ**) completed the purchase of it for nearly \$20 billion -- the largest acquisition in J&J's history. Market watchers cheered the deal, which will expand the company's stable of high-margin orthopedic products. J&J, which has endured a series of **reputation-sullyng recalls** and lawsuits in recent years, specifically cited Synthes's "culture" and "values" as evidence of its appeal, even as former Synthes executives awaited sentencing on charges of grievous conduct.

In 2009 the U.S. attorney in Philadelphia accused the company of running illegal clinical trials -- essentially, experimenting on humans. Between 2002 and 2004, Synthes had tested a product called Norian XR, a cement that has a unique capacity to turn into bone when injected into the human skeleton. The Food and Drug Administration explicitly told Synthes not to promote Norian for certain spine surgeries, but the company pushed forward anyway. At least five patients who had Norian injected into their spines died on the operating-room table. One was Barbara Marcelino.

The indictment of Synthes and its executives shook the health care industry. What occurred is a classic example of corporate malfeasance, but set inside an insular corporation run by a reclusive and autocratic Swiss multimillionaire, the provider of the largest individual gift in the history of Harvard University. The case offers a rare, sometimes disturbing, glimpse inside the shrouded world of medical devices, where surgeons occasionally turn for advice during operations to twentysomething sales representatives.

Most of all, this is a story about a company that repeatedly ignored evidence of potential lethal consequences. Interviews with more than 20 former employees and surgeons involved in the Norian project, hundreds of pages of court transcripts, and company documents submitted in the case reveal that Synthes not only disregarded multiple warnings that it was flouting the rules, but also brushed off scientists' cautions that the cement could cause fatal blood clots.

The Department of Justice targeted four high-ranking executives, all of whom pleaded guilty to a misdemeanor under an unusual provision of health care law called the Responsible Corporate Officer Doctrine. They accepted responsibility for the



A colored CT scan of a single vertebra (as seen from above) during a vertebroplasty. The term refers to a procedure, used to treat compression fractures, in which a surgeon injects bone cement (the white material coming out of the needle) into the spine to reinforce the bone and prevent future damage.

company's crime of running unauthorized clinical trials and for engaging in off-label marketing, or promoting products for unapproved uses, without conceding that they were involved in the crime. At the time, no executive had ever gone to prison for such a charge. (Lawyers for the four executives declined to make their clients available for interviews or to comment on the facts of the case.)

Off-label marketing is so common among drug and device makers that it's often dismissed as the equivalent of driving slightly over the speed limit. During the past decade, pharmaceutical behemoths such as **Merck (MRK)**, Pfizer (**PFE**), Abbott Labs (**ABT**), and GlaxoSmithKline (**GSK**) have paid billions in fines to settle charges that they engaged in **off-label drug promotion**. Yet cases continue to happen, in part because the potential profits often exceed the fines.

But this wasn't the typical off-label marketing case. Nor was it typical of trials for medical devices or drugs. Patients sometimes die during such clinical trials -- but only after being advised of the risks and then granting their consent. In hiding the unapproved status of the cement, prosecutors argued, Synthes denied patients the right to choose whether they wanted to be test subjects.

For the Justice Department, the Synthes case posed an unprecedented opportunity. It could finally hold individual businessmen accountable for their actions. Mary Crawley, the assistant U.S. attorney who led the prosecution, urged the court to send the executives to jail for their "venal crime." The "callous disregard of patient safety," she argued, "warrants the highest sentence the law will allow."

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Synthes is based about 25 miles west of Philadelphia, but its roots lie in Switzerland. In 1958 four Swiss surgeons founded a research organization devoted to their belief -- controversial at the time -- that broken bones could be better fixed internally with implants. They developed products, branded with the name "Synthes," that they licensed to a pair of Swiss manufacturers.

In the 1970s one of the founding surgeons bought an airplane from an enigmatic Swiss businessman named Hansjörg Wyss (pronounced hans-yerg vees). The son of a mechanical-calculator salesman, Wyss boasted a worldly résumé. He had worked in Turkey, Pakistan, and the Philippines, and had graduated from Harvard Business School. When he met the surgeon, he was working for a chemical company and selling planes on the side. Wyss struck a deal to become head of Synthes's U.S. operation.

Wyss later became CEO of the entire company and over the next 30 years built it into an industry giant that specializes in making plates and screws to stabilize broken bones. Along the way he became a multibillionaire, splitting his time in the U.S. among homes in Pennsylvania, Martha's Vineyard, Mass., and Tucson. He was CEO until 2007 and remained chairman of the company, which has 12,000 employees, until it became part of J&J (where it's now in the renamed DePuy Synthes division). Last year Synthes generated \$4 billion in sales. Until the J&J acquisition, Wyss and his family owned nearly 50% of Synthes's shares.



Wyss was an intimidating, hands-on CEO, former employees say. He is also one of the wealthiest men in the world.

of success, I would say he has a surprising amount of contact with what's going on." (Her grand jury testimony, like other such testimony mentioned in this article, was excerpted in a public court filing; she did not respond to requests for

Wyss, 76, shuns the limelight. Unassuming, with wavy gray hair and owl-like glasses, he often wore baggy corduroys to work and drove an old Volvo for years. Wyss has generally shied away from the press, telling a Swiss newspaper in a rare interview last year, "Nobody knows me, and I hope that it stays like this." In a phone interview with *Fortune*, Wyss declined to comment on the central issues in this article but did address several smaller points. A Synthes spokesperson declined to discuss the Norian case.

Wyss donates heavily to liberal-leaning nonprofits and in 2008 gave \$125 million to Harvard to fund a biological-engineering institute. An avid hiker and outdoor enthusiast, he has poured millions of dollars into preserving land in the Rocky Mountain states, a region he fell in love with as a student.

Former Synthes employees portray Wyss as an intimidating, hands-on leader. Nisra Thongpreda, the manager first assigned to the Norian project, would testify before a grand jury that "for somebody who is at his level and his level

comment.) Several former Synthes staffers recall meetings where Wyss probed the minutiae of their projects. "It would feel like he wasn't paying attention," says a former employee. "Then, all of a sudden, he'd turn and raise a question that was far in the weeds -- maybe the single dollar amount of something you proposed."

Wyss's level of control could verge past micromanagement. Several former employees say he wouldn't let the company provide Internet access in the mid-2000s; workers who wanted to go online had to sign in to a single computer in front of everyone. Maria Maccicchini, who was president of biomaterials at Synthes for eight months in 2004, says the CEO was fixated on the brand of toilet paper used in company restrooms, the color of the desks, and the shape of the plates in the cafeteria (he insisted that they be square).

One former employee recalls how, as he was walking into Synthes's headquarters on a fall day, he saw Wyss hunched over in the foyer. The CEO was picking up leaves off the floor, one by one, and then putting them outside.

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In the late 1990s a fledgling biotech company called Norian popped up on Wyss's radar. The startup, based in Cupertino, Calif., had developed a calcium-phosphate-based cement, also called Norian, with almost miraculous qualities. When implanted in the skeleton, the cement not only fills cracks but also gradually transforms itself into actual human bone.

Synthes bought the company in 1999 for about \$50 million. At that point Norian had already obtained FDA approval to market two versions: Norian SRS, for use in the arm, and Norian CRS, for use in the skull.

There was a third potential application for the cement -- one that Synthes executives hoped could be extremely lucrative -- and it's this use that would eventually prove disastrous: filling fractures in the spine. In the 1990s specialists were increasingly touting the benefits of a procedure called a vertebroplasty. To perform the surgery -- typically done to treat vertebral compression fractures, or VCFs, a common side effect of osteoporosis -- surgeons inject cement into the spine. At the time, the procedure was performed with acrylic cement, which contained a material used to build aquariums. Norian, with its unique properties, seemed like a superior alternative.

When Synthes acquired Norian, the company did not yet have permission to sell it for use in the spine. As is true any time a company wants to market a high-risk medical device (and under FDA rules, the cement was considered a device) for a new purpose, Synthes would have to convince regulators that the new use was safe and effective.

The government's response was discouraging. An FDA representative told Synthes in a conference call that it would "almost definitely" need to pursue a path that typically necessitates clinical trials, according to minutes of the call. To do that, the company would have to obtain an Investigational Device Exemption, or IDE, from the FDA. (In FDA jargon, the "exemption" grants the manufacturer the right to conduct human tests.) Then Synthes would have to persuade a large number of patients to undergo experimental treatment and conduct a lengthy and expensive clinical study.

Instead of preparing a clinical study, Synthes made the first of a series of fateful choices, deciding to launch right into market research. In February 2000, Wyss announced at an all-hands meeting that there would be a strong push for vertebroplasty, according to factual findings by the judge in the criminal case. In March, employees in Synthes's spine division began interviewing spine surgeons about Norian. Their report, which was shared with executives, pointed out that Americans suffer more than 500,000 VCFs each year and that the "market potential" was "considerable." It concluded, "There is excitement about using Norian for vertebroplasties."

Whispers of the project began spreading, prompting the first -- but not the last -- alarm within Synthes. A strait-laced regulatory staffer named Michael Sharp was appalled when he learned, in a chance conversation, about the plan to promote Norian. Companies are explicitly barred from marketing products for uses that haven't been authorized by the FDA. Even mentioning unapproved uses to surgeons is prohibited.

Sharp fired off an e-mail to Tom Higgins, the president of Synthes Spine, and Richard Bohner, vice president of operations at Synthes, expressing his concern that the company was testing Norian without going through the proper channels. "Regulatory is unaware that this is even being considered," he wrote.

→ THE EXECUTIVES

Four former Synthes managers were sentenced last year for their roles in the company's illegal clinical trials. (Tom Higgins, the ex-president of Synthes Spine, is not pictured.) All four pleaded guilty under the Responsible Corporate Officer Doctrine, accepting responsibility for the crime without admitting they were involved.



MICHAEL HUGGINS

The head of Synthes North America, Huggins expressed concerns about Norian, then continued with the project.



RICHARD BOHNER

As VP of operations, Bohner oversaw regulatory affairs. He was warned by one of his staff that Synthes was on shaky ground.



JOHN WALSH

Walsh, another regulatory executive, approved a brochure for Norian that omitted a required FDA warning.

Higgins met with Sharp. The regulatory staffer says he made it clear that Synthes employees shouldn't discuss Norian with spine surgeons. Higgins assured him, Sharp recalls, that the company wasn't going to promote the product for use in the spine. "At that point," says Sharp, "I thought the issue was entirely put to bed."

But the project didn't die there. In February 2001 a surgeon in Santa Monica used Norian to perform two procedures on elderly patients with vertebral compression fractures. In both cases, according to company documents, the patients experienced rapid drops in blood pressure shortly after the surgeon injected the cement, and an anesthesiologist had to administer drugs to keep them from dying.

When Sharp learned about the surgeries, he e-mailed Bohner again. Bohner alerted his boss, Michael Huggins, the head of Synthes's North American division, who sent a cautionary message to the sales force about the dangers of off-label marketing. Prosecutors would later dismiss Huggins's e-mail as "anything but strongly worded" and "confusing at best."

Despite the warnings, the vertebroplasty project rolled on. Sharp left the company for reasons, he says, having nothing to do with Norian. In April 2001, Higgins organized a focus group in Cupertino with surgeons who were interested in using Norian to treat VCFs. The doctors discussed the operations that had gone wrong in Santa Monica, according to minutes of the meeting. Dr. Sohail Mirza, a surgeon at the University of Washington, suggested that Norian could be causing problems if it entered the bloodstream. The spine contains multiple blood vessels, and any leakage into them could send cement to the lungs and heart, causing a fatal clot. Mirza said it was critical that Synthes conduct an animal study before using Norian in human patients. The company agreed to fund a small study.

Meanwhile, Synthes's top brass was scheduled to meet with Wyss in November to decide whether to proceed with plans to sell Norian for use in the spine. A few weeks before the meeting, Higgins asked a regulatory employee to mock up a clinical trial for using Norian in vertebroplasty. The staffer estimated it would take three years and cost about \$1 million. He told Higgins that Synthes needed government approval to test Norian on people -- a fact that was common knowledge, according to prosecutors and several former Synthes employees.

That November, Huggins, Higgins, and their colleagues met with Hansjörg Wyss in Tucson. It was judgment day for the vertebroplasty project. The attendees discussed the prospect of doing a clinical study, according to the meeting's minutes. Then Higgins asked whether Synthes should get an IDE and conduct trials.

The answer, according to the minutes, was no: "Decision made not to pursue an IDE study, but to get a few sites to perform 60-80 procedures and help them publish their clinical results." No explanation was mentioned. Synthes wasn't taking the onerous -- but expected -- route of getting an IDE. Instead, it would get a few doctors to do the procedure on their own, which the company hoped would popularize the product. It was, prosecutors later alleged, an end run.

The implications of the minutes are clear. But their passive construction raises a question. "Decision made" -- by whom? Nisra Thongpreda, the manager in charge of Norian, later told a grand jury that Wyss had made the call. (Wyss declined to comment.) Prosecutors, who never charged her, asked how she knew it was the CEO. "Because I was there at the meeting," Thongpreda said. She later added, "Tom Higgins asked Mr. Wyss ... about the IDE study and Mr. Wyss said no."

The prosecutor pressed for more. "Was that about it -- just no?"

"Just no," said Thongpreda.

Former employees describe Synthes as highly regimented -- the kind of place where employees do what they're told. "Everybody's just a sort of a worker bee," says one former staffer. Wyss was known for handpicking young executives, typically men who had gone to top-notch schools, and guiding their careers. Several former employees say Huggins and Higgins, who had attended, respectively, Wharton and Harvard, belonged to that group. "He picked these guys and cultivated them," says a former Synthes manager. "They were all fiercely loyal."

They also knew, former staffers say, that the man everyone called "Mr. Wyss" didn't tolerate dissent. Several recall a story, well known at Synthes, about the CEO attending a meeting at a Marriott hotel. Wyss asked a hotel employee for a banana. When the worker ignored his request, Wyss was "boiling," says a former employee who was in the room. Days later the company announced that henceforth Synthes employees could not stay at Marriott hotels. (Wyss says he banned the chain because it didn't donate the leftover food from Synthes's meeting to a homeless shelter.)

Wyss had rejected clinical trials. But there was a less-demanding form of regulatory approval, a process intended for modifications of permitted devices. Synthes applied for this type of approval and sure enough, in December 2001, the FDA blessed the use of Norian in the spine. But there was a crucial caveat. The FDA said that Norian could not be mixed with another substance before it was injected into the spine -- which is precisely what vertebroplasties require. (Defense attorneys would later assert that the FDA's language was confusing.)

The general clearance effectively prohibited Synthes from promoting Norian for vertebroplasties -- but did give it a foot in the door to spine surgeons' operating rooms. It's almost as if, to use a benign analogy, Synthes bought nosebleed tickets to a football game and then tried to sneak into the VIP section.

In the spring of 2002, Thongpreda received an unsettling e-mail from Dr. Jens Chapman, an orthopedic surgeon at the University of Washington who was working, along with his colleague Mirza, on the animal study funded by Synthes. The early results were alarming. Chapman informed her that when Norian was injected into the bloodstream of a pig, "the entire pulmonary artery system had clotted off." As he put it, "We were expecting to kill the pig ... but not suddenly and with a relatively small dose." (Chapman declined to comment; Mirza did not respond to requests to be interviewed.)

Over the next few weeks, according to prosecutors, top executives at Synthes held a series of meetings about Norian. On May 13, 2002, Huggins and Higgins met with Wyss and decided to proceed with their plan to informally test it for vertebroplasties. On May 22, Huggins and Higgins met again. This time there was "high concern about SRS in spine test market," according to a document assembled by an employee who didn't attend the meetings. On May 28, Huggins spoke with Wyss, and they "agree[d] to go ahead with Vertebroplasty Test Market."

Then, a couple of days later, the whole project almost blew up. One of Synthes's medical consultants at the time was an orthopedic surgeon named Ken Lambert. An old friend of Wyss's, Lambert had been doing work for Synthes for decades, even briefly sitting on the company's board. One afternoon he was in Synthes's offices when he stumbled across a box of Norian. Lambert noticed that the shipping label was addressed to a spine surgeon. "I was starting to smell a rat, so I said, 'Let's open it up,'" he says. "And there it was: directions on how to mix it." Lambert called Huggins, who assured him he would look into the matter.

Huggins was shaken. On May 30, 2002, he e-mailed Higgins and Bohner and told them he had talked to Lambert and was having "second thoughts" about the plan to promote Norian. "We discussed about the need to perform a real study to test Norian," he wrote. "It seems Spine is bypassing the needed blocking and tackling without thinking this all the way through."

Huggins's apparent crisis of conscience caused a stir in the lower ranks. By then Thongpreda had transferred responsibility for the project to Josi Hamilton, a 26-year-old product manager. Hamilton was rattled. She began assembling a timeline that would document the internal approvals, hoping it would protect her if she got into trouble.

→ THE PATIENTS

From left: Lois Eskind (seen in framed photo held by her husband, Ike), Ryoichi Kikuchi, Barbara Marcelino, and Joan Bryant, who all died after Norian was injected into their spines. The families of the four are suing Synthes. They allege that the patients were never warned about the experimental nature of the surgeries and the risks that accompanied them.



For a moment it seemed as though Huggins might kill the vertebroplasty project. But then, without any sign of explanation in the record, he let the issue drop. An internal e-mail shows only that the executive met with Wyss a few days after expressing his doubts.

Lambert, meanwhile, was still spooked. On June 10, 2002, he sent a late-night e-mail to Thongpreda. "In my respectful opinion, giving SRS directly to a surgeon for him to use without any protocol [control] is not a controlled study; given the other issues I have mentioned, this action amounts to human experimentation whose only defense seems to be that it will be a small study," he wrote. He forwarded the e-mail to Huggins and Higgins, adding that the company could "suffer serious consequences" if it didn't conduct proper studies.

The next day Lambert forwarded the e-mail to his old friend Wyss. "Dear HJW," he wrote. "I'm never sure what information gets to your level but some things have happened recently that could have serious consequences. If you are aware of all of this, then the system works."

Lambert was the second person to explicitly caution the company against testing Norian for unapproved uses. But like Sharp's earlier warnings, Lambert's went unheeded. He says he didn't hear back from the CEO, and his phone calls went unanswered. Eventually, Lambert says, Wyss contacted him -- to inform him that Synthes would not be renewing his contract. (Wyss says the contract ended for unrelated reasons.)

Two weeks later Jens Chapman and his colleague sent the final results of their study to Higgins. The first test involved mixing Norian with human blood in test tubes, then watching how quickly clots formed. The scientists noted that "a relatively small amount of Norian results in the formation of a very large volume of clot," which could block the flow of blood inside the heart or lungs.

The final word on the pig test was equally worrisome. The surgeons had injected Norian into a large vein leading to the animal's heart to simulate what would happen if the cement leaked during vertebroplasty. The pig's blood pressure plunged. When the scientists cut into it after its demise, they noted that volumes of blood clot containing Norian had amassed in its lungs. The animal had died in less than 30 seconds.

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The FDA does not regulate doctors' activity; as a result, off-label prescribing is ubiquitous. A 2006 study in the *Archives of Internal Medicine* examined hundreds of millions of prescriptions and found that more than 20% were written for off-label use. "A surgeon can prescribe anything," says a former Synthes employee. "If he says, 'Let's put a bowling ball in your body,' he can do it." Physicians are quick to note that, because the FDA's approval process can be frustratingly slow, off-label drug and device usage is a crucial part of health care.

Surgeons regularly use devices in unapproved ways. The culture of orthopedic surgeons is particularly aggressive. Predominantly male, "orthopods" are the jocks of the surgical world. Sales representatives tell stories of doctors playing loud rock music in the operating room and throwing instruments at the wall when they get frustrated. Several surgeons tell *Fortune* they simply don't have time to pore over labels. Lambert offers a blunt appraisal: "'Off-label' is not at all a pejorative term -- it's almost the opposite. Reading the label is for people who read labels."

Surgeons don't always listen to the FDA, but they do heed the young sales representatives who bring them devices and routinely watch them operate. "It sounds ridiculous, because here's a guy who went to medical school and did his

residency, and he's listening to some guy in the back of the room," says one former Synthes salesperson. Another adds: "It's not uncommon to have a surgeon with a drill in his hand, about to drill a hole, looking over his shoulder at you saying, 'Is this right?' "

In the summer of 2002, Hamilton, the young Norian product manager (who had recently graduated from business school), began training spine surgeons to mix SRS with barium sulfate in order to perform vertebroplasties -- an act explicitly prohibited by the label. During this preliminary trial, which Synthes employees called "test market phase 1," a select group of surgeons conducted several dozen surgeries using the mixture, SRS-R.

Hamilton later testified that she knew she was on thin ice. The FDA's warning was unambiguous: They weren't supposed to talk about mixing SRS. But whenever they brought up their concerns with their managers, they were assured that everything would be fine. Hamilton, who was later granted immunity from prosecution in exchange for her cooperation, explained that it was understood at Synthes's spine division that off-label marketing was the status quo: "This is the way that it's done. And it happens every day."

The SRS-R test market proceeded successfully. Dozens of surgeries went off without a hitch, and Synthes was ready to move on to phase 2. That September, Hamilton gave a presentation to several executives -- including Wyss -- about the vertebroplasty project. "Wyss inquired about the test-market setup and how surgeons, who are interested in the product, were to be trained," the minutes of the meeting stated.

That winter, employees in the regulatory division were tasked with getting the FDA to approve the mixed version of Norian, rechristened as Norian XR, for general use in the spine. It was a touchy subject. The FDA had recently issued a public notification that stressed the off-label nature of vertebroplasties. In December 2002 it approved the mixed version. But Synthes was still stymied: The FDA ordered it to include a warning on its label that said XR should not be used to treat vertebral compression fractures.

The fact that Synthes couldn't promote XR for its target market didn't seem to bother its executives. Higgins sent the vertebroplasty team a celebratory e-mail. "Let me take a moment to congratulate the four of you [on] getting XR approved," he wrote. "Very Well Done!"

Less than a month later Dr. Barton Sachs, a spine surgeon in Texas, used Norian to treat a VCF. His patient, a 70-year-old Oklahoma native named Lois Eskind, said beforehand that she was in excruciating pain and that she'd "rather have surgery than live like this." Fifteen seconds after Sachs injected the cement into her spine, Eskind's blood pressure plummeted. As a Synthes sales representative looked on, Sachs attempted to resuscitate her for 30 minutes before she died. (Sachs declined to comment.)

→ THE EVIDENCE

Numerous Synthes documents emerged during the sentencing process. From top:
• An excerpt from a memo touting the lucrative market for vertebroplasty
• A portion of an e-mail in which Huggins expressed reservations about the Norian plan
• Part of the FDA-approved label, which warned against using Norian XR to treat VCFs

3) CONCLUSIONS

The use of the vertebroplasty is on the rise. The technique has tremendous potential, as it fills a void in the treatment of vertebral body compression fractures. There are over ½ million of these fractures a year in the U.S. The technique is only starting to be publicized in the surgical community; its use will no doubt rise within the next few years.

In addition, I had a long phone conversation with Dr. Lambert who is very concerned about the Spine plan. I am now having second thoughts. Please make that shipments are stopped until we can discuss and resolve all the issues.

WARNINGS

- Do not manipulate site during the 10-minute Setting Time.
- Remove excess material in adjacent soft tissue.
- Do not mix Norian XR Bone Void Filler with any other substance.
- Highly pressurized application of Norian XR Bone Void Filler into a tightly confined space with ready venous or arterial access is not recommended, as the potential for formation of emboli is unknown.
- Not intended for treatment of vertebral compression fractures.

PRECAUTIONS

Hamilton and Thongpreda called the doctor to find out what had happened. Sachs said he didn't know the cause of death; the family had not requested an autopsy. He didn't blame Norian, but he was concerned, according to minutes of the call:

"He did the technique the way he was supposed to and the outcome was catastrophic."

Whenever a death or injury occurs that may implicate a medical device, the manufacturer is obligated to report what happened to the FDA. Synthes did not report Eskind's death. According to an internal document, the company's regulatory staffers decided that, because Sachs didn't conclusively blame Norian for his patient's death, they didn't have to send a report.

If Synthes staffers were disturbed by Eskind's death, they didn't show it. That month a group of employees met to discuss a sales plan for Norian. The document they put together predicted revenue of at least \$20 million by 2005, with after-tax profit margins of 50%.

In mid-August, Hamilton and her team launched the next phase of its test market with a surgeon forum in San Diego. Spine doctors from around the country flew in (their travel expenses were paid for by Synthes, which also organized a dinner and golf outing). Hamilton handed out binders of information about Norian XR, her business cards tucked inside. Sachs delivered a keynote address. There was a training session where surgeons practiced injecting XR into the vertebrae of cadavers. "The takeaway from the course was that this stuff is safe, and it works, and there's very little downside risk," says one of the surgeons Synthes trained.

For the moment everything seemed to be going fine. The forum was a huge success. Several surgeries went smoothly. Then, on Sept. 19, disaster struck again. Dr. Paul Nottingham, a surgeon based outside San Francisco, was operating on Ryoichi Kikuchi, an 83-year-old prize-winning physicist. Shortly after Nottingham injected him with XR, Kikuchi's blood pressure sank. The doctor couldn't resuscitate him, and he died on the table.

Nottingham couldn't ascertain why his patient had died, and Kikuchi's family didn't request an autopsy. But unlike the previous surgeon to lose a patient, Nottingham was quick to point a finger at Norian, which had apparently leaked during the operation. When Hamilton called Nottingham to discuss what had happened, the surgeon erupted. "He claimed the sales consultant 'pushed' this product on him and was unclear as to its status on the market," she wrote in minutes of the call. This time Synthes did file a report to the FDA. But it was vague and left out key details.

Nottingham asserts that the company misrepresented the product to him. "Synthes is very much to blame for pushing a product that they didn't have the indications [i.e., approvals] for," he says, adding that he never used Norian again. "I used it once -- that was enough."

Hamilton also called Nottingham's partner, Dr. Hieu Ball, to discuss what happened. Ball had more experience with Norian; according to prosecutors, he had assisted on one of the failed surgeries that took place in 2001 in Santa Monica. He had also performed five operations using Norian, Hamilton wrote. "Based on his own experience," she added, "he will continue to use XR."

In December 2003, John Walsh, who had just become head of regulatory affairs at Synthes Spine, signed off on Norian XR's technique guide, a brochure that was given to surgeons. The guide omitted the warning that the FDA had ordered Synthes to include on the label, which said that Norian shouldn't be used to treat VCFs.

It also included two "case examples" -- real X-rays of anonymous patients who had had surgeries with Norian. One of the X-rays belonged to a 41-year-old male. The other came from a 70-year-old female. The female, prosecutors later revealed, was Lois Eskind. Unbeknownst to the surgeons who received the brochure, the case study came from a woman who had died after being injected with Synthes's product.

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On Jan. 21, 2004, Barbara Marcelino checked into a hospital near San Francisco for spine surgery. Her daughter, Georgia, called her that evening to see how she was doing. Georgia had wanted to fly out for the surgery from her home in Salt Lake City, but her mother insisted that she didn't have to because it was an "easy" procedure. "She said, 'I think this is going to help me a lot and make me feel a lot better,'" recalls Georgia.

Their conversation was light. Marcelino, an avid reader who enjoyed Proust, complained about the Stephen King novel she was reading. Petite, with soft white hair and a small, heart-shaped mouth, Marcelino fretted about spilling a glass of water in her hospital bed.

Her surgeon was Hieu Ball. At 10:30 that night, according to prosecutors, Ball started to operate. A Synthes sales representative -- the same one who witnessed Kikuchi's death -- was in the room. Ball injected the cement into Marcelino's spine at 11:10 p.m. Her blood pressure immediately plummeted. At 11:12, Ball attempted CPR. At 12:12 a.m., Marcelino was pronounced dead. An autopsy later revealed foreign material in the blood vessels in her lungs, though the results were inconclusive because of the prolonged CPR.

Ball declines to comment on why Marcelino died. He says he was unaware of Synthes's animal studies involving Norian and believes he used Norian in an approved manner. "We were using it based on the recommendation of the company." (Ball's lawyer adds that "of the 20-30 times he used Norian, there was only one instance of complication.")

When the company received news of Marcelino's death, Hamilton quickly drafted a letter to surgeons that stated, "Synthes is stopping the distribution and usage of Norian XR." Her letter was never sent. Instead, Walsh, the spine division's new regulatory chief, helped put together a different letter for surgeons. This version simply stated that "deaths have been reported." Norian, it said, should not be used to treat VCFs -- but Synthes would "continue to explore new approaches to the treatment of vertebral compression fractures." The letter did not mention a recall, and Synthes continued to sell Norian.

Rumors about the deaths quickly spread at headquarters, and staffers began to panic. Then, on the morning of May 11, 2004, the project finally imploded. Capt. Joseph Despins, an FDA investigator, arrived at Synthes headquarters and announced that he had received a tip that the company had engaged in off-label marketing.

Over the next month, Despins conducted a series of interviews. Synthes's staffers denied almost everything. Bohner said he knew nothing about a vertebroplasty test market for SRS. Hamilton disputed having encouraged surgeons to use Norian off label. Huggins told Despins that he didn't recall what was discussed at meetings.

Despins didn't buy it. His 143-page inspection report concluded that the company had violated FDA rules. Synthes, he wrote, should have applied for an IDE before testing Norian. Despins accused the company of off-label marketing.

Around the same time, Chapman -- the surgeon who had conducted the study in which a pig had died only seconds after being injected with Norian -- came back into the picture. (It wouldn't be the last time.) The surgeon wrote a letter at Huggins's behest that defended the cement, according to prosecutors. They later pointed out that Chapman had recently been named to the Hansjörg Wyss chair at the University of Washington, which received a \$2 million endowment from Synthes's CEO. The prosecutors concluded: "So we submit the letter should be taken with a grain of salt."

* * * * *

It took nearly five years of FDA proceedings, investigation, and grand jury hearings before federal prosecutors were ready to move. By 2009 they were prepared to indict not only Synthes but also four individuals: Huggins, Higgins, Bohner, and Walsh. The executives' attorneys negotiated a deal in which the men would plead guilty to a misdemeanor under the Responsible Corporate Officer Doctrine. The U.S. Supreme Court has ruled that the Food, Drug, and Cosmetic Act allows prosecutors to charge individuals who lack actual knowledge of a crime simply because they are "standing in a responsible relation to a public danger."

When Synthes was charged, as noted earlier, the doctrine had never been used to send an individual to prison. Most people expected the four executives to receive fines, or possibly probation.

On June 16, 2009, the grand jury handed up an indictment against Synthes and the executives. It was a doozy. Norian, the company, was charged with 52 felony counts, including lying to the FDA and intent to defraud. Synthes, its corporate parent, was charged with 44 misdemeanors. Though the U.S. attorney's office charged the four businessmen with just a single misdemeanor for their roles as "responsible corporate officers," it outlined in excruciating detail the history of the Norian XR test market and deaths. The U.S. attorney's office issued a press release peppered with lurid details, including the allegations that Synthes had performed "human experimentation."

The defense attorneys were furious. They believed they were the victims of a bait and switch. In their view, their clients had agreed to take general responsibility for their company's actions only to find themselves charged with a litany of misdeeds -- without any need for the prosecutors to prove that the executives had committed those acts. There was no reason, they argued, that the judge should consider the prosecution's allegations in his sentencing decision.

The assistant U.S. attorney who prosecuted the case, Mary Crawley, disagreed. Just because the government didn't have

to establish that the executives were involved in the crime didn't mean it couldn't do so if it wanted, she argued. In a filing, she wrote: "[The] four individuals seek to transform the responsible corporate officer doctrine from a sword intended to achieve maximum adherence to the U.S.' food and drug safety laws into a shield insulating the genuinely culpable parties from the consequences of their own intentional wrongdoing."

The war between Crawley and attorneys for the executives raged on for two years. Meanwhile, in October 2010, Synthes pleaded guilty, agreeing to pay \$23 million in fines and divest Norian. In exchange, the Justice Department promised not to bring any new criminal charges against Synthes employees.

That included Wyss. He was not charged in the indictment, but he was mentioned. The prosecutors cited "Person 7" as making the initial decision not to pursue an IDE study. A key on the last page identified Person 7 as Synthes's "CEO and major shareholder." The U.S. attorney's office declined to comment on why it didn't charge Wyss, but the answer may be simple: The CEO's name appears multiple times in e-mails and meeting minutes, but only as a recipient and attendee. Wyss's name also turns up in documents less and less as events reached their peak.

Around the time of the guilty plea, Synthes was quietly exploring a sale. In late September 2010, Wyss met with top executives from Johnson & Johnson, including **Alex Gorsky**, then head of its medical devices unit and now its CEO. The company saw the opportunity to achieve dominance by buying one of the highest-margin players in a growing market. Seven months later, on April 27, 2011, J&J announced that it was buying Synthes for about \$20 billion. (J&J declined to comment for this article.) The deal, which formally closed in June 2012, valued the Wyss family stake at about \$10 billion.

* * * * *

In Nov. 21, 2011, the four Synthes executives appeared for sentencing in a federal courthouse in Philadelphia. Huggins went first. His lawyer touted Huggins's devotion to his family and his community service. The judge, Legrome Davis, told Huggins to stand, and the packed room fell silent.

Huggins's conduct, the judge said, was "egregious" -- so egregious that he was going to send him to prison for nine months. "I think that a lesser sentence would not speak to the harm that has been done here," Davis said. It was the first time in his 25-year career, he continued, that he had sentenced someone above the federal guidelines, which suggested Huggins get no more than six months in jail.

"But I do it because it is necessary," he boomed. "Because what has occurred in this case, in terms of wrongfulness -- it's 11 on a scale of 10." Davis denied Huggins's request that he be allowed to turn himself in later. Instead, as his wife and daughters watched, Huggins was placed in handcuffs and led directly into custody.

Davis sentenced the next executive, Higgins, to nine months. The third man to face the judge was Bohner. His lawyer, Brent Gurney, took a surprising tack when asked about Bohner's guilt. "There is another person who is not present in this process who may have a bearing in answering your question, Your Honor," he said. That person, he continued, was none other than the man who ran Synthes during the illegal clinical trials: Wyss.

It was Wyss, Gurney continued, who made the initial decision to test the bone cement without doing proper clinical trials. It was Wyss, he charged, who created a corporate culture where people could not "stand up and stop things that were wrong, especially when they were coming from the top." Gurney cited Synthes employees who told the grand jury that the chairman was "hands-on," "forceful," and an "800-pound gorilla" who refused to brook dissent.

Davis seemed unconvinced. Then, just as the judge was laying into the executives' "shameful behavior," the confrontation took a bizarre turn: Gurney suddenly collapsed, hitting his head on a table as he fell. For a moment he lay on the floor, bleeding. When he regained consciousness, the lawyer -- who declined to discuss the episode -- was taken to a hospital. The hearings continued, and the judge sentenced the fourth executive, John Walsh, to five months.

Gurney recovered and returned to court in December for his client's rescheduled hearing. This time he made no mention of Wyss, and Davis sentenced Bohner to eight months. Gurney asked if he could delay Bohner's sentence so that his client wouldn't have to spend the holidays in a detention center. Davis said no. "To me, jail is not a question of personal convenience to the defendant," he said. "In the scheme of things, it's an incredibly brief sentence." He sent Bohner straight to prison.

* * * * *

The jail sentences in the Synthes case stunned the industry, sparking fears of increased risk for executives. Some defense lawyers warn that the government's strategy could backfire. "Now that executives realize that they may be facing real jail time, they may be reluctant to plead guilty," says Adam Hoffinger, the attorney at Morrison & Foerster who represented Tom Higgins.

Government lawyers counter that prosecuting individuals is the only way to stop off-label marketing, because companies have come to view fines as a cost of doing business. As a result, the Responsible Corporate Officer Doctrine, which was mostly dormant throughout the 1990s, is resurgent. In 2007 the government used it to pursue charges against **three officials at Purdue Pharma**. In 2011 the former CEO of KV Pharmaceutical was sentenced to 30 days in jail. The Justice Department used the Synthes case to send a message: The threat of incarceration is real.

As for the convicted former Synthes executives, Walsh was released from a Pennsylvania prison camp in late April after serving a five-month sentence. Huggins, Higgins, and Bohner were all released at the end of the summer.

Synthes itself suffered little from the Norian debacle. After settling with the government, the company sold the bone cement unit to Kensey Nash, a small manufacturer located just down the road, for \$22 million (just \$1 million less than its fine). Today J&J's DePuy Synthes unit is the product's exclusive distributor.

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The civil litigation over Norian is far from over. The families of Barbara Marcelino and Ryoichi Kikuchi jointly sued Synthes, the four executives, and Wyss. Their lawyers, Greg Rueb and Joseph Motta, called the defendants' conduct "reprehensible, despicable, deceptive." Wyss's attorney has filed a motion to dismiss the suit, arguing that the families "failed to allege any specific facts indicating that Wyss had any personal involvement" in the purported crime.

Eskind's daughter, Eva Sloan, filed suit against Synthes in late July. "One of the most offensive things was the little piddly sentence they got for this," she says. "They could have gone to 7-Eleven and stolen a six-pack of beer and got more time." Like the Kikuchi and Baddley families, the Eskinds say they were kept in the dark about the circumstances of their relative's death for nearly a decade.

These disasters didn't put an end to the use of Norian in the spine. Three years ago, an article in the *New England Journal of Medicine* concluded that vertebroplasties are basically ineffective. But many spine surgeons still believe in the procedure.

In June of this year, another death came to light. A man from Enumclaw, Wash., named Russell Bryant filed a suit against Synthes alleging that his wife, Joan Bryant, had died after being injected with Norian. This lawsuit described events similar to the others, but with a troubling twist: Bryant's surgery took place on July 6, 2009 -- three weeks after the government had filed charges against Synthes. Even more shocking, one of the two surgeons named in the complaint was Jens Chapman, the same person who had studied Norian in the early 2000s and observed the rapid death of a pig injected with the cement. (Chapman's lawyer declined to comment.)

The complaint's version of the facts is as follows: Chapman first attempted surgery on June 29, 2009. After he started operating, Bryant began bleeding profusely and had to be transferred to the intensive-care unit. On July 6, Chapman tried again (according to a report filed by the company, a Synthes sales representative was in the operating room). After Chapman injected Norian into Bryant's back, she experienced cardiovascular collapse and died.

Bryant's suit asserts that his wife, who was 58, was healthy when she went into surgery. She reported on a hospital questionnaire that she "felt full of life, felt calm and peaceful and felt happy all the time."

A few weeks after Bryant's death, two reports were submitted to the FDA. One described a fatal surgery that took place on July 6, 2009 -- Bryant's death, according to the complaint. The other report recounted a death that had occurred nearly two years earlier, on Aug. 17, 2007. It stated that a woman injected with Norian had died during spine surgery; an autopsy found cement fragments in her lungs.

The belated timing of the second report caught the attention of Bryant's lawyer, Dan Hannula, who suspected that Chapman had submitted both notifications. With the help of an investigator, Hannula found a woman from Enumclaw whose operation and death matched the description in the report. Reba Golden died on Chapman's operating table on Aug. 17, 2007, according to her daughter Cindy. She was 67. Until this summer, Cindy says, she had no idea that Norian might be implicated in her mother's death. She plans to sue.

--Reporter associate: Doris Burke

This story is from the October 8, 2012 issue of Fortune.

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