THE CANCER LETTER

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How Medical Devices Do Harm

By Matthew Bin Han Ong

Friends call him The Hoomanator, a darkly comical conflation of his first name, Hooman, and morcellator, the medical device he has aggressively campaigned against.

Enemies—who are great in number—call him much worse.

Over the past two years, Hooman Noorchashm, a cardiac surgeon at Thomas Jefferson University Hospital, has been accused of launching a "campaign of distortions," threatened with legal action, subjected to security searches and publicly chastised.

Over a two-year investigation, The Cancer Letter tracked Noorchashm and his wife, Amy Reed, as they challenged FDA, Congress, hospitals, the gynecology profession and manufacturers of medical devices. Their struggle began with a routine hysterectomy, during which a device called a power morcellator disseminated Reed's undetected sarcoma. Today, as Amy's aggressive disease spreads, the couple continues to draw public attention to the blind spots in the U.S. medical device regulatory system.

Reed and Noorchashm's campaign reveals how the system works and how it fails. As a direct result of the outcry stirred up by the couple, FDA has restricted the use of power morcellators, finding that one in 350 women undergoing hysterectomies or myomectomies have an unsuspected uterine malignancy.

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Editorial

The Year in Review

By Paul Goldberg

As the New Year approaches, we are preparing to revamp our website and launch an app. The work on it is almost done—a January launch seems likely.

In 2015, we got to report some cool stories, win national journalism awards and successfully deflect Amgen's attack on our First Amendment rights.

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The Cancer Letter is taking a publishing break, and will return Jan. 8, 2016

How Medical Devices Do Harm

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The couple and their supporters argue that the lives of this minority of women are being sacrificed for the convenience of the majority. Critics say the controversy was blown out of proportion by the media, and as a result, women are more likely to be harmed by more invasive open surgeries that FDA's restrictions have made the standard of care for most women. However, in a statement to The Cancer Letter, FDA said it stands by its guidance.

On Dec. 18, Rep. Mike Fitzpatrick (R-Pa.) sent a letter to the FDA Office of Criminal Investigations, requesting an investigation of the "failure" of FDA's Medical Device Reporting regulations with regard to specific hospitals and manufacturers.

"As you may be aware, hundreds, if not thousands, of women are dead because of a medical device known as a laparoscopic power morcellator," Fitzpatrick wrote. "Despite the long history of this device on the market, only recently has the FDA put out guidance that the use of laparoscopic power morcellator increases the risk of spreading unsuspected cancers.

"It appears that these patient safety regulations may not be working as intended, leaving patients in danger."

Fitzpatrick's letter can be downloaded here.

The questions that remain extend beyond power morcellators, encompassing the entire landscape of medical device regulation. Patients can be harmed and never learn that the device is to blame. Doctors, hospitals, and manufacturers can, as a practical matter, conceal the fact that a device has caused harm. No one will catch them, because no one is looking.

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Here is what The Cancer Letter's investigation shows:

• FDA doesn't assess the risk posed by the vast majority of medical devices. Instead of focusing on risk, FDA's Class II 510(k) process clears products for the market based on "substantial equivalence" to comparable devices that are already on the market. The power morcellator is one example where preemptive risk assessment by the agency might have gauged the potential for harm to a subset of women, experts said to The Cancer Letter.

• Hospitals and manufacturers are required to "self-report" adverse outcomes to FDA, but the agency doesn't actively look for those that don't. The agency says it focuses on "encouraging" more reporting, which means that manufacturers and hospitals can often get away with not reporting adverse outcomes. This matter has become the focus of probes by Congress, the FBI, and the Government Accountability Office.

• FDA doesn't have a postmarket surveillance system for tracking all medical devices available in the U.S. Experts say the agency does not have a system analogous to the National Drug Code Directory, which assigns unique identifiers to each drug product. Without a data system that can be used for active safety surveillance, FDA, manufacturers, providers, and patients cannot quickly identify potential safety issues. Unique device identifiers exist, but investment is needed before payers, providers and hospitals can report UDIs in claims data and electronic medical records.

• Manufacturers of the highest-risk medical devices are shielded from product liability lawsuits. The 1976 Medical Device Amendments—along with a 2008 Supreme Court ruling—sharply limit the types of recourse patients might have for injuries from medical devices. This applies to Class III products, which go through premarket approval, FDA's highest bar for demonstration of safety and effectiveness.

Lawsuits can be filed for injuries caused by Class II devices, which include power morcellators. At least 50 such suits have been filed in the U.S. since Reed and Noorchashm brought the issue to light. The couple has filed their own lawsuit claiming medical malpractice on the part of the device manufacturer, Karl Storz, and Brigham & Women's Hospital, the institution that performed Reed's surgery. Hospital officials declined to comment on the lawsuit.

2015 was a rough year for Reed. The 42-year-old mother of six has had three surgeries, chemotherapy, and three runs of stereotactic radiation for five metastases of leiomyosarcoma in her spine, lung and pelvis. The latest occurrence was removed on Dec. 16.

The Cancer Letter's video interview with Reed and Noorchashm is posted here.

Driven to obtain justice for Reed, as well as to protect future patients from unnecessary harm, Noorchashm took on the entire establishment.

"We have to find a way out of this hole. I'm committed to doing whatever it takes to figure out a way," Noorchashm said. "But I fear that my best may not be good enough."

Two Docs who Broke the Code

By Matthew Bin Han Ong

Hooman Noorchashm sends out several scathing emails each day.

Consider the subject lines of some recent emails that went to hospital administrators, with copies to members of Congress and the press: "Your ethical lapse and negligence." "Outrageous!" "Your corruption." "The Fouled Ethics of Your Specialty." "Do read with care."

"The time for diplomacy has passed," Noorchashm said to The Cancer Letter. "I have no time to play politics. I have a wife with advanced cancer and six young children."

His wife, Amy Reed, is battling advanced leiomyosarcoma. Since her undetected cancer was spread via power morcellation performed at Brigham & Women's Hospital in October 2013, Reed has been in treatment for metastatic disease.

"Every time I see her go through these different phases and I think about the implications of it, it gives me a little bit more resolve to look at the root cause of this thing and hit it as hard as I can," Noorchashm said.

The Cancer Letter's video interview with Reed and Noorchashm is posted here.

Noorchashm's blistering, in-your-face tactics abandon the decorum of academic debate usually expected of Harvard physicians. He says his indignation grew in response to what he describes as the initial stonewalling he received from his former employer, Brigham & Women's Hospital—and the medical community at large—for speaking up.

"It's probably fair to say that we went from being straight-laced professionals on a certain path, to becoming activists," Noorchashm said. Reed was formerly employed as an anesthesiologist at Beth Israel Deaconess Medical Center, and Noorchashm was formerly employed as a cardiothoracic surgeon at Brigham.

Angered and disillusioned, Reed and Noorchashm turned to the press, regulators and legislators.

"It took heroic measures on mostly Hooman's part to be heard," Reed said to The Cancer Letter. "They weren't reaching out to us. You know the number of emails alone that he sent, and the number of phone calls—it was like three full-time jobs, what he was doing to get the FDA to move in that direction. And that's not even thinking about the 20 years that this was on the market with no recourse for these patients."

Within a year, FDA published a guidance to severely limit the use of power morcellators in the vast majority of women getting these procedures. An analysis by the agency found that one in 350 women who undergo hysterectomy or myomectomy for fibroids have an unsuspected uterine sarcoma (The Cancer Letter, Nov. 26, 2014).

The FBI and the Government Accountability Office have launched investigations. And now, members of Congress are writing letters to determine who knew what, and when.

"The reality is, this succeeded because there were two things: there was a fundamental truth underlying it, and because the press engaged it," Noorchashm said. "The Wall Street Journal and The Cancer Letter did a great public health service, and I think in both professional domains, both outlets got recognition by their colleagues that this was something significant that was accomplished.

"The third was because we were hitting this problem from inside the establishment."

Having undergone two surgeries in November and December, Reed is focusing on recovery, and her family.

"What's immediately next is, for me, what's immediately in front of me," Reed said. "As Hooman said, we're working hard to make a cure or at least turn this into a chronic condition.

"I'm lucky that I started off this in relatively good health, so hopefully I'll be able to withstand all the treatments that are thrown at me, and you know, raise the kids, dog, chickens.

"The biggest lesson I've learned this year is that this is just one example of many. We always come across things in life that don't seem right. There were countless times when people could've intervened in the past 20 years that wouldn't leave us sitting here.

"It's very easy to stand by or look the other way. That's very easy; that's the default—but you can really make a difference to one person by not doing so. It's not always pleasant, and it certainly doesn't win you any popularity contests or help keep any mainstream jobs, but it can really make a difference to people.

"I hope I've done true to my word and stayed to the cause and spoken up."

What Did Brigham and J&J Know?

In the initial months after Reed's October 2013 hysterectomy at Brigham, the couple was stunned to discover that upstaging of Reed's disease was not an unlucky, statistical anomaly. Other women must have been similarly harmed.

Power morcellators have been on the market for about 20 years, and were used to perform routine hysterectomies and myomectomies on about 100,000 women a year in the U.S. (The Cancer Letter, July 4, 2014).

At the time of Reed's surgery, no one had publicly made the connection between the mechanical shredding of uterine tissue and the dissemination of hidden malignancies.

It was a painful discovery for Reed and Noorchashm, and it happened only because of the couple's medical expertise—both physicians have PhDs in immunology, and Noorchashm, now a cardiac surgeon at Thomas Jefferson University Hospital, has a working understanding of medical devices.

The couple immediately alerted Brigham to the problem, believing that the Harvard-affiliated hospital would ban the procedure, set an example, and thereby protect women across the world from avoidable harm.

Their concerns were met with silence in the beginning, Reed and Noorchashm said, not only from Brigham, but also professional gynecological societies and device manufacturers.

Noorchashm and Reed are suing Brigham, claiming medical malpractice.

Hospital officials declined to comment. "We will not be answering any further questions," a spokesperson said.

As media across the country picked up their story, letters and phone calls from other patients and their families poured in, confirming the couple's suspicions.

In the past two years, over 300 patients and families have come forward claiming harm, and at least 50 lawsuits have been filed.

Reed and Noorchashm subsequently learned that Brigham doctors—as well as the Johnson & Johnson leadership—knew of the dangers and risk estimates of power morcellators prior to Amy's surgery.

But no one, it appears, had informed FDA as per Title 21, Section 803 of the Code of Federal Regulations, which mandates adverse outcomes reporting by user facilities and manufacturers.

"Failures in many domains had created this monster that was sacrificing one in 300 to 400 women to the altar of corporate medicine," Noorchashm. "An individual who has been hit by this and is dying in your hospital and you don't take any real steps to protect others in your own hospital? You're criminally negligent."

The press started asking questions, and the momentum reached the House Subcommittee on Oversight and Investigations (The Cancer Letter, Nov. 20), which launched an inquiry focused on reporting of adverse outcomes.

In a statement to The Cancer Letter, J&J subsidiary Ethicon said it didn't know of the dangers of power morcellators prior to December 2013, when Reed and Noorchashm filed a Medical Device Report to FDA. Whistleblower Robert Lamparter, a retired pathologist from central Pennsylvania, disagreed, and produced documents from 2006 proving that he had reported to J&J a near-miss case as well as risk estimates similar to FDA's numbers (The Cancer Letter, Nov. 20).

In November 2014, The Cancer Letter first reported on Brigham's role in upstaging Erica Kaitz's leiomyosarcoma via power morcellation performed in 2012. Kaitz died on Dec. 7, 2013, nearly two months after Reed received her cancer diagnosis at Brigham (The Cancer Letter, Nov. 26, 2014).

In a study by Brigham physicians Michael Muto and Michael Seidman published November 2012 in PLOS ONE, the authors identify four patients—out of 1,091 patients—who showed evidence of peritoneal dissemination of leiomyosarcoma after undergoing power morcellation. Three of the four patients died, with an average post-diagnosis survival of 24.3 months.

It is not publicly known where the four patients were treated.

Responding to questions at a House subcommittee hearing, Jeffrey Shuren, director of the FDA Center for Devices and Radiological Health, said FDA wasn't informed of Kaitz's death or any other adverse outcomes prior to Reed's report in December 2013 (The Cancer Letter, Nov. 20).

"Campaign of Distortions"

In August 2014, Karl Storz, a German manufacturer of power morcellators, warned Noorchashm to cease his campaign against power morcellation or face legal action (The Cancer Letter, Aug. 27, 2014).

"Should we get to know further public statements from you that our device and/or management would be responsible for your wife's or any other women's uterine cancer, and/or any aggravation of their cancerous situations, we would not hesitate to take appropriate legal actions to protect our good name and our rights," the letter states.

A scuffle erupted in November 2015, when a Brigham administrator declared Reed and Noorchashm a security threat and subjected them to a physical search.

Noorchashm had to submit to being tailed by a security guard while his wife was undergoing an urgent cancer surgery (The Cancer Letter, Nov. 3).

"Do you know what it's like to have a hospital administration threaten your health care proxy with being forced out of the hospital, when you are six hours from home and family, and could potentially be left without anyone to speak for you in person, because of some arbitrary hospital rules that have been made up and apply only to them?" Reed wrote in a Nov. 13 letter to Brigham COO Ron Walls. "Threatening? Yes. Terrifying. You should be ashamed of yourselves for penalizing patients and their families for speaking up. For saying something's wrong. For saying that there was a real patient safety issue, and when no one listened, called them on it."

The couple sought a restraining order against Brigham for engaging in "retaliatory action"—the next day, a Boston Superior Court judge ordered the hospital to lift all security requirements, finding that "both plaintiffs will suffer irreparable harm."

In a Nov. 5 letter to Brigham, Rep. Mike Fitzpatrick (R-Pa.) wrote that he was "deeply concerned about what appears to be an effort to retaliate against [Reed and Noorchashm's] advocacy and silence their First Amendment Rights."

Walls replied, saying that the hospital stands by his decision, because of Noorchashm's "disturbing and threatening" emails to hospital faculty and staff.

"I undertook these precautions with full knowledge that he would use them to distort the truth and once again publically criticize the hospital," Walls wrote to Fitzpatrick Nov. 10. "Responding to the safety and security needs of our faculty, staff, our patients and their families is far more important to me than the impact of Dr. Noorchashm's campaign of distortions."

Top Gynecologists Challenge FDA Guidance

Many prominent gynecologists and some patient advocates are opposed to FDA's restrictions on morcellation, saying that more invasive open surgeries would harm more women than power morcellation.

That exchange was sparked by a recent study, led by William Parker, director of minimally invasive surgery at UCLA Medical Center, and published by The American College of Obstetricians and Gynecologists in the December 2015 issue of Obstetrics & Gynecology.

Titled, "U.S. Food and Drug Administration's Guidance Regarding Morcellation of Leiomyomas: Well-Intentioned, But Is It Harmful for Women?" the study, authored by top gynecologists in the nation, disputes FDA's estimate that one in 350 women getting a hysterectomy or a myomectomy have unsuspected uterine malignancies.

The group's letter to FDA can be downloaded here.

The authors, representing a 46-member review group, "disagree with the FDA's methodology in reaching their conclusion and provide clinical recommendations for care of women with leiomyomas who are planning surgery."

A recent and "more rigorous analysis"—the authors argue—of 133 studies determined that the risk of finding leiomyosarcoma among women having surgery for presumed fibroids was one in 1,960, or 0.051 percent. Another estimate puts the risk at one in 4,320, or 0.023 percent.

"There are serious gaps in the studies used [by FDA] to estimate the frequency of finding unexpected LMS where the device might be used," said Matthew Siedhoff, director of minimally invasive gynecologic surgery at the University of North Carolina, Chapel Hill. "Our research suggests that, rather than abandon the clear benefits minimally invasive surgery affords women, future research efforts ought to focus on better preoperative identification and new techniques, such as placing specimens in bags before removing them."

Ironically, another study published in the same issue of the journal produces estimates that wildly differ from those in the Parker et al. paper.

That study, titled "Occult Uterine Sarcoma and Leiomyosarcoma: Incidence of and Survival Associated with Morcellation," identified 125 hysterectomies with occult uterine sarcomas among 34,728 hysterectomies performed for leiomyomas. The study finds that the incidence of occult uterine sarcoma and leiomyosarcoma is one in 278 and one in 429, respectively—numbers that fall within range of FDA's estimate.

"Morcellation is associated with decreased early

survival of women with occult leiomyosarcomas," the authors conclude.

In 2014, Brigham launched a controversial study that combined power morcellators with "containment bags" intended to capture tissue during the minimally invasive procedure. The study was led by Jon Einarsson, the Brigham surgeon who performed the "open"—unbagged—version of the procedure on Erica.

Designed to enroll 400 women, the study was suspended after The Cancer Letter reported that the hospital did not seek an FDA Investigational Device Exemption—the agency's license allowing clinical testing of potentially high-risk devices.

In July 2014, several panel members of the FDA Obstetrics and Gynecology Devices Advisory Committee said that the safest way to perform a hysterectomy or myomectomy would be to remove the specimen intact, i.e. via the vaginal route, to preclude the need for a containment system (The Cancer Letter, July 25, 2014).

Responding to the Parker et al. paper, an FDA spokesperson said that the agency's recommendations have not changed.

"Prior to issuing recommendations concerning the use of power morcellation for the treatment of presumably benign uterine fibroids in November 2014, the FDA convened a public meeting of the Obstetrics and Gynecology Medical Device Advisory Committee," FDA said in a statement to The Cancer Letter. "At the meeting, patients, family members, health care providers, researchers, device manufacturers and other stakeholders—including some of the authors from the recent paper—presented information and provided their perspectives.

"The FDA's November 2014 recommendations considered these perspectives and that of the Advisory Committee. At this time, the Agency's recommendations have not changed.

"We continue to believe that inclusion of a boxed warning and contraindications to the use of power morcellation for uterine fibroid removal in the majority of women is both appropriate and necessary.

"We welcome the continued scientific dialogue concerning the available evidence about benefits and risks associated with power morcellation and will notify the public if our recommendations change."

FDA's November 2014 guidance preserves the use of power morcellators for younger women who are interested in maintaining their ability to have children or wish to keep their uterus intact after being informed of the risks.

"By recommending these labeling changes, the FDA believes it will reduce the risk of unsuspected cancer spread," the spokesperson said. "But, even for that very narrow patient population who are not included in these contraindications, doctors should thoroughly present the risks of such surgery to these patients.

"There is evidence to show that women over 50 years old have a higher risk of having underlying cancer, and morcellation carries a higher risk than previously thought of spreading and upstaging such cancer. According to the medical literature, women 50 to 54 years old are five times more likely to have uterine cancer compared to women under 40. That risk continues to increase with age."

Power morcellators should not be used in younger women, Noorchashm said.

"The FDA says that power morcellators have a role in younger women hoping to preserve their fertility. This is a misrepresentation by the gynecological industry," Noorchashm said. "There is absolutely no reason for why young women wishing to undergo a fertility-preserving myomectomy should need a power morcellator. When you can't rule out a cancer for sure, the power morcellator would still pose a danger."

Noorchashm was infuriated by the Parker paper, sending out what might be called a Hooma-gram to over 50 people. His subject line: "Ethical/Legal Lapse in Gynecology—Do Read With Extreme Care."

"Dr. Parker and company, your position stands as ethically and legally compromised and weak," Noorchashm wrote.

Responding, Parker said that he had blocked Noorchashm's emails for over a year.

"Please be advised that, for more than a year, I have my server reject all of his email before it is delivered or read," wrote Parker, hitting "Reply All."

In the same exchange, Carla Dionne, executive director of the National Uterine Fibroids Foundation, said she would report Noorchashm to Google.

"On May 5, 2014, you and your wife were explicitly asked to cease and desist all email communication to me," Dionne wrote Dec. 14. "These latest 2 emails sent from you to me (and others) today is a direct violation of that request. At this point, I will be reporting your breach to abuse @ gmail. Cease and desist and STOP attempting to email me for ANY reason whatsoever immediately."

"Feel free, Ms. Dionne," Noorchashm replied.

The Root Causes of Harm From Medical Devices

By Matthew Bin Han Ong

The FDA Office of Criminal Investigations is being asked to determine why the agency has failed to detect the upstaging of cancers in women who had been operated on with a power morcellator.

These devices, widely used to shred uterine tissue in minimally invasive gynecological surgery, are now known to upstage undetected cancers that, according to FDA, occur in one of about 350 patients undergoing hysterectomies and myomectomies.

It took over two decades for the agency to realize that thousands of women may have died from metastatic uterine sarcoma upstaged by power morcellators, Rep. Mike Fitzpatrick (R-Pa.) wrote in a Dec. 18 letter to the agency.

"For over two decades since the power morcellator was cleared for use on patients, the FDA's Medical Device Reporting regulations failed to catch the severe dangers posed to women's health by morcellation," Fitzpatrick wrote. "It appears that these patient safety regulations may not be working as intended, leaving patients in danger."

The letter includes 26 questions concerning possible failures to report adverse events at Brigham & Women's Hospital, Rochester General Hospital, University of Rochester Medical Center, and Johnson & Johnson subsidiary Ethicon, the largest manufacturer of power morcellators.

"It should not have taken a family devastated by this device to raise the issue to the FDA," wrote Fitzpatrick, the House member who represents Hooman Noorchashm and Amy Reed, the physician couple who first focused the attention of the public on the hazards of power morcellators.

Fitzpatrick's letter can be downloaded here.

Fitzpatrick joins the FBI and the Government Accountability Office, which have launched separate investigations posing similar questions to FDA, device manufacturers and hospitals nationwide.

"FDA cannot comment on any planned or ongoing investigations," an agency spokesperson said to The Cancer Letter.

Over 300 patients and families have come forward claiming harm, and at least 50 lawsuits have been filed. Critics say the press has overblown the issue, causing a knee-jerk reaction on the part of the agency, which led to restrictions and black box warnings on the use of power morcellators. As a result of an FDA guidance published in November 2014, women are now getting more invasive surgeries. (The Cancer Letter, November 26, 2014.)

In a two-year investigation, The Cancer Letter found that patients aren't always told that they have been harmed by medical devices. Though federal statutes require hospitals and manufacturers to report adverse outcomes to the agency, no such reports were filed until Reed and Noorchashm's Medical Device Report in December 2013. Reed's undetected sarcoma was upstaged during power morcellation at Brigham and Women's Hospital two months earlier.

Experts on FDA regulation point to flaws in the system for regulation of medical devices and the agency's implementation of existing laws:

• **Bill Vodra, a former FDA associate chief counsel for drugs,** says that the agency's Class II 510(k) clearance process for medium-risk devices—a category that includes the power morcellator—is inadequate, because it does not focus on risk assessment. Instead, the process relies on "substantial equivalence" to predicate devices, thereby allowing subsequent iterations of a device to introduce risk without active FDA surveillance.

• **Larry Pilot, one of the original authors of the 510(k) legislation,** says that patients are being harmed because FDA doesn't commit sufficient resources to enforce federal requirements for hospitals and manufacturers to report adverse outcomes caused by medical devices. Pilot said the agency has the authority to demand more robust data when clearing power morcellators for the market.

• **Gregory Daniel, fellow and managing director of the Center for Health Policy at the Brookings Institution,** says that devices aren't tracked with the same rigor as drugs. FDA does not have a data system that can reliably track medical devices and identify potential safety problems. A good postmarket surveillance system would pick up signals of harm through claims data and electronic health records, thereby reducing the need to rely on reporting of serious adverse events.

A Clash Over Standards

As is the case with FDA laws, regulations and guidances, the standards for clearance and approval of devices are often disputed.

FDA uses a three-tier classification process for medical devices. Class I includes devices with the lowest risk, such as elastic bandages and examination gloves. Class II devices are cleared through the 510(k) process, which applies to new devices that are based on comparability to devices already in use. Power

morcellators were placed into this category.

Only Class III high-risk devices require an FDA premarket approval application. These include pacemakers and HIV diagnostic tests.

The vast majority of devices go through the 510(k) process—about 3,900 Class II devices were cleared for the market in fiscal 2013. By comparison, only about 45 devices are approved every year through the Class III premarket approval process.

The power morcellator is a good example of how the 510(k) process fails to protect the American public, said Bill Vodra, a retired partner at the Washington, D.C., law firm Arnold and Porter.

"The current test for clearance of a 510(k) is, 'Is the proposed device substantially equivalent to another device—the predicate device or device chain—that has been marketed?' The answer may be yes, but that does not tell you much about risk of the proposed device or its predicates," Vodra said to The Cancer Letter. "For a comprehensive evaluation of the 510(k) process, see the Institute of Medicine report in 2011. The whole premise of the IOM criticism was, if FDA doesn't ask about the risks, it's not necessarily going to get answers about risk."

The 2011 report, titled "Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years," was authored by an IOM committee asked by FDA and Congress to review the legislation in 2009.

Vodra helped draft many agency regulations still in use, including those implementing the Controlled Substances Act and FDA's rules for Good Manufacturing Practices, Good Laboratory Practices, Good Clinical Practices, bioequivalency and the Orange Book.

FDA should revamp the 510(k) process to categorize devices into several risk-based groups, Vodra said. This could allow for differentiation of surgical tools like power morcellators from products like acupuncture needles.

"You start by having a question in the preclearance process: what do we know about the risk posed by this device and its predicates?" Vodra said. "That could mean breaking apart the current Class II devices into a much larger universe of disparate device groups, because different groups of devices present risks similar to each other, but distinct from other groups of devices."

A conversation with Vodra is posted here.

FDA disagrees with the IOM recommendation to splinter Class II devices into multiple categories.

"While FDA does not agree with IOM's recommendation to create a new system, we do believe that we can make improvements to the current system and we have worked to do so over the past four years," Dayle Cristinzio, acting associate commissioner for legislation at FDA, wrote in a Nov. 12 letter to Fitzpatrick.

"FDA believes that for certain medical devices, comparison to a predicate device is an efficient and scientifically sound method of product evaluations. Tens of thousands of medical devices cleared through the 510(k) program function well for U.S. patients."

Risk shouldn't be used as the sole classifier, said Larry Pilot, one of the original authors of the 510(k) process.

Devices shouldn't be classified according to the risk they pose, because the legislation was designed to provide "reasonable assurance" of safety and effectiveness—a higher threshold than "risk," Pilot said to The Cancer Letter.

"I disagree with the agency's position and in particular, the IOM on the characterization of the classification process as risk-based," Pilot said. "It is not risk-based, and I have said this many times, because the criteria that applied to each one of the three classes was in the context of reasonable assurance of safety and effectiveness.

"A subset of safety is risk, yes, but this low, medium and high risk is fabrication.

"The statutory language, which didn't change, is quite clear that it is about safety and effectiveness, whereas functionally—if people want to look at risk—it's inappropriate for the agency to use risk as a surrogate for the explanation, when safety and effectiveness are the criteria.

"For drugs, it's absolute safety and effectiveness, whereas in the statute applicable to devices, it's reasonable assurance. That was a distinction that was made during the legislative process, because the objective was to avoid pigeonholing this industry into the criteria that applied to drugs."

A conversation with Pilot is posted here.

Pilot: Enforcement Needed at User Facilities

There is no need to revamp the 510(k) process, Pilot said. The agency should instead enforce existing laws to make device manufacturers and user facilities report adverse outcomes.

"It's a good system we have now, but FDA needs to allocate more resources to enforcement, especially for user facilities," Pilot said. "That's why FDA, with its authority, and this opportunity to put the emphasis on reporting to the user facility required by law, and then by specific regulation, should be going for money

penalties for user facilities that do not abide by the reporting requirement.

"I know for almost 10 years, many user facilities have not been keeping records, and did not have the required written procedures for evaluating whether a complaint justified an MDR.

"And FDA didn't know that? They haven't looked at any of this? How has FDA been managing what these user facilities are doing? What has the agency been doing?

"Because people like Amy [Reed] are being hurt by this. If she knew that it was, instead of one in 10,000, a one in 300 chance, she'd probably say no. This is an embarrassment to the agency.

"Going back to the responsibility of the external community, the users and manufacturers—I expect the FDA to have done a better job."

According to FDA, failure to comply with medical device reporting requirements will render a device "misbranded," and may result in the issuance of a warning letter or more severe penalties such as seizure of the device or monetary penalties.

In FDA's letter to Rep. Fitzpatrick, Criztinzio said that the agency generally focuses its enforcement on manufacturers, and not on user facilities.

"We have found that encouraging more reporting—and more complete reporting—by user facilities is a good use of our limited resources in this area," Criztinzio wrote.

Pilot said he is "astounded" by Criztinzio's letter.

"What? That surprises me, because I believe too much of the agency's resources go to manufacturers and are wasteful," Pilot said. "Encourage? I could never write a letter like that to Congress.

"That letter must have passed through [FDA Center for Devices and Radiological Health Director Jeffrey] Shuren's office. He had to have seen that letter that says, 'Oh, we have a voluntary system for the user facility community, but with the industry, we have a mandatory system.' You've got to be kidding me.

"This kind of judgment or failure to exercise judgment has been harmful to the agency and more importantly, to the public. This is our world—FDA's world—and we need to at least have some minimal understanding of surveillance, or when it's important to step up surveillance.

"If Brigham at Harvard isn't reporting, what about other groups and other user facilities?"

Vodra said that adverse outcomes reports are "extremely difficult to identify, capture, investigate and interpret."

"That's why I'm not so judgmental, off the top of my head, that a company should or should not have reported a medical problem until I know the facts of a particular case," Vodra said.

However, in the 2006 whistleblower case involving Johnson & Johnson subsidiary Ethicon, the reporting of a power morcellation near-miss case should have led to warnings, additional research, and to discussions with FDA, Vodra said (The Cancer Letter, Nov. 20).

"The near-miss case [reported by Robert Lamparter, a retired pathologist from central Pennsylvania] should probably have led a manufacturer to reassess the potential risks," Vodra said. "I'm not giving the company a full pass."

FDA: We Are Not Aware of Criminal Prosecutions

FDA officials say the agency has investigated cases of failure to report and taken enforcement actions.

"But we are not aware of criminal prosecutions that have resulted from a failure to report adverse events," FDA said in a statement to The Cancer Letter.

The most recent example of prosecution for failure to submit reports to FDA was the TMJ Implants case involving joint prostheses. This case is referenced in the draft guidance titled "Medical Device Reporting for Manufacturers," dated July 9, 2013.

A summary of the outcome noted: "One court agreed that although some of these consequences may be deemed clinically insignificant, they are considered to be serious injuries when coupled with the interventions, e.g. administration of antibiotics or other medications, explant, reconstruction, debridement, or revision surgery." (TMJ Implants, Inc. v. U.S. Department of Health & Human Services, 2009.)

In another 2009 case, the FDA issued warning letters to 17 LASIK ambulatory surgical centers after inspections revealed inadequate adverse event reporting systems at all the centers. Under adverse outcomes reporting legislation passed in 1990, user facilities are required to have a written protocol for adverse event reporting.

The inspections did not identify problems with the use of the LASIK devices—which permanently change the shape of the cornea with laser—at these facilities.

"FDA has an active industry training program, consisting of presentations, webinars, and numerous web resources," an FDA spokesperson said. "We also receive and address hundreds of questions from industry each year related to what should be reported and how to report.

"Congress recognized the challenges of user facility reporting and in the 1997 FDA Modernization Act provided FDA with the opportunity to design and implement a national surveillance network composed of well-trained clinical facilities that can provide high-quality data on medical devices in clinical use."

According to FDA, about 250 hospitals participate in the Medical Product Safety Network—also known as the MedSun program—which provides webinars, presentations, online trainings, and videos.

"Such tools help hospitals understand how identifying and reporting device problems to FDA early on can impact public health and improve patient safety in their hospitals," FDA said. "These facilities are trained to not only submit reports required by the MDR regulations but also to submit 'potential for harm' events that would otherwise be considered voluntary reports to FDA.

"We are also currently working with 20 hospitals from our MedSun Network to develop software capabilities to export real-time adverse event data with device identifiers from hospital incident reporting systems. The ASTER study demonstrated that facilitated 'triggered reporting' increased the number of adverse events reported by clinicians.

"The FDA has taken a number of recent steps to modernize the adverse event reporting and analysis systems including the development of automated adverse event reporting systems. We are also working to increase the number of reports submitted electronically with a goal of reaching an electronic submission rate of 95 percent of all reports submitted."

Daniel: No Reliable Data System for Tracking Devices in U.S.

Experts say devices aren't tracked with the same rigor as drugs, because FDA doesn't have a reliable medical device tracking system analogous to the National Drug Code Directory, which assigns unique identifiers to each drug product.

"On the drug side, the NDCs are great, because they are ubiquitous in electronic health data," said Daniel, fellow and managing director of the Center for Health Policy at Brookings. "NDCs are included in claims data, they're included in electronic medical records, and because of that, it's very efficient to go to large claims data sources in electronic medical records and quickly identify unique drug exposures and then link those exposure to outcomes.

"That doesn't exist on the device side," Daniel said to The Cancer Letter. "Unique device identifiers did not exist—but now the system exists, but the challenge is that just having the identifier on the device itself doesn't help us better identify devices in the electronic health care data systems."

FDA is working on improving its postmarket surveillance system for devices in collaboration with Brookings—an effort that Daniel said would reduce reliance on spontaneous reporting of adverse outcomes.

The initiative, called the National Medical Device Postmarket Surveillance System, or MDS, will use unique device identifiers, insurance claims data and electronic medical records to create a database that can track devices and link them with patient outcomes.

"I think that the major impetus [for this program] is a realization that there isn't at all an existing sustainable data system in the United States that one can use to track and understand how medical devices are performing across different patient populations, across clinical settings," Daniel said.

"First, without having such a data system that can be used for active safety surveillance—i.e., safety monitoring that doesn't rely on reporting of adverse events by providers or manufacturers—it is challenging to quickly identify potential safety issues with devices early on.

"Second, without such a system, it is very costly and resource-intensive to develop longer term evidence on the effectiveness and impact on patient outcomes of medical devices. Better systems for developing evidence on safety and effectiveness could also help support innovation through enabling more streamlined and routine data collection that would be required for regulatory decisions."

The MDS is at least five years away from full deployment. The new system should eventually make it easier for FDA and other stakeholders to pick up adverse outcomes resulting from medical devices such as the power morcellator, Daniel said.

"Generally, I think it is safe to say that with better, more robust postmarket surveillance that the MDS can provide, certainly in a lot of cases, this would enable the accumulation of evidence on the devices much more rapidly and in much larger populations than is currently available right now," Daniel said.

"You get a better understanding of what's happening sooner. If there is a safety issue that's happening out there, this would improve the accumulation of evidence in terms of speed and quantity.

"Also, the system will not rely on reporting of serious adverse events as the data that will be leveraged will automatically include them as they are identified from claims, EHRs, and registries, not

on spontaneous report data."

Before the MDS can work, stakeholders need to invest in systems for documenting and reporting unique device identifiers, Daniels said.

"Providers, payers, patients need to use the UDIs and document them, mostly on the provider and payer side into the electronic medical record in the claims data in order to be able to much more efficiently identify unique devices in the data themselves.

"So the NDC is a good example on the drug side of how that can be done. We do have tremendous amounts of drug safety surveillance, comparative effectiveness research, quality reporting, etc.—and we learn a lot about drugs, not only initially when the drugs are on the market, but drugs that have been on the market for 10, 20 years. We have a wealth of data available to really understand how that drug performs in a variety of different patient populations, thanks to the ubiquitous nature of the NDC.

"We'd like to be able to get there on the device side, but it will take a lot of investment up front by payers, providers, and hospitals to develop the data capability and infrastructure to be able to document and report those UDIs in the claims in the electronic medical records."

With a system like the MDS, medical device registries will become obsolete, Vodra said.

"I don't see any major improvements in the voluntary self-reporting system that will vastly improve our ability to detect and fix problems, though I hope that some of the initiatives underway at FDA and in the medical community will make a difference," Vodra said. "Voluntary reporting remains valuable for providing insight. The guy who says 'I think this may be a problem' often has thought long and hard about it, and has generated a hypothesis."

To test this hypothesis, the medical device community needs to move from the current system to a Big Data network, where one can process vast amounts of claims data and link it up with specific devices, Vodra said.

"Instead of going to the spontaneous reporting database, FDA can go to claims data and say, 'Let's run this through the computer and get results,'" Vodra said. "If there is upstaging of cancer, and if this is more commonly associated with use of a particular drug or device over others, you should be able to see these trends more rapidly because you have a huge amount of data.

"From 2015 to 2025, I would argue that Big Data is the way we're going to head."

Conversation with The Cancer Letter

Vodra: 510(k) Does Not Assess Risk; Needs to be Split Into Multiple Risk Groups

FDA's Class II 510(k) clearance process for medium-risk devices—a category that includes the power morcellator—is inadequate, because it does not focus on risk assessment, according to Bill Vodra, a former associate chief counsel for drugs at FDA.

Instead, the 510(k) process relies on "substantial equivalence" to predicate devices, thereby allowing subsequent iterations of a device to introduce risk without active FDA surveillance.

"A huge variety of devices are now in Class II, and they pose extraordinarily different kinds of risk," Vodra said. "The current test for clearance of a 510(k) is, 'Is the proposed device substantially equivalent to another device (the predicate device or device chain) that has been marketed?'

"The answer may be yes, but that does not tell you much about risk of the proposed device or its predicates."

Vodra, a retired partner of Washington, D.C. law firm Arnold and Porter, helped draft many FDA regulations still in use, including those implementing the Controlled Substances Act and FDA's rules for Good Manufacturing Practices, Good Laboratory Practices, Good Clinical Practices, bioequivalency and the Orange Book.

"You start by having a question in the preclearance process: what do we know about the risk posed by this device and its predicates?" Vodra said. "That could mean breaking apart the current Class II devices into a much larger universe of disparate device groups, because different groups of devices present risks similar to each other, but distinct from other groups of devices."

Vodra spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: *What is the difference between how drugs and devices should regulated? What are the primary reasons for why drugs and devices have different pathways for regulation?*

Bill Vodra: With all medical interventions, the goal is to assure that they provide a reasonable assurance that they will deliver the benefit they promise (i.e., are effective), and that the risks they present are outweighed by these benefits (i.e., are safe). But how

one develops the evidence of safety and effectiveness differs markedly between drugs and devices.

Fundamentally, I would call it a matter of *n*, the numbers of humans on which you can test a new technology in a reasonable period of time.

With drugs, the process for developing a drug starts with an identified and well-characterized molecule—sometimes with biologics that's not quite true—but normally, you know exactly what it looks like, and you analyze it in a laboratory.

You can control the dosage of drugs very specifically, and then you can give that in a staged fashion, first to normal subjects. These are people who are not sick in any way, shape or form, and you're looking for the things that animals can't tell you—rats and mice don't talk to you about headaches, dizziness or nausea.

You're really looking for safety issues. There are things you learn in phase I studies working the dosage up until you're well into the range where you're expecting therapeutic effects.

Then you go to people with the disease you are trying to study in phase II trials and that you're trying to get this drug to work in. You start with a small number of patients, and monitoring them extremely closely, often in the clinical setting, to determine if these patients react differently than normal subjects would.

Once you establish the doses, you then take the drug into larger populations, essentially the phase III studies, often with 3,000 to 5,000 people in them. And now we're into Bayesian statistics, adaptive design trials and so forth, where you look at who responds and who doesn't respond, and ask why. Studies can be modified or tailored to the patients who predictably should respond.

That's the drug model, and it relies on the availability of a large number of people in whom to test the drug in a reasonably fast manner.

Go to the device situation: generally, the number of available patients in a given period of time, and the existence of a thoroughly standardized product throughout that period, are radically different.

You would use animals first, but obviously, when you finally get to humans, you don't go to phase I normal subjects. You go right to phase II, and when you find a device doesn't work, you go back and tinker with the product and make changes.

You may have many generations of products out there before you settle on the one you want to launch in the marketplace, and then you learn from the marketplace that you need more modifications. Look how frequently you get Microsoft updates—that's very typical of what they're doing in all engineering areas. The device continues to evolve in a way that a drug does not.

The model for drugs simply does not work for devices. So we have developed an alternative system in which a few high-risk devices are reviewed by FDA via a premarket application with extensive safety and effectiveness data, others are reviewed by a 510(k) submission with limited clinical data, others are reviewed by a 510(k) submission without clinical data, and even others are not reviewed at all before entering the marketplace.

MO: *Can you explain the 510(k) process we have today?*

BV: When the law was being drafted in 1976, it originally had only two classes—one was going to be preclearance through the premarket approval process (the current Class III), and one was going to be essentially without any review whatsoever (the current Class I). Because of that, there was a concern that FDA would put everything into the preclearance mode, which was going to break the whole system down and burden many devices unnecessarily.

So the drafters came up with this intermediate Class II system, under which access to the market would be by showing conformity to a set of regulatory standards (e.g., diagnostic sensitivity and specificity, or wavelength and focal point size of a therapeutic laser). In the interim, pending development and promulgation of regulatory standards for Class II devices, and requirements for PMAs for Class III devices, a "temporary" mechanism was established, under which new devices could enter the market by demonstrating "substantial equivalence" to a device on the market in 1976. That then morphed over time to become a permanent feature for Class II devices.

In practice, the assumption that if the risk was acceptable to the previous devices, it is acceptable for this device, does not even ask, "Have we made any steps to reduce that risk?" It only asks whether the risk any worse with the new product.

And if the answer is not obviously "yes," the product gets cleared. That makes no sense to me. That's not focusing on the risks actually posed and attempting to manage or reduce those risks.

This story is laid out very clearly in the appendix to the IOM report in 2011. Both FDA and the industry are wedded to the "substantial equivalence" standard, which is perceived to be something that was far less demanding for gaining marketing access for Class

II products than the premarket application process required of Class III devices.

MO: *We've talked in the past about whether the 510(k) clearance process adequately protects patients from harm. Advocates are now saying that a more reliable risk-based evaluation system needs to be instituted. What could that be? Is it possible to come up with something that's better than what we have?*

BV: The short answer is, yes, we can do more than we're doing. The current test for clearance of a 510(k) is, "Is the proposed device substantially equivalent to another device (the predicate device or device chain) that has been marketed?" The answer may be yes, but that does not tell you much about risk of the proposed device or its predicates.

The implicit assumption of the substantial equivalence standard for the 510(k) is: "We've lived with that earlier device; therefore we can live with this one." In fact, we know from a number of case studies that the risks of the predicate device (or devices) might never have been identified or understood.

For a comprehensive evaluation of the 510(k) process, see the Institute of Medicine report in 2011. The whole premise of the IOM criticism was, if FDA doesn't ask about the risks, it's not necessarily going to get answers about risk.

For specific proposals on how to look into existing databases that the agency or the industry to determine whether or not risks have been identified properly in the past, refer to a FDLI Food and Drug Policy Forum that I wrote later that year. I note that manufacturers and FDA have a variety of historic records that can be explored to look at this question.

MO: *What is your fix for this? How do you actively and proactively assess risk?*

BV: You start by having a question in the preclearance process: what do we know about the risk posed by this device and its predicates? That could mean breaking apart the current Class II devices into a much larger universe of disparate device groups, because different groups of devices present risks similar to each other, but distinct from other groups of devices.

A huge variety of devices are now in Class II, and they pose extraordinarily different kinds of risk. Consider just diagnostic tools: you have in vitro diagnostics that do not come into contact with the human body, diagnostics that work by passively collecting information through contact with the body, diagnostics that work by emitting energy into the body, and in vivo diagnostics that are placed inside the body. All diagnostics must provide accurate information, of course, but beyond that, the different categories can raise unique risks not found in the other categories. The same analysis could be applied to implanted and external devices to affect heart rhythm, or contraceptive devices, or lasers for therapeutic use, and so on. We now have almost 40 years of regulating devices, which was not available in 1976. Surely we don't need any longer to lump all of these disparate tools into a single "Class II" with a single standard of clearance, based fundamentally upon substantial equivalence to a device sold before 1977.

And yet, we don't differentiate those devices and ask questions like, "What are the risks that we know about this, or that group of products, and what have we done to address those risks?"

MO: *Would this require more premarket testing of devices?*

BV: Not necessarily. As I stated before, there is a fundamental difference between drugs and devices in terms of the number of patients you can study before you make a decision about proceeding to routine medical use. In drugs, you can get 5,000 patients, sometimes 10,000 patients, in premarket studies. In the device arena, it may be 300 to 500 patients or less.

If you're looking for something that occurs in the incidence of one in 1,000—you're not going to find it necessarily in the first 500 patients.

David Feigal, former CDRH director, has proposed what he called the "Lifecycle Iteration of Medical Devices" in which you use version 1.0 as the test model for version 2.0—find out what you can about version 1.0 through postmarket surveillance and experience, and then fix those things for version 2.0. Postmarket surveillance on version 2.0 tells you what changes you need to make for version 3.0, and so on.

What Feigal is suggesting is: Use the postmarket surveillance for the first-generation product, and then design the second-generation product.

With that, you're studying what you know about this product, whereas currently, if version 2.0 is no riskier than version 1.0, it'll go out on the market, and we don't ask the question of, "Have we addressed the risks identified for version 1.0 and reduced those risks?"

MO: *How is the IOM 2011 proposal different from Feigal's proposal?*

BV: The IOM Committee was looking at a broader series of things than just that. Feigal was proposing how to use existing experience to improve devices, one device at a time.

We were looking at this systemically: What is the adverse outcomes reporting system like, and how can that be used to assure the safety of products in the marketplace, which is a little bit different, because it's not, "How can you improve one particular product?" but simply, "How do you learn about what's out there?"

For example, "How do you learn whether the morcellator is causing upstaging of cancer?" That was the kind of question we were focusing on. And we were saying that you can't improve the 510(k) process, which was what we were charged with doing, without having a well-functioning postmarket surveillance system, which we don't really have yet.

MO: *FDA wrote in a Nov. 12 letter to Rep. Mike Fitzpatrick (R-Pa.) that the agency disagrees with IOM's recommendation about changing the 510(k) process. What is your take on that?*

BV: FDA issued a statement like that the day the IOM published the report. The agency had received copies of the report a week prior to its public release, and had had a chance to consider it.

In fairness to everybody, I think that FDA did not expect what it got from our IOM panel. They were looking for a checklist of, "Tweak this, tweak that," and not a "Throw the whole thing out" which, I fear, is how FDA first read the report. The IOM Committee said that FDA needs to fundamentally rethink it. There are places where the 510(k) process with "substantial equivalence" still makes a lot of sense.

I believe that FDA was taken totally off-guard and put in an awkward place. First, FDA certainly didn't want the political problem of dealing with such a sweeping idea on the eve of having to renegotiate the user fee requirements for 2012. Industry was equally unwilling to address the idea, and legislative changes were just not politically possible. Secondly, what the IOM report basically said is that the 510(k) process is not doing as much to protect the public as the public perceived. That conclusion required a lot of people within the agency to swallow and say, "You mean everything we've done for the last 10 or 20 years is worthless?" It's not quite the right interpretation of the IOM message, but that's the way it could come across to the dedicated career staff at the agency.

At the end of it, FDA just said, "No, thank you." But I've been told that there is an awful lot in the IOM report that FDA does agree with that and that it will seek to implement over time.

The IOM process itself is partially to blame. If we had been able to lay out a vision for what a new process or processes might look like, it might have been easier for FDA and industry to deal with it. As it happened, the committee was given a very strict timetable that could not be extended. By the point we had realized the fundamental deficiencies in the 510(k) system, we lacked the time to develop alternatives. My regret is that we didn't have another year to come up with some additional suggestions. It would have been a lot easier for them to deal with. Plus, we could've gotten it out after the 2012 user fee negotiations, in which case FDA and industry would have had several years to think about it before the next round of device user fee legislation.

In short, to everyone's misfortune, I fear the IOM put a dead fish on the table and FDA disposed of it quickly. But this is all speculation on my part.

MO: *Other proponents of the 510(k) process say that scrapping or changing it further would stifle medical device innovation.*

BV: I've heard that cry for my entire career. "Regulation stifles innovation!"

There are two answers to this, both extremely relevant. First, regulation frequently stimulates innovation. The requirement for adequate and well-controlled clinical studies for approval of new drugs after 1962 led (after a period of adjustment lasting to the early 1980s) to three decades of enormous productivity in pharmaceuticals. This golden age was significantly due to the developments in the way drugs were developed to meet the new regulatory standard. Secondly, innovation is not always inevitably beneficial. When you look at products that had gotten into the market that injured or killed patients, you have to acknowledge that innovation is a risky exercise.

In my experience, there are not many things that aren't improved by having a second set of independent eyes looking at it. Whether it's planning to invade Normandy in 1944 or to launch a new artificial heart, having somebody else look at the plans and ask questions is a very constructive process.

MO: *You're saying that this argument that regulation stifles innovation has a long beard.*

BV: Yes. To prove that argument, you have to show where in the world we've got more medical progress with less regulation.

In the 1970s, we had a debate called "drug lag," which was an argument that new drugs were getting on the market much sooner in Europe than in the U.S., because the 1962 law had toughened things up, and took far more time to get new drugs through FDA than elsewhere. The advocates held up some examples of products, and FDA challenged them. I'm not sure either

FDA or the drug lag advocates prevailed based on the experience of the 1970s. But by the end of the 1980s, the debate had evaporated, as FDA demonstrated consistently shorter review times and more drug approvals than all other advanced nations.

I'd like to see a similar evidence-based debate over the effect of FDA regulation on the development and entry of new devices to the U.S. and foreign markets, and the medical costs and benefits of the devices.

The ideology that regulation destroys innovation—I've been through it, and I've thought about it, and it doesn't persuade me as more than rhetoric and speculation.

MO: *Let's talk about the federal mandate for adverse outcomes reporting. Does the system work? Is it effective?*

BV: Getting someone to report an adverse outcome to a manufacturer or FDA is about step 3 or 4 in a multi-step process.

First, you have to have somebody who has an adverse outcome and recognizes an adverse outcome. Usually, that means an outcome that is not expected with the disease. If you're dealing with a drug or device intended to prevent heart attack, and the patient dies of heart attack, you don't necessarily focus on, "Could the drug or device have caused the heart attack?" People don't tend even to recognize that there is something unusual, if it seems part of the disease being treated.

The second step is, somebody has got to recognize that, not only is the outcome is untoward, but that it might also be associated with the exposure to some sort of intervention—a drug or device. So if the patient has a heart attack but you weren't expecting that they would, you've got to say, "Could it have been the pacemaker? Or could it have been a drug he's taking?" To connect the dots and say, "Gee, I wonder if that could've been a relationship"—somebody at the frontline, usually a patient, doctor or caregiver, has to make that association.

Usually, if there is a temporal relationship, like immediately after taking a drug, it's more obvious. Where you've got something implanted in the body for a long time, it may be a lot harder to link the event with the device. That recognition may require seeing the same event in several patients.

Once somebody makes that association—that, maybe this intervention is related to that untoward outcome—then they have to be motivated to report it. Our entire system relates to voluntary reporting. We don't have, with the exception of some user reporting requirements, a mandatory reporting system, in which everybody reports everything that happens to the patients. Some people argue that fear of malpractice liability inhibits voluntary reporting by physicians and hospitals; and others contend that plaintiffs' attorneys in the area of product liability stimulate inappropriate and inaccurate reporting. So you have biases that can influence the frequency and quality of voluntary reports.

The next step is to get the report to someone who is responsible for collecting and investigating such reports. In America, there are three bodies that are charged with doing this: the manufacturers of the products, the FDA, and private registries that track certain types of devices. But reports may die in the pathway to these bodies. Patients tell doctors, who decide not to report; doctors tell hospitals, who decided not to report; and reports can simply go astray.

Once somebody voluntary reports an untoward event and its possible association to the manufacturer of the device, however, the company is legally required to investigate that report and determine whether it meets criteria for reporting forward to the FDA. Not every event is required to be reported to the agency.

The company is also charged with looking for patterns. It has been said that one case is an accident, two cases are a coincidence, but three cases suggests a pattern. Looking for patterns is a pretty sophisticated science, under the heading of epidemiology. The pharmaceutical industry has whole departments under the heading "pharmacoepidemiology." Unless the device industry has changed radically in the last three or four years, my experience is that smaller device companies frequently don't even have an epidemiologist on staff or on call.

So this sequence must all to fall into place in order to get that light bulb going off that says, "Yes, we've got a probable causal relationship here, or at least an association that is worthy of study."

Individual companies have a further challenge, in that they follow only their own products. Absent publicly available registries or use of FDA's public databases on medical device reports, it is impossible for a company to know whether the reports about its products are comparable to, or out of line with, those of competing products.

MO: *In summary, you're saying that it's difficult to capture adverse outcomes with voluntary reporting.*

BV: Extremely difficult to identify, capture, investigate and interpret. That's why I'm not so judgmental, off the top of my head, that a company

should or should not have reported a medical problem until I know the facts of a particular case.

MO: *What about power morcellation? A whistleblower alerted Johnson & Johnson in 2006 to a risk estimate of one in 300—a number similar to FDA's estimate—as well as a near-miss case, where a patient would likely have experienced an upstaging of her uterine cancer if she had undergone the procedure?*

BV: With the morcellator, I understand from you (but have not otherwise confirmed) that FDA had raised the issue of upstaging with the manufacturers during the review process and discussed whether the labeling should address the issue. If so, because people were already concerned about upstaging, the company should probably have been looking for that. That's an unusual situation, however.

My initial reaction to the "whistleblower" situation as you describe it, however, is that this was not a mandatorily reportable case. There was no actual case or event to report. The situation involved a potential future event, because in this case the morcellation was not performed. They did a standard surgical removal; found cancer cells, and realized that they had dodged a bullet.

FDA does not require reporting on "what might have been"—except where a device actually malfunctions without causing a reportable injury but if it similarly malfunctioned in another similar situation, it could have resulted in death or serious injury.

Think of an X-ray machine that unexpectedly exceeds its radiation emission control limit during a warm up, when no patient is exposed; had the same dose of radiation hit a patient, it would have killed him. In this case, the morcellator was not used and did not malfunction.

The underlying philosophy is that attention and limited resources should be focused on real problems, those actually seen. FDA, industry, and physicians should, of course, consider potential risks, but all would be overwhelmed if every conceivable risk was reported.

I know this philosophy is not satisfying to consumer safety advocates, but there are other systems that should address potential risks. A postmarket study of morcellator use in removal of fibroid tumors, looking for upstaging, might have been appropriate, for example. The Medical Device Reporting system, however, is to look at actual experiences.

Let me be very clear: I'm only saying that the "case study," as you have described it, did not, in my view, trigger a legal obligation to report to FDA under the MDR regulations, because the device was not used and did not lead to an injury or malfunction, which are the essential predicates for an MDR reportable event.

In light of the pre-existing recognition of the risks of upstaging, the near-miss case should probably have led a manufacturer to reassess the potential risks, and perhaps led to warnings, to additional research, and to discussions with FDA. I'm not giving the company a full pass, just focusing on the MDR reporting question.

MO: *I'm going to jump ahead and circle back. Do you know whether federal requirements for adverse outcomes reporting are different for drugs and devices?*

BV: The regulations are different and they're designed for different kinds of things, and the reporters are frequently different. There are differences in the basic structures of federal regulations, yes. They also differ in terms of what is a reportable event.

For drugs, there is no required reporting by anybody except the manufacturers. Hospital or as we call it, end user reporting, is only required for certain devices, partially because in the device arena, you have frequently a disconnect between the ordinary physician and the user facility—a lot of X-ray centers, MRI centers, things like that are independent of the doctor, and so the doctor would not necessarily know whether the machine had failed or things like that.

Another point is, the device regulations are looking for machine failures that would cause injuries if they occurred later on. In the drug arena, that's not the way the formulation of language is used.

Individual practitioners are not held liable for reporting in the device or drug arena.

MO: *User facilities i.e. hospitals are required to report adverse outcomes resulting from medical devices—but why not drugs?*

BV: I think it has to do with the special ability of the user facility to identify device-related events, at least as perceived at the time the regulations and laws were enacted. We are talking about specialized equipment like X-rays, MRI machines, CAT scans, radiation-beam therapeutics, etc.

If there's a problem with the machine, the operators are more likely to know, and those are located in the user facilities, hospitals or MRI clinics—which would be required to report. The referring physician might not be likely even to detect a problem.

Now that doesn't mean that hospitals don't report drug-related adverse events. An Institute of Medicine report in the late 1990s discussed how many adverse events were caused by misprescribing, misdispensing and drug interactions, often in hospitals. As a result,

many hospitals established risk committees to look into the utilization of drugs and adverse events. Now that hospitals have centralized identification of drug-related adverse events, they're probably reporting more voluntarily than they did before.

MO: *Patient advocates are saying that individual practitioners should also be mandated to report. What do you think?*

BV: It's going to lead to a lot of litigation, as to when this or that doctor should have recognized the first case they had, and proving that the drug or device did this or that.

I've been involved in a number of litigations where they go after the company, and the plaintiffs always want to allege that the company should've known when the first case came in, that the drug was the cause of harm. And that, from a scientific standpoint, is rarely possible.

It is even more problematic for individual physicians. For every untoward outcome, she would have to determine, was it an accident, or part of the natural course of the disease, or drug-related? The default mode would be to report everything, regardless whether it was realistic. You don't get in trouble for over-reporting, only failing to report.

Plus, consider the burden on FDA to police the medical community. Today, FDA has legal jurisdiction over the handling of food in most restaurants, yet relies on state and local food inspectors to inspect and monitor retail operations. FDA could not possibly find the resources to conduct routine inspections of physicians for possible failure to report an adverse event.

MO: *So you're saying that it's just too difficult because, generally speaking, individual physicians could be embroiled in a problem that they genuinely have no knowledge of?*

BV: Remember, failure to report, on the federal level, is a crime. It's not a civil thing like damages that your insurance companies pay for. It's a crime. You want to encourage voluntary reporting, in which the doctor thinks about the case. If the only safeguard is to report everything bad, then public safety is not advanced by mandatory physician reporting.

A general philosophical standpoint is, the federal government, at least from FDA's standpoint, does not try to regulate the practice of medicine or what doctors do. That's left to the states.

MO: *Advocates also say that companies should be required to track the first wave of high-risk devices via a registry and report outcomes to FDA. Is this feasible?*

BV: It is feasible, but it is very expensive. In the 1980s, the NIH established a patient registry for pacemakers; it died within 10 years, because the government could not afford to maintain it. In tracking patients, you have to get the doctors or hospital staff to fill out the paperwork (sometimes literally in the operating room), then collect the information and enter it into a database, and then follow the patients for an extended period of time. With the Unique Device Identifiers and electronic medical records, it's going to become a lot easier to get accurate information on the implanted device and the patient, but somebody still has to transmit the information to the manufacturer (or registry operator), who must put the patient on the registry, and follow the patient through routine contacts with the patient or her treating physician.

This alone presents real issues of confidentiality. Patients might not want to be in the registry or otherwise refuse to cooperate. Years ago, an organization tried to set up a registry for breast implants; they met enormous pushback from women who did not want even their husbands to know they had a breast implant. If a researcher wants to test a hypothesis that involves getting non-anonymized patient information, HIPAA restrictions also kick in.

My bottom-line position is registries are generally not cost-effective. A company-oriented registry collects on its product, but not comparative data, because it's not shared with other manufacturers. You can only have comparative data with a registry that covers all products in a certain category (e.g., pacemakers, hip implants) across the board. That's a better way of doing it, and a number of independent registries covering all products in a given class (e.g., hip implants, heart rhythm devices) have been established by academic or professional groups. But if the manufacturers are going to participate in these arrangements, you have to resolve issues such as sharing the cost among companies, allowing access to the data, and determining whether data might be used for competitive (not health) purposes.

As you can tell, I am not a fan of registries today.

MO: *Is there a better way of doing it?*

BV: The way to move forward, in my view, is a comprehensive medical device postmarket surveillance system that utilizes claims data and electronic health records. Just think about how medical reimbursement records could be used in the era of Big Data.

Let's take morcellators as an example. Suppose you were to code (accurately and with high granularity)

all patients who were treated with morcellators vs. other types of surgical interventions for the same medical conditions. It would be possible to probe the data to look for how many patients had treatments for uterine fibroid tumors and who subsequently were treated for uterine cancer in the next succeeding 12 or 24 months. You could then compare those treated with morcellators to those treated by other interventions. If—if—morcellation increased the risk for upstaging, it might appear very quickly from this type of query, with a minimum of cost and complications. It seems to me that if FDA and the manufacturer were concerned about the potential for this particular risk, instead of a registry or a small-sized postmarket study, they could agree on periodic probes into the medical reimbursement records to test the hypothesis. This approach would be much cheaper and faster than either a registry or a postmarket study.

Now and increasingly in the future, with electronic medical records and claims data, you don't have to enter the patient into a registry of people. You can identify and study things no one has previously considered. With Big Data, you don't need to collect the first 1,000 or 2,000 patients in a registry. That, to me, is the way of the future.

MO: *Let's try and summarize. We've got two physicians-turned-patient-advocates, a controversial high-profile medical device, an FDA that acknowledges that this is a reporting of adverse outcomes issue, and a Congressional inquiry. What is the root cause of this problem, and what preemptive steps could have been taken to prevent the morcellator disaster?*

BV: What the IOM report essentially said: FDA should focus more on risk at the time it's looking at the products for preclearance. Move away from the simple 510(k) "substantial equivalence" evaluation, and concentrate more on the risks we know or associate with the device, and what are the risks we think could potentially be associated with the device.

And then, FDA should spell out the appropriate criteria for deciding whether to let that product and similar ones on the market. As I said, these criteria could be articulated in the context of groups of similar devices, rather than treating all Class II devices as a single group. In fairness, FDA does do this in practice, but the statutory standard of "substantial equivalence" applies to all Class II devices equally.

Once FDA has cleared the product, it and the manufacturer should both periodically revisit the product to determine whether there are safety concerns, either foreseen or not.

As the manufacturer makes modifications to the product, FDA should consider whether the modifications also respond to confirmed safety issues. Much of the burden for answering these questions will lie with the manufacturer, of course.

Basically, the IOM Committee wanted to introduce the concept of risk-management throughout the lifecycle of the device as a regulatory requirement. You're not going to prevent all bad things from happening. What you hope to do is to reduce the number of casualties and the duration before you catch the problem at fix it.

That's your goal. Detect it early and intervene to prevent further harm.

MO: *So that's the preemptive part. Do you think the federal mandate for self-reporting right now is the best that it can be?*

BV: Yes, unfortunately. I think we've had a lot of experience with self-reporting in the drug arena, and to some extent in the device arena. It's just very difficult to collect a lot of good data.

When you look back at the last 40 years, you can see that we've been unlucky in that we missed some problems for years or even decades, that it took a long time to recognize that this drug or that device was causing a health problem, and then to figure out why and how it was causing that problem.

I don't see any major improvements in the voluntary self-reporting system that will vastly improve our ability to detect and fix problems, though I hope that some of the initiatives underway at FDA and in the medical community will make a difference.

Voluntary reporting remains valuable for providing insight. The guy who says "I think this may be a problem" often has thought long and hard about it, and has generated a hypothesis.

But to test such a hypothesis, we need to move from the current system to Big Data, where you take a huge amount of claims data and link it up with particular devices, and then look at the health claims filed by patients in the months of years later to see what happens after a particular device put in or used on them, in comparison to other similar devices or to other forms of treatment not involving a device. Instead of going to the spontaneous reporting database, FDA can go to claims data and say, "Let's run this through the computer and get results."

If there is upstaging of cancer, and if this is more commonly associated with use of a particular drug or device over others, you should be able to see these trends more rapidly because you have a huge amount

of data. From 2015 to 2025, I would argue that Big Data is the way we're going to head.

Registries will become a thing of the past, and we won't have to rely on voluntary reporting terribly much.

Pilot: Don't Change 510(k), Put More Money Into Enforcing FDA Reporting Laws

Patients are being harmed because FDA doesn't commit sufficient resources to enforce federal requirements for hospitals and manufacturers to report adverse outcomes caused by medical devices, according to Larry Pilot, one of the original authors of FDA's 510(k) device clearance process.

There is no need to revamp the 510(k) process, Pilot said. The agency should instead enforce existing laws to make device manufacturers and user facilities report adverse outcomes.

"It's a good system we have now, but FDA needs to allocate more resources to enforcement, especially for user facilities," Pilot said. "That's why FDA, with its authority, and this opportunity to put the emphasis on reporting to the user facility required by law, and then by specific regulation, should be going for money penalties for user facilities that do not abide by the reporting requirement.

"How has FDA been managing what these user facilities are doing? What has the agency been doing?

"Because people like Amy [Reed] are being hurt by this. If she knew that it was, instead of one in 10,000, a one in 300 chance, she'd probably say no. This is an embarrassment to the agency.

"Going back to the responsibility of the external community, the users and manufacturers—I expect the FDA to have done a better job."

Pilot received the FDA's Award of Merit in 1977 for his contributions to the development of the agency's medical device programs. He is a contributor to the Competitive Enterprise Institute in Washington, D.C.

Pilot spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: *Patient advocates and the IOM report in 2011 say that the 510(k) process does not adequately protect the public from harm. What did you have in mind when you designed the 510(k) in the 70s?*

Larry Pilot: For that regulation, I would never say that I wrote it, because it's a team of people; I was one of the supervisors, of course. What its intent was—and how it's been altered through legislation, and sometimes altered not always for the benefit of the public by the bureaucracy, over the years and decades.

First, I disagree with the recommendation of the IOM, and I did publish a piece for the Competitive Enterprise Institute titled "Stifling Medical Device Innovation," and I explained my position in that document.

Initially, the premarket notification process—the 510(k)—was implemented in order to identify to the FDA what was to be entered into commercial distribution in 90 days. It was a notification process, and the objective of the notification process was to enable the FDA to look at what the intended use of the device was and whether or not it fit into one of the three categories.

There was no requirement of feedback to the notifier, the submitter, unless the agency believes it was useful to convey some kind of message back to them. And there was no order attached to that, which is where we now move from 1976 to 1990, where there are extensive changes to the law, one of which stipulated that the 510(k) notification process now was to require the issuance of an order from the FDA in order to commercially distribute the device.

Before that, and I represented clients who submitted notifications to the agency, got no response whatsoever, and marketed devices in the 90th or 91st day. I did have clients who got notification, and for which the agency was maintaining that they had to go through premarket approval or something else, and for which the client to disagree and discard that recommendation, including for devices that were in Class III.

That was because of the particular nature of the transitional process, because devices which were in Class III—say, a heart valve—had not been manufactured by any other manufacturer; that new entity could market after the 90-day notification.

The company can market unless the device did not fall within the description, or the agency believed that it was not reasonably safe or effective. Because there was a three-year period during which those manufacturers of heart valves marketing on the day of the enactment, they could continue marketing, but by the end of that three-year time, they must have submitted an application for which then the agency would decide whether or not they could continue on the basis of the evidence that they provided to support the reasonable assurance of safety and effectiveness. If not, the agency may believe that it was imperative

to reclassify what had been classified.

Then we move into back into the 510(k) process. The idea was to submit information to the agency to enable them to know who was marketing what and from where. That moved along fairly well from 1979 up to 1990, although there were some hearings and some events that suggested that perhaps there should be a better process, which led to, of course, 1990 amendments. That is the order process.

Now, with that process, the agency had much more leverage now over who sent in what, but in addition to requiring this issuance of an order, the requirement for standard was broadened into a special controls category, where the special control could be identified by the agency and for which those who were marketing Class II devices—there was no standard, and that was one of the impediments to the success of that venture into standards. Then the agency could identify what the special controls ought to be for which the agency would then review against what would be an order if they agreed.

From my perspective, both from the inside, the start of this program, through all the years that I have been in practice, CDRH has plenty of authority to stop what enters into the marketplace or to accelerate a remedial activity, including possible withdrawal of the device from the marketplace.

Over the years, it accomplished more feedback approaches to safety and effectiveness than were available for the drug side, where there is no requirement to report any adverse outcomes unless it were subject to a New Drug Approval.

For all devices—whether they were approved or cleared or never cleared but in commercial distribution—federal reporting regulations requires not only manufacturers, but subsequent to the 1990 amendments, user facilities to report incidents related to death or serious injury. Those are the controls or the expansion of controls that gave to the agency much more ammunition to correct what the agency believed was necessary to provide a reasonable assurance of safety and effectiveness.

My take on this is—relating to how the 510(k) process was implemented, first through the statute and then ultimate regulation—I disagree with the agency's position and in particular, the IOM on the characterization of the classification process as risk-based.

It is not risk-based, and I have said this many times, because the criteria that applied to each one of the three classes was in the context of reasonable assurance of safety and effectiveness. A subset of safety is risk, yes, but this low, medium and high risk is fabrication.

The Europeans have a risk-based system, and what they rely on to clear or approve a device on is safety. They leave it up to the consumer and user or the intermediary practitioner the evaluation of effectiveness, whether the device is effective for its represented, intended use. For instance, a pacemaker needs to be safe—it's not going to shock people inadvertently, it's not going to fail when it's needed. Now the medical community will decide the effectiveness of that device.

That is a risk-based system. But to me, that's a lower standard that what we have here now, which is safety, which includes risk, and effectiveness, which goes beyond risk.

The risk-based system, which the FDA continues to advocate and incorporate into their websites—that's a fabrication, many years after the three-tier classification was created. It became more intense at some point in time where I began to notice, and that was probably back around 2009, when Jeffrey Shuren testified before a Congressional committee.

I received an advance copy of that and I communicated with the staff person on the committee and I said, "This is not right. You should have somebody questioning him—what does he mean by risk? How is that incorporated into what the statute expresses?"

The statutory language, which didn't change, is quite clear that it is about safety and effectiveness, whereas functionally, if people want to look at risk, fine, but it's inappropriate for the agency to use risk as a surrogate for the explanation, when safety and effectiveness are the criteria.

For drugs, it's absolute safety and effectiveness, whereas in the statute applicable to devices, it's reasonable assurance. That was a distinction that was made during the legislative process, because the objective was to avoid pigeonholing this industry into the criteria that applied to drugs.

MO: *You are saying that the 510(k) process is not responsible for clearing devices that are potentially harmful. Who is at fault, then, for the deaths and harm to women by power morcellators?*

LP: I know from what I've read that the manufacturer, the subsidiary of J&J, may have had information to suggest that there was a nexus between the use of the morcellator and possible sarcoma upstaging. If the subsidiary of J&J had that,

the subsidiary was responsible for looking into that and saying, "Look, if this is true, is this going to be a reportable event?"

A good judgment could indicate, yes. I've represented companies who have been faced with these kinds of questions: "We just got this report, our device has been approved by the FDA, within the first five week, this has happened, what should we do?"

If you can't figure it out, and this is advice I've given clients, "Well, let's go to the FDA, don't be afraid to go to them, because maybe they know something from their experience that we don't know." So we enlarge the scope to include the agency.

As for Brigham & Women's Hospital, they were obligated, in my view, to notify the agency. If it's true that the J&J subsidiary had enough information to be able to submit within 30 days, and if it's true that the user facility had the information, and they didn't report, both of them probably could be successfully prosecuted for failing to comply with the requirements of law.

If you go back further and you take the classification process and the review of the morcellator—how is it that a surgical instrument, which is different from the kind of surgical instrument that had existed in 1976 or 1979 when it was classified, is that substantially equivalent to what power morcellators are now?

That's a judgment that the manufacturer, the sponsor, and the agency have the opportunity to resolve and make. Now what kind of an improvement in the legislative or the regulatory process can be made to that kind of judgment?

Somebody there should've said, "You know, this one, when you scratch it, it doesn't give off any real perfume, and there might be a little smell to it."

FDA needs to recognize that we've got special controls here, maybe that the agency should ask them about some of the clinical data, or require agreement on some kind of a study to evaluate whether grinding up pieces of stuff inside the abdomen that might be malignant, and say, let's get some more information on that.

Part of the agency's responsibility, at least when I was there, was, if we thought there was a signal that we should give to somebody, whether it was in a 510(k) or compliance context, we give them the signal.

Those are the kinds of judgment exercises that weren't available in 1979, but could've been used in conversation with the applicant of the 510(k) and said, "Have you thought about this, do you have anything on that?" instead of, "Look, you haven't done this, and we want to ask 1,000 questions."

For Class II devices that might be on the fringe in the context of the application of that definition, if there is suspicion or belief, it has to be reasonable and supportable on the part of the agency, that some additional special controls—clinical studies—need to be undertaken before we can clear this device for the market.

Don't you think they should've asked for something a little bit more in terms of evidence of safety when the morcellator was cleared over 20 years ago?

Registry trials do work to a certain extent, but not through a formal statutory requirement. The agency has the flexibility—special controls for the Class II devices—to track devices. The agency should judge the need and undertake that function.

I believe there were some people who were concerned about the power morcellator years ago. Why not tack on to that postmarket surveillance, and say, "Let's work together and evaluate over time the performance of these devices?"

From my perspective, and having been one of the few people to start the process and review its performance on an experimental basis up until 1976 and in the real world after that, there's more than enough authority for the agency to do what it needs to be done if the agency is administered by competent individuals who have a knowledgeable staff understand what the provisions of law and regulation are, and discharge their responsibility correctly.

MO: *Patient advocates are saying that individual practitioners—not only manufacturers and user facilities—should be required to report adverse outcomes. What do you think?*

LP: If the agency cannot manage the present system for information supplied by user facilities and manufacturers, how can you expect a multiplier of 100,000 physicians all across the country? No.

If the agency would manage, in cooperation with the health care community and the industry, the responsibility it has over the medical device reporting system, you don't need individual practitioners. But individual practitioners can always be encouraged to voluntarily report to the agency, and I think that's a good thing.

Mandatory reporting? Can you visualize what millions of reports a year might be like? Impossible.

And FDA imposed on itself an unreasonable burden at the time they were beginning to apply the medical reporting regulations, because they took some very strict interpretations of what an adverse event was.

I had one client, maybe they'd send in 10 or 20 a month but they were conscientious about those few. The response they got from the agency's counsel was, "Oh no, you have to send all those in." But that would be a thousand a month, so they go from sending in 120 that are good reports, because they're substantive, to junk. What are you going to do with 1,200 reports? And that's just one company, so it ballooned up to the hundreds of thousands. At one point they had 200,000 reports coming in.

No, individual practitioner mandatory reporting would just complicate things for the agency enormously. It's better to filter it through the user facility or manufacturer—report to them if you don't want to report to the government, because the conscientious reporting is required by law.

Litigation is usually the best tool for regulating an activity. If you look at other incidents, even during the time I was at the agency, the plaintiffs bar had a much greater influence on determining what would be in the marketplace than the FDA. When I preach and lectured on this subject, I'd say, "You ought to be more worried about the plaintiffs bar, than you do the FDA."

However, it should be the agency that is the monitor of that and the facilitator for the patient. I haven't witnessed much improvement since Jeffrey Shuren has been there, or since that IOM report was issued. It's unfortunate, all the missed opportunities, and that goes to the management of the organization.

MO: *How, then, can FDA more reliably pick up signals that patients are being harmed, when voluntary reporting hasn't worked in the case of power morcellators? The agency said that it is unaware of the dangers until Hooman Noorchashm and Amy Reed filed a Medical Device Report in December 2013.*

LP: It's a good system we have now, but FDA needs to allocate more resources to enforcement, especially for user facilities.

The scientists evaluate the reasonable assurance of safety and effectiveness. The enforcement side of the agency is to detect whether a violation or possible violations have occurred.

And there's a crossover when you have the medical device reporting problem, if it exists, where the hospital or manufacturer did not report these events as they should have.

The reporting is necessary as a signal, an early warning, for which then the scientists have to get involved, and the medical, technical people in the agency to evaluate, "Is it one in 300, or is it one in 10,000?" to establish what is a reasonable approach to the availability of the product in the marketplace, and the judgment that is exercised by the user community as through the advisory committee process.

That's why FDA, with its authority and this opportunity to put the emphasis on reporting to the user facility required by law and then by specific regulation. The agency should be going for money penalties for user facilities that do not abide by the reporting requirement.

I know for almost 10 years, many user facilities have not been keeping records and did not have the required written procedures for evaluating whether a complaint justified an MDR, and FDA didn't know that? They haven't looked at any of this?

How has FDA been managing what these user facilities are doing? What has the agency been doing?

Because people like Amy are being hurt by this. If she knew that it was, instead of one in 10,000, a one in 300 chance, she'd probably say no. This is an embarrassment to the agency.

Going back to the responsibility of the external community, the users and manufacturers—I expect the FDA to have done a better job.

MO: *You're saying that FDA needs to do more surveillance of user facilities, but how can this be done when the agency has limited resources? In a recent response to inquiry from Rep. Mike Fitzpatrick (R-Pa.), FDA wrote, "We have general focused our enforcement resources on manufacturers—who are required under law to investigate any MDR-reportable complaint they receive—and not on user facilities. We have found that encouraging more reporting—and more complete reporting—by user facilities is a good use of our limited resources in this area."*

LP: What? That surprises me, because I believe too much of the agency's resources go to manufacturers and are wasteful. Again, this is a topic I know very well, from inside and outside through many different experiences.

When I was at the agency, I lectured on this subject and on inspections, I said, "No inspection should last more than two days, I don't care about the size of the company."

Within two days, a good inspector should be able to determine—and we're talking about the application of Good Manufacturing Practices, which nearly every manufacturer must comply with, almost totally with limited exceptions—if something is a little bit odd, or jump to the company's records.

If it's more than two days and if it's a good inspection, then you're on track at the very least an

eventual warning letter.

Since my time, I've read warning letters where the agency has been in the facility for a month, sometimes with two inspectors, and then a warning letter goes out sometimes six months later. What is the importance of something six months later, after you've spent all the resources and time?

At the very least, take some of those huge resources you now have that we didn't have at the time, and apply them to evaluating the user facility community, whether it's hospitals for stay or ambulatory facilities.

Go out there and develop a statistical base for what you're doing to evaluate: one, how many user facilities have written procedures, two, how are they following their procedures, and three, in following their procedures, are they making reports based on what is in the regulation itself as the criteria and their own procedures in implementing that.

If Brigham would've been inspected at any time in the past few years—let's assume that they did have procedures but people sort of after awhile forgot about them—they would have picked that up in the inspection.

So I'm astounded by that kind of response, because it's, "Oh, we put more of our resources here, but on this very important function, what we do is kind of encourage people."

Encourage? I could never write a letter like that to Congress. And this is their associate commissioner for legislation. That letter must have passed through Shuren's office. He had to have seen that letter that says, "Oh, we have a voluntary system for the user facility community, but with the industry, we have a mandatory system." You've got to be kidding me.

This kind of judgment or failure to exercise judgment has been harmful to the agency and more importantly, to the public. This is our world—FDA's world—and we need to at least have some minimal understanding of surveillance, or when it's important to step up surveillance.

If Brigham at Harvard isn't reporting, what about other groups and other user facilities?

MO: *In summary, what do you think is the root cause, then, for what happened to patients and families who were affected by power morcellators? And what can we learn from this case study?*

LP: It is a failure of FDA to properly administer the flexible authority and the required authority that it has. The root cause here is the failure on the part of the community to get the information to the FDA.

It's not a fault of the statute, or even the implemented regulations. It's the failure of the agency to responsibly evaluate the performance in the marketplace.

Now, if people are going to be dishonest on either side, whether it's in the agency or within the industry, then they should be punished, and we're going to make them as an example that is administratively and judicially fair.

It is a disappointment to me, as someone who has been in this arena from its inception in 1970 to the present, and seeing it from both sides, because I'd rather have a more congenial relationship between the agency and the health care community and the industry.

It's much more effective, instead of the "us vs. them" mentality the agency has now.

MO: *Let's circle back to your relationship with FDA. How did you become involved in creating FDA medical device legislation in the 1970s?*

LP: My interest in the topic on medical device legislation began 1969 when I joined the government and then shifted over to FDA. Medical device regulatory processes were minimal then—it literally hadn't been looked at since 1938, when the term device was identified.

So then we moved forward to do what it took to get to the 1976 amendments, and that was an almost six-year process. To implement the regulations, of which we were able to accomplish most by 1979, and that's when I left the agency.

Another fellow, David Link and I were the two people who were assigned the responsibility in 1970 to plan for and interact with those who would ultimately write and approve the legislation. We created the Office of Medical Devices, which ultimately became the Bureau of Medical Devices, and which is now the Center for Devices and Radiological Health.

I was responsible, as a surrogate to Dave, who was the director, on all matters relating to regulatory issues, but in that context of implementing the regulations, Dave and I both were intimately involved in everything across the board, including the 510(k) process. I still practice law.

MO: *You wrote the existing three classes for medical devices with David Link?*

LP: That concept was introduced—not exactly three classes—as a result of an intradepartmental task force for Ted Cooper was the chairman, and he was the director of the Heart and Lung Institute at the time. But this task force was directed upon the request of President Richard Nixon and his consumer message in

1969, where he suggested that the agency take a look at its authority over the medical device industry as a complement to the regulation of drugs.

That's what the task force was set up for, and they completed their work in 1970 and issued what is known as the Cooper Committee Report, which laid the foundation for what ultimately became the Medical Device Amendments of 1976.

And the concept of this tiering, that ultimately became Class I, II and III, was recognized among this industry or this practice of medicine that the breadth and depth was clearly much different than anything that existed in the drug arena—because we're looking at Band-Aids all the way to heart valves, so to speak.

That's how the legislation developed into the necessity to classify devices, that is devices that were in commercial distribution at the time of the enactment on May 28, 1976—we're getting up to 40 years now.

Dave and I thought we'd get a head start on the process in the early 70s and Commissioner Charles Edwards said, "Go do it!" so we organized two test panels, one in the orthopedic arena, and one in the circulatory system—cardiovascular, thoracic—to evaluate how a committee consisting of physicians, scientists, engineers, industry, consumer, could work together to develop a plan to evaluate distinctions based on what were adequate controls to provide reasonable assurance of safety and effectiveness.

So obviously, for a tongue depressor, the floor would be Device Registration and Listing, Good Manufacturing Practices, etc. But for those devices for which something more was necessary to provide that reasonable assurance of safety and effectiveness, the concept of compliance with standards would be the Class II devices—Class I being general controls, Class II being standard.

It was contemplated at the time that standards would be rather broad—maybe electrical safety, sterility—some broad categories applicable to the particular device or group of devices for which safety and effectiveness would be reasonably compliant.

And then the third group, for those devices that met the definition of Class III—life-sustaining, life-supporting or for which there was not a reasonable risk of illness or injury associated with the use.

With those two test panels, we were able to agree on a questionnaire system to be used by the individuals who were on the advisory committee, and then subsequently, after their work was done, to publish in the Federal Register a notice to promulgate a rule by regulation.

That's how the process began before 1976. So all the 10 or 12 advisory committees that we had had looked at approximately 1,800 different classes of devices to place them into one of these applicable slots.

But when the amendments were enacted on May 28, we had enough background to hold a formal, public hearing to have the panel agree on recommendations, which then were published in the Federal Register as a proposal for the public to comment, and for the agency—then it was the Bureau of Medical Devices as part of the FDA—to evaluate those comments and publish a final rule with explanatory text. That became the official classification process for devices.

It took from 1976 to the mid-80s before all those proposed regulations were completed and finalized. That formed the basis for the formal classification system.

If devices were developed after that time and for which they couldn't slot into one of those three categories, because they might be completely novel—say, an artificial pancreas, what would you do with an artificial pancreas? Or if there was a pre-enactment device before 1976 that had been in lawful commercial distribution, but not known to the agency or the committee at the time, then those would ultimately have to be classified, because they were pre-enactment.

MO: *On a separate issue, the Supreme Court ruling in Medtronic v. Lohr (1996) generally held that FDA approval of a Class III medical device preempted state product liability law. What was the rationale of that ruling, and why does it sharply limit the types of recourse a patient might have for injuries?*

LP: Before *Medtronic v. Lohr*, there was another case involving the 510(k) process. The immunization from products liability is with reference to the premarket approval process.

That's what the intent was back in 1976, so that when FDA approves a device, manufacturers wanted some protection from frivolous lawsuits. The companies said, "If you are going to approve the PMA device, we want some insulation here, because this judgment-making process, while it's mutual, FDA is giving us the green light that there's a reasonable assurance of safety and effectiveness. We don't want any frivolous lawsuits for the PMA devices."

The Class III approved devices are entitled to this exemption, but it does not apply to Class I or II devices. The Supreme Court has ruled on its application, and it would take a Congressional amendment to the statute to modify or eliminate the exemption.

This exemption from liability suits would be

difficult to accomplish. If there was to be some fraud associated with the Approval process, this could be the basis for some further litigation as to application of the exemption. At present, there could be other avenues for judicial relief that may be possible, but I am not aware of any.

I really respect what Hooman and his wife, as well as what some of the others have done, but I disagree with his penchant for a legislative change.

FDA should use present resources to provide greater surveillance over how user facilities are complying with the MDR regulation. If either the manufacturer or user facility failed to comply with the regulation, they could be subject to civil and/or criminal penalties as well as lawsuits from plaintiffs for negligence per se.

It's within the authority of the agency to detect violations, but better, to prevent by trying to understand what's going on the in the marketplace before waiting for an incident.

Daniel: FDA Does Not Have A Reliable Surveillance System For Medical Devices

Devices aren't tracked with the same rigor as drugs, because FDA does not have a data system that can reliably track medical devices and identify potential safety problems, according to Gregory Daniel, fellow and managing director of the Center for Health Policy at Brookings Institution.

"Without having such a data system that can be used for active safety surveillance—i.e., safety monitoring that doesn't rely on reporting of adverse events by providers or manufacturers—it is challenging to quickly identify potential safety issues with devices early on," Daniel said.

FDA is working on improving its postmarket surveillance system for devices in collaboration with Brookings—an effort that Daniel said would reduce reliance on spontaneous reporting of adverse outcomes.

The initiative, called the National Medical Device Postmarket Surveillance System, or MDS, will use unique device identifiers, insurance claims data and electronic medical records to create a database that can track devices and link them with patient outcomes.

"I think that the major impetus [for this program] is a realization that there isn't at all an existing sustainable data system in the United States that one can use to track and understand how medical devices are performing across different patient populations, across clinical settings," Daniel said. "Generally, I think it is safe to say that with better, more robust postmarket surveillance that the MDS can provide, certainly in a lot of cases, this would enable the accumulation of evidence on the devices much more rapidly and in much larger populations than is currently available right now."

Daniel spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: *How did Brookings become involved in FDA's efforts to develop and expand the Center for Devices and Radiological Health medical device postmarket surveillance system?*

Gregory Daniel: Brookings has a longstanding partnership with FDA on facilitating the discussions around a lot of the high-priority topics for the agency.

We started working with the CDRH in our role in developing the Unique Device Identifier implementation roadmap, which is the strategy for how stakeholder groups can implement and begin using the Unique Device Identifiers on devices.

That work helped launch our role into convening the planning board, and we did that by essentially responding to an RFA that was released by the agency.

MO: *When did CDRH start working on this, and when did you join the project?*

GD: CDRH included this in their strategic priorities in 2012, which also included establishing the UDI system. We began working on the National Medical Device Evaluation System by convening the planning board in 2014.

MO: *Why did CDRH decide to enhance its postmarket surveillance capabilities for medical devices?*

GD: It's multifactorial. I think that the major impetus is a realization that there isn't at all an existing sustainable data system in the United States that one can use to track and understand how medical devices are performing across different patient populations, across clinical settings.

First, without having such a data system that can be used for active safety surveillance—i.e., safety monitoring that doesn't rely on reporting of adverse events by providers or manufacturers—it is challenging to quickly identify potential safety issues with devices early on.

Second, without such a system, it is very costly and resource intensive to develop longer term evidence on the effectiveness and impact on patient outcomes

of medical devices. Better systems for developing evidence on safety and effectiveness could also help support innovation through enabling more streamlined and routine data collection that would be required for regulatory decisions.

So developing such as system can substantially improve the ability of FDA, manufacturers, providers, and patients to get better and more timely evidence on safety and effectiveness, and help support innovation.

I think the promise of such a system to deliver on more robust and efficient data collection led the FDA to make this such a high priority.

MO: *What initiatives are Brookings and CDRH proposing, and how does it work? In a nutshell, what's the plan, and how will it be implemented?*

GD: Over the last year, Brookings convened the National Medical Device Evaluation System Planning Board. The planning board was put together through a public call for nominations—we had an independent selection committee to determine who would be selected for the board membership.

We spent the last year working with the planning board to articulate what the national vision should be for such a data system and what the system should look like, and what functions it should have. That report came out in February earlier this year.

At the same time, the National Medical Device Registries Task Force, led by Duke University and the MDEpiNet partnership, developed priorities for improving the use of registries—which are one of the modes for collection important data on devices and outcomes—specifically for developing evidence on safety and effectiveness. This effort was largely focused on methods and data collection.

Now we're in phase two, which is continuing to work with the planning board on the actual implementation plan and strategy for the NMDES, incorporating the planning board's report and the registries task force report—so getting to the details of data coordinating center, the function of this center and its governance, and the sustainability and business plan for the system.

MO: *What needs and concerns were important to you in the process of developing the blueprint?*

GD: That's a great question. One of concerns was that—neither FDA nor the planning board wanted this to be a brand new, one-off data system that's built from scratch. We have too many of those right now.

The vision for the system was that it would leverage and collaborate with existing data models and systems that are already out there, like FDA's Sentinel System, a national electronic data system to actively monitor the safety of FDA-regulated medical products, but most useful for drugs and vaccines and the Patient-Centered Outcomes Research Institute's PCORnet, a national collaborative research infrastructure focused on comparative effectiveness research that matters to patients. There are many great medical device registries that are also up and running. These are important building blocks and data systems that could enable the MDS to function.

So that's one, the coordination of existing data networks.

Number two was patient privacy and data security. With the way that electronic health data are generated across the health care system, there are a lot of novel ways to appropriately utilize these data to generate medical evidence. This system should make sure that it develops evidence in a way that is compliant and is appropriately protective of patient privacy and data security.

And number three—not in order of importance; probably in reverse order—is the patient should be at the center of this. This is all about improving the evidence to inform patient and provider decision-making about high quality care, and this is about evidence that can help identify what works in the system and what doesn't.

MO: *How will FDA be using the system of networks? Will it be through Sentinel via tracking UDIs?*

GD: Sentinel is certainly a good model in being able to partner with large private health plans and other systems that have majority access to the claims data. That will be an important part of the system. I don't think Sentinel will be the keystone of the system necessarily, simply because Sentinel does not have a lot of clinical data around the particular devices themselves and right now, claims data do not include UDIs so that makes it nearly impossible to use that data to identify specific brands or models of devices. It would be fundamentally enabling if UDIs were included in claims data, but that doesn't exist today.

So we have to design better, other ways to be able to identify specific devices and link them to long term outcomes, and that will be including claims data, but also registry data and electronic medical record data.

The planning board didn't envision that FDA would own or lead this system. Rather a coordinating center managed by a public private partnership with an independent governance structure would need to be created to coordinate this system's development and

use. This would enable many stakeholder groups to be an important part of the system.

MO: *How would MDS improve FDA's ability to track medical devices and keep up with reporting of adverse outcomes in the future?*

GD: What we're hoping the system will be able to do is that when there is a potential concern about safety on a particular device, or there are questions about the benefits that a particular device can bring to a patient population—having a system like this will enable FDA or a sponsor or a provider group to formulate what their question is of the data and our system will be able to coordinate the necessary data in order to efficiently ask those questions and get answers. For safety questions, this would be a big step forward because the FDA would be able to evaluate safety issues without relying on providers or manufacturers to report adverse events. This will be an active system in which the data such as the claims, EHRs, and registries automatically and routinely collect safety and effectiveness information as medical encounters occur.

MO: *What is the overall approach on how drugs and devices should be regulated? Are Brookings and CDRH using the National Drug Code Directory as a reference point?*

GD: On the drug side, the NDCs are great, because they are ubiquitous in electronic health data. NDCs are included in claims data, they're included in electronic medical records, and because of that, it's very efficient to go to large claims data sources in electronic medical records and quickly identify unique drug exposures and then link those exposure to outcomes.

That doesn't exist on the device side. Unique device identifiers did not exist—but now the system exists, but the challenge is that just having the identifier on the device itself doesn't help us better identify devices in the electronic health care data systems.

Providers, payers, patients need to use the UDIs and document them, mostly on the provider and payer side into the electronic medical record in the claims data in order to be able to much more efficiently identify unique devices in the data themselves.

So the NDC is a good example on the drug side of how that can be done. We do have tremendous amounts of drug safety surveillance, comparative effectiveness research, quality reporting, etc.—and we learn a lot about drugs, not only initially when the drugs are on the market, but drugs that have been on the market for 10, 20 years. We have a wealth of data available to really understand how that drug performs in a variety of different patient populations, thanks to the ubiquitous nature of the NDC.

We'd like to be able to get there on the device side, but it will take a lot of investment up front by payers, providers, and hospitals to develop the data capability and infrastructure to be able to document and report those UDIs in the claims in the electronic medical records.

MO: *Should there be a difference between how drugs and devices are regulated? And has this evolved over time?*

GD: Drugs and devices are different. Drugs, once they're on the market, their chemical structure is consistent, and it stays the same over the life of that drug.

When a device gets on the market, version A gets approved and is used, but then there's version B and version C that are slight modifications, for instance, based on surgeons' input using the devices as part of surgery.

So the device development continues to evolve in an iterative fashion, even after the devices are on the market. They're different, so the regulatory pathways need to accommodate those fundamental differences in how drugs are developed versus how devices are developed.

I think we don't have a one-size-fits-all regulatory approach—I don't necessarily think that that's right—but an approach that recognizes the differences between drugs and devices, and diagnostics are clearly part of this, too.

It is important that the reviewers and the folks at FDA—whether they're on the drug side or the device side—that they have the deep understanding of the therapeutic areas of the disease process within the body, the biological underpinnings of disease and an understanding of patient experiences and preferences in order to best be able to evaluate the benefits and risks in the patient population.

MO: *Should adverse outcomes reporting be different for drugs and devices, and is it?*

GD: If you're talking about the spontaneous report data requirement on manufacturers and providers, I'm not sure how different they are between devices and drugs.

MO: *There has been a lot of controversy over the past two years on whether FDA medical device regulations adequately ensure patient safety. The Class II 510(k) clearance process has been the focal point in the debate, and critics say that a more reliable risk-based system needs to be instituted.*

Since the legislation clears products based on predicate devices without premarket testing, patient advocates say that the potential for patient harm is embedded in the 510(k) process, because there is no rigorous risk assessment mandate for subsequent iterations of equivalent Class II devices.

How does the MDS address those concerns?

GD: In the specific example that you're talking about, I think that with the 510(k) and the PMA processes, there is some form of a risk-based system.

The question is: How well are we doing in identifying what products go through which process? And how well are we accumulating and generating the best highly reliable and quality data to support both pathways?

The MDS doesn't change the regulatory pathway, but we certainly need to look at the pathways and make sure that they are the most appropriate for improving quality and reducing the risk of harm.

For the MDS, that does and will improve the availability of high quality data for regulatory decision-making, whether that's premarket decisions or postmarket decisions.

Leveraging the constant availability of clinical and administrative data from real patient experiences with these devices can help much more than before identify safety concerns much earlier in the process. It helps companies and providers better understand the right patient population where the benefits are outweighing the risks the most, and guide care in that context. Most importantly these data do not rely on reporting. The data are automatically collected as part of routine care.

So there are a number of improvements in the decision-making ability of regulators, providers and patients that these kinds of data—that are generated from actual patient experiences—can bring into the system.

MO: *I've got a proposal from patient advocates that I'd like to bounce off you. Some advocates say that perhaps the most effective way to protect patients is to require manufacturers to track the first wave of high-risk devices via a registry—sample size to be determined—and report outcomes to FDA.*

Can you juxtapose that proposal against the MDS and weigh the pros and cons?

GD: The proposal you're talking about is requiring high-risk devices to automatically have a registry that continues to collect postmarket data on these devices. Is that right?

MO: *Right, as an active way of reporting back to FDA instead of waiting for adverse outcomes to be reported.*

GD: This is a prime example of how valuable something like the MDS could be. Because, requiring a company to automatically start collecting this data—that's pretty expensive to do for the company and the health system.

Generally, what that means is a brand new registry needs to be created. And to get the data into the registry, the providers and clinical staff need to manually add data to the registry at the point of care and typically during any follow up visits. That's actually very burdensome on providers and their clinical staff.

For some medical device implant procedures, it can take longer to fill out the data forms for the registry than performing the procedure itself.

The vision for the MDS is that it will enable coordination and use of ongoing national data systems and registries to eliminate or minimize the need to start a brand new registry from scratch, thereby enabling the evidence to be developed more efficiently.

For some questions on safety and effectiveness, a registry may not be needed because we'll be able to use claims and EHR data, potentially as they are collected and made available for Sentinel and PCORnet, for example. However, for other questions that require specific clinical data elements, registries will be an important component—but by also leveraging claims and EHRs, the burden on the providers can be reduced.

There's a lot of work right now exploring how to more efficiently automatically include claims data and electronic medical records into a registry so that you alleviate the burden on the provider allowing them to spend more time with their patients.

If there is a requirement on a company to capture specific outcomes data, the MDS could be the data infrastructure backbone, eliminating the need to build a new registry from scratch.

So it's a longwinded way to say that this system could be a much more cost effective and efficient and flexible way to meet regulatory requirements on collecting postmarket safety and effectiveness evidence of medical devices. That's a major goal of this system.

MO: *What do device companies think of the MDS? What have you heard from industry?*

GD: We have some industry members on the planning board. Generally, they are very supportive of having this national system that brings stakeholders around the table to develop and coordinate the right kind of data systems that we need to generate better evidence.

There are, as you've mentioned, a lot of

regulatory requirements for collecting data—they see the value in a system like this being able to do that more efficiently.

It's sort of a blueprint right now, it's not a reality yet, so support from FDA and federal partners to launch this system to begin generating evidence can really then provide back to industry proof that this system can be valuable and is worth investment.

MO: *What are the milestones for the blueprint, going forward?*

GD: Generally, what we're trying to do over the next year is identify the characteristics and functions of the coordinating center, including the organizational and data a governance models and to stand this coordinating center up. Then further refinement and development of the data strategy, business model, and operating policies will need to be supported along with early evaluations to demonstrate the value of the system. A full-blown system operating as envisioned by the planning board will take at least five years to really develop. A lot will need to go into bringing disparate data together and using it for medical devices.

MO: *Circling back to the genesis of this story, if the MDS had been in place, say, in 2010, how would it have prevented patients from being harmed by power morcellators in recent years?*

Also, how would it have impacted adverse outcomes reporting, considering that these devices were on the market for two decades before patients—not manufacturers and user facilities—reported harm to the FDA?

GD: Generally, I think it is safe to say that with better, more robust postmarket surveillance that the MDS can provide, certainly in a lot of cases, this would enable the accumulation of evidence on the devices much more rapidly and in much larger populations than is currently available right now.

You get a better understanding of what's happening sooner. If there is a safety issue that's happening out there, this would improve the accumulation of evidence in terms of speed and quantity. Also, the system will not rely on reporting of serious adverse events as the data that will be leveraged will automatically include them as they are identified from claims, EHRs, and registries, not on spontaneous report data.

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Capitol Hill

Congress Passes Omnibus Bill Funding Gov't Through Sept. 2016, Boosting NIH Budget by $2 Billion

By Conor Hale

Congress passed a $1.1 trillion government spending bill Friday morning, increasing the NIH budget by $2 billion. The measure now moves to the president's desk for approval.

The omnibus spending bill includes a $680 billion tax cut package—which was voted on separately by the House Thursday afternoon, and passed 318 to 109. Virtually all Republican House members, 241 total, voted for the tax cut package.

The vote for the larger appropriations bill, which funds the government through Sept. 30, 2016, passed the House by 316 to 113, with 150 Republicans and 166 Democrats voting in favor. Ninety-five Republicans and 18 Democrats voted against.

The Senate took up the bill shortly afterwards, approving it with a 65-33 vote.

Presidential candidates Sens. Ted Cruz (R-Texas), Rand Paul (R-Ky.) and Bernie Sanders (I-Vt.) voted against the bill; Sen. Lindsay Graham (R-S.C.) voted yes. Sen. Marco Rubio (R-Fla.) missed the vote on the bill.

The tax cut portion of the bill postpones two taxes set in the Affordable Care Act for two more years. One is on expensive health care insurance plans, the other, a 2.3 percent excise tax on the sale of medical devices.

The omnibus bill mandates a two-year delay on the implementation of draft recommendations by the U.S. Preventive Services Task Force on breast cancer mammography screening.

The task force had given a C rating to routine screening of women ages 40–49, and a B to screening women ages 50–74 every other year. The Affordable Care Act requires private insurers to cover procedures given grades of B or higher by the task force.

The bill also caps multiple procedure payment reductions to Medicare reimbursement for interpretation of advanced imaging scans performed on the same patient in the same session on the same day, according to the American College of Radiology.

In recent years, the Centers for Medicare & Medicaid Services applied a 25 percent MPPR to the professional component of these services. Beginning Jan. 1, 2017, the bill caps any reduction at 5 percent, the ACR says.

The votes come just before Congress' scheduled winter recess, following weeks of pushing back deadlines and passing multiple short-term resolutions to keep the government open while leaders hashed out the larger budget deal.

"It is so important to see this proposed increase in support of life saving cancer research," said Louis Weiner, director of the Georgetown Lombardi Comprehensive Cancer Center.

"Dollars spent in biomedical research – and particularly cancer research—is directly associated with a decrease in the number of people who die from cancer. Therefore, the health of America is directly related to our investment in research," Weiner said. "An increase in NIH funding will boost progress and restore the pace of discoveries."

The full omnibus bill was made public late Tuesday night, generating praise from professional societies and research advocacy groups. The Federation of American Societies for Experimental Biology urged Congress to pass the appropriations bill.

"The legislation includes a $2 billion increase for the National Institutes of Health, $119 million increase for the National Science Foundation, $279 million increase for the Department of Energy Office of Science, $41.8 million increase for Veterans Medical and Prosthetic Research, and $25 million increase for the Agriculture and Food Research Initiative," FASEB said in a statement.

"We are very pleased to see the $2 billion dollar increase for NIH in the FY 2016 Omnibus Appropriations bill," said FASEB President Parker Antin. "I appeal to scientists across the United States to contact their representatives and urge speedy passage of this essential legislation."

Marc Casper, speaking for United for Medical Research, said, "We are very pleased with the critical funding Congress has included for NIH.

"Boosting the NIH budget to just over $32 billion is a significant increase over 2015—more than five percent—and demonstrates the strong bipartisan support for biomedical research as an engine for innovation and a pathway to hope for patients. United for Medical Research commends those members of Congress who worked tirelessly to make this possible," said Casper, president and CEO of Thermo Fisher Scientific.

Mary Woolley, president and CEO of Research!America, said: "The FY16 omnibus and the tax extenders measure bring a healthy helping of glad tidings for patients with a significant boost in funding for medical research and tax provisions that will advance innovation.

"The bills help accelerate the pace of medical progress in profoundly important ways; working to defeat Alzheimer's, cancer, heart disease and other serious conditions, bringing new lifesaving treatments and ultimately cures within our reach.

"In particular, provisions in the bills that bolster funding for the National Institutes of Health, the National Science Foundation, the Centers for Disease Control and Prevention, and the Food and Drug Administration, suspend the medical device excise tax and make the Research and Development tax credit permanent, signal a solid bipartisan commitment by members of Congress determined to reduce the prevalence of deadly and disabling disease, and protect the health of Americans.

"Unfortunately, funding for the Agency for Healthcare Research and Quality remains below what is necessary to address inefficiencies in health care delivery.

"Among the many congressional champions who took decisive action on behalf of patients, Senators Roy Blunt (R-MO), Orrin Hatch (R-UT), Patty Murray (D-WA) and Ron Wyden (D-OR), and Representatives Tom Cole (R-OK), Kevin Brady (R-TX), Rosa DeLauro (D-CT) and Sandy Levin (D-MI) merit special recognition for their extraordinary vision and leadership.

"We urge Congress to approve the package to ensure we continue to make headway in finding solutions to pressing health challenges.

Editorial

The Year in Review

(Continued from page 1)

My colleague Matthew Bin Han Ong squarely earned the nickname "Scoop" by winning three awards for his coverage of the controversy over power morcellation:

• The first place National Press Club Award in the NPC's annual journalism competition;

• The Sigma Delta Chi Award for Public Service in Journalism in the newsletter category;

• A first place 2015 Dateline Award for Excellence in Local Journalism in the newsletter category from the Society of Professional Journalists, Washington, D.C., Professional Chapter.

His series on power morcellation and FDA regulation of medical devices continues in this issue of The Cancer Letter.

The year began with a story I had been waiting to break for well over four years: a whistleblower—a brave medical student named Brad Perez—had warned Duke University administrators about troubles in the lab of its star scientist Anil Potti (The Cancer Letter, Jan. 8).

Had Duke listened to Perez's warning, it would have avoided a lot of trouble. Duke got a lot of ink in 2015. One highlight was an interview with a Duke patient who disagrees with the university's assertion that no one was harmed in the trials that utilized fraudulent genomic predictors (The Cancer Letter, May 22).

Duke settled a lawsuit brought by patients who were enrolled in its clinical trials, and Potti received a light penalty in a deal with the Office of Research Integrity (The Cancer Letter, Nov. 13). Potti, who now practices in North Dakota, will not be able to engage in unsupervised research for five years.

Also in 2015, The Cancer Letter had to defend itself against an effort by Amgen Inc. to force me to answer questions related to a 2007 story that sparked a class action suit by investors and triggered a change in FDA regulations of erythropoiesis-stimulating agents.

Judge Amit Mehta, of the U.S. District Court for the District of Columbia, quashed a subpoena filed by Amgen that sought information related to my reporting of a story about an important clinical trial showing that patients who received Aranesp did worse than patients who did not. (The Cancer Letter, Sept. 4).

The ruling, dated Aug. 21, is posted here.

Our readership has grown dramatically.

Unless this issue goes viral—which it likely will—this year we will have logged 490,000 visits, a 54 percent increase over the previous year. Page views will be over 1.3 million and the volume of downloads will be over 1,100 gigabytes, nearly 60 percent more than in 2014.

In 2014, we averaged about 12,600 unique visitors a month—this year we averaged over 21,000, an increase of over two-thirds.

These numbers show explosive growth. In 2014, we had 307,350 visits, page views were just under 1.1 million, and 673 GBs were downloaded.

With over 130 institutional subscriptions, the vast majority of cancer centers and pharma companies now have access to our publications. Our coverage and ads placed on our website reach the entire top tier of oncology—the leading healthcare providers, pharma companies, and government agencies.

The number of stories and briefs in each issue of The Cancer Letter and The Clinical Cancer Letter has grown tremendously, thanks to Conor Hale. Conor anchors our coverage of Capitol Hill, our videos, and production of every issue.

Finally, dear reader, if you find yourself in Washington Feb. 2, come to my reading from my debut novel, The Yid, at Politics & Prose. The Yid has nothing to do with oncology. It's a dark comedy set in Moscow in 1953. If you like things Russian and Shakespeare in Yiddish, a good time will be had.

In Brief

DuBois Named Dean at MUSC College of Medicine

RAYMOND DUBOIS was named the next dean of **The Medical University of South Carolina College of Medicine**. DuBois will assume his new role effective March 1, 2016, with an academic appointment as professor while also holding an appointment in the Hollings Cancer Center.

DuBois currently serves as executive director of the Biodesign Institute at Arizona State University. Prior to his appointment at Arizona State, DuBois was provost and executive vice president at MD Anderson Cancer Center, overseeing all research, education, training and faculty development.

Prior to joining MD Anderson, DuBois was a professor at Vanderbilt University Medical Center in the departments of Internal Medicine and Cancer Biology, director of the Vanderbilt-Ingram Cancer Center, and prior to that, chief of Gastroenterology, Hepatology and Nutrition.

DuBois has served in many leadership roles, among them as past president of the American Association for Cancer Research and the International Society for Gastrointestinal Cancer. DuBois will continue his leadership in cancer discovery through his ongoing research, engagement with the NCI, and through partnership with the Hollings Cancer Center. He also currently serves on the Executive Management Committee for the Stand Up to Cancer Foundation, and is the president and chair of the AACR Foundation Board.

JOHN "DREW" RIDGE was elected president of the medical staff at **Fox Chase Cancer Center – Temple Health**. Ridge serves as chief of Head and Neck Surgery and Louis Della Penna Family Chair in

Head and Neck Oncology.

In this role, Ridge will work with Richard Fisher, president and CEO, and hospital administration to improve physician credentialing and privileging processes, and select physician representatives to committees that oversee patient safety and quality control.

Ridge has been co-chair of the NCI Head and Neck Steering Committee, as well as president of the American Head and Neck Society and of the American Radium Society. He has held leadership positions in the Eastern Cooperative Oncology Group and NRG cooperative groups.

BHRAMAR MUKHERJEE was appointed associate director for population science research at **The University of Michigan Comprehensive Cancer Center**, effective Jan. 15, 2016.

Mukherjee is the John D. Kalbfleisch Collegiate professor of biostatistics and a professor of epidemiology at the U-M School of Public Health. She also serves as the associate chair for biostatistics.

In her new role, she will oversee the center's research on screening, detection and prevention, as well as research on outcomes, disparities and new models of cancer care delivery.

Mukherjee joined the University of Michigan faculty in 2006. She has received the U-M School of Public Health's Excellence in Teaching Award and was the recipient this year of the University of Michigan's Faculty Recognition Award. She is the founding director of a cross-disciplinary summer institute at the School of Public Health to train undergraduates at the intersection of big data and human health. She is also an elected fellow of the American Statistical Association.

Her cancer research has focused on how the interaction between genes and the environment impacts cancer risk. She has studied the roles of diet, physical activity and lifestyle factors, and their interplay with the genetic architecture of an individual.

The associate director for population science position was last held by Stephen Gruber, who is now the director of the University of Southern California Norris Comprehensive Cancer Center.

JOSEPH SMITH JR. received the Huggins Medal from **The Society of Urologic Oncology**, the society's highest honor, for his lifetime contributions to treatment for patients with genitourinary neoplasms. Smith is a professor of Urologic Surgery at Vanderbilt University Medical Center.

The Huggins Medal is named after Charles B. Huggins, who was awarded the Nobel Prize for Physiology or Medicine in 1966 in recognition of his work on the hormonal treatment of prostate cancer. It is the second major award for Smith from the SUO, having been awarded the SUO Medal in 2006.

Smith received the medal and presented the Huggins lecture at SUO's 2015 annual winter meeting in Washington, D.C. He was also recently named the next editor of The Journal of Urology.

Smith performed Vanderbilt's first robotic surgery in 2003 and has completed more than 7,000 prostatectomies since that time. With Smith, VUMC has established itself as a leader in robotic surgery and indications have extended in urology to radical cystectomy, partial nephrectomy and bladder suspension.

RICHARD ADAMSON received the 2016 Founders Award from the **Society of Toxicology**.

The society also named over three dozen other award recipients, who will be formally honored during its annual meeting and ToxExpo in New Orleans, which begins March 13, 2016.

The Founders Award recognizes a society member who has demonstrated outstanding leadership in fostering the role of toxicological sciences in safety decision making, helping illuminate the difference between safe and unsafe exposure levels for humans to chemical and physical agents.

Currently of TPN Associates LLC, Adamson's career spans more than four decades. For newborns, Adamson demonstrated that not only was weight a factor in administration of a dose to infants, but allowing for the development of drug metabolizing enzymes in the infant was also a major factor to reduce sensitivity to drugs.

In the use of antibiotics in surgical procedures and myasthenia gravis, he and his colleagues demonstrated the synergy between some antibiotics and neuromuscular blocking agents as very important interactions between muscle relaxants.

In studying absorption, distribution, metabolism, and excretion of folic acid antagonists, he found dichloromethotrexate was metabolized by liver enzymes and Methotrexate was generally excreted by the kidneys. This suggested that DCM was the better folic acid antagonist for use when renal function is impaired, or in the case of immunosuppression, such as cases of kidney transplantation.

In working with the National Research Council,

Adamson was invited to a committee to investigate the safety of platinum catalytic converters in cars. The committee concluded that the platinum and palladium emitted from automobiles was small and the chemical form and lack of methylation by microorganisms posed no known threat to the environment or individuals.

His work with a Department of Health and Human Services committee reviewed the benefit and risks of fluoride in the use for prevention of dental cavities. The committee supported the use of fluoride in drinking water, toothpastes, mouth rinses and fluoride dietary supplements at optimal levels.

He has also investigated the carcinogenic potential of food additives, food contaminants, and pesticides. His long-term study of the use of saccharin led in part to various regulatory agencies to remove saccharin from their lists of carcinogens. He helped determine that MOPP combination chemotherapy for Hodgkin's disease caused toxicity due partly to the use of procarbazine, which led to the development by oncologists of other first-line therapies for Hodgkin's disease. Working with Japanese investigators, he found that heterocyclic amines resulting from cooking meat were carcinogenic and determined that certain methods of cooking could reduce their formation. More recently, he has spoken out about the safety and benefits of caffeine consumption.

"Toxicologists are involved in research that both assesses the safety of chemicals and compounds and determines the mechanisms, or ways, in which chemicals and compounds affect the body. The 2016 SOT awardees are among the best and brightest of our scientists whose work in these areas has greatly impacted public health—or soon will," said Peter Goering, SOT president. "We also are pleased to honor exceptional individuals who are educating the next generation of scientists and who are making toxicology more accessible to all."

The honorees represent various disciplines, which all factor into toxicological research. *The 2016 SOT Award recipients are:*

Raymond Nagle, University of Arizona Health Sciences Center; *SOT Honorary Membership*

Lauren Aleksunes, Rutgers University; *SOT Achievement Award*

Alan Boobis, Imperial College London; *SOT Arnold J. Lehman Award*

I. Glenn Sipes, University of Arizona; *SOT Distinguished Toxicology Scholar Award*

Kenneth Reuhl, Rutgers University, and **John Wise Sr.**, University of Louisville; *SOT Education Award*

Warren Casey, NIH; *SOT Enhancement of Animal Welfare Award*

Cheryl Lyn Walker, Texas A&M Institute of Biosciences and Technology; *SOT Leading Edge in Basic Science Award*

Melvin Andersen, The Hamner Institutes for Health Sciences; *SOT Merit Award*

Steven Gilbert, Institute of Neurotoxicology & Neurological Disorders, and **Gary Ginsberg**, Connecticut Dept. of Public Health; *SOT Public Communications Award*

Richard Beger, FDA-NCTR; *SOT Translational Impact Award*

Mohamed Salama, Mansoura University, Egypt; *SOT Translational/Bridging Travel Award*

Antonio Baines, North Carolina Central University; *SOT Undergraduate Educator Award*

Jessica Ray, Michigan State University; *SOT Undergraduate Intern Travel Award*

David Pamies, Johns Hopkins Bloomberg School of Public Health, and **Lei Yin**, University of Georgia; *Colgate-Palmolive Grant for Alternative Research*

Shih-Yu Chang, University of Washington, and **Tshepo Moto**, University of Pretoria, South Africa; *Colgate-Palmolive Award for Student Research Training in Alternative Methods*

Katherine Dunnick, The Hamner Institutes for Health Sciences; *Colgate-Palmolive Postdoctoral Fellowship Award in* In Vitro *Toxicology*

Thomas Luechtefeld, Johns Hopkins Bloomberg School of Public Health; *Syngenta Fellowship Award in Human Health Applications of New Technologies*

The SOT Board of Publications for the Best Paper in Toxicological Sciences *Award* goes to: "A Systems Biology Approach Utilizing a Mouse Diversity Panel Identifies Genetic Differences Influencing Isoniazid-Induced Microvesicular Steatosis" (*Toxicological Sciences*, 2014, 140(2) 481–492); Authors: **Rachel Church**, **Hong Wu**, **Merrie Mosedale**, **Susan Sumner**, **Wimal Pathmasiri**, **Catherine Kurtz**, **Matthew Pletcher**, **John Eaddy**, **Karamjeet Pandher**, **Monica Singer**, **Ameesha Batheja**, **Paul Watkins**, **Karissa Adkins**, and **Alison Harrill.**

The Pfizer SOT Undergraduate Student Travel Award goes to: **Sarah Burnett**, University of Arkansas; **James Ding**, University of Texas at Austin; **Benjamin Alan Elser**, Indiana University; **Emily Fabyanic**, West Virginia University; **Laura Fisch**, Montana State University; **Eduardo Aztlán**

González, University of California Davis; **Mina Huerta**, Oberlin College; **Haydee Jacobs**, University of Massachusetts Amherst; **Rachael McMinimy**, Oberlin College; **Danyelle Osowskib**, University of North Dakota; **Lizbeth Perez-Castro**, University of Puerto Rico at Cayey; **Jiwon Seo**, John Jay College of Criminal Justice; **Carolyn Anne Smith**, United States Coast Guard Academy; **Stephanie Thiedeb**, Purdue University; **Nancy Ly Tran**, Bates College; **Jamie Weimer**, Northern Kentucky University.

THE ALBERT EINSTEIN CANCER CENTER and the **Montefiore Einstein Center for Cancer Care** received a Ruth L. Kirschstein NRSA Institutional Research Training Grant from NIH, which will provide $1.18 million in funding over five years.

This new competitive program is designed so that surgical residents in training spend two additional years in hands-on training as research fellows focused on the study of malignant tumors, the role of the immune system in tumor growth inhibition and the identification of emerging novel targets.

The 15 faculty members guiding this training, both as educators and mentors, represent six clinical and four basic science departments. Participating research fellows are expected to submit at least two abstracts to national meetings and at least one original manuscript for peer review by the completion of their training.

THE KNIGHT CANCER INSTITUTE at Oregon Health & Science University and **Cancer Research UK** formed an international collaboration focused on the early detection of cancer.

The collaboration seeks to address research models for the earliest stages of the disease; shortages of tissue samples available for research, especially samples from higher risk patients; and the need for a better understanding of the biology of early cancer and appropriate technologies to detect its features.

The collaboration will host an annual international conference series; in 2016, the conference will be titled "Cancer Research UK and OHSU Knight Cancer Institute present the Sondland-Durant Early Detection of Cancer Conference" in recognition of generous support from the Gordon D. Sondland and Katherine J. Durant Foundation.

ST. JUDE CHILDREN'S RESEARCH HOSPITAL opened its **Red Frog Events Proton Therapy Center**, the first proton therapy center in the world dedicated solely to children with cancer.

The $90-million center includes the linear accelerator, a synchrotron, a three-story rotating gantry, powerful magnets and other equipment. The system features advanced imaging technology, including cone-beam CT to provide a 3-D image of the patient's anatomy to achieve precise positioning for treatment. FDA cleared the features unique to the St. Jude proton therapy system Nov. 2.

The center also contains three proton therapy treatment rooms, treatment preparation and recovery rooms for patients plus a musical staircase that leads to a rain forest-inspired waiting room. The center's multidisciplinary staff includes specialists from oncology, radiation therapy, imaging, nursing, child life and other disciplines.

The center is located in the Kay Research and Care Center, which opened earlier this year and also houses a state-of-the-art surgery and intensive care unit, the Marlo Thomas Center for Global Education and Collaboration, and other facilities.

In 2013, the co-CEO's of Red Frog Events, Kunkel and Joe Reynolds, pledged to raise $25 million to bring proton beam therapy to the hospital's campus. Red Frog Events brands include the Warrior Dash obstacle race series, Firefly Music Festival, and Chicago Beer Classic.

INDIANA UNIVERSITY MELVIN AND BREN SIMON CANCER CENTER is seeking high school and college applicants for its 2016 Summer Research Program.

The annual program, held in partnership with the Indiana University-Purdue University Indianapolis Center for Research and Learning, places students with a mentor physician or researcher for nine weeks. Students work with faculty who are conducting studies in cancer research.

The program's primary goal is to increase the number of underrepresented populations engaged in basic, clinical and prevention and control cancer research by providing positive and meaningful first-hand exposure to those fields. Each student receives a stipend of $3,200 and is responsible for their own housing and transportation arrangements.

The program allows students to interact with any of the cancer center's research programs, shared facilities and investigators; gain exposure to a wide range of basic science, translational and clinical research activities; and attend weekly career development workshops related to gaining admission to graduate and professional programs of study.

Students are selected based on interest in biomedical or behavioral science, academic performance and personal interviews. High school students who participate must have completed at least their junior year and have maintained a grade point average of at least 3.0 on a 4.0 scale. Undergraduates in the program must have completed 24 hours of college credit, be majoring in a biomedical or behavioral science, and have maintained a grade point average of at least 3.2.

The application deadline is Feb. 26, 2016. Those students selected as finalists will be invited to campus for an interview in April 2016.

THE HEALTHWELL FOUNDATION launched a fund to provide financial assistance to underinsured patients suffering from multiple myeloma, providing grants up to $10,000 to assist patients with copayment or premium costs.

Multiple myeloma patients who are insured and have annual household incomes up to 500 percent of the federal poverty level are eligible under the fund. http://www.HealthWellFoundation.org

"A substantial number of multiple myeloma patients face significant hardship when it comes to treatment choices and the ability to cover out-of-pocket drug copayment and premium expenses," said Sharon Saias, Vice President Marketing and Communications, Multiple Myeloma Research Foundation. "The financial lifeline being offered through the HealthWell Foundation addresses a critical need for these patients and allows them to access medical treatments that are vital to managing their disease."

Drugs and Targets
FDA Approves Bendeka

FDA approved Bendeka (bendamustine hydrochloride) injection, a 10-minute infusion formulation of bendamustine.

Bendeka is approved for the treatment of patients with chronic lymphocytic leukemia and for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. Efficacy relative to first line CLL therapies other than chlorambucil has not been established.

Bendeka is contraindicated in patients with a known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine. Bendeka is also contraindicated in patients with a known hypersensitivity to polyethylene glycol 400, propylene glycol, or monothioglycerol.

Bendamustine hydrochloridecaused severe myelosuppression in 98% of patients in the two NHL studies. Three patients (2%) died from myelosuppression-related adverse reactions.

Teva Pharmaceuticals, the sponsor, expects to make Bendeka available to patients in the first quarter of 2016. Bendeka was granted Orphan Drug Designations for both CLL and indolent B-cell NHL.

Stem Cell Theranostics and CapellaBio established a cardio-oncology collaboration to discover novel drug therapies to prevent cardiotoxicity associated with various oncology drugs.

By combining CapellaBio's SMarTR computational analysis platform with SCT's iPSC-derived cardiomyocyte discovery platform, advanced drug leads have been identified in the first of a series of programs.

The first collaborative program is focused on discovering cardioprotective drugs to prevent anthracycline-induced cardiotoxicity. There is currently only one FDA-approved agent, Dexrazoxane, but this has limited indication approval and has not been widely used due to concerns that it may interfere with the anti-tumor activity of anthracyclines. Novel cardioprotectants with improved efficacy and safety profiles that could be used across multiple indications would offer significant clinical benefit.

Amgen entered into a definitive agreement with GSK to reacquire all of its remaining rights to Prolia (denosumab), XGEVA (denosumab) and Vectibix (panitumumab) in 48 countries in Asia, South America, Europe, Australia and other regions.

GSK has held select regional rights to Prolia and XGEVA since 2009 and to Vectibix since 2010 under license from Amgen. In 2014, GSK generated approximately $111 million in combined sales from these licenses. Amgen will make undisclosed milestone payments to GSK on signing and on the successful transition of the products back to Amgen. Amgen will book all product sales following this transition.

Amgen will work closely with GSK to enable a seamless transition for customers and patients. GSK will continue to hold the license and sell and distribute the products for an interim transition period that will vary by country. The majority of markets are planned to be transitioned back to Amgen within a 12-month period.