How a botched acquisition by Pfizer helped turn America’s chronic drug shortage into a full-blown crisis. 

BY ERIKA FRY
moved past such practices decades ago. Such shortages may seem unfathomable in America where, when it comes to health care, we seemingly spare no expense—shelling out $3.3 trillion in 2016—and must about the promising future of precision medicine. But even in our staggering costly and ambitious health care system, the bupivacaine shortage is not an outlier. Rather, it’s the new norm. Increasingly, the low-cost essential medicines that we’ve used for years—a category known as generic sterile injectable drugs, considered the “bread and butter” of hospital care—are in short supply.

As of last count, there were 202 medicines on the drug shortage list. They include a hazily wide array of medical staples such as epinephrine, morphine, and sterile water. Already in short supply, the nation’s stocks of saline—the saltwater solution used to administer other drugs through IV lines—fell perilously low after Hurricane Maria crippled its main manufacturer’s ability to get product and empty bags out of Puerto Rico. Sodium bicarbonate, another indispensable product—essentially baking soda in solution—that is used in heart surgeries and for kidney-failure patients, was likewise in critical shortage last summer. (Austrlian imports have helped, but the product remains on the shortage list today.) This year hospitals are struggling to get injectable opiates, which hospitals and hospices use to manage the pain of serious injury, surgery, and terminal disease.

In Ohio, at Dayton’s Miami Valley Hospital, a top-tier trauma center, ER nurses can’t get their hands on medicines they’ve used for years. They’re short of ondansetron, a first-line anti-nausea medication, for which they’ve had to substitute another drug that can cause side effects and irritate some patients’ veins. There isn’t any diltiazem, a one-time staple to treat rapid heart rate. (The drug doctors now use instead—metoprolol—isn’t safe for some people.)

“We’ve stepped back in time,” says Karen Pearson, who has worked on the ward for 38 years. When patients say they have allergies to the only available drugs, Randy Marriott, an emergency physician, now feels he has to press them: Is this a true allergy or just a sensitivity? “It’s ridiculous,” he tells Fortune. “This is not an infrequent conversation I have. Can I give you this drug that will give you miserable side effects to relieve your pain? Because today I don’t have another drug to give you.”

The problem is testing health care networks, large and small. Chris Snyder, Cleveland Clinic’s seasoned drug shortage specialist, says the situation is as bad as it has ever been; on average, a shortage crops up at the state-of-the-art system every weekday. According to an October survey from the Institute for Safe Medication Practices, shortages have prevented 71% of practitioners from providing recommended drugs or treatment and frequently delay care. “Our primary responsibility is taking care of patients,” fumes Debbie Simonson, VP of pharmacy services at Ochsner Health System in Louisiana, “That becomes a challenge when we’re making sure we can get a drug to take care of them.”

There’s another thing these drugs have in common, though. They’re almost all produced by America’s largest pharmaceutical company, Pfizer (No. 57 on this year’s Fortune 500). Indeed, as of May 11, the company, which is also the world’s largest maker of sterile injectable drugs, had 370 products that are depleted or in limited supply, 102 of which the company has indicated will not be available until 2019.

The simple answer to why America currently has so many shortages of generic sterile injectable drugs: America’s leading manufacturer of generic sterile injectable drugs hasn’t been making them.

**ALL STREET CHEERED**
When Pfizer announced its intention to buy Hospira, the world’s leading maker of generic sterile injectable drugs, for $17 billion, in early February 2015. The deal had been done after a hasty courtship—Pfizer CEO Ian Read reached out to Hospira chief Mike Ball in mid-December, and at a meeting six days later, Read offered to buy the company at a 30% premium, or $82 per share. By mid-January the Chicago-area Hospira had negotiated it up to $90. Two weeks later the parties had signed a definitive merger agreement.

Pfizer’s press release made clear its hopes of soon dominating the generic sterile injectable drugs market, a segment where global sales were projected to reach $70 billion by 2020. Perhaps even more tantalizing, Hospira was a leading player in the fledgling biosimilar market. Biosimilars are essentially generic versions of large-molecule “biologics,” the often phenomenally
Once the hospital products division of Abbott Laboratories, it had been spun off in 2004. With aging facilities, the sterile drug-maker muddled along, and then in the depths of the recession, launched an aggressive efficiency initiative dubbed “Project Fuel.”

Fourteen hundred jobs were shed as part of the exercise. According to former employees and a shareholder suit filed in 2011 (and settled three years later for $60 million), the cuts gutted the company’s quality and technical staff.

What followed is not terribly surprising: Between 2009 and 2015, the company received eight FDA warning letters and announced a steady drumbeat of recalls. At Rocky Mount, the North Carolina plant that management called the company’s “crown jewel,” FDA inspectors took issue with a comprehensive array of problems, from a lack of proper testing and control procedures to inadequate training of employees to poor design of buildings and manufacturing equipment.

By 2011, Hospira had new management, and at the company’s investor day, they offered some straight talk. “Let’s just be real with each other,” senior VP of operations Jim Hardy told the audience. “We understand we have issues to fix.”

Fixing them wasn’t easy though. To the team management brought in to clean up the mess, it became clear that getting Rocky Mount alone up to snuff was at least a three-year job. One described the plant as “a disaster.” It had so many batches awaiting testing that the company needed to lease additional warehouse space to store them. Recalls proliferated—the company tallied 239 recalls between 2012 and the start of 2015, according to FDA data—with sterile products already in the marketplace being found to contain everything from human hair to glass to “orange particulate matter.” The saga served as a relative lull in the news media’s drum roll for the pharmaceutical trade press, which followed the company’s every recall and disciplinary action with gusto.

Still those at Hospira felt they were getting somewhere. They had made improvements in plants, and thawed relations with the FDA; CEO Mike Ball himself regularly showed up for meetings with the agency. In earnings calls, Ball often referred to the company’s manufacturing woes as “gators,” and when asked by an analyst for a “Gator update” in February 2014, the executive declared something akin to mission accomplished: “I never say never in terms of gators, but I think we’ve got the swamp drained. There might be one or two hiding deep in the mud, but I think we’ve pretty much dug them out.”

When Pfizer bought the company, management was confident it had things under control. Key members of Hospira’s cleanup crew were let go. While Pfizer made some investments, it also laid off hundreds of workers at Rocky Mount alone. The string of recalls didn’t stop, however; there have been at least 45 more since the sale went through in September 2015. Hospira’s 41-year-old facility in McPherson, Kans.—which, together with Rocky Mount, produced the bulk of America’s sterile injectable drug supply—drew increasingly harsh reviews from government inspectors. In June 2016 the FDA issued a “483” for the site—a post-inspection memo—that was 23 pages of biting criticism. It chronicled instances of complaints that had been inadequately investigated and product that looked, well, not like ye’d want your sterile injectable drugs to look.

As to one particular batch of dobutamine, a drug that helps the heart pump blood, hospitals had complained that the medicine, typically clear, “rapidly changed…to a dark pink color after a few hours,” or it was “peachy-colored” with “little flakes, like eraser dust.”

The McPherson site, which sits at the periphery of an old railroad town, got an FDA warning letter eight months later, in February 2017. The comprehensive 2,500-word document took issue with a gamut of things—and recounted an incident in which the plant received a complaint about particulate matter found in an injection of the antibiotic vancomycin. (Pfizer itself later assessed it to be cardboard.) Despite additional complaints, Pfizer hadn’t recalled the lot of not-so-sterile product for five months. The FDA’s letter ended with a flourish of sweeping condemnation: “Repeated failures at multiple sites demonstrate that your company’s oversight and control over the manufacture of drugs is inadequate.”

The McPherson plant is where Pfizer, which makes 7% of America’s injectable opioids, produces most of those drugs. It’s also the production site for a major share of the nation’s anesthetic, including bupivacaine—the drug Columbia anesthesiologist Ruth Landau administers to delivering mothers every day. At Columbia, Landau and her colleagues have established conservation measures to make a limited supply last for months. Though bupivacaine is used as a local anesthetic across the hospital, for all sorts of procedures, Columbia now reserves it for obstetrics. “We understand we have issues to fix.”
SHORTAGES MAY sound like a problem from a bygone era or a dysfunctional facet of socialist economies, but they’ve been a stubborn problem in the U.S. for years. The country experienced a rash of them at the start of the decade. In 2011, a then-record 257 medications were added to the University of Utah’s authoritative shortage list, joining the 184 medicines that were already in short supply. That prompted congressional hearings and a series of reports from the Government Accountability Office. The shortages exposed the fragility of the American health care supply chain, which, as many in the system will tell you, has long been on the verge of buckling.

The medications most vulnerable to running short have a few things in common: They are generic, high-volume, and low-margin for their makers—not the cutting-edge specialty drugs that pad pharmaceutical companies’ bottom lines. Companies have little incentive to make the workhorse drugs we use most.

Congress’s response was to pass legislation in 2012, requiring manufacturers to give more notice ahead of anticipated shortages—but that seems to miss the point: What we’ve been witnessing, in slow motion, is market failure. It boils down to a lack of economic incentives.

Manufacturers of widely used, inexpensive drugs make relatively little off the products, whose prices are largely determined in contract negotiations between drugmakers and group purchasing organizations (or GPOs), which exist to broker better deals for hospitals. That makes this a high-volume, low-cost game, a reality that has driven consolidation in the market. It’s also a highly regulated and somewhat costly industry, which has chased some companies out. The economics make it hard to invest in the business or in building supply chain redundancy. When shortages happen, the financial losses tend to be marginal and temporary; there are too few players for customers to take their business elsewhere. What’s left is a system with just enough inventory to get by if nothing goes wrong.

Last year, a lot went wrong.

After Hurricane Maria decimated Puerto Rico’s power grid in September, a cascade of problems for the health system followed—not just on the island, but across the United States. What’s more, it caught everybody off guard. Puerto Rico is home to a significant share of drug manufacturing and much of the nation’s production of saline solution, a central component to hospital care. “More and more, we’re hearing about shortages where there aren’t natural substitutions—or where the identification of substitutions is harder—and that’s leading to cascading shortages,” says an official in the office of the Assistant Secretary for Preparedness and Response at the Department of Health and Human Services. Erin Fox, who runs the University of Utah’s shortage list, says that after Hurricane Maria when people couldn’t get small bags of saline, there was a run on large bags, then syringes, vials, and sterile water.

That natural catastrophe landed in the middle of Pfizer’s man-made one.

In spring of 2017, Pfizer began sending “Dear Customer” letters, warning of anticipated product shortages—largely owing to issues at the McPherson facility—every few months. Particularly grave were the issues surrounding syringes filled with drugs. Over a seven-month span, the company relayed vague news of additional setbacks in production, with each notification pushing back the arrival of the next shipment. (It didn’t help that the company closed the McPherson plant from January through March to upgrade the facility and make repairs.)
Injectable narcotics, in particular, were in desperate short supply—a function of not only the dysfunction at McPherson but also of Pfizer’s near-complete grip on the market. Because these opioids are controlled substances, they are subject to a quota managed by the Drug Enforcement Administration. The agency restricts the amount of the core ingredient that is available each year, and it strictly allocates that supply to manufacturers based on past sales. What this meant was that, even if other companies had the capacity to produce the narcotics and fill the void left by Pfizer, they couldn’t get the raw material to make them.

In late February, five medical groups, from the American Society of Health-System Pharmacists to the American Society of Clinical Oncology, petitioned the DEA to adjust the quota in order to address the problem. (In March, Pfizer surrendered a portion of its allotment, which the DEA reallocated to other suppliers.)

Pfizer, whose list of drug back orders is well over 300 items long, says it takes its responsibility seriously and that it’s working feverishly to resolve its supply issues. (After Hurricane Maria, the company also stepped up production of certain drugs to make up for competitors’ shortages.)

The challenge is substantial. The Rocky Mount facility, for example, makes up to a half-billion sterile injectables each year, enough to fill 20 semitrailers every day. Workers there make 500 different products, fitted into syringes, vials, and ampoules. They span a human life, from the vitamin K used to prevent blood clotting in new babies to the morphine used to ease the pain of terminal illness.

The plant, though, has only 26 manufacturing lines, meaning that any given line is likely to be running something different every day. Each line, moreover, has to be FDA-qualified for the drugs made on it, a costly and lengthy vetting process. Schedules are typically planned weeks in advance and can be scuttled for any number of unforeseen events, from a snow day to a worker’s illness to components that don’t arrive at the factory on time.

Because of the testing and paperwork involved, it takes batches three to six weeks to leave the factory. And each batch generates a 200- to 400-page stack of paper that documents the process. These, of course, are merely logistical wrinkles. Achieving a sterile environment—essential for medicines that are shot directly into the bloodstream—is the true challenge.

So as not to disturb the airflow, employees in aseptic spaces move slowly and deliberately, their arms raised as if in an act of surrender. They are fully covered, dressed in white boxy bunny suits that they’re allowed to don only after months of mastering the gowning technique. (In the 1970s, workers suited up for the job in a smock and paper cap.) They are separated from the slightly less sterile areas by windows streaked with disinfectant. Watching workers ploddingly unwrap instruments and tend to their machinery is like watching a lunar landing.

In the midst of this logistical labyrinth come the never-ending demands of the world outside. To instill a sense of urgency, managers sometimes post photos of babies above the manufacturing lines.

Pfizer is doing its best to meet that demand, says Kirsten Lund-Jurgensen, its executive VP of global supply. “We don’t ever want to have significant supply shortages again,” she says. “The mission is really clear to us.” That means Pfizer managers now have routines much like those of hospital doctors: They huddle every week, she says, to assess the shortages and to prioritize drugs considered “medically necessary” and “medically significant.”

Both the costs and effects of these drug droughts, it goes without saying, are also medically significant.

Even to cobble together a B-list of drugs and medical supplies requires an inordinate amount of pharmacist hours and some creativity. The goose chase involves calling around for scarce medicines and supplies, identifying multiple alternatives and ordering them before others do, and optimizing available drugs by compound- and repackaging them on site. Then there’s the Herculean task of communicating the changes to the hospital staff.

And in the melee of ERs, the race to find alternative medications and use them appropriately can sometimes lead to mistakes. The Institute for Safe Medica-
tion Practices has amassed a great deal of anecdotal evidence that shortages result in medical error. An October 2017 survey of some 300 practitioners revealed nearly 100 instances over the previous six months when mistakes were made—many of them involving administering medicines in incorrect doses or concentrations.

Another concern is disaster preparedness. “The clock is ticking as we approach hurricane season,” says Dave Harlow, chief pharmacy officer at Martin Health System in Stuart, Fla. “The situation is an emergency waiting to be a disaster.” Harlow is currently managing 275 shortages. He notes that Martin is within an ambulance-drive range from Mar-a-Lago and that when it comes to the nation’s drug shortages, they don’t discriminate.

A number of people interviewed for this story—notably who work at Pfizer, suggested that the march of progress in quality control has gone too far, or at least that it should be tempered a bit. Back in a simpler, less scrutinized era, providers got the drugs they needed, and no one seemed to suffer the effects of a drug not passed through automated visual inspection equipment.

“In efforts to make better, even potentially perfect products, we may lose sight that being without some of these medications could be life threatening,” says Chris Snyder, the Cleveland Clinic shortage specialist. “We need to ask, What does this look like when we’re taking care of patients? How are all these hospitals dealing with it?” Nobody wants to look behind that curtain.

Others argue the level of regulatory nit-picking has backfired in a dangerous way. By stalling production at factories that make sterile drugs—and the FDA pointedly denies that it has—the regulator has pushed hospitals into a task many of them aren’t equipped to handle: compounding drugs in a sterile environment.

On Fortune’s visit to the Cleveland Clinic, Snyder channels his laid-back dude. Tall and jolly by nature, the Ohio native says he has been so preoccupied by drug shortages of late that he sometimes dreams about them. On what he calls a typical day, Snyder is in his basement cubicle calling around to colleagues across the system to check on their inventories of essential, short-supply drugs. He is anxiously awaiting a shipment of potassium chloride, which its supplier says was loaded on a boat in Puerto Rico weeks ago, bound, he thought, for Miami. It’s hard to fathom that it hasn’t arrived. “You can get from Fort Lauderdale to the Yucatán peninsula in a week—with stops all along the way,” Snyder quips to the other pharmacists. “I need to go on vacation.”

If it doesn’t turn up soon, the pharmacy staff will have to change concentrations of the chemical solution—a step that will force the hospital’s IT team to reconfigure the systemwide electronic medical records. The prospect elicits audible groans from the team. Snyder is also managing other shortages that day, including a mass recall of syringes—the CDC had linked them to bacterial contamination.

He seems to take it all in stride, and as he ticks through multiple issues at drug manufacturers, what is most striking is his lack of outrage. Snyder admits it has become business as usual. Then, he asks with resignation, “What choice do we have?”

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**DRIP, DRIP, DRIP**

Shortages of essential medicines have left IVs empty and hospitals scrambling for alternatives. Here are three drugs that are hard to replace.

**DILTIAZEM**

A drug used to reduce rapid heart rate. Pfizer’s ongoing supply issue stems from a problem with a supplier that recently stopped providing the company with an excipient used in the drug’s formulation. Pfizer is working with the FDA to find a solution.

**SODIUM BICARBONATE**

A lifesaving drug for patients threatened by blood acidification, such as in kidney failure or cardiac arrest. Pfizer ran short last year when a supplier issue was compounded by a technical one. Pfizer is making it again, but it remains on drug-shortage lists.

**HYDROMORPHONE**

Used for surgeries and to manage the pain of serious injury and disease. Pfizer considers the ongoing shortage—which stems from the company’s reduced output owing to plant upgrades and then the investigation of a syringe component—a top priority.