Beware Compounded Drugs -- Especially Under Trump's FDA

A burgeoning and little-regulated private industry that specially mixes drugs at so-called compounding pharmacies poses a public-health hazard that the Trump administration is about to make a whole lot worse.

BY RENA STEINZOR DECEMBER 8, 2016

President-elect Donald Trump has pledged to eliminate 70 to 80 percent of all federal regulations, and the Food and Drug Administration's (FDA) rulebook is near the top of his list. Close Trump adviser Newt Gingrich has denounced the FDA as the nation's leading "job killer," and has called the agency "a major prison guard stopping the breakout in health."

If the Trump administration makes good on these threats, an already weakened FDA could approach paralysis, exposing millions of patients to unsafe medications. Particularly at risk will be those who receive ostensibly "sterile" injections for back and neck pain, among other ailments, from compounding pharmacies. Essentially small businesses with overweening national ambitions, compounders were implicated in a deadly meningitis outbreak in 2012, and continue to manufacture potentially dangerous drugs administered to millions of Americans. Federal prosecutors have accused them of defrauding government health-care programs of hundreds of millions of dollars. The Obama administration failed to get a solid grip on regulating the industry, even when serious quality control problems emerged, and the Trump administration is likely to turn its back on the problem entirely, setting the stage for another fatal outbreak.

How did local businesses finagle their way into selling tens of thousands of doses of medicine made in small facilities that often fail to meet rudimentary safety standards? And why have Congress and federal regulators done nothing to stop it? The story is a troubling one that grew out of the epic pressures on modern health-care costs that began well before this election. The protagonists are an industry that has grown ever greedier, dysfunctional federal and state regulators, and a Congress that passed a law it should have known would not work.

A public health catastrophe made the problems with compounding pharmacies headline news in 2012, when a virulent outbreak of fungal meningitis was traced back to the New England Compounding Center (NECC) in Framingham, Massachusetts. The NECC shipped 17,676 vials of contaminated methylprednisolone to health-

care facilities in 20 states. Injections were administered to 14,000 patients, killing 64 and severely sickening 753. Fungal meningitis develops one to four weeks after exposure, and produces inflammation of the brain or central nervous system. Even if the disease doesn't kill the patient, it can persist for years.

> Compounding, defined as the mixing of drug doses tailored to the individual patient, has existed as long as people have made medicine.

Up until recently, American compounders worked at the local level. In the early 1990s, hospitals eager to avoid the headaches of making compounded drugs in-house turned to these independent pharmacies, dramatically expanding their customer base. The most entrepreneurial among them saw the opportunity to also expand their boundaries, mixing and selling large quantities of medicine across state lines without individual prescriptions. The NECC was able to get licenses to sell medicine in 44 states. A former manager who spoke on the condition of anonymity told *The New York Times*: "It was a license to print money. I've never seen a business grow so fast."

The NECC produced the tainted injections in a so-called "clean room" that was actually startling in its squalor.

The air conditioning was turned off at night; equipment was rusted; swabs showing contamination of work surfaces were ignored; and test tubes sprouted visible black growths floating in otherwise transparent liquid. As federal and state regulators converged on the facility, the family members who owned the NECC and its sister company, Ameridose, surrendered their pharmacy licenses and shut down.

In December 2014, federal prosecutors indicted 14 NECC employees; the two most senior members of the group face second-degree murder charges applied through the Racketeer Influenced Corrupt Organizations Act. The case has yet to go to trial, although *The Boston Globe* reports that proceedings may start in January 2017.

COMPOUNDING SOLVES SEVERAL MEDICAL and economic problems. Some patients are allergic to components of mass-produced products and need special mixtures that omit these ingredients. Children and the elderly may need doses of medicine not found in standardized products. Drug shortages can drive health care providers to compounding pharmacies that provide substitutes. Last but by no means least, compounders price their products low enough to undercut the costs of standardized medicines sold by the major drug companies.

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The International Academy of Compounding Pharmacists, an industry trade association, estimates that 3,000 firms produce sterile preparations. Sales have grown by leaps and bounds. According to a report by the Health and Human Services Department's Office of the Inspector General, between 2006-2015, Medicare

expenditures grew by 333 percent for compounded intravenous drugs, and by 285 percent for compounded injectable drugs. The NECC outbreak and its aftermath had very little effect on these developments.

Because the industry is dominated by under-regulated small businesses that grew very rapidly, fraud was almost inevitable. Federal prosecutors have indicted 25 defendants for selling unnecessary compounded medications to TRICARE, the health insurance program that serves 9.4 million military service members. TRICARE experienced a "massive surge" in claims for "unnecessary and costly compound drugs" in 2014 and the first half of 2015, with costs eventually reaching more than $1 billion in just the first four months of 2015. Compounded drugs accounted for only 0.5 percent of the volume of medications supported by the program, but totaled 20 percent of total costs. In May 2015, when TRICARE implemented stricter screening to ensure that all the drugs it pays for are safe and effective, the monthly total dropped precipitously to $10 million.

No publicly funded health-care system can afford such rip-offs. But the problem with compounders is not just that they squander money.

> The 2012 NECC outbreak uncovered widespread quality control problems that cried out for a national crackdown that never took place.

At first, despite severe funding gaps, the FDA appeared poised to act. The agency selected 31 facilities across the country for "risk-based" audits based on adverse event reporting by health care professionals and historical

inspection data. Inspectors discovered safety problems at 30 of the 31 facilities, including "inappropriate or inadequate, or both, clothing for sterile processing, lack of appropriate air filtration systems, insufficient microbiological testing, and other practices that create risk of contamination." The FDA sent "warning letters" to 18 of these compounders. Such letters explain what a company is doing wrong but only threaten future legal action.

Then Congress got involved. Despite low approval ratings and a well-deserved reputation for gridlock, Congress has a history of passing landmark legislation in the aftermath of national emergencies. The 1970 Clean Air Act responded to reporting on blankets of thick smog over Rust Belt cities. The Clean Water Act passed in 1972 after the Cuyahoga River caught fire. When a sulfa "wonder drug" containing anti-freeze killed 100 people in 1937, many of them children, Congress produced the Food, Drug, and Cosmetics Act. And in November 2013, Congress sent the Drug Quality and Security Act (DQSA) to President Obama's desk.

Unfortunately, the bill was a bipartisan compromise that further undermined FDA enforcement. When Congress began the debate, it seemed to be heading in the direction of traditional reforms, including tougher penalties, stronger safety rules, and more vigilant FDA oversight.

But relatively late in the game, following a high-dollar lobbying campaign by the compounding pharmacy

industry, a peculiar compromise emerged. The new law allowed the owners and operators of compounding pharmacies to decide whether or not their businesses meet the new law's definition of an "outsourcing facility" that should pay to register with the FDA. If a company decides not to turn itself in, the FDA could prosecute it for dispensing medications without a prescription written by a doctor for a specific patient. But if the company never registers and violates the law by selling compounded drugs across state lines without prescriptions, the FDA confronts a catch 22: it cannot chase violators it has not identified.

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THE RATIONALE OFFERED FOR THIS compromise was that the market could take care of the problem. Health-care facilities would insist that the compounders who provided their sterile medications were registered and under FDA oversight. This assumption was fatally flawed. Today, three years after the law's enactment, about 66 facilities-or about 2 percent-have registered out of the 3,000 compounders estimated to be making sterile drugs. This registration number has fluctuated at the margins, with a few compounders de-listing themselves and a handful joining the list for the first time each year.

The bottom line is that if the FDA happens to discover problems at any of the 2,900 remaining pharmacies, these facilities could be subject to sporadic enforcement. But in the absence of registration and the resources to inspect every pharmacy on a regular basis, the FDA must depend on whistle-blowers, physician reports of adverse incidents, or customer complaints to identify problems.

Quality control problems persist. Of the 66 pharmacies that are now registered with the agency voluntarily, 52 have been notified of potential violations spotted during compliance inspections. Thirteen of the remaining 14 compounders have not yet been inspected, meaning that only one of the registered firms has managed to pass inspection without sending up any red flags. In 2015, the most recent year for which data are available, the FDA inspected 215 pharmacies, up from 92 in 2014, but still only 10 percent of the estimated total.

The FDA has been inordinately hesitant to bring violators to court. Between October 2012 and August 2016, FDA enforcement staff brought only four cases, winning permanent injunctions against violations in each case. Three additional firms, including NECC, face criminal charges.

The FDA's curtailed role leaves state pharmacy boards on the front lines of oversight for this burgeoning industry. The boards are composed of pharmacists serving part-time who are assisted by small staffs. Their primary purpose is to license individual applicants, not to inspect pharmacies to verify safety measures. Even in a state with a reputation for progressive oversight like Massachusetts, this set-up proved woefully inadequate.

Federal and state regulators were well aware of the NECC's sanitation problems as early as 2002-2003, when inspectors visited the facility repeatedly. They developed a list of serious violations that needed to be fixed. But FDA regulators withdrew from a formal role in the case, ceding responsibility for follow-up to the state board. That board required the NECC to hire a third-party auditor to furnish a detailed report of the steps needed

to make the "clean" room safe. The audit team discovered the same problems as the regulators had, but nevertheless recommended that the board take the NECC off probationary status. The board approved this faint slap on the wrist in 2006.

In February 2016, the Pew Charitable Trusts released a report on state oversight of compounding pharmacies that revealed dangerous gaps in the states' performance. Only half of the 43 states that responded to the Pew survey required compounders to conform to widely recognized quality control standards established by the U.S. Pharmacopeial Convention. The majority (26 of 43) did not require pharmacies to report serious adverse events associated with sterile compounding. Twenty-eight of the 43 states that responded to Pew allow compounders to manufacture compounded medicines without patient-specific prescriptions.

The Obama administration has always supported the FDA's mission, and appointed highly qualified commissioners to lead the agency. But the president fell short when it came to defending the agency against harsh attacks by GOP critics on Capitol Hill, leaving the agency short of desperately needed additional funding. Given Trump's vow to roll back government regulations and shift federal money to defense, federal oversight of compounders will probably be even less effective under the next administration.

In fact, President-elect Trump seems likely to appoint industry executives or conservative policy wonks to head agencies that protect public health, worker and consumer safety, and the environment. They are likely to low-ball operating budgets and discourage aggressive enforcement. Inevitably, the day will arrive, probably sooner than later, when contaminated compounded drugs cause another string of illness outbreaks and fatalities. But this time, Trump political appointees will

be the ones sitting in the hot seat as bipartisan and irate members of Congress excoriate them.

Public health crises that result in the death of constituents have always been very bad news for presidents, regardless of which party controls Congress. Trump's pledge to douse regulation is intended to mollify such business groups as the U.S. Chamber of Commerce and the National Association of Manufacturers, and they will undoubtedly applaud these initiatives. But, as Secretary of State Colin Powell once said of federal service, "you break it, you own it." The government that president-elect Trump loves to hate will be his albatross when it fails to protect patients.

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