Prescription for Danger

How Unsafe Drugs Produced by Compounding Pharmacies Are Putting American Lives at Risk

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Executive Summary

The fungal meningitis outbreak caused by contaminated steroidal injections that has killed 53 people to date and sickened more than 720 is one of the worst public health disasters the nation has seen in recent history. The tainted injections came from a drug manufacturer doing business as a "compounding pharmacy," a classification which allowed them to evade the regime of safety rules, inspections, and oversight that keep our drug supply safe. And according to an analysis of warning letters sent to other compounding pharmacies by the FDA from 2002 to 2012, there is a long history of similar violations that have in many cases led to unnecessary illness, injury, and even death.

The letters clearly show that compounding pharmacies have been exploiting loopholes in the regulatory system for decades. This public health crisis starkly highlights the difference in how compounding pharmacies are regulated compared to pharmaceutical companies, and the need for reform.

Our Key Findings

Prescriptions are regularly compounded at pharmacies, after a doctor writes a prescription for a compounded drug. However increasingly compounding pharmacies are behaving like pharmaceutical companies, producing drugs in bulk, but are not inspected or regulated like the pharmaceutical industry. Due to this lack of oversight, many compounding pharmacies have not adhered to safe manufacturing practices, and shown little regard for consumer safety. In the FDA warning letters, the most frequent violations cited included misbranding drugs; producing unapproved new drugs; producing drugs under unsanitary conditions; repackaging sterile drugs; and using unapproved, potentially unsafe ingredients. Some of the most egregious violations by compounding pharmacies included:

- In 2002, consumers complained about arthritis pain relief injections from Lee Pharmacy in Fort Smith, Arkansas the FDA analyzed the injections and found they were all contaminated with pennicilliium rugulosum, a fungus that can cause death.

- In 2009, Hopewell Pharmacy in Hopewell, New Jersey was found to be using a solvent called diethylene glycol monoethyl ether in sterile injections used for the treatment of varicose veins. This ingredient is not approved by the FDA for use in drug manufacturing and is normally used in industrial cleaners.

  In 2005, University Pharmacy in Salt Lake City, Utah was investigated, because a 25 year old woman lapsed into a coma and died from using Photocaine, a topical anesthetic cream produced by the pharmacy without the approval of the FDA.

Recommendations for Policy Makers

The FDA must be given the power to regulate compounding pharmacies that produce drugs in high volume whether sterile and non sterile. These pharmacies are acting as pharmaceutical manufacturers and should have to play by the same rules as pharmaceutical. Consumers must be able to rely on the safety of their drugs, regardless of where they are produced.

Recommendations for Consumers

Before any clinical or surgical treatment, talk to your doctor about the drugs that are going to be used and if they are compounded. If they are compounded drugs ask your doctor if an FDA-approved drug is available and appropriate for your treatment instead. If that is not possible ask where the compounded drug is made and check for safety alerts and warnings on the FDA website. If you experience any problems or adverse events with a medication, contact your doctor or pharmacist immediately. Report any adverse events experienced while using the product to FDA's MedWatch program.

Introduction

Nearly six months after the initial discovery of steroids tainted with fungal meningitis, new infected victims are still emerging each week. This deadly outbreak, which has killed 53 people to date and sickened more than 720, is one of the worst public health disasters the nation has seen in recent history.[1]

The Food and Drug Administration investigation of the facility that made the tainted drugs not only found contamination problems, but FDA investigators saw "thick residues," on areas used to prepare sterile drug products. They also found "multiple insects" within just a few feet of where supposedly-sterile drug were being made – they even saw a bird flying inside the building, near where the drugs were packed and stored. In the sterile preparation room, used to make the steroid injections, counters were stained, a leaky boiler led to pools of standing water, and the entrance mat was brown and soiled.[2]

Every day millions of patients across American are given compounded drugs. And yet due to lax oversight and failures of regulation, this compounding pharmacy's reckless disregard for safe practices went undetected until tragedy struck.

Ultimately, the fungal meningitis outbreak was linked to a contaminated drug, a steroidal injection called methylprednisolone acetate that had been produced and distributed by a compounding pharmacy in Massachusetts, the New England Compounding Center. 14,000 people in 23 states were exposed to the drug and unfortunately the death toll may continue to rise, due to new worries that the incubation period for the illness may be longer than anyone thought. The states that had the most consumers affected were Florida, Michigan, Indiana, Maryland, North Carolina, New Jersey, Ohio, Tennessee, and Virginia according to the U.S. Centers for Disease Control.[3]

This public health crisis starkly highlights the difference in how compounding pharmacies are regulated compared to pharmaceutical companies. If the New England Compounding Center (NECC) had to comply with the same regime of safety rules, inspections, and oversight as most drug manufacturers, this tragedy may have been prevented. However, because NECC classified itself as a "compounding pharmacy" rather than a traditional drug maker, it was largely able to avoid the common-sense rules that keep our drug supply safe.

The meningitis outbreak was not a one-off aberration – it is simply the latest and deadliest in a long line of errors and risky practices by compounding pharmacies, which for years have acted as a shadow

pharmaceutical industry. In every relevant respect, large compounding pharmacies now behave exactly like drug manufacturers, but they exploit legal uncertainty and loopholes in the law to escape oversight.

Warning letters issued by the FDA show that compounding pharmacies have been violating federal drug safety rules for over a decade.[4] Violations have included manufacturing unsafe or ineffective drugs that have been removed from the market; making less-effective or unsafe copies of a commercially available drug; mislabeling or misbranding drugs; selling adulterated or contaminated drugs; and selling new drugs that have never been deemed safe and effective by the FDA.[5]

Consumers should be able to expect that their drugs – whether a brand-name drug, a generic or a compounded drug – are manufactured to the highest standards and are safe and effective. Allowing compounding pharmacies to manufacture drugs without being subject to adequate safety rules or oversight puts lives at risk. The industry has exploited gray areas between federal and state law to evade regulation, leading to an unacceptable status quo. It's past time for compounding pharmacies that act as drug manufacturers to be held to the same standards as their competition.

<u>Findings</u>: According to over 40 warning letters issued by the FDA between 2002 and 2012 to separate compounding firms, each firm made multiple violations that include:

- 11 violations of good manufacturing practices
- 18 violations for behaving like pharmaceutical companies, producing drugs in bulk without prescriptions;
- 21 violations for adulterated drugs i.e. drugs that were less potent with inferior or unsuitable ingredients;
- 38 violations for misbranding drugs;
- 36 violations for producing unapproved new drugs;
- 16 violations for producing drugs under unsanitary conditions or repackaging sterile drugs;
- 16 violations for making unauthorized knock-off copies of FDA approved drugs; and
- 22 violations for using unapproved, potentially unsafe ingredients.

<u>What are Compounding Pharmacies?</u>

Compounding of pharmaceuticals has long been a part of the practice of medicine. "Compounding" simply means taking mass-manufactured drugs and other active ingredients and tailoring them to fit an individual patient's needs. For example, compounding might be used to:

- Adjust a medication when a patient is allergic to certain ingredients of the drug, such as dyes;
- Change the dosage of medications;
- Combine several medications to make it easier for a patient to take all of them at once;
- Change the form of a medication to make it easier for the drug to be administered (for example, turning a pill into a liquid for a patient who has trouble swallowing); or
- Add flavors to make ingestion easier, especially for children.

Prescriptions are regularly compounded at pharmacies, after a doctor writes a prescription for a compounded drug. For example, a common compounded drug is Prevacid, which is used to treat babies with acid reflux, in a liquid or suspension form. It only comes in capsules and tablets from the drug

manufacturer, so a pharmacist must prepare it in a liquid form. However, compounded drugs are no longer simply made to order for particular patients: hospitals and medical clinics often stock compounded drugs and use them in day to day treatments: examples include injectables, chemotherapy solutions, and IV and parenteral i.e. through the vein nutrition fluids.[6]

Compounding pharmacies are required by law to use FDA-approved active pharmaceutical ingredients and active ingredients covered by the United States Pharmacopeia for these processes. Without this requirement, compounding could potentially introduce ingredients that are impure, unsafe, or ineffective.[7]

Traditional compounding has a long history and because it is typically performed on a patient-by-patient basis it would be inappropriate to subject these methods to the same high standards as wholesale drug manufacturers. However, the 1990s saw the rise of so-called "non-traditional compounding," in which compounding pharmacies began behaving like traditional drug manufacturers by producing large quantities of uniform drug products and selling in bulk to hospitals and other institutional customers. An exact definition of non-traditional compounding has yet to be agreed upon by either the FDA or the National Association of Boards of Pharmacy, but the FDA has suggested a number of factors that indicate if a pharmacy is engaged in non-traditional compounding: [8]

- If the pharmacy produces medications in bulk or high volume;
- If it manufactures exceptionally complex medications, including sterile drugs such as vaccines and shots;
- If it ships drugs outside the state in which they were produced;
- If it produces medications before a prescription has been presented (this is known as anticipatory compounding); or
- If it sends its drugs to middlemen, rather than the patient who will ultimately take the medication.

Over the years, the compounding industry has grown progressively more involved in the mass production of drugs. These pharmacies can dramatically increase their bottom line by making illicit copies of drugs that are then able to compete against the products of FDA-regulated drug manufacturers. Because they are not subject to the same level of oversight and scrutiny and they do not pay registration fees like a drug manufacturer or conduct rigorous testing and research like traditional pharmaceutical companies, they are often able to undercut the prices of drugs from traditional manufacturers.

Drug Regulation in the United States

At the turn of the 20th century there were no federal regulations to protect consumers from dangerous drugs in the marketplace. The market was filled with so called nostrums, elixirs, and patent medicines, including weird concoctions such as "Benjamin Bye's Soothing Balmy Oils to Cure Cancer." Most of the products on the market were useless remedies that fleeced consumers; in many instances these products were also dangerous.[9]

The Food, Drug, and Cosmetic Act (FDCA) was passed in 1938 after 107 people died from a chemical equivalent of antifreeze in a product called Elixir Sulfanilamide. One of the victims was a six-year-old girl from Tulsa whose mother wrote to the President, spurring him to act.[10]

An important provision of the act required manufacturers to show that a drug was safe before it was marketed. In 1951, the Durham Humphrey Amendment was passed requiring certain drugs to be labeled for prescription only. The act was further strengthened in 1962, when in response to the Thalidomide scare, in which more than 8,000 children worldwide were born with birth defects,[11] the Kefauver-Harris Amendments to the FDCA were enacted to require that manufacturers had to prove a drug was not only safe, but also effective.[12] Drug approvals had to be based on sound science. Companies had to monitor safety reports that emerged after the drugs went to market, and adhere to good manufacturing practices that would lead to consistently safe products. The amendments not only benefited consumers - they helped industry raise their scientific standards and eventually ushered in today's strong regulatory systems for pharmaceutical manufacturers.

Since then the pharmaceutical industry has become a multi-billion dollar industry that is rigorously regulated by the Food and Drug Administration. After years of laboratory and animal testing pharmaceutical companies submit an Investigational New Drug Application for FDA review prior to testing in humans. The company then performs a series of clinical trials in humans in three phases, which the FDA monitors, to see if the drug is effective and safe for humans. Next, the company sends its data from all these tests to FDA's Center for Drug Evaluation and Research in a New Drug Application. A team of CDER physicians, statisticians, toxicologists, pharmacologists, chemists and other scientists review the data and proposed labeling. If this review establishes that a drug's benefits outweigh its known risks for its proposed use, the drug is approved for sale.[13]

Ensuring that the drugs in your grocery stores and pharmacies are safe is a lengthy and costly process. For example it can cost a brand name pharmaceutical company as much as an estimated $1.2 billion over ten to fifteen years to develop and gain approval for a single new drug.[14]

Then after a drug is on the market, the FDA monitors its performance in a number of ways, most notably through MedWatch, the agency's safety information and adverse event reporting program, which receives reports of suspected adverse reactions from consumers, health care practitioners and pharmaceutical companies. [15]

By comparison, the compounding pharmacy industry falls into a gray area between state and federal regulatory oversight. Traditional compounding pharmacies are not registered with the FDA as drug manufacturers. This continued confusion in regulatory oversight is a huge problem. It allows the industry to behave more and more like drug manufacturers, but without the strong protections for consumers. There are now internet pharmacies and mail-order pharmacies producing and providing medications directly to consumers, providers and hospitals without prescriptions or safety checks. However, while the FDA has clear authority to regulate the development and manufacture of drugs by the pharmaceutical industry, the compounding pharmacy has been regulated mainly by state pharmacy boards in an inconsistent manner with regulations varying from state to state.[16]

State law generally controls recordkeeping, certifications, and licensing for compounding pharmacies in the retail setting. However, states have differing laws and rules in this area. Some states, like Minnesota, have inspectors who are licensed pharmacists and have training and expertise in compounding, while other states don't do routine inspections at all and only inspect pharmacies as a result of complaints. In general, the states have made clear that they are only comfortable with regulating traditional compounding pharmacies and do not feel they have the resources to monitor non-traditional compounding.[17]

Hospital pharmacies, home care agencies and skilled nursing facilities that compound sterile products have even less oversight, as they are not comprehensively regulated by states or the FDA. These facilities are usually accredited by a voluntary organization.

The states have consistently been unable or unwilling to perform the level of safety-related oversight necessary for compounding pharmacies. And the FDA has been struggling to address this problem for more than two decades. In 1992, FDA Commissioner David Kessler warned of the explosion of unapproved drugs and a "shadow industry."[18] The FDA also issued a Compliance Policy Guide that year attempting to clarify the distinction between traditional compounding and bulk drug manufacturing. This culminated in 1997, with Congress enacting the FDA Modernization Act, a comprehensive overhaul of the 1938 FDCA. Section 503A required all drug manufacturers including compounding pharmacies to come under the authority of the FDA. This section drew severe resistance from the compounding industry, resulting in lawsuits against this section of the law. The industry was successful in its litigation and due to a Supreme Court ruling in 2002 confusion over the FDA's role persists to this day.[19]

Another attempt was made to strengthen regulation of compounding pharmacies through the Safe Drug Compound Act of 2007. The bill would have required the FDA to regulate and inspect all compounding pharmacies, curtail all interstate distribution and sale of compounded drugs, and require all clinicians to document when compounded medications are needed. Unfortunately, due to fierce opposition again from industry, this bill failed.[20]

Currently, the FDA's authority is generally limited to reacting to problems identified by others and it is often unclear who is responsible for the inspections of actual pharmacy sites. If a site is found to be unsanitary and producing contaminated drugs, it is also often unclear which regulatory body is responsible for fixing the problem. [21] Even during this time of heightened awareness, FDA inspectors are being delayed in their work or denied full access to records at some of the facilities they are inspecting.[22] Industry efforts at self-policing have also been ineffective. Compounding pharmacies are accredited by the Pharmacy Compounding Accreditation Board. This organization is made up of industry associations including the American College of Apothecaries, National Community Pharmacists Association, International Academy of Compounding Pharmacists, National Home Infusion Association, National Association of Boards of Pharmacy and United Pharmacopeia.[23] At best, this system is an example of industry policing industry – these special interests have little incentive to hold compounding pharmacies accountable. In addition, the entire system is voluntary – accreditation is optional, and providers such as hospitals and clinicians are only encouraged, but not required, to purchase drugs from accredited pharmacists.

Compounding Pharmacy Industry Are a Powerful Special Interest

The rapid increase in non-traditional compounding has created a dangerous environment for consumers. As the compounding industry grows so too does its influence over lawmaking bodies in the U.S. There are approximately 56,000 community based pharmacies in the U.S. and also 50 percent offer simple compounding services to doctors and patients and about 7,500 pharmacies perform advanced compounding services and roughly 3,000 of those perform sterile compounding.[24] The compounding industry makes up 1 to 3 percent of prescription drug sales in the United States. Although this does not sound substantial the annual sales for the prescription drug market is around $300 billion, which means

that the compounding industry generates around $6.5 billion a year.[25] If the regulatory gap that compounding pharmacies are exploiting is not fixed, the industry's share in the market will continue to increase, as will the potential for dangerous drugs to harm consumers. In addition, the larger the industry grows, the more difficult it will be to stop.

The main lobbying arm of the industry is the International Academy of Compounding Pharmacists (IACP). It was formed by a group of compounding pharmacies in the early 2000's and has since grown to over 2,700 members of the compounding community.[26] The group began making substantial political contributions in 2008, which have been tracked by the Center for Responsive Politics.[27]

- In 2008, the IACP spent $71,300 in political contributions.
- In 2010, the IACP spent $63,499 in political contributions.
- In 2012, the IACP spent $109,250 in political contributions.

The IACP will continue to pour more and more money into political campaigns in the future in order to sustain the dangerous practice of unregulated non-traditional compounding. The only way to stop this alarming cycle is to convince Congress to close the regulatory gaps and loopholes that the industry is taking advantage of.

Unsafe Practices, Unsafe Drugs

This report looks at warning letters issued by the FDA over a ten-year period from 2002 to 2012. The results are in Table A. We found that compounding pharmacies regularly broke the law and violated the Food, Drug, and Cosmetic Act in numerous ways.

There were 43 warning letters issued to compounding pharmacies over the ten-year period. That is an average of four per year, which means a compounding pharmacy was caught breaking the law on average every three months.

From examining the letters we found that all the compounding pharmacies that received warning letters from the FDA were not adverse to breaking the law and violating the Food drug and Cosmetic act with multiple violations. In fact:

- 12 pharmacies made up to 4 violations;
- 4 pharmacies made up to 5 violations;
- 6 pharmacies made up to 6 violations and;
- 2 pharmacies made up to 7 violations.

The most important of these violations, because they can cause injury, illness or death, included repackaging sterile drugs; producing drugs under unsanitary conditions; marketing and selling drugs that have been shown to be dangerous or sub-potent; producing unapproved untested new drugs; and producing drugs with unapproved ingredients.

Case Studies of Violations under the Food, Drug, and Cosmetic Act

These are specific case studies from the FDA's warning letters.

Failure to Follow Good Manufacturing Practices

Adherence to Good Manufacturing Practices (GMP) for production and testing helps ensure a quality product. The Food, Drug, and Cosmetic Act outlines the GMP systems a pharmaceutical company must follow. The goal is to safeguard the health of the patient through safe and effective medicines.

Gentere, Inc. – Ohio – July 2004
The FDA and the Ohio State Board of Pharmacy found that Gentere was in violation of good manufacturing practices related to sterile compounding procedures. The firm was producing large volumes of injectable drugs without approval from the FDA and without valid prescriptions from patients.

The drugs that were being produced without prescriptions were Dexamethasone Sodium Phosphate, which is given to cancer patients undergoing chemotherapy, and Estradiol Cypionate, which is used for symptoms of menopause. The firm was supplying the drugs to doctors and clinics as "office stock," which is not permitted under Ohio law. The firm also did not have proper procedures in place to prevent microbiological contamination of the drugs made. The FDA and Ohio State Board of Pharmacy found that "equipment and utensils are not cleaned at appropriate interval to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product."

Adulteration and Misbranding of Drugs

Adulteration is the production of drug products that are impure, unsafe, or sub-potent. Misbranding a product involves using deceptive pictures, testimonials, misleading lists of components, or wrong brand or trade names on a product's label.

Monserrat Pharmaceuticals, Inc. – Puerto Rico – January 2004
Inspections by the FDA in 2004 with the Puerto Rico Health Department found that Monserrat Pharmaceuticals was behaving like a drug manufacturer and thereby operating illegally under Puerto Rico law. The firm was misbranding drugs; producing new drugs without FDA approval; producing adulterated drugs; and their processing, packing and holding of drugs did not comply with good manufacturing practices. The firm was producing inhalation solutions such as ipratropium bromide and albuterol sulfate, drugs that are used by patients with asthma and lung disease. The FDA found there was no guarantee that these drugs, which were being sold to unsuspecting consumers, met the standards of "identity, strength, quality and purity at time of use."

PharMEdium Services – Illinois – April 2007
PharMEdium Services was involved in a number of violations including producing adulterated and misbranded drugs. In March 2005, a patient at a New Jersey hospital became infected with Serratia marcescens, a bacterial infection, after he was given a Magnesium Sulfate in Dextrose injection compounded by the pharmacy's Houston, Texas site. Soon, five more patients at the

hospital showed the same symptoms. In April, a patient in a South Dakota hospital who was recovering from surgery was given one dose of the same product and within hours showed "signs of sepsis" and died. The South Dakota hospital laboratory cultured blood samples from the deceased patient and found the same bacterial contaminant. Six cardiac patients were also infected after surgery at a Kaiser Permanente Medical Center in Los Angeles. Overall, at least 18 patients across five states were infected with the same bacteria from the contaminated injections.[28]

In 2006, a patient at an Arizona hospital was given an epidural injection of what the clinicians believed based on the labeling of the product was Fentanyl Citrate and Bupivacaine HCL. Soon after the epidural the patient showed symptoms of "decreased consciousness, hypoxia, and hypotension." The hospital's toxicology lab tested multiple unopened samples of the injections and found the presence of Morphine Sulfate instead of Fentanyl or Bupivacaine. It was discovered that PharMEdium's Cleveland, Mississippi, facility had misbranded the product.

Unsanitary Conditions

Unsanitary Conditions are present when a drug is prepared or packed in a facility which is not clean or properly sanitized. The compounding pharmacy is also not following the protocols outlined by the FDA to keep drugs safe and contaminate free.

Lee Pharmacy, Inc. – Arkansas – October 2003
Consumer complaints led to an investigation of Methylprednisolone Acetate shots produced by Lee Pharmacy. The FDA analyzed a batch of the shots, which are used for pain relief in arthritis patients, and found they contained penicilliium rugulosum, a fungi known to cause death. The batch of injections tested violated the FDCA, because they consisted in whole or in part of "filthy, putrid or decomposed substance." The FDA also discovered sub-potent samples of Triamcinolone Acetonide, a synthetic corticosteroid that is mainly used to treat skin conditions, such as poison ivy.

B. Braun Medical, Inc., Central Admixture Pharmacy Services (CAPS) – Pennsylvania – 2006
Testing by the FDA and CDC found bacterial contamination in unopened bags of cardioplegia solution, a solution used during cardiac heart surgery. The bags were produced by a CAPS facility in Maryland and used primarily at Mary Washington Hospital in Virginia. The contaminated solutions used during surgery led to six patients dying and four injuries in Virginia.[29] One worker in the Kansas City facility in MO was caught "smoking outside the facility while still wearing the clean room gown and then re-entered the area without changing his gown."

Franks Lab – Florida – May 2012
During FDA inspections of Franks Lab in March and May of 2012, inspectors found injections of Brilliant Blue G dye to be "filthy, putrid or consisted of decomposed substances." The contaminated shots were linked back to nine patients with fungal endophthalmitis, a serious inflammation of the eye. The initial investigation, led by the Los Angeles County Department of Public Health, determined that in all cases patients had undergone a vitrectomy, a procedure that uses Brilliant Blue G to remove some of the vitreous fluid, or gel, from the eye. In total, 33 people became infected in seven states.[30]

Opening and Repackaging Sterile Drugs

Opening and repackaging sterile drugs into smaller vials without proper sterile procedures and precautions can make them unsterile and potentially introduce contamination.

Infupharma, LLC – Florida – July 2012

Infupharma was cited in 2012 after dangerous repackaging practices contaminated their production of Avastin, a cancer drug that is used off-label for eye conditions. Many retina specialists use Avastin because, at $50 per shot, it costs $2,000 less than Lucentis, its mainstream competitor.[31] Lucentis is manufactured by the same company that makes Avastin.

In order to meet this off-label use, Infupharma was opening up vials of Avastin and repackaging them into smaller vials that they then sold to medical providers in Florida.

While the original vials were sterile, the repackaging process introduced a bacterial infection, Streptococcus mitis/oralis, into the newly packaged smaller vials. The FDA discovered contamination in the vials during inspections from July to September 2011.

They also found that the repackaging was being done under unsanitary conditions where the drugs were "contaminated with filth," and where employees failed to practice effective aseptic processes to keep the vials sterile.

Twelve Florida patients were identified with endopthalmitis, a serious eye inflammation, after receiving an injection of the repackaged Avastin. All twelve patients lost significant amounts of vision and several were blinded by the infection. One patient's family sued Infupharma, because they believe the infection permanently damaged the brain of their father, 77-year-old Lloyd Mason Sylvis, who came in walking and talking and is now in a permanent vegetative state.[32]

Unapproved New Drug

An unapproved new drug is when a firm produces a completely new drug with no testing for safety and effectiveness of the drug or prior approval from the FDA.

University Pharmacy – Utah - December 2006

In 2005, investigators from the FDA and Utah State found that University Pharmacy was compounding an unapproved new drug product in bulk quantities called Photocaine gel without FDA approval. The drug was also misbranded, the labels were false and the drug safety information leaflet did not contain warnings for elderly or pediatric groups where safety precautions need to be stronger.

Topical anesthetic creams can be dangerous as they are toxic and addictive in high doses. There is also a narrow range between the optimal therapeutic dose and the dose at which they

become toxic. This product caused the death of a 25-year-old Arizona woman, Blanco Bolanos, who lapsed into a coma in January 2002 after applying Photocaine gel to her legs in preparation for a laser hair removal treatment. She spent nearly two years in a coma before dying.[33]

Triangle Compounding Pharmacy – North Carolina – December 2006
Shiri Berg was a 22 year college student who went to a spa in North Carolina for laser hair removal. The spa, Premier Body Laser Services asked her to apply a pain numbing gel called Lasergel to her body before coming to the spa for treatment. On the drive down to the spa Shiri Berg had seizures and she fell into a coma and died eight days later. [34] An autopsy revealed that Shiri Berg died of anoxic brain injury due to lidocaine toxicity. Lidocaine is a topical anesthetic that can be applied to the skin to reduce the immediate feeling of pain and produces numbness, but in high doses is dangerous.

Like a pharmaceutical manufacturer Triangle Compounding Pharmacy developed unapproved anesthetic drug products called Lasergel and Lasergel Plus 10/10. Both drugs were misbranded as the information leaflets they were sold with were copies of a drug safety leaflet that belonged to a FDA brand name drug. Lasergel and Lasergel Plus 10/10 were in no way similar to the brand name drug, whose leaflet they were being marketed with. Both drugs had high doses of Lidocaine and Tetracaine in them and this was not mentioned in the safety leaflets.

Pharmacy Creations - New Jersey - 2006
Pharmacy Creations was discovered to be illegally producing adenosine-5-monophosphate, a drug that can be used for nerve pain. This drug was withdrawn from the U.S. market in 1973 by the FDA as it was not considered safe or effective.

The pharmacy was also producing Domperidone capsules and Polidocanol injections under unsterile manufacturing conditions, potentially producing contaminated drugs. Domperidone is a drug increasingly used off-label by moms to increase breast milk. However it is not approved by the FDA or any country for increasing breast milk production. In fact there have been several reports and case studies of cardiac arrthymias, cardiac arrest and sudden deaths in patients using Domperidone. European Union drug regulators announced in March 2013 that they have begun a review of Domperidone because of concerns about its adverse cardiac effects.

Production Similar to Drug Manufacturer

Compounding pharmacies threaten public health when they produce drugs in bulk or high volume without the necessary safety and aseptic conditions, or adherence to good manufacturing practices that include research on drug safety and effectiveness.

ComputeRX/BronchoDose – Connecticut – March 2007
FDA inspections found that ComputeRX was not operating like a retail pharmacy, but more like a large pharmaceutical manufacturer. They were mass producing budesonide inhalation, an asthma drug , in various strengths and formulations that were not “medically therapeutic.” The drugs were misbranded and labeled at a stronger dosage then they actually were. Further testing by the FDA found the drugs produced by the firm to be sub-potent.

The pharmacy was also not following sterile manufacturing practices to prevent microbiological contamination of the drugs. The firm was selling these sub-potent and potentially contaminated drugs across twelve states to unsuspecting consumers who could have died from a serious asthma attack.

Delta Pharmacy, Inc. – Mississippi – September 2004
Delta Pharmacy was involved in large scale production of injectable drugs that did not meet the criteria for safe drug manufacturing. The firm was making large volumes of methylprednisolone acetate, a drug for arthritis, dexamethasone sodium phosphate, an anti-inflammatory medication that is used for cancer patients during chemotherapy, and promethazine hydrochloride, a drug that has since been linked to severe tissue injury, including gangrene.

None of the firm's products were directly dispensed to patients - instead they were sold to physicians as "office stock." The FDA also found the pharmacy was working with a wholesaler to obtain physicians' orders for products. Delta also failed to prevent microbiological contaminations of sterile drug products and failed to establish sterile conditions for drug compounding.

Unofficial and Illegal Copies of Brand Name Drugs

Some compounding pharmacies have been producing unofficial and illegal copies of FDA-approved brand name drugs. This is done by substituting approved ingredients with dangerous unapproved substances or changing the strengths to untested or unapproved dosages.

Plum Creek Pharmaceuticals, Inc. – Texas – October 2003
Inspections by the FDA and the Texas State Board of Pharmacy found that Plum Creek Pharmceuticals was producing Fentanyl and Naloxone lollipops. These are flavored lollipops loaded with narcotic pain-killers for treatment of end-stage cancer patients suffering from breakthrough pain. The lollipops were dispensed to patients without proper safety features or warning labels. In comparison, the FDA-approved brand name Fentanyl lollipops have locks on the bags and other safety features to avoid accidental pediatric exposure and possible death.

The firm was also selling a Mizadolam lollipop, which was a new drug being produced without approval from the FDA. Midazolam is a benzodiazepine that slows down the nervous system and is usually given under the immediate supervision of a doctor trained to use this drug in pediatric and pre-surgical procedures.

Using Unapproved Ingredients

The use of unapproved ingredients can be extremely dangerous, causing allergic reactions or even death. All compounding pharmacies are required to compound drugs only using approved active pharmaceutical ingredients and active ingredients covered by the United States Pharmacopeia.

Hopewell Pharmacy and Compounding Center - New Jersey - 2009
Hopewell Pharmacy was found to be using unapproved ingredients in their production of Sodium Tetradecyl Sulphate injections, which are used to treat varicose veins. The FDA sampled vials of the injections and found them to contain diethylene glycol monoethyl ether, a cleaning

solvent used commonly in wood cleaners and industrial cleaners. This chemical solvent has never been tested for safety for use in drugs or injectables and is not an approved active pharmaceutical ingredient.[35]

Conclusion

There continues to be a legitimate, important role for traditional compounding to play in the practice of medicine. These activities should continue to be licensed and regulated by State Boards of Pharmacy.

However, there is a shadow industry that has evolved and is exploiting ambiguities in the law to escape proper regulation. The magnitude and complexity of these operations have outpaced the current patchwork of state regulation. As the recent meningitis outbreak dramatically illustrates, the risks to consumers have increased, and states are ill-equipped to regulate these companies. This shadow industry must be bought under the umbrella of regulatory oversight to protect the health and safety of American consumers.

Recommendations for Policy Makers

The FDA must be given the power to regulate compounding pharmacies that produce bulk drugs without prescriptions. These pharmacies are acting as pharmaceutical manufacturers and should have to play by the same rules as other drug makers. In order to ensure that consumers can rely on the safety of their drugs, regardless of where they are produced, the following recommendations should immediately be put into effect:

- The same federal safety and manufacturing standards that are applied to pharmaceutical manufacturers should be applied to firms that compound bulk drug products in advance of or without a prescription and ship them interstate. The FDA must have clear authority to proactively inspect all compounding pharmacies' operations and records to ensure that they are complying with these rules.

- The National Association of State Boards of Pharmacy should set minimum uniform national standards for regulatory oversight for traditional compounding and in particular for sterile compounding. A national database of compounding pharmacies should be developed, which would include a complete history of disciplinary actions and violations. This database will help state and federal agencies track outbreaks and repeat violators and should be publicly accessible.

- The FDA should have the authority to bar the compounding of complex and high risk products, which can only safely be made by FDA-registered drug manufacturers under an approved new drug application.

- The FDA should enforce the requirement that compounded drugs only use approved active pharmaceutical ingredients and active ingredients covered by the United States Pharmacopeia.

It is a violation of the FDCA to use other ingredients and the FDA should make this absolutely clear to the industry.

Recommendations for Consumers

While legislative and regulatory action will be necessary in order to solve the problem of potentially unsafe drugs being manufactured by compounding pharmacies, in the meantime there are steps consumers can take to protect themselves:

- It might be difficult to always know when you are being given a compounded drug. Always make sure that you ask your doctor or pharmacist if the drug you are using or being administered is compounded. Also ask why it is being compounded, who produced it, and where it is being produced. Then check the FDA Compounding Pharmacy website to check for recent actions on unsafe drugs.[36]

- Before any clinical or surgical treatment, talk to your doctor about the drugs that are going to be used and if they are compounded. If they are compounded drugs ask your doctor if an FDA-approved drug is available and appropriate for your treatment instead. If that is not possible ask where the compounded drug is made and check for safety alerts and warnings on the FDA website.

- If your doctor or pediatrician writes a prescription for a compounded drug, check with the pharmacist to see if he or she is familiar with compounding the product in your prescription, and whether he or she has the training, equipment, and processes in place to compound that product safely using FDA-approved ingredients.

- If you experience any problems or adverse events with a medication, contact your doctor or pharmacist immediately. Report any adverse events experienced while using the product to FDA's MedWatch program.[37]

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