According to the FDA, the term "compounding includes the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug" (21 USC 353b – The Compounding Quality Act or Drug Quality and Security Act of 2013). Compounded drug products serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product such as for a patient who has an allergy and needs a medication to be made without a certain dye (or preservative or flavoring) contained in an FDA-approved drug, or an elderly patient or a child who cannot swallow a pill and needs a medicine in a liquid form that is not available in an approved product. Drugs for identified individual patients can be compounded by licensed pharmacists in state licensed pharmacies and federal facilities and by licensed physicians operating under Section 503A of the FD&C Act. Sterile drug products can also be compounded by outsourcing facilities for distribution to health care practitioners across state lines without receiving prescriptions (continued on pg. 2)....

Potential Positive Impact on Innovation

1. Physicians prescribe compounded medications to satisfy patient needs that are not addressed by approved products available from drug companies. As such, compounding provides for medical innovation that would not otherwise be possible or economically feasible. (continued on pg. 2)...
under Section 503B of the FD&C Act. One to three percent of prescriptions filled in the U.S. by community pharmacies are estimated to be for compounded medications; the percentage of compounded drugs used in hospitals, especially those for intravenous therapy, is significantly greater.

Many have called for the FDA to do more in light of several instances of significant quality concerns, especially from “industrial compounders” of sterile drugs. However, the FDA’s hands have been tied by Congress and the courts, leaving the primary responsibility to the states, which have incomplete and inconsistent policies and enforcement practices. So, how can appropriate regulation and oversight of pharmaceutical compounding be performed to ensure patient safety without severely limiting the supply of customized products and intravenous therapies that are not available from drug companies?

### Purports To Do (continued from pg. 1)

- Pharmaceutical manufacturing. FDA-approved drugs that serve a limited population are often discontinued by manufacturers. In most of these cases, the only option left for doctors and their patients is to have a compounding pharmacist make the discontinued drug from scratch using pharmaceutical grade ingredients.

- Compounding satisfies the needs of physicians to prescribe extemporaneous sterile compounded medications in response to the impact of ongoing drug shortages limiting the availability of many injectable medications, including prefilled ready-to-use injectables.

### Potential Positive Impact on Innovation (continued from pg. 1)

- Valuable treatments. The trade-off is that the innovation must be offered individually by each compounding pharmacy, as opposed to when drug products are approved by the FDA and manufactured for large scale distribution.

### Unintended Consequences (continued from pg. 1)

In the last 11 years, three separate meningitis outbreaks have been traced to purportedly “sterile” steroid injections contaminated with fungus or bacteria, which were made by compounding pharmacies:

- As reported in Forbes, “in a particularly egregious and infamous case in 2012, 64 people were killed and more than 700 made ill” (in twenty states) “from fungal meningitis by steroid injections prepared under grossly improper conditions by the New England Compounding Center (NECC). For a decade leading up to the deaths there were clear signs the NECC was a bad actor—adulterating and misbranding drugs, selling copies of commercially available drugs, making products under improper conditions, lying to regulators, and on and on.

- As Kurt Eichenwald wrote in a Newsweek expose on the NECC, a “seemingly innocuous pharmacy in a Framingham [Massachusetts] strip mall was making millions of dollars by cutting corners, fabricating records and ignoring laws designed to keep contaminated drugs off the market.”

- As stated in a July 2016 draft FDA guidance document, “the FDA has also identified many pharmacies that compounded drug products under insanitary conditions whereby the drug products may have been contaminated with filth or rendered injurious to health and that shipped the compounded drug products made under these conditions to patients and health (continued on pg. 3)...
Unintended Consequences (continued from pg. 2)

care practitioners across the country, sometimes in large amounts."

c. As outlined by Janet Woodcock (Director, FDA Center for Drug Evaluation and Research), in 2013 to the House Subcommittee on Health Committee of the House Energy and Commerce, “sadly, NECC was not an isolated incident. Indeed, over the past 20 years we have seen multiple situations where compounded products have caused deaths and serious injuries:

- In 1997, two patients were hospitalized with serious infections after administration of contaminated riboflavin injection prepared by a Colorado pharmacy.
- In 2001, 13 patients in California were hospitalized and received medical care following injections from contaminated vials of a steroid solution. Three patients died as a result.
- In 2002, five patients in North Carolina suffered from fungal meningitis resulting from contaminated methylprednisolone acetate made by a South Carolina pharmacy. One person died.
- In 2005, contaminated cardioplegia solution, made by a firm located in Maryland, resulted in five cases of severe system inflammatory infections; three of these patients died.
- In 2007, three people died from multiple organ failure after a Texas compounding sold super-potent colchicine that was as much as 640 percent the labeled strength.
- In 2010, FDA investigated a cluster of Streptococcus endophthalmitis bacterial eye infections in patients who received injections of Avastin repackaged by a pharmacy in Tennessee.
- In 2011, there were 19 cases of Serratia marcescens bacterial infections, including nine deaths, associated with contaminated total parenteral nutrition products.
- In 2012, 43 patients developed fungal eye infections from contaminated sterile ophthalmic drug products. At least 29 of these patients suffered vision loss.
- Recently, in 2013, FDA investigated reports of five cases of eye infections in patients who received Avastin repackaged by a pharmacy in Georgia. The Avastin was contaminated with bacteria."

d. Although no patients were injured, Med Prep of New Jersey was shut down in 2013 because of particles and visible mold found in sterile bags of magnesium sulfate for injection that were shipped to thirteen hospitals in Connecticut, Delaware, New Jersey and Pennsylvania.

2. “Several studies, including a survey conducted by FDA in 2001, have reported quality problems with various pharmacy-compounded drugs, including sub-potency, super-potency, and contamination. To explore these quality issues, FDA conducted an additional survey of compounded drug products in 2006. FDA collected both active pharmaceutical ingredient (API) and finished compounded drug product samples during unannounced visits to compounding pharmacies located throughout the country. The samples were sent to FDA field laboratories for chemical analysis to measure identity of active ingredients, potency, and uniformity of dosage:

- The analytical methods used were generally United States Pharmacopoeia (USP) or modified-USP methods. Once all analyses were complete, FDA staff evaluated the analytical data and methods corresponding to all samples that failed at least one analytical test.
- Gathered during FY2006, 125 were APIs and 73 were compounded finished drug products. The samples comprised three major drug classes: female hormone products, inhalation products, and local anesthetic products. All 125 API samples passed analysis. Of the 73 compounded finished drug products, sixteen samples were not analyzed because the expiration dates on the samples elapsed before analysis. The remaining 57 samples were analyzed, but the results of the analyses for 21 of these samples were deemed unusable for various reasons and excluded from the survey.

- Of the remaining 36 samples, 12 (33%) failed analytical testing using rigorously defensable testing methodology. Most of the products that failed analysis did so due to sub or super-potency, called assay, or a lack of uniformity of individual dosage units, called content uniformity. Potency ranged from 67.5% to 268.4% of the amount of drug declared on the product labeling. For content uniformity analysis of products containing multiple active components, both sub- and super-potent active components were found within the same product samples. Such variability can lead to uncertainty in dosing and raises concern for patient therapy. The results of the survey suggest that problems with the quality of compounded drugs occur throughout the country.

- Of note is that all APIs passed analytical testing, supporting the notion that the observed failures of the finished drug products may be causally related to the compounding processes at pharmacies.”

3. Fraud and abuse:

a. In February of 2016, the Wall Street Journal reported that the “Justice Department is investigating what authorities suspect is half a billion dollars in health-care fraud linked to specialty creams used to treat pain and other ailments, and believe an insurance program for (continued on pg. 4)...
veterans may have been the biggest victim. Sales of these so-called compounding creams have surged recently thanks in part to a marketing blitz, including pitches by retired NFL quarterback Brett Favre, that has promoted them to the elderly, athletes and others. Investigators are looking into allegations that some of the products provide little to no medicinal value, and that some pharmacies sent more product than was ordered, overbilled, or automatically refilled prescriptions without being asked, according to people familiar with the matter. Some companies charged more than $10,000 for a single tube or prescription of cream. The creams are often pitched on the Internet or by telemarketers as a safe way to help athletes heal quickly or alleviate types of pain or cramping, according to officials investigating the industry. The creams also are often marketed to seniors as a way to ease the aches of aging, they said.

• The product promoted by Brett Favre is called RxPro made by World Health Industries Inc. of Jackson, Miss; it also does business as Aspire Rx, ‘the pre-eminent provider of compounding pharmacy services in the U.S.’ Mr. Favre, who retired from football after the 2010 season, said in an appearance on a sports talk show on SiriusXM in 2013 that Rx Pro was ‘a safe way to treat some of your ailments,’ adding, ‘it even works with cramps, stomach pain.’

• Investigators have found many instances in which a single customer’s account for pain cream racked up bills of tens of thousands of dollars, according to the people. According to Defense Department data, Tricare (a healthcare program of the US Department of Defense Military Health System) paid $1.75 billion for compounded drugs including creams during its 2015 fiscal year that ended in September—18 times the amount paid three years earlier. Investigators suspect most of those bills are fraudulent, according to people familiar with the matter. Tricare has implemented new internal controls to crack down on fraudulent billing. The products made by compounding pharmacies, which mix pharmaceutical and prescription ingredients to meet specialized medical needs, often for people who have difficulty taking pills, aren’t as tightly regulated as mass-market drugs. Compounded creams frequently aren’t approved by the Food and Drug Administration because they are mixed in very limited amounts, and it is considered impractical to test all the variations.

• Under federal law, compounding pharmacies don’t have to prove the efficacy or safety of their products. The industry is primarily regulated by states, which exercise varying degrees of scrutiny. The International Academy of Compounding Pharmacists said ‘legitimately prescribed and dispensed compounded topical creams and gels bring tremendous relief to those suffering from bone and joint pain. They have the added—and very significant—benefit of being non-addictive. IACP believes public and private health care payers should aggressively address health care fraud, including taking aggressive action against any health care provider that has allegedly broken the law.’ In Mississippi, investigators suspect some of the creams that were sold have no medical value.’

b. As reported in a 2015 article by Managed Care, “The recent growth in compounded drugs has been dramatic—and very expensive. They now sit as the third most costly drug category in Express Scripts’ latest drug trend report. The company says the annual trend for compounded drugs was 128.4%, highest of the traditional therapy classes. The average cost per script was $1,164. From 2012 to 2014, the quarterly spend for compounded medications increased from $28 million to $171 million.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>$97.67</td>
</tr>
<tr>
<td>High blood cholesterol</td>
<td>$48.73</td>
</tr>
<tr>
<td>Compounded drugs</td>
<td>$46.04</td>
</tr>
<tr>
<td>Pain/inflammation</td>
<td>$45.98</td>
</tr>
<tr>
<td>High blood pressure/heart disease</td>
<td>$36.06</td>
</tr>
<tr>
<td>Heartburn/ulcer disease</td>
<td>$33.40</td>
</tr>
<tr>
<td>Asthma</td>
<td>$29.59</td>
</tr>
<tr>
<td>Attention disorders</td>
<td>$27.97</td>
</tr>
<tr>
<td>Depression</td>
<td>$25.98</td>
</tr>
<tr>
<td>Mental/neurological disorders</td>
<td>$24.85</td>
</tr>
</tbody>
</table>

Express Scripts says pain creams are the most common type of compounded medication, incorporating ingredients such as gabapentin, baclofen, cyclobenzaprine, progesterone micronized, and propylene glycol.

The problem with compounded drugs is that there is no FDA approval process to say that these mixtures work, and there can be adverse reactions, overuse, and overdoses,’ says Jo-Ellyn Abou Nader, an audit and fraud executive at Express Scripts. Express Scripts says it has implemented a multistage approach to rein in compounded drug costs that includes blocking payment for more than 1,000 bulk powders that it says do not provide a clinical benefit over traditional medications. The country’s largest PBM says (continued on pg. 5)
its strategies will save its clients more than $1.9 billion in 2015. ‘Our clients want safety and many of them have opted in,’ says Abou Nader. But Abou Nader says when the company limited the use of bulk powders, the pharmacies started to crush tablets and capsules: ‘We saw one claim for a pain cream for migraines with multiple ingredients, including tramadol and zolmitriptan, that had over 2,000 tablets in it.’

A new business model for compounding pharmacies is also contributing to costs. Compounding has expanded from the original practice of individual prescriptions for specific patients to large-scale manufacturing and aggressive nationwide marketing of standardized concoctions for the general public. Compounding pharmacies are promoting their products with direct-to-consumer telemarketing campaigns and DTC websites. ‘We have received tips through the fraud hotline that patients are being called by telemarketers asking if they take pain medication and if so, they are told that compounds may be a better solution,’ says Abou Nader.

In February, CBS aired a report about a patient who received a monthly supply of three compounded medications he did not authorize, costing $18,000. Abou Nader adds there’s another possible fraudulent practice in the telemarketing campaigns. ‘If the patients are receiving cold calls that don’t fully disclose what is going on, they are likely to be suspicious and less likely to be paying their copays. Forgiving copays could be a fraudulent practice and we audit the pharmacies for compliance.’

c. According to a July 2016 article in Medcity News, “Spending on compounded drugs in Medicare’s Part D program rose 56 percent last year, with some of the costliest products, including topical pain creams, priced at hundreds or thousands of dollars per tube. The federal workers’ compensation program has also seen a recent spike in spending. Some of the prescriptions may not have been medically necessary — or even dispensed at all, notes the report, which also details recent fraud cases brought by U.S. attorneys in several states. In Medicare’s drug program, known as Part D, the number of Medicare beneficiaries getting compounded drugs has grown 281 percent since 2006 to nearly 280,000 in 2015. Spending on such drugs in Medicare’s Part D grew 625 percent between 2006 and 2015, to $509 million, according to the OIG report. That is still a tiny fraction of the program’s total spending on drugs. The fastest-growing category of compounded drugs are topical creams and gels, often used for pain. Spending on those increased 3,466 percent in the Medicare program since 2006, the report said, while the average cost per prescription hit $331, up from $40 in 2006. Nationally, since 2012, pharmacies have been required to report all the ingredients they used to make a compounded drug. The idea was to provide insurers with more information about what they were being billed for and to make sure there were no hidden ingredients. A few unscrupulous pharmacies began adding more ingredients so they could charge more.

‘They are [creating] combinations of things that have never been tested together,’ said Glen Stettin, senior vice president for clinical research of Express Scripts. ‘We saw a diaper cream that was billed at $1,000, where a patient could get one over the counter for $2.50.’ In California, federal investigators say a marketer for one pharmacy paid doctors to write prescriptions for compounded pain creams formulated to include a ‘five-pack’ of the most expensive ingredients. Then the pharmacy could bill California’s worker’s compensation program $3,000 per tube for creams it cost about $20 to make, according to a federal indictment filed in June. In Florida, federal prosecutors also in June unsealed an indictment against a doctor who allegedly was given kickbacks — including a $72,000 BMW — for sending prescriptions to a particular pharmacy, which then billed Tricare, Medicare and other government health programs for compounded creams. Prices ranged from about $900 to $21,000 for a one-month supply, according to court documents.”

4. Pre-filled syringes provided by drug manufacturers are tested for stability of the drug in the container system and expiration dates are provided. No such testing is required for compounded injectables in closed container systems (syringes). Larger hospitals typically perform stability testing through third-parties (e.g., Dynalabs). When testing is performed, the beyond use date is not recorded in a public database so that stability information regarding drugs prepared and stored in various closed containers can be shared.
Potential Negative Impact on Innovation (continued from pg. 1)

demonstrate safety and effectiveness and are not produced in accordance with current good manufacturing practice (CGMP) requirements or labeled with adequate directions for use.” In addition, drug developers “might also be less likely to seek approval of an ANDA for a generic drug if compounders were permitted to compound drugs that are essentially copies of commercially available drugs without going through the abbreviated new drug application (ANDA) process.”

2. “When Turing Pharmaceuticals raised the price of a drug used for patients with compromised immune systems from $13.50 a pill to $750 last year, for example, one of the nation’s largest pharmacy benefit managers partnered with a compounding pharmacy to produce its own version for $1 a pill. ‘Some compounding we should be happy for,’ said Glen Stettin, senior vice president for clinical research of Express Scripts.” While this was a beneficial and welcome development in light of the unprecedented unscrupulous pricing policy of Turing, the act of compounding drug product from API does deter the development of innovative products and subsequent formal FDA approval.

3. Physicians may be reticent to prescribe customized formulations of drugs via compounding - they may then have to settle on drugs that are FDA approved, but that are not their first choice for the patient.

Discussion (continued from pg. 1)

business practices that increase drug prices, and (3) the dispensing of products that may not have clinical activity. The most concerning issue from a patient safety perspective is the preparation of sterile products.

Who regulates compounding pharmacies?

“Although the US Food and Drug Administration (FDA) has clearly delineated jurisdiction over drug companies and products manufactured under Good Manufacturing Practice (GMP) regulations to ensure quality, potency, and purity, compounding pharmacies are regulated by the State Boards and are not registered by the FDA.” (Chest. Apr;143(4):896-900. Compounding pharmacy conundrum: “we cannot live without them but we cannot live with them” according to the present paradigm.) “The states are the primary regulator of pharmacies, including community drug stores, large chains, and specialty pharmacies.” (Int J Pharm Compd. 2014 Mar-Apr;18(2):101-11. Pharmaceutical compounding or pharmaceutical manufacturing? A regulatory perspective.)

“All pharmacies and pharmacists are licensed and strictly regulated by state boards of pharmacy, which regularly update their standards. In almost every state in the country, a pharmacy that sends medications to patients or health care professionals in another state must also have a license there as well. Compounders follow established U.S. Pharmacopeia practice guidelines, USP chapter <795> (non-sterile preparations) and USP chapter <797> (sterile preparations), as well as requirements under Section 503(a) of the Federal Food, Drug and Cosmetic Act.” (International Academy of Compounding Pharmacies – Backgrounder on Compounding Pharmacy.) Approximately 2.9% (454 of 15,700 compounding pharmacies in the US) obtain accreditation from organizations such as the PCAB (Pharmacy Compounding Accreditation Board).

FDA Authority

The FDA has authority to regulate compounding under its broad jurisdiction over drug manufacturing. However, as stated by Janet Woodcock (FDA Director, Center for Drug Evaluation and Research), in 2013 to the House Subcommittee on Health Committee of the House Energy and Commerce, “the FDA’s ability to enforce Section 503A (21 USC 353a) has been called into question by several court rulings that have produced conflicting case law and amplified the perceived limitations and ambiguity associated with FDA’s enforcement authority over compounding pharmacies... A look at FDA’s attempts to address compounding over the last 20 years shows numerous approaches that were derailed by constant challenges to the law. As a result, presently, it is unclear where in the country Section 503A is in effect.” [This provision of the law exempted compounded drugs from three critical provisions of the FD&C Act: the premarket approval requirement for “new drugs”; the requirement that a drug be made in compliance with current good manufacturing practice (cGMP) standards; and the requirement that the drug bear adequate directions for use, provided certain conditions are met.]

In a risk-based approach to regulating compounding pharmacies in the wake of the NECC scandal, the agency proposed, and Congress passed, a new law (Compounding Quality Act or Drug Quality and Security Act of 2013 ~ Section 503B, 21 USC 353b), which addressed uncertainties in Section 503A of the law that were introduced by court challenges, and which allows an entity that compounds sterile drugs to register as an outsourcing facility. In a February 27, 2014 Joint Commission sponsored webinar that featured a presentation by Janet A. Axelrad, Associate Director for Policy, FDA Center for Drug Evaluation and Research, it was apparent that the changes to 503A addressed in the Compounding Quality Act were not sufficient; (continued on pg. 7)...
The New Law Leaves Some Issues Unresolved

- Compounds may seek to hide out in the traditional compounding category and escape detection
- The lack of clarity in section 503A over whether a state or FDA has primary responsibility over a particular pharmacy remains

The following is a summary of the law found on the FDA website:

**Compounding Quality Act**

**Title I of the Drug Quality and Security Act of 2013**

On November 27, 2013, President Obama signed the Drug Quality and Security Act (DQSA), legislation that contains important provisions relating to the oversight of compounding of human drugs.

Title I of this new law, the Compounding Quality Act, removes certain provisions from section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) that were found to be unconstitutional by the U.S. Supreme Court in 2002. Section 503A describes the conditions under which certain compounded human drug products are entitled to exemptions from three sections of the FDCA requiring:

- Compliance with current good manufacturing practices (CGMP) (section 501(a)(2)(B));
- Labeling with adequate directions for use (section 502(f)(1)); and
- FDA approval prior to marketing (section 505).

By removing the unconstitutional provisions, the new law removes uncertainty regarding the validity of section 503A, which will be applicable to compounding pharmacies nationwide.

In addition, the new law creates a new section 503B in the FDCA. Under section 503B, a compounding pharmacy is allowed to prepare sterile drugs for individual patients and hospitals is allowed to morph into a large-scale drug manufacturing or a “outsourcing facility.” An outsourcing facility will be able to qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from CGMP requirements. Outsourcing facilities:

- Must comply with CGMP requirements,
- Will be inspected by FDA according to a risk-based schedule, and
- Must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound.

If compounding pharmacies register with the FDA as outsourcing facilities, hospitals and other health care providers can provide their patients with drugs that were compounded in outsourcing facilities that are subject to CGMP requirements and federal oversight.

If a compounding pharmacy chooses not to register as an outsourcing facility and qualify for the exemptions under section 503B, the compounding pharmacy could qualify for the exemptions under section 503A of the FDCA. Otherwise, it would be subject to all of the requirements in the FDCA applicable to conventional manufacturers. FDA anticipates that state boards of pharmacy will continue their oversight and regulation of the practice of pharmacy, including traditional pharmacy compounding. The Agency also intends to cooperate with State authorities to address pharmacy compounding activities that may be violative of the FDCA.

FDA has initiated actions to implement the new law.

In a letter to state officials after the law was passed, “Dr. Hamburg (former Commissioner of the FDA) asked them to consider how they can encourage compounding pharmacies located out of state that ship compounded sterile drugs into the state to register with FDA as outsourcing facilities. FDA noted that registration of pharmacies as outsourcing facilities, a voluntary exercise, will help FDA identify and more effectively regulate these facilities. As to hospital purchasers of compounded products, Dr. Hamburg told them that they can play an important role in improving the quality of compounded drugs by requiring compounding pharmacies that supply drugs to register as outsourcing facilities. Once they register, such facilities and the patients they serve, said FDA, can be assured that FDA will inspect these facilities on a risk-based schedule, hold them to CGMP requirements, monitor the adverse event reports they are required to submit to the agency, and require appropriate labeling.”

But, the FDA cannot mandate that compounding facilities producing sterile drugs for interstate sale register as outsourcing facilities because Congress did not include this in the law. Why should industrial compounding pharmacies volunteer to do so, thereby committing to being held to GMP standards? Of course, an economic incentive would induce outsourcing facilities to register if, for example, hospitals refused to purchase from compounding pharmacies that are not registered with the FDA, or states mandated registration with the FDA as a condition of licensure.

But, the FDA has been empowered by Congress only to partake in enhanced communications with the states – The Compounding Quality Act requires the Secretary to establish a mechanism to receive (continued on pg. 8)
submissions from state boards of pharmacy concerning certain actions taken against compounding pharmacies or expressing concerns that a compounding pharmacy may be acting contrary to section 503A. This section is to be implemented in consultation with the National Association of Boards of Pharmacy (NABP). In addition, state boards of pharmacy must be notified when the Secretary receives certain state submissions or makes a determination that a compounding pharmacy is acting contrary to section 503A. States that wish to provide this information to FDA should submit the information by email to the following mailbox: StateCompounding@fda.hhs.gov. FDA intends to follow up with states that provide this information and to notify other states about the receipt of the information in accordance with the law.

What are the differences between traditional compounding and compounding outsourcing facilities?
The following table summarizes the differences between traditional compounding and outsourcing facilities with respect to FDA regulation:

<table>
<thead>
<tr>
<th>Activity / Issue</th>
<th>Human Drug Compounding Outsourcing Facility (21 USC 333a and FD&amp;C Section 503A) – Non-traditional Compounding</th>
<th>Compounding Pharmacy (21 USC 333a and FD&amp;C Section 503B) – Traditional Compounding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounding activities permitted</td>
<td>Traditional compounding plus any sterile compounding in advance of, or without receiving, a prescription, where the drug is distributed out of the state in which it was produced.</td>
<td>Traditional compounding - combining, mixing, or altering of ingredients to create a customized medication for an individual patient with an individualized medical need for the compounded product, in response to a valid patient-specific prescription or order from a licensed practitioner documenting such medical need.</td>
</tr>
<tr>
<td>Prohibited activities</td>
<td>Products that (1) are essentially copies of FDA-approved drugs, absent a shortage justification based on the drug appearing on FDA’s shortage list; and (2) are complex dosage forms such as extended release products, transdermal patches, liposomal products, most biologics, and other products as designated by FDA.</td>
<td>Cannot be contaminated or made under insanitary conditions – FD&amp;C 501(a)(2)(A); FDA will issue 483 findings of CGMP infractions only if a drug is not compounded in accordance with conditions in section 503A.</td>
</tr>
<tr>
<td>FDA operating standards</td>
<td>Must follow current Good Manufacturing Practices (CGMP) for both sterile and non-sterile drugs – FD&amp;C 501(a)(2)(B)</td>
<td>Individual patients for whom the prescriber indicates the rationale for which the compounded drug produces a clinical difference.</td>
</tr>
<tr>
<td>Customers</td>
<td>1. Physician’s offices and healthcare facilities (e.g., hospitals and hospices) to be used in many patients with common conditions for which the compounded drug produces a clinical difference; 2. Individual patients for whom the prescriber indicates the rationale for which the compounded drug produces a clinical difference.</td>
<td></td>
</tr>
<tr>
<td>FDA Inspections</td>
<td>Risk-based schedule</td>
<td>None specified – at any time</td>
</tr>
<tr>
<td>Interstate supply</td>
<td>No volume restriction</td>
<td>Cannot exceed 5% of the total prescription orders dispensed or distributed</td>
</tr>
</tbody>
</table>

(continued on pg. 9)...
### Discussion (continued from pg. 8)

<table>
<thead>
<tr>
<th>Activity / Issue</th>
<th>Human Drug Compounding Outsourcing Facility (21 U.S.C Section 353B and FD&amp;C Section 503A) - Non-Traditional Compounding</th>
<th>Compounding Pharmacy (21 U.S.C Section 353A and FD&amp;C Section 503B) - Traditional Compounding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event reporting</td>
<td>Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.</td>
<td>None specified</td>
</tr>
<tr>
<td>FDA Registration</td>
<td>Annual registration</td>
<td>No registration requirement</td>
</tr>
<tr>
<td>Reporting requirements</td>
<td>Biannual reporting of a list of drugs compounded during previous 6 months – active ingredient; source of the active ingredient, National Drug Code number of the source or drug or bulk active ingredient, strength of active ingredient per unit, dosage form and route of administration, package description, number of individual units produced, and National Code number of final product.</td>
<td>No specified requirements</td>
</tr>
<tr>
<td>Labeling requirements</td>
<td>Comprehensive – “this is a compounded drug”; name, address, phone of outsourcing facility; lot or batch number; established name of drug; dosage form and strength; quantity/volume; date of compounding; expiration date; storage and handling instructions; National drug Code number; “not for resale”; if not for an individual patient, then marked “Office Use Only”; list of active and inactive ingredients with quantities and proportions.</td>
<td>No specific requirements</td>
</tr>
<tr>
<td>Bulk (API) Substances</td>
<td>Produced by establishments registered with the FDA under 21 USC 360 (significant reporting requirements to the FDA and biennial inspections by FDA); comply with USP, NF (National Formulary) or other monographs compendium recognized by the Secretary (of Health and Human Services)</td>
<td></td>
</tr>
<tr>
<td>Non-bulk substances</td>
<td>USP, NF or other monographs compendium recognized by the Secretary</td>
<td></td>
</tr>
<tr>
<td>Accreditation</td>
<td>No requirement to be accredited by the PCAB (Pharmacy Compounding Accreditation Board) or other accrediting body.</td>
<td></td>
</tr>
</tbody>
</table>

### State Regulation of Compounding Pharmacies

The states are the principal regulators of pharmacy practice, including pharmacy compounding activity. With respect to sterile drug compounding practices and policies, state boards of pharmacy rely on US Pharmacopeia Chapter <797> -

United States Pharmacopeia Chapter has developed standards to help compounding practitioners adhere to widely accepted, scientifically sound procedures and practices. USP standards can be legally enforceable when incorporated into or referenced by state laws or regulations. The USP Chapter <797> provides procedures and requirements for compounding sterile preparations. It describes conditions and practices to prevent patient harm resulting from microbial contamination, excessive bacterial endotoxins, variability in intended strength, unintended chemical and physical contaminants, and ingredients of inappropriate quality in compounded (continued on pg. 10)...
sterile preparations. Chapter <797> describes appropriate sterile gowning, cleaning procedures, environmental controls such as airflow, and monitoring practices to detect and prevent unsafe levels of contaminants in the air and on equipment and surfaces. Adherence to quality standards is essential to the safe preparation of sterile drugs. Of note, the USP is currently working to update its standards for sterile compounding and published a proposed revision to Chapter <797> in September of 2015. The USP is also working to develop Chapter <800>, which will cover the compounding of hazardous drugs.

In February 2016, PEW Charitable Trusts conducted a review of publicly available information from state pharmacy board websites, as well as a survey, to which 43 of 51 state boards (50 states plus the District of Columbia) responded. Here are some of the findings:

1. Most regulatory bodies (34 of 43 states, or 79 percent) referenced or incorporated USP standards for sterile compounding in their laws and regulations. However, 13 of these 34 respondents (or 38 percent) indicated that the state does not require USP in its entirety. Seven of the eight states reporting that they do not require USP indicated that they will require the standard under pending policy changes. Just over half of respondents (representing 24 of 43 states, or 56 percent) reported that their states tracked the number of pharmacies that perform sterile compounding.

2. At the time of the study, there were notable differences in how respondents defined compounding for the purposes of meeting USP standards. State definitions included varying criteria, such as the combination of two or more ingredients, repackaging, reconstitution, diluting, or pooling. As a consequence, drugs prepared in one state may not be held to the same standard as those prepared in another, depending on the definition of compounding. This has implications for the quality standards applied to products shipped across state lines. For example, a repackaged sterile product made in a state that does not consider this compounding, and thus not subject to USP standards, could be sent to a state that does require USP compliance for sterile repackaging. This presents an additional challenge for state regulators, who are already confronted with the task of how to best ensure the safety of compounded drugs shipped from other states. Minimum quality standards that are consistent across both drug preparation activities and states would help ensure that compounders within and outside of the state prepare safe drug products and protect the public from potential harms.

3. In response to questions regarding training requirements for pharmacists conducting sterile compounding, a majority of respondents (28 of 43 states, or 65 percent) reported that they did not mandate specific expectations for specialized training in sterile compounding, beyond what is currently required in USP, as a condition of competency for pharmacists engaging in such activity. Ten states (23 percent of respondents) reported specific training requirements: Alabama, California, Idaho, Louisiana, Maryland, Missouri, New Jersey, New Mexico, South Carolina, and Texas. For example, as of September 2015, Texas indicated that it will require all pharmacists and pharmacy technicians who conduct sterile compounding to complete annual training in this practice. The number of hours required will depend on whether the practitioner is engaged in low- and medium-risk sterile preparations (two hours) or high-risk sterile preparations (four hours). Both Texas and New Jersey clarified in their questionnaire responses that they assess compliance with specific sterile compounding training requirements during facility inspections. Research suggests that many pharmacy schools and educational programs for pharmacists and technicians lack appropriate hands-on training in aseptic technique and sterile compounding. In 2005, 82 accredited U.S. pharmacy schools were surveyed regarding the extent to which they provided didactic and laboratory instruction related to compounded sterile preparations. Among the 53 schools that responded, 88 percent taught students about USP; however, only 13 percent felt that their students had been adequately trained in sterile compounding prior to graduation. Given this potential gap in education, it is possible that some pharmacists may not recognize deficiencies in their own sterile compounding practices.

4. The majority of respondents (representing 26 of 43 states, or 60 percent) said their states did not require pharmacies to report serious adverse events and reactions related to sterile compounding.

5. Twenty-eight respondents (65 percent) said their states allowed pharmacies to compound without patient specific prescriptions. Most of these states (21 of the 43 respondents, or 49 percent) had specific limits on this practice, but with varying degrees of restriction. State policies permitting compounding without a prescription for human use conflict with recently clarified federal law.

6. Nine respondents (21 percent) said their state required pharmacies to have a separate license or registration to perform sterile compounding.

7. The number of pharmacies per inspector ranged from 40 to 900, with a mean of 230 (standard deviation = 159) and a median of 183. It is worthwhile to note that differences in state policy and...
inspector workload allocation also affect how oversight is conducted. In addition, in some cases states may outsource inspections to third parties to improve their oversight reach. Twelve respondents (28 percent) reported that when inspecting sterile compounding pharmacies in the state, they prioritized inspections for pharmacies where high-risk sterile compounding occurs. Five respondents (12 percent) reported that they did not verify the compliance of out-of-state sterile compounders.

8. Majorities of respondents reported that their states required that inspectors who assess sterile compounding be licensed pharmacists (70 percent), have prior experience within a pharmacy (60 percent), and have training on applicable USP standards (58 percent). Interestingly, among states that mandated full or partial compliance with USP (21 and 13 respondents, respectively) for sterile compounding, only 14 of 21 (67 percent) and 6 of 13 (46 percent) required that their inspectors be trained in applicable USP standards. Lack of a requirement does not mean that states never secure such training for inspectors, but insufficient training can undermine the state’s ability to recognize a violation through inspection.

9. The study found variability in the authority of states to share information about inspections, investigations, and enforcement concerns related to drug compounding with in-state, out-of-state, and federal officials. Twenty-six, 28, and 30 respondents reported that they could share information with instate, federal, and other state officials, respectively (corresponding to 60 percent, 65 percent, and 70 percent of the 43 respondents). One respondent reported no authority to share information. Third parties, such as the National Association of Boards of Pharmacy, are engaged in efforts to establish clearinghouses of inspection information for states to access, and to facilitate state recognition of one another’s inspections through harmonized inspection checklists.

10. Sterile compounding sometimes takes place in physician offices or clinics, which are normally regulated by a state board of medicine. When asked, only one state reported that their state had a mechanism to track non-pharmacy locations where sterile compounding occurs, and only seven respondents (17 percent) reported that physician offices were held to the same compounding quality standards as pharmacies.

Why is pharmaceutical compounding an issue today?
The most important restriction contained in FD&C Sections 503A and 503B is that compounding pharmacies and outsourcing facilities cannot produce drugs that are “essentially a copy of one or more approved drugs.” Although compounded drugs can serve an important need, they also pose a higher risk to patients than FDA-approved drugs. Compounded drug products are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality. Therefore, if an FDA approved drug is available, it should be given to patients in lieu of a compounded drug.

In July 2016, the FDA issued two guidance documents for the implementation of Sections 503A and 503B, respectively, which provide additional details regarding the definition of a “copy of an approved drug.” On July 18, 2016, an article in Forbes entitled, “Lax FDA Oversight Of ‘Compounded Drugs’ Is A Matter Of Life And Death” was highly critical of the two new guidance documents. It called for the FDA to do more -

…the FDA’s attempt to address these issues is far from adequate. There remain gaping loopholes in the proposed guidance that rogue compounding pharmacies will exploit. The FDA proposes to allow pharmacies to make a “limited,” 30-day supply of drugs in advance of a prescription, but that smacks of “drug manufacturing,” rather than the customized, patient-specific drug preparation that is the essence of compounding. It should, therefore, be subject to the rigorous quality and procedural standards that manufacturers must adhere to.

In order to create an acceptable (continued on pg. 12)
risk-benefit paradigm for drug compounding, FDA needs to increase its scrutiny over compounding pharmacies. When a pharmacy is allowed to morph into a large-scale drug manufacturer without adequate oversight, it's a matter of life and death.

But, the FDA cannot do what the courts prohibit it from doing, and what Congress will not authorize it to do.

The FDA also announced on July 12, 2016 that it will be changing its inspection policy as of August 1, 2016 with respect to traditional compounding pharmacies:

For companies that compound human drugs in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (i.e., human drug compounders that are not registered with FDA as outsourcing facilities under section 503B), effective 1 August 2016, “FDA investigators will make a preliminary assessment of whether such entities are compounding their human drugs in accordance with certain conditions of section 503A before closing the inspection.”

The change comes as FDA says that “in the substantial majority of cases, inspected human drug compounders not registered as outsourcing facilities were compounding at least some of their drugs not in accordance with section 503A, subjecting their drugs to CGMP requirements.”

And, on August 3, 2016, the agency put forth a draft guidance document on insanitary conditions at compounding pharmacies based on observations made during inspections.

Clearly, better regulation of compounding pharmacies that prepare sterile drugs for individual patients and hospitals is needed. But, is it fair to assign the sole responsibility for regulating compounding pharmacies to the FDA? Further, has the FDA been sufficiently empowered by Congress to effect and enforce appropriate regulation?

**Recommendations (continued from pg. 1)**

1. Provides a summary of state requirements and recommendations for inspections of compounding pharmacies. Requires outsourcing facilities to register with the FDA, thereby, mandating operation under CGMP requirements. Such action will allow inspections of such facilities to be governed by the FDA (rather than state pharmacy licensing boards), which has the potential to drive closure of sterile compounding facilities not in compliance.

2. Congressional legislation that mandates adverse event reporting and complete product labeling by all compounding pharmacies, not just registered outsourcing facilities (including both date compounded and expiration dating).

3. State pharmacy licensing boards require that industrial compounders comply with Section 503B (that is, to register with the FDA as outsourcing facilities) as a condition of state licensure.

4. State pharmacy licensing boards require that all compounding pharmacies are accredited by the Pharmacy Compounding Accreditation Board (PCAB) via the Accreditation Commission for Health Care (ACHC), or equivalent body (e.g., Joint Commission Accreditation for Specialty Pharmacy), using USP (United States Pharmacopoeial convention) standards, as a condition of state licensure. Only 2.9% of compounding pharmacies are PCAB accredited.

5. Payers (e.g., Medicare, Medicaid, Tricare, private insurers, etc.) provide a higher level of payment for drugs compounded by pharmacies that are PCAB accredited and/or registered with the FDA as outsourcing facilities.

6. FDA publicly recommends that hospitals, physicians, and patients purchase sterile compounded drugs ONLY from establishments that have registered as a Human Drug Compounding Outsourcing Facility (62 entities in the US have registered to date).

7. FDA requires outsourcing facilities to register with the FDA, thereby, mandating operation under CGMP requirements. Such action will allow inspections of such facilities to be governed by the FDA (rather than state pharmacy licensing boards), which has the potential to drive closure of sterile compounding facilities not in compliance.

8. Congressional legislation that mandates adverse event reporting and complete product labeling by all compounding pharmacies, not just registered outsourcing facilities (including both date compounded and expiration dating).

9. State pharmacy licensing boards require that industrial compounders comply with Section 503B (that is, to register with the FDA as outsourcing facilities) as a condition of state licensure.

10. State pharmacy licensing boards require that all compounding pharmacies are accredited by the Pharmacy Compounding Accreditation Board (PCAB) via the Accreditation Commission for Health Care (ACHC), or equivalent body (e.g., Joint Commission Accreditation for Specialty Pharmacy), using USP (United States Pharmacopoeial convention) standards, as a condition of state licensure. Only 2.9% of compounding pharmacies are PCAB accredited.

11. Payers (e.g., Medicare, Medicaid, Tricare, private insurers, etc.) provide a higher level of payment for drugs compounded by pharmacies that are PCAB accredited and/or registered with the FDA as outsourcing facilities.
Recommendations (continued from pg. 12)

The state boards provide for sharing of information regarding results of inspections, adverse events, and the results of stability testing (beyond use dating) of closed container storage systems.

Address Inquiries to:

Joseph Gulfo, MD, MBA, Executive Director - Lewis Center for Healthcare Innovation and Technology

jvgulfo@fdu.edu