



First, do no harm

Compounds in Comp: A New Look at Patient Safety, Efficacy and Cost

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Introduction

CompPharma published "[Compounding is Confounding Workers' Compensation](#)" in 2014. That research paper, like this one, was written by pharmacists and government affairs professionals employed by several of the member pharmacy benefit management (PBM) companies of CompPharma. Many of the pharmacists who worked on both papers have extensive training and experience in the art of pharmaceutical compounding.

The original paper was well received by the workers' compensation community, and over 2,000 copies have been downloaded from the [CompPharma](#) website as well as those of the member companies. In addition, the paper was presented at several industry forums including the [International Association of Industrial Accident Boards and Commissions](#) (IAIABC) and the [American Insurance Association](#) (AIA).

However, the paper was not well received by a few pharmacists who interpreted it as an attack on both the necessity and the science of state-of-the-art pharmaceutical compounding.

The authors never intended to examine all areas of pharmacy compounding in the 2014 paper. Instead, we focused on the confusion and expense that compounding for injured employees was causing the workers' compensation industry. We want to make sure readers do not mistake our concern for injured patients and their employers as a criticism of clinically appropriate, patient-specific compounding. The right for a pharmacist to compound is protected by law in all 50 states, and we support this right when it is executed with the patient's best interest in mind.

In fact, we believe that modern day compounding can play an important role in medicine. Appropriate uses of compounding include the sterile compounding of intravenous drugs for in-patient use, the extemporaneous preparation of radioisotopes for nuclear medicine procedures, and the compounding of oral preparations for individuals with allergies to ingredients found in manufactured drugs. It is also appropriate to compound custom dosages of medications for patients with special needs or in patient-specific cases where commercially available products have been used and the therapy has failed. CompPharma supports the use of compounding when prescribed by a licensed practitioner with knowledge of evidence-based medicine supporting the use of a compound for a single patient with special needs that prevent the use of a drug approved by the Food and Drug Administration (FDA).

Workers' compensation PBMs have worked extensively to protect the best interests of patients by using established programs such as formulary management, clinical intervention and prior authorization. These programs improve patient outcomes and reduce the financial burden on payers by eliminating the use of unnecessary drug therapies, both compounds and otherwise.

However, like the first CompPharma compound paper, PBMs have come under fire. Ironically, a chief criticism is that by acting as intermediaries, PBMs profit from the use of compounds and other over-priced medications. In reality, the clinical management programs employed by these companies actually decrease PBMs' top-line revenue. It is also important to note that based on a research update published by the California Workers' Compensation Institute in December of 2015, 97.5% of all denials for the approval of compound prescriptions were upheld by independent medical review, lending further support to the use of PBM programs to challenge the necessity of these compounded drugs.

In addition to concerns about its use in workers' compensation, compounding has found itself in the crosshairs of both the Department of Justice (DOJ) and the US Government Accountability Office (GAO) for reasons related to excessive use, prohibitive costs and violations of the Stark Act. Therefore, this compound

paper directs the readers' attention to adverse consequences arising from the actions of bad actors involved in compounding who seek to profit by taking advantage of laws written to protect the best interest of patients, providers and employers.

Some compounding pharmacies promote their interests by introducing concepts that may further confuse injured patients, workers' compensation payers, and lawmakers. For example, some marketers have tried to conflate The United States Pharmacopeia (USP) compliance with FDA approval. Compounded drugs are not approved by the FDA.

This paper seeks to clear up confusion surrounding compounding medications in workers' compensation. It clarifies research on the efficacy of compounds and explores how a pricing benchmark that was never intended to be applied to pharmaceutical grade chemicals has been manipulated to drive compounding prices and profits. We examine how certain business practices violate the traditional physician-patient-pharmacist triad, which has safeguarded patient interests for almost two centuries in this country. We also provide updates to legislative and regulatory actions addressing compounding in workers' compensation. Finally, we examine the consequences of what can most accurately be described as a greed-driven practice that has resulted in tragic deaths as well as the prosecution of numerous physicians and pharmacists.

One of the authors' goals is to educate the industry so that employers and other payers, providers, policy makers, and other stakeholders can take steps to address inappropriate compounding, a far-too common practice that risks patient safety and drives costs in the workers' compensation system.

The current research paper is intended as a stand-alone product rather than a continuation of the original paper. For ease of use by different audiences, it is divided into two sections: Part 1: Patient Safety and Considerations for Providers and Part 2: Regulatory and Financial Concerns Related to Prescription Drug Compounding. However, the authors encourage all stakeholders to carefully consider and incorporate patient safety when dealing with matters related to compounds.

PART 1: Patient Safety and Considerations for Providers

The Physician-Patient-Pharmacist Triad

The first college of pharmacy was established in this country in 1821, and since then a triad relationship has evolved among the physician, patient and pharmacist. Simply stated, the physician examines and diagnoses the patient's condition, and if appropriate, prescribes a drug. The physician is free of any conflict of interest if he or she does not profit from this prescription. The patient – free of any undue influence by the prescriber – then takes that prescription to the pharmacist of his or her choice. (Even in this era of preferred pharmacy networks contracted with workers' compensation PBMs, this patient/injured employee may still choose any pharmacy without penalty or undue pressure in the vast majority of states.)

The pharmacist then fulfills that prescription within the confines of various state laws as they may pertain to generic substitution, patient counseling, etc. Please note that nothing stated above is intended to impede a pharmacist's professional and ethical obligation to conduct drug utilization review at the time of dispensing and alert the prescriber of any clinical concerns that must be addressed and could affect the drug selection process. Nor is it intended to be confused with a PBM's role in enforcing clinical guidelines especially as they pertain to pain management and/or patient safety for an injured employee.

Unfortunately, this time-tested triad has been under assault from many fronts in recent years, including direct-to-consumer advertising, physician dispensing, "detailing" to prescribers on compounding, as well as physician ownership in pharmacies or kickbacks from same. These tactics have resulted in harm to some patients and produced egregious profits for many compounding pharmacies and extremely high and unnecessary costs for employers and taxpayers. The authors want policy makers and decision makers involved in workers' compensation to consider the role of the triad relationship in avoiding conflicts of interest when evaluating policy and/or statutory changes.

Concerns Over Safety

CompPharma's 2014 compound research paper stated, "Pharmacies have received FDA warnings regarding topical lidocaine in concentrations greater than 5% and other topical anesthetics." Some compounding pharmacists responding to the 2014 paper characterized this statement as a misrepresentation. The authors stand by the statement and back it with the following details: The FDA sent warning letters to five pharmacies demanding those pharmacies stop compounding and distributing standardized versions of topical anesthetic creams (essentially, stop functioning as manufacturers). Copies of the warning letters are found in Appendix B.

A 2006 FDA press announcement said, "FDA is concerned about the serious public health risks related to compounded topical anesthetic creams. Exposure to high concentrations of local anesthetics, like those in compounded topical anesthetic creams, can cause grave reactions including seizures and irregular heartbeats. Two deaths have been connected to compounded topical anesthetic creams made by Triangle Compounding Pharmacy and University Pharmacy, two of the five pharmacies receiving warning letters. Similar topical anesthetic creams are compounded by the other firms, and today's action serves as a general warning to firms that produce standardized versions of these creams."

Concerns Over Effectiveness

Much of pharmacological evidence-based decision support in the workers' compensation arena is driven by established guidelines specific to this particular population of patients. The Work Loss Data Institute's Official Disability Guidelines (ODG) and the Reed Group's MDGuidelines are two nationally recognized guidelines for medical and pharmacy treatment in workers' compensation. In addition, Washington State and others have

begun to ideate and model state formularies based on the recommendations established by guidelines and evidence-based medicine with regard to medications in workers' compensation.

While the craft of pharmaceutical compounding may offer many advantages for specific patients in general pharmacy practice, the use of topical compounded products is not recommended as first-line treatment for workers' compensation patients. Per ODG: "Custom compounding and dispensing of combinations of medicines that have never been studied is not recommended, as there is no evidence to support their use and there is potential for harm."¹

ODG does recommend topical nonsteroidal anti-inflammatory drugs (NSAIDs) as an option in specific conditions when the active ingredient (the NSAID) is supported for the prescribed indication by either the FDA approval process or adequate medical and scientific evidence in medical literature. ODG recommends considering each specific ingredient contained within the compounded pharmacy product to determine whether or not all components meet this criteria.

ODG typically limits topical NSAIDs to short-term use (up to 12 weeks) due to the lack of sufficient data related to safety and efficacy for long-term use. Recommendations are restricted to conditions that include acute pain (particularly soft tissue injuries) and osteoarthritis and tendonitis in joints amenable to topical treatment (i.e., knee, elbow, hand) for which there is evidence-based support for using these agents.

A 2010 literature review conducted by Haroutiunian et al² identified various clinical trials and systematic reviews that pointed to the variation in efficacies and outcomes, as well as some of the differences in pharmacokinetic (how the drug moves through the body) and pharmacodynamic (what the drug does to the body) properties, with the use of topical NSAIDs for specific conditions. The review concluded that topical NSAIDs exhibit variability in absorption kinetics and pharmacodynamic effects, and that evidence supports some topical NSAID formulations as more effective than placebo or comparable to the efficacy of oral NSAIDs for single joint osteoarthritis and acute muscle injuries (in studies up to 12 weeks in duration). However, evidence did not support use for acute or chronic low back pain, widespread musculoskeletal pain, or in peripheral neuropathic pain syndromes.

It is understood that pharmacokinetics and systemic availability of topically applied drugs can be affected by several factors. The layers of skin through which a topical drug would need to pass include the stratum corneum (uppermost layer, predominantly lipophilic), epidermis (devoid of blood vessels, mainly aqueous), the basal membrane, and the dermis (contains blood vessels) after which absorption into the systemic circulation or penetration into deeper tissues could occur. Differences in absorption and penetration through the skin can vary based on the active medication, the delivery vehicle (i.e., gel, solution, cream, ointment), pH, lipid characteristics and drug solubility in the vehicle, carrier-mediated transport, and penetration enhancement. (A thorough discussion of the anatomy of the skin and absorption of topical medications can be found in CompPharma's earlier compound research paper.) Other studies evaluating the effect of vehicles on NSAID skin penetration are summarized in Table 1.

Table 1. Study Summary

Citation	Key Points
Sallam MA, Motawaa AM, Mortada SM. An insight on human skin penetration of diflunisal: lipogel versus hydrogel microemulsion. Drug Dev Ind Pharm. 2015;41(1):141-7.	<ul style="list-style-type: none"> +Lipogels delivered higher total drug amount through the skin vs. the hydrogel. +Composition of lecithin seemed to have effect on skin permeability enhancement ability of the lipogel, with those containing a higher amount of phosphatidyl ethanolamine providing for better transdermal delivery.
Hoppel M, Ettl H, Holper E, Valenta C. Influence of the composition of monoacyl phosphatidylcholine based microemulsions on the dermal delivery of flufenamic acid. Int J Pharmaceutics. 2014;475(1-2):156-162.	<ul style="list-style-type: none"> +Water-rich microemulsion resulted in significantly higher in vitro skin penetration of flufenamic acid. +Monoacyl phosphatidylcholine appears to be a skin-friendly emulsifier with the ability to stabilize microemulsions.
Goh CF, Lane ME. Formulation of diclofenac for dermal delivery. Int J Pharmaceutics. 2014;473(1-2): 607-16.	<ul style="list-style-type: none"> +Reviewed studies analyzing various dermal delivery enhancers and skin permeability for diclofenac. +Studies used doses which are higher than those used clinically, however, it was found that only a small amount of diclofenac permeates.
Gee CM, Watkinson AC, Nicolazzo JA, Finnin BC. The effect of formulation excipients on the penetration and lateral diffusion of ibuprofen on and within the stratum corneum following topical application to humans. J Pharm Sci. 2014;103(3):909-19.	<ul style="list-style-type: none"> +In vivo ibuprofen solution applied onto human forearm with octisalate (OS) showed greater tendency for lateral diffusion compared to ibuprofen dosed with propylene glycol (PG) or polyethylene glycol 200 (PEG 200). +Recovery of ibuprofen from the stratum corneum after 24 hours was $25.3 \pm 8\%$ with added excipients (OS, PG, PEG 200) and $55.5 \pm 18.6\%$ without (suggesting permeation enhancement effects of excipients), with a 2- to 3-fold enhancement in ibuprofen flux in vitro when applied with excipients.
Liu KS, Hsieh PW, Aljuffali IA, Lin YK, Chang SH, Wang JJ, Fang JY. Impact of ester promoieties on transdermal delivery of ketorolac. J Pharm Sci. 2014;103(3):974-86.	<ul style="list-style-type: none"> +Ketorolac ester prodrugs with tert-butyl (KT), benzyl (KB), heptyl (KH), and diketorolac heptyl (DKH) were synthesized for percutaneous penetration comparison. +Lipophilicity increased in the following order: ketorolac < KT < KB < KH < DKH. +KT showed the highest skin permeation, and the flux of KT and KB were 2.5-fold and 2-fold greater than ketorolac, respectively. +KB, KH, and DKH increased transepidermal water loss (TEWL) after 7-day consecutive administration, while ketorolac and KT showed no influence on TEWL. +Balance between lipophilicity and aqueous solubility is important in the design of a successful prodrug.
Gujjar M, Banga AK. Vehicle influence on permeation through intact and compromised skin. Int J Pharmaceutics. 2014;472(1-2):362-8.	<ul style="list-style-type: none"> +Mineral oil (lipophilic vehicle) and 10mM phosphate buffered saline (hydrophilic vehicle) were used with diclofenac diethylamine. +Phosphate buffered saline vehicle resulted in higher permeation into and across skin vs. mineral oil vehicle for all simulated models of compromised skin.
Carter SG, Zhu Z, Varadi G, Veves A, Riviere JE. Vasomodulation influences on the transdermal delivery of ibuprofen. J Pharm Sci. 2013;102(11):4072-8.	<ul style="list-style-type: none"> +Peripheral vasodilators, tolazoline, or papaverine were added to transdermal drug delivery vehicles in rabbits. +Penetration enhancer (PE) complex enhanced plasma ibuprofen level ~7-fold vs. control, and tolazoline+PE increased plasma levels of ibuprofen another 2-fold compared with PE. +PE increased plasma ibuprofen 3.7-fold vs. control in the next set of experiments, and papaverine+PE increased plasma ibuprofen an additional 3.3-fold compared with the PE formulation.

Summary of studies that evaluate the effect of vehicles on NSAID skin penetration.

In 2012, a study was conducted comparing the efficacy and skin permeability of nine topical NSAIDs.³ The study used preparations available in the European Union, and evaluated the in vivo anti-inflammatory effect in rat models of acute and chronic inflammation. The skin permeability of the preparations was evaluated in vitro using mouse skin. The preparations included four patch formulations (ketoprofen 20 mg/70 cm², diclofenac 180 mg/140 cm², flurbiprofen 40 mg/140 cm², and piroxicam 14 mg/70 cm²) and five gel formulations (ketoprofen 2.5%, diclofenac 1.16%, piroxicam 1%, niflumic acid 5%, and ibuprofen 5%).

The anti-inflammatory effect of the topical NSAID preparations on hind paw edema and tissue PGE₂ levels was recorded and compared to a control for statistical significance. Only ketoprofen and flurbiprofen patches and ketoprofen and diclofenac gel resulted in significant differences in swelling rate and PGE₂ level reduction versus control. Ketoprofen and diclofenac patches and gels resulted in significant differences in analgesic effect versus control in terms of increased pain threshold. Overall, the order of anti-inflammatory effect was ketoprofen > flurbiprofen > diclofenac ≥ piroxicam for the patches, and the order of analgesic effect was ketoprofen > diclofenac > flurbiprofen ≥ piroxicam for the patches and ketoprofen > diclofenac > niflumic acid ≥ piroxicam and ibuprofen for the gel preparations. Skin permeation in vitro results showed maximum cumulative permeation for ketoprofen patch, followed by (in descending order) flurbiprofen patch, diclofenac patch, and piroxicam patch. Ketoprofen gel also showed maximum permeation, followed by (in descending order) diclofenac gel, ibuprofen gel, niflumic acid gel, and piroxicam gel.

In general, topical NSAIDs have a high safety profile with a lower incidence of severe gastrointestinal effects compared to oral therapies. However, toxicity by dose has not been established because the maximum recommended dose to avoid toxicity in most compounds is not known. Based on available study data, it has been demonstrated that inter-individual variability exists in transdermal drug penetration, and skin and connective tissue differences may alter the topical absorption of drugs. The addition of carriers and/or penetration enhancers or use of multiple-dose administration could also contribute to higher systemic concentrations.

For FDA-approved topical NSAID preparations, a maximum dose is established for each particular diclofenac formulation. However, the practice of compounding topical NSAID products often involves various non-standardized “recipes” for extemporaneous preparation for which drug-related effects, optimal dose or vehicle, bioavailability, and clinical endpoints are rarely examined on a scale or with a study design that would correlate to strong or quality evidence-based results for each particular product. This variability, along with a lack of definitive efficacy data for application of topical NSAIDs outside of specific acute conditions, contributes to the difficulty in recommending compounded topical NSAID products for first-line use in most patients.

Quality Questions

Quality assurance (Q/A) continues to be an area of concern. While there currently are no specific end-product testing requirements for non-sterile compound products, the United States Pharmacopeia (USP) 795 Standards include Q/A recommendations for compounded medications.⁴ The standards further state that a pharmacy engaged in compounding should have a Q/A program that includes the following: training; standard operating procedures (SOPs); documentation; verification; testing; cleaning, including safety and disinfecting; containers and packaging, including repackaging, labeling, and storage; outsourcing if used; and responsible personnel.

USP 795 standards recognize that testing every compound is not necessary or practical. The standards do recommend regular testing during the compounding phase as well as testing of the final product when appropriate. Further, USP provides the following recommendations for numbers for end product testing⁵:

Table 2. Number of Articles to be Tested (USP Recommendations)⁶

Injections		Noninjections		Devices		Solid Bulk Preparations	
Batch Size	No. of Articles to be Tested	Batch Size	Number Tested	Batch Size	Number Tested	Batch Size	Number Tested
<100	10% or 4	<200	5% or 2 articles	<100	10% or 4 articles	<4	Each container
100-500	10	>200	10	100-500	10	4-50	20% or 4
>500	2% or 20	N/A	N/A	>500	2% or 20	>50	2% or 10
Large-volume	2% or 10	N/A	N/A	N/A	N/A	N/A	N/A
Antibiotic solids (<5g)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Antibiotic solids (>5g)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A = not applicable							

USP Recommendations for the number of articles to be tested.

It is recommended that when a pharmacist initially makes a new compound formulation, two batches should be made to assess the stability and sterility of the product over the expected course of treatment.⁷ If in-house testing is not feasible for compounding pharmacies, there are commercial entities that can complete USP 795 standards testing and provide completed reports. Although outsourcing Q/A may be costly, it may be a warranted cost for larger compounding pharmacies to help answer questions of quality.

Each compounded product is required to have a documented step-by-step manufacturing process, Q/A procedure, and end product inspection. This documented process should clearly outline each step of the compounding procedure so as to make it reproducible.⁸ Thoroughly documented Q/A may help overcome some of the concerns related to content and uniformity of compounded products.

The Q/A portion of the compounding documentation should include at least one of the following reference documents⁹:

- Peer reviewed, published clinical studies regarding stability
- Stability/sterility testing on the final product (laboratory or in-house testing)
- National compendia with stability data
- Extrapolation of above references based on professional judgment

The citation of reference documents is the crux of the issue regarding compounded medications since there is a lack of evidence-based efficacy or stability data to support the use of multi-ingredient topical compounds. Further, there are no peer-reviewed studies available for compounds with four or more active ingredients. As a result, compounding pharmacies frequently provide peer-reviewed clinical studies from oral formulations in an attempt to support topical efficacy.

This leaves clinical reviewers wondering if it is appropriate to use extrapolation of references based on professional judgment as the sole basis for supporting topical compounding efficacy. This is where the professional judgment of some compounding pharmacists in selecting ingredients may be questioned. For example, tramadol is frequently included in topical compounded agents yet it is a prodrug that requires activation by the liver in order to release the active drug. As topical application bypasses the liver, the rationale behind the use of tramadol in topical compounds is not evident. Such questions regarding the efficacy, safety, and stability of individual ingredients and their combination in multi-ingredient topical compounds remain unanswered.

The list of pharmacies on the FDA Compounding, Inspections, and Other Recalls¹⁰ website highlights the need for further review of the quality of compounded medications. More than 100 pharmacies have been issued warnings under an FDA inspection. Many citations pertain to sterile compounding, but other citations address a lack of Q/A documentation in non-sterile compounding pharmacies. Patient safety remains the most important factor in all pharmacy compounding, and steps to assure that safe, effective, and stable products are provided should remain the primary concern of all compounding pharmacists.

Despite quality concerns, a 2012 survey conducted by the National Community Pharmacists Association indicated that 85.5% of the responding pharmacies perform compounding. Among these compounders, only 69.95% participate in ongoing training and educational courses. Unfortunately, none of the 2012 survey questions addressed the use of Q/A processes or end-product testing.¹¹

Verification of accreditation with an accrediting body for compounding pharmacies may help patients and payers assess compliance to current compound standards (please refer to section on Pharmacy Compounding Accreditation).

Cases Against Providers

There have been numerous cases of healthcare fraud linked to compounding, mainly outside of workers' compensation. However, just as this paper was finalized, an April 21, 2017 WorkCompCentral.com story¹² reported a \$23.2 million kickback scheme in workers' compensation. Husband and wife Christopher and Tanya King of Beverly Hills, California allegedly masterminded a scheme that paid \$2.1 million in kickbacks to providers who prescribed compound creams. Twenty-one physicians and a physician assistant were involved, and two pharmacists face charges for mass-producing compound transdermal creams that were provided to approximately 13,000 injured employees.

According to the Orange County District attorney, the Kings purchased 30-gram tubes of the compounds (a three-day supply) from the pharmacy and provided them to doctors to dispense to injured workers on the condition that the doctors would also prescribe a second, 120-gram tube that the pharmacy would mail to the injured workers. Carriers were billed between \$700 and \$1,000 per 120-gram tube (originally purchased for \$40), and providers were supposed to receive 70 to 90% of the net profits. Tanya King purportedly specified the ingredients for the pharmacy to compound based on formulas that were profitable under the fee schedule. Between 2011 and 2015, the Kings allegedly bought more than \$1.2 million in compound creams from one pharmacy, received \$3.7 million from workers' compensation payers and paid more than \$2.3 million in kickbacks to providers. The compounds were part of a \$40 million kickback scheme involving the King's three medical management companies and that also included repacked drugs and unnecessary urine toxicology tests.

Previous investigations involved other payer types with TRICARE, the health insurance program for U.S. military personnel, veterans and their families, considered the biggest victim. The FBI and Defense Criminal Investigative Service (DCIS) along with other agencies are investigating a \$100 million fraud involving TRICARE claims for compounded pain and scar creams. According to a July 2016 Health.mil¹³ article, TRICARE experienced a huge surge in the claims for unnecessary and costly compound drugs in 2014 and the first half of 2015. For perspective, TRICARE's compound drug spend in 2004 was \$5 million. In 2014, it was \$514 million, and within the first four months of 2015, TRICARE had spent over \$1 billion on compound drugs. The Health.mil article said, "Many compound products were of dubious or no clinical value, and some may have been dangerous."

This scheme allegedly used a sham medical study through which TRICARE beneficiaries received monetary compensation in exchange for obtaining compounded drugs with their TRICARE prescription benefits. CCMGRX, LLC, a Dallas company, marketed compounded pain and scar creams to TRICARE beneficiaries on behalf of several compounding pharmacies. Payments to beneficiaries were disguised as “grants” for participating in the “study,” which was supposed to evaluate the safety and efficacy of compounded drugs. Several physicians allegedly participated in the scam, one writing thousands of prescriptions for patients he never met in person. At least four compounding pharmacies in TRICARE’s network paid CMGRX employees kickbacks for sending prescriptions. By October 2016, 35 doctors, pharmacy owners and marketers had been arrested.^{13,14} If convicted, each defendant could face 10 years in federal prison, a \$250,000 fine and forfeiture of any property traceable to the offense.

On February 7, 2016, the Wall Street Journal (WSJ) reported that the Justice Department was investigating healthcare fraud linked to compounding in Mississippi.¹⁵ The alleged fraud could amount to as much as a half billion dollars, and TRICARE, Medicare, Medicaid, and private insurers are potential victims. The Mississippi Bureau of Narcotics, FBI, DCIS, Internal Revenue Service, and U.S. Postal Inspectors conducted a series of raids in January 2016, resulting in the seizure of \$15 million in property. Raids also occurred in Alabama, Utah and Florida. Court documents filed in the U.S. District U.S. District Court Southern Division of Mississippi allege that three pharmacies in Jackson, Hattiesburg and Ridgeland, Mississippi “conspired to commit health care fraud, mail fraud and wire fraud associated with the marketing and sale of compounded medications,” according to a February 19, 2017 Clarion Ledger article.¹⁶ The pharmacies purportedly engaged marketers to persuade doctors to write prescriptions for compounded drugs and send patients to the pharmacies, which filled them through private and government health care plans. The doctors, marketers and beneficiaries allegedly received kickbacks. The pharmacies automatically filled prescriptions even when patients asked them not to and billed for the prescriptions in smaller amounts to avoid insurance price caps, according to the complaint. However, as of February 2017, no criminal charges have been filed and some of the property has been returned.

Just a few days after the WSJ article, on February 10, 2016, the Dallas Morning News reported on a new Texas state law designed to help investigators identify financial arrangements between physicians and pharmacists that may actually be illegal kickbacks.¹⁷ State Senator Charles Schwertner, R-Georgetown, who is both a pharmacist and an orthopedic surgeon, has been a critic of financial arrangements between compounding pharmacists and physicians for years. The bill he helped pass will allow the Texas State Board of Pharmacy to “inspect a pharmacy’s ‘financial records’ in response to a specific complaint against the pharmacy.”¹⁸ Prior to this law that was not possible.

Leading up to this law was a report that podiatric doctors had (as of early 2014) been enticed by investment offers from two different chain pharmacies that were owned by the same person, Lifecheck America and Healthscripts of America. These doctors would write prescriptions to an affiliated compounding pharmacy under the same ownership. These “investors” could then receive a generous share of the pharmacy’s profits without being directly compensated by the pharmacy in which they invested.

Compounding pharmacies in Texas were also soliciting doctors to enroll patients in studies of pain creams the pharmacies make, also with the promise of large payments. The CEO of one company says that they are in full compliance with all state and federal guidelines. One possible question is whether they are in line with the ethical codes of the American Medical Association. These concerns were voiced during the Texas Committee on Public Health hearing on April 14, 2014.¹⁹ Notes from the hearing include:

Discussions also took place regarding physician ownership of pharmacies. Mary Robinson, executive director of the Texas Board of Medical Examiners, spoke about pharmacy and physician relationships.

She stated that the only time the medical board will be involved is when the doctor in question requests a prescription from a pharmacy that he owns or partially owns.

Some compounding pharmacies advertise to physicians to invest in their pharmacy which can lead to physicians referring patients to that pharmacy to obtain specific products. There are anti-kickback laws in place, namely the Texas Solicitation of Patients Act, to prevent this sort of activity; however, the law is complicated and detailed and includes exceptions which may exempt certain physician-pharmacy relationships. The only requirement for physicians who fall under this exemption is that they must disclose to the patient that they have a financial investment in the entity to which they are referring the patient.

One of the problems with investigating these relationships or imposing further regulations is that currently there is no database or list of physicians or pharmacies who participate in these activities. Texas Medical Board (TMB), Texas State Board of Pharmacy (TSBP) and legislatures will continue to tackle this issue.

Senator Schwertner characterizes such relationships between physicians and pharmacists as potentially unethical and possibly illegal. The State of Texas does allow a physician to own or invest in a pharmacy but the physician must disclose that relationship if he or she refers a patient to that pharmacy. However, “federal Stark law prohibits physicians from referring Medicare and Medicaid patients to a health care company if the physician or an immediate family member has a financial relationship with the company.” As other states consider passing similar laws, special attention must be placed on the impact such arrangements have on workers’ compensation.

The following cases highlight the types of compounding schemes that have been prosecuted and/or are under indictment and include the dollar amount of healthcare fraud involved as well as the geographic location. Fraud in the workers’ compensation system has not received the same attention as that committed against TRICARE, Medicare and others. Only just recently have the federal workers’ compensation programs, administered through the Department of Labor (DOL), started to pay attention to this issue. Testimony from the Inspector General for the DOL indicates that the federal workers’ compensation programs have experienced a dramatic increase in provider abuse and costs of compounds, particularly pain relief creams. Current investigations are focusing on collusion between prescribers and pharmacies - where in one such case, they have identified fraud involving nearly \$100 million.²⁰

Muscle Shoals, AL: In July of 2016, 63-year-old pharmacist Rodney Dalton Logan pled guilty to obstructing a Medicare audit and agreed to pay a \$2.5 million penalty to the government.²¹ Many readers of this research paper are aware that a pharmacy must bill for the national drug code (NDC) of the drug actually dispensed to the patient, and failure to do so may result in charges of mislabeling the prescription or even fraud. This case is interesting in that Medicare Part D prohibited reimbursement for bulk compounding powders in February of 2009. After that date pharmacist Logan billed for compounded products, mostly topical pain gels, through PBM CVS/Caremark for Medicare Part D beneficiaries. Most of the compounds were for topical pain gels. CVS/Caremark conducted a federal audit on behalf of Medicare and determined that pharmacist Logan had billed for NDC numbers that corresponded to tablet or capsule forms of the ingredients rather than the bulk powders that are prohibited under Medicare Part D. Logan was sentenced to six months of home confinement and one year of probation, during which he is not allowed to work as a pharmacist.

Houston, Texas: Four residents were indicted on charges of conspiracy to commit wire fraud, and unlawfully distributing a controlled substance on 12/8/2015.²² The scheme ultimately resulted in \$17 million in fraudulent healthcare claims over a two-year time period. Tamara Mitchell owned two pharmacies: Diamond

Pharmacy and Save Rite. The pharmacies allegedly paid Dr. Michael Kelly thousands of dollars a month to provide “pre-signed” prescriptions of compounded creams containing controlled substances such as ketamine without examining the patients. These pharmacies would then bill the insurance companies for these compounded creams containing controlled substances. Priscilla Orosco, a technician, and Joyce Ann Gilmore-James, a pharmacist, were also involved in this indictment.

New Port Richey, Florida: Co-conspirators allegedly used A to Z Pharmacy Inc., located in New Port Richey, as well as several Miami-area pharmacies including Medplus/New Life Pharmacy, Metropolitan Pharmacy, Havana Pharmacy, Jaimy Pharmacy, and Prestige Pharmacy to cause the submission of false and fraudulent reimbursement claims for prescription compounded medications to private insurance companies, Medicare and TRICARE from approximately October 2012 through December 2015.²³ The pharmacies allegedly submitted \$633 million in claims for compounded prescriptions and received \$157 million in payment. The claims were allegedly based on prescriptions generated as a result of illegal kickbacks and bribes, prescriptions that were not based on legitimate provider/patient relationships, and misuse of patient information. Additionally, the reimbursement claims allegedly represented that medications contained certain pharmaceutical ingredients when they did not.

Tampa, Florida: the United States is seeking a money judgment in the amount of at least \$5.3 million as proceeds of the conspiracy and health care fraud offenses and forfeiture of a 2015 BMW in an indictment charging Dr. Anthony Baldizzi (52, Tierra Verde) with one count of conspiracy to defraud the United States, 21 counts of health care fraud, one count of money laundering, one count of making a false statement, and one count of receiving illegal kickbacks.²⁴ According to the indictment, Baldizzi entered into an agreement with the owners and operators of Lifecare Compounding Pharmacy to receive kickbacks for each prescription he wrote and directed to Lifecare for filling. In addition, the principals of Lifecare and Baldizzi entered into another kickback relationship whereby Baldizzi agreed to become a Centurion “in-network” doctor and write prescriptions for compounded creams marketed by Centurion and filled at Lifecare. Baldizzi received a kickback equal to approximately 10% of the after-cost amount of paid claims. Many of these prescriptions were written for TRICARE beneficiaries.

Jacksonville, Florida: United States Attorney A. Lee Bentley, III announced that two compounding pharmacies and four physicians agreed to pay the government a total of approximately \$10 million to resolve allegations involving TRICARE.²⁵ The four physicians, Manish Bansal, Mehul Parekh, Marisol Arcila, and Syed Asad, created pharmacies Topical Specialists and WellHealth allegedly to create revenue for themselves when the pharmacies would bill tens of thousands of dollars for topical pain and scar creams which only cost 4-5% of the submitted charge. TRICARE also contends that many of the patients did not even use the creams.

Part 2: Regulatory and Financial Concerns Related to Prescription Drug Compounding

Concerns Over Cost

Average Wholesale Price (AWP) is the universal benchmark for prescription drug reimbursement in the United States today. It was originally introduced in California in the late 1960s with the intent of creating competition among manufacturers and thereby decreasing drug costs. It also replaced the cost-based reimbursement that existed prior to that time. Pricing typically involves a mark-up over AWP or a discount off AWP, plus a nominal dispensing fee (typically represented mathematically as $[Quantity \times AWP] \pm \% + \text{dispensing fee}$).

While AWP has come under considerable scrutiny since its inception, it has survived and remains the universal benchmark today. The basis of that scrutiny is outside the scope of this paper, but its impact on the reimbursement methodology used for compounds does merit attention.

The cost-based reimbursement model remained in place for drug compounds for decades after the implementation of on-line adjudication and reimbursement by PBMs for manufactured drugs. Several factors contributed to this delay, notably:

- The chemicals used in compounding, known as active pharmaceutical ingredients or APIs, lacked an NDC number until after 2000. Like AWP, NDC is key data requirement to process a prescription on-line.
- In addition, APIs lacked an AWP.
- Compounds were somewhat of an anomaly with regard to the development of transaction standards for prescription processing. These standards are created by the National Council for Prescription Drug Programs (NCPDP), which is a member-driven ANSI-accredited organization. They were developed with a preconceived notion that a prescription number has a one-to-one relationship with a drug. Compounds may have a one-to-many relationship because a compound may contain multiple APIs. This relationship prevented the appropriate electronic processing of compounds for many years.

In order to overcome these obstacles in the short term, compounding pharmacists requested manufacturers and distributors of APIs assign both an NDC number and an AWP value to their products. In addition, the pharmacist determined the only way to successfully process a multi-ingredient compound for reimbursement was to submit one ingredient per prescription number. Although this solution technically worked, it introduced two new problems:

- Drugs not included in the transaction could not be evaluated by the PBM for clinical concerns, and
- A pharmacy might not be adequately reimbursed for the cost of all ingredients in a particular compounded prescription.

The former concern could be partially overcome by a pharmacist providing adequate counseling on all ingredients plus a manual evaluation of potential drug-drug interactions or drug-disease state contraindications. However, this has considerable implications for liability since the pharmacist conducting a paper-based review may not have access to all the digital information available to a PBM.

The latter concern was often overcome simply by inflating the AWP values of APIs so that reimbursement based on an AWP calculation for one ingredient would be sufficient to provide reimbursement for the all the other lower cost ingredients in that compound.

If compounding had remained a customized solution for patients with unique needs, the workarounds described above probably would have remained viable. However, as the number of compounding prescriptions increased, it became apparent that the industry needed a better prescription processing solution to the one-to-many dilemma.

NCPDP developed and implemented a solution in 2012 as part of its updated standard set known as Telecommunications Standard Version D.0. Among other things, version D.0 allowed the on-line processing of prescriptions that contained more than one drug or API. Compounding pharmacists were now able to process and therefore bill for all ingredients in a compound. Unfortunately, there was no corresponding correction to the inflated AWP that came into use prior to D.0. This led to significant increases in the cost per compound prescription essentially overnight. This paper will examine AWP further in the section regarding Controls on Drug Compounding and make a case for reimbursement caps as a potential solution to this problem.

Evidence-based and State-specific Guidelines for Use of Compounded Medications in Workers' Compensation

A number of national and state-specific workers' compensation guidelines and regulations address the use of compounds in the injured worker population and the commentary in this paper examines only those related to workers' compensation. This is not intended as a comprehensive assessment of the practice of compounding across all patient populations.

ODG, upon which a number of state workers' compensation treatment guidelines are based, specifically states that compounds are "not recommended as a first-line therapy for pain."²⁶ In general, commercially-available, FDA-approved drugs should be given an adequate trial. If these are found to be ineffective or are contraindicated in individual patients, compound drugs that use FDA-approved ingredients may be considered." This ODG guidance and the ODG formulary have been incorporated into regulatory language in a number of states, some of which also incorporate additional guidance on compounds or reference the Reed Group's MDGuidelines.

States may place additional limits on compound use in workers' compensation, including capping reimbursement for pharmacy compounding fees, requiring prior authorization, and/or requiring documentation of medical necessity. States may also adopt the language of ODG or MDGuidelines in formularies or employ state-specific formularies, evidence-based clinical guidelines, or other tools. A comprehensive state-by-state review of workers' compensation compounding guidance is beyond the scope of this paper, however, a map and chart displaying certain limits are included in this paper. For example, Colorado caps prescription-strength compounded topical medications according to the drug class of the ingredients and²⁷ and Kansas requires prior approval from the carrier for compounds.²⁸

Review of Pharmacy Compounding Regulatory Framework and Practice Standards

The FDA and State Boards of Pharmacy increased their scrutiny of pharmacy compounding practices after the New England Compounding Center (NECC) outbreak of fungal infections in 2012-2013. The NECC tragedy was described in the previous CompPharma research paper on compounding, and a summary is not repeated in this paper. However, it is important to understand the regulatory framework and practice standards that relate to both sterile and nonsterile compounding.

From a practice-standard perspective, professional obligations for sterile compounding are outlined in USP <797> Pharmacy Compounding- Sterile Preparations;²⁹ those for nonsterile compounding are found in USP <795> Pharmacy Compounding- Nonsterile Preparations.³⁰

USP <795>- Pharmacy Compounding- Nonsterile Preparations

USP <795> defines good compounding practices for various nonsterile preparations and includes guidance on the responsibilities of the compounder, the compounding facilities and equipment, component selection and handling, stability and beyond-use-dating of nonsterile preparations, documentation requirements, training of compounding personnel and patient counseling.

Nonsterile compounding is divided into three different risk categories, each of which has different requirements for experience, training and facilities. The categories are Simple, Moderate, and Complex, depending on the complexity of the preparation, literature and compendial support for preparation and stability and type of dosage form. For example, captopril oral solution would usually be considered Simple, morphine sulfate suppositories may be considered Moderate, and preparation of transdermal or modified-release dosage forms may be considered Complex. The requirements for bulk component ingredients used in compounding are enumerated, as are requirements for equipment function and cleanliness, compounding personnel hand hygiene, and required personnel protection. Facility requirements for lighting, plumbing, ventilation, temperature, and humidity are mentioned, though not in as proscriptive a manner as USP <797>. From an ingredient perspective, compounders are encouraged to use USP, National Formulary (NF) or Food Chemicals Codex (FCC) sourced components, stored under compendial conditions and attempt to obtain them from an FDA-registered facility. If the component cannot be obtained from an FDA-registered facility, then the compounder shall use professional judgment in selecting a reliable source and require certificates of analysis to establish purity and safety. For example, American Chemical Society (ACS) grade or reagent grade chemicals do not consider whether impurities represent human or animal safety concerns.

USP <797>- Pharmacy Compounding - Sterile Preparations

USP <797> objectives more specifically describe conditions and practices to prevent harm, including death, to patients from compounding and describes minimum practice and quality standards for pharmacy compounding of sterile preparations. The standards in USP <797> are intended to apply to all persons and all places in which compounded sterile preparations (CSPs) are prepared. Not limited to pharmacies, these include other healthcare facilities, physician offices and hospital nuclear medicine departments.

USP <797> defines risk levels for compounding, compounding personnel responsibilities including training and competency assessment, types of compounded sterile preparations, environmental quality and control, suggested SOPs, final preparation release checks, facility requirements, maintaining sterility and purity, adverse or patient event reporting, patient and caregiver training, among others. A large portion of USP 797 defines the physical and facility requirements and the competency and training requirements involved in compounding. Risk levels are defined in terms of low-, medium- and high-risk CSPs, as well as immediate use CSPs, depending on the complexity, compounding environment, type of ingredients and testing.

The type of engineering controls, including laminar flow hoods, biological safety cabinets and aseptic compounding isolators are described, along with the ISO classifications for each and for the room in which the engineering control is placed. Personnel requirements for hand hygiene, garbing, aseptic technique validation and training are described in detail. Facility design elements to facilitate cleaning and disinfection are outlined, as are the expectations for cleaning and documentation. Environmental sampling and other quality assurance testing expectations are documented, including expectations for specific types of equipment and requirements for sterility testing and establishment of beyond-use dating. Sample appendices in the USP <797> chapter may be useful for developing SOPs. These include sample forms for assessing hand hygiene and garbing, as well as cleaning and disinfection.

State Boards of Pharmacy

In most cases, the practice of pharmacy compounding is regulated by the board of pharmacy in the licensure state(s). Traditionally, state boards have recognized the right to compound by a pharmacist (or physician, depending on the state) for a specific patient upon a prescription from the prescriber who has a relationship with the patient. Note: The FDA definitions and regulation of compounding are discussed in a different section of this paper.

State boards of pharmacy have adopted USP <797> language for sterile compounding either by direct reference or indirectly through incorporation into state-specific requirements for sterile compounding. Although an in-depth review of each state is beyond the scope of this paper, Critical Point, a provider for pharmacy continuing education and resources for sterile compounding, includes a comprehensive map³¹ of state board of pharmacy adoption of USP <797>. As of August 8, 2016, 28 states reference USP <797> directly and 21 indirectly. Pennsylvania does not currently have language related to sterile compounding and USP <797>.

Following the NECC compounding catastrophe, many state boards of pharmacy conducted surveys to assess which pharmacies within their states were performing sterile and nonsterile compounding. Some state boards require different types of licenses and different types of inspections for pharmacies that perform sterile compounding. Some state boards have specific continuing education requirements for sterile compounding, as well.

To facilitate state board of pharmacy adoption of USP <797> and inspection of pharmacies, the National Association of Boards of Pharmacy (NABP) has adopted Model Pharmacy Act and Model Rules³² language that references USP <795> and <797>, as well as a uniform inspection form that incorporates the requirements specified in those chapters. The uniform inspection document is designed to help state boards of pharmacy crosswalk their existing inspection forms against the USP 797 and 795 standards, as well as the Verified Pharmacy Program standards and identify any gaps. The use of this “Multi-state Model Inspection Blueprint”³³ is expected to gain traction as more states standardize regulations and as the NABP advisory committee gains experience with its use. Because many states require current inspections to be on file for out-of-state pharmacies that ship compounds into a state, the NABP has also created a “Verified Pharmacy Program” that facilitates recordkeeping and inspection requirements.

Food and Drug Administration Regulation of Compounding

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.³⁴ 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 deleting the unconstitutional provisions, the new law removes uncertainty regarding the validity of section 503A, which is applicable to compounders nationwide. Generally, state boards of pharmacy continue to have primary responsibility for the day-to-day oversight of state-licensed pharmacies that compound drugs in accordance with the conditions of Section 503A of the FDCA, although FDA retains some authority over their operations. However, outsourcing facilities that register under section 503B are regulated by FDA and must comply with CGMP requirements and will be inspected by FDA according to a risk-based schedule.

503(A) Pharmacy Compounding of Human Drug Products

In July 2014, the FDA issued a guidance document, “Pharmacy Compounding of Human Drug Products” under Section 503A of the Federal Food, Drug and Cosmetic Act (FDCA).³⁵ This guidance document outlines several requirements, including:

- Compounding for an identified individual patient, based on the receipt of a valid prescription order, or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient.
- The compounding is performed by a licensed pharmacist in a state licensed pharmacy or Federal facility or by a licensed physician on the prescription order for an individual patient made by a licensed practitioner authorized by state law to prescribe drugs. The provision also specifies limited quantities may be prepared before the receipt of the prescription based on history of compounding and based upon an established relationship between the physician, patient and pharmacy.
- The requirement that the drug product is compounded in compliance with USP <797> or <795> using bulk drug substances, as defined in 21 CFR 207.3(a)(4), that comply with standards of an applicable USP or National Formulary (NF) monograph if one exists, or be a component of an FDA-approved human drug product if the monograph does not exist and be listed on a list of bulk drug substances for use in compounding developed by the FDA.
- Use of bulk drug substances that are manufactured by an establishment registered with the FDA
- Bulk drug substances must have a valid certificate of analysis for each bulk drug substance.
- Ingredients that are not bulk drug substances must comply with the standards of USP or NF monographs and with USP chapters on pharmacy compounding.
- The drug product does not appear on the list in 21 CFR 216.24 of products removed from the market and deemed unsafe or not effective.
- The pharmacist or physician does not compound regularly in inordinate amounts that are essentially copies of commercially available drug products (allows compounding in shortage situations).
- The drug product is not identified as one that is demonstrably difficult to compound or that demonstrates adverse effect on safety or effectiveness of the drug product.
- The state has entered into an memorandum of understanding (MOU) with the FDA to address distribution of compounds, as well as investigation into complaints; if an MOU is not on file, then not more than 5% of total prescription orders dispensed or distributed by a pharmacy can be compounded under this section.

The guidance document also describes enforcement actions when sections of 503(A) are not met, including definitions for producing adulterated, misbranded or unapproved new drugs.

DQSA- 503B Outsourcing Facilities

The Drug Quality and Security Act also created a new section 503B in the FDCA under which a compounder can become an “outsourcing facility.” The law defines an “outsourcing facility” as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of section 503B. Repackaging or compounding of nonsterile drugs does not fall within this definition of an outsourcing facility.

An outsourcing facility can qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from current 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 a compounding facility does not register with FDA as an outsourcing facility, it will not qualify for the section 503B exemption from the FDA approval requirements and the requirement to label products with adequate directions for use. If that compounding facility also fails to satisfy the conditions for the section 503A exemption, it will be subject to all of the requirements of the FDCA that are applicable to drugs made by conventional manufacturers, including the new drug approval, adequate directions for use, and CGMP requirements.

On August 12, 2015, the FDA issued a guidance document for facilities that are considering whether to register as outsourcing facilities.³⁶ (Similar documents^{37, 38} outline requirements to register as outsourcers and a draft guidance document outlines current good manufacturing requirements for outsourcers.)

According to this guidance document, an outsourcing facility is not required to be a licensed pharmacy and may or may not obtain individual patient prescriptions. Outsourcing facilities are subject to current CGMPs and are inspected based on those requirements. Inspections will be conducted according to a risk-basis established by the FDA. The August 2015 guidance document defines specific situations that exempt outsourcers from the drug approval requirements in section 505 of the FD&C Act (21 U.S.C. 355), the requirement for products to be labeled with adequate directions for use in section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)), and the track and trace requirements in section 582 of the FD&C Act (21 U.S.C. 360eee-1). However to qualify, a number of conditions outlined in the guidance document must be met.

As of November 2016, there were 65 registered outsourcing facilities listed on the FDA website, with FDA Form 483s cited (inspection findings document) for almost 80% of those listed.³⁹

Pharmacy Compounding Accreditation

There are a number of ways for pharmacies to become accredited providers of compounding services. The process of accreditation demonstrates a pharmacy's adherence to quality standards and written SOPs as well as to training and competency testing of compounding personnel. Accreditation, which can encompass compounding of sterile or nonsterile pharmaceutical products, generally involves a specific review of adherence to standards found in USP <797> Pharmaceutical Compounding – Sterile Preparations and USP <795> Pharmacy Compounding - Nonsterile Preparations along with requirements of the accrediting organization's standards.

A review of pharmacy compounding accreditation options follows and Appendix A contains the websites of relevant accreditation organizations. Payers and providers are encouraged to understand whether a compounding pharmacy is accredited and to determine if there are any unfavorable state board of pharmacy or FDA inspection findings against the pharmacy.

ACHC Pharmacy Accreditation

Pharmacy Compounding Accreditation Board (PCAB) is a service of Accreditation Commission for Health Care (ACHC), a nonprofit accreditation organization. ACHC administers PCAB accreditation for non-sterile and sterile pharmacy compounding pursuant to a prescription from a physician for an individually identified patient. PCAB accreditation assesses the compounding process based on a specific set of standards that concentrate on the quality and consistency of medications produced.

ACHC's accreditation process includes a site survey of compounding practices conducted by an ACHC surveyor, who is a licensed pharmacist, as well as a complete review of SOPs developed according to USP 797 and 795 standards, as well as those required by PCAB. ACHC also accredits infusion pharmacy (IRX), Ambulatory Infusion Centers (AIC), Specialty Pharmacy (SRX), Infusion Nursing (IRN), Community Retail Pharmacy (CR), Long Term Care Pharmacy (LTC), with specific standards for each site survey and SOP review. ACHC also may be contracted by boards of pharmacy to conduct out-of-state pharmacy inspections of pharmacies that compound and ship sterile pharmaceuticals into the state.

United Compounding Credentialing and Accreditation Program (UCAP)

The National Association of Boards of Pharmacy (NABP) administers the United Compounding Credentialing and Accreditation program for Focus Script, formerly United Compounding Management. This accreditation program includes a review of business practices, attestation to a code of conduct, and compounding-specific requirements, including adherence to USP <797> and <795> requirements. By undergoing UCAP accreditation, compounding pharmacies can meet regulatory inspection requirements for nonresident licensure in several states.

Other Accreditation Options

The Joint Commission (TJC) accredits a number of healthcare entities, including ambulatory health, laboratories, hospitals, and home care. While TJC is not specifically focused on pharmacy accreditation, pharmacies offering infusion or specialty services may choose to pursue this accreditation route.

The Center for Pharmacy Practice Accreditation (CPPA) accredits community and specialty pharmacies for patient care services. Although not specific to compounding services, its accreditation process focuses on clinical pharmacist services that improve patient outcomes. The quality management survey process includes a Continuous Quality Improvement (CQI) review, including quality and safety procedures and processes for adherence to USP <797> and <795>.

URAC also accredits community pharmacies and other pharmacy practices, but does not focus on pharmacy compounding as part of the review and survey process. URAC accredits a variety of healthcare entities that provide utilization review and healthcare services, including health plans, PBMs, mail service pharmacies, and pharmacy quality management programs. In general, URAC accreditation focuses on patient-centered activities and health and quality outcomes.

Compounding Kits

The use of compounding kits, sometimes called FDA Convenience Kits, continues to increase, perhaps to avoid compounding controls imposed by states and PBMs. Convenience packs or CoPacks contain a combination of active and inactive ingredients that are intended to be mixed at the pharmacy or prescriber's office to compound a final product. These convenience kits may be intended for either sterile or non-sterile compounds.

Compounding kits contain pre-weighed amounts of the bulk substance active pharmacy ingredient (API) and excipient or base and some include the compounding supplies (stirrer, vessel, etc.) needed to prepare the drug along with directions for mixing. The majority are not FDA approved.

Although the kits contain multiple ingredients, they are not identified as compounds at the point of sale because they are packaged together as a unit of dose and have a single NDC number. Typically, the topical ingredient kits are intended for use in the workers' compensation population, with various proposed indications and may contain ingredients such as analgesics, muscle relaxants, steroids, anti-inflammatories, or other drugs. Examples include Enova-Rx lidocaine HCl 5% or 10% or Enova-RX baclofen 1% cream.

Some compounding kits are marketed to compounding pharmacies as a convenience to the staff to save time, decrease waste and improve compliance, reproducibility and accuracy. These are intended to be used to prepare a compound for a specific patient upon receipt of a prescription from that patient's physician.⁴⁰

Other kits seem to be directed more toward physician dispensers and describe use at the point-of-care by a licensed professional.⁴¹ Some directions clearly state that the kit is intended for use in compounding and not intended as the final dosage form, while others are less clear and reference point-of-care dispensing.

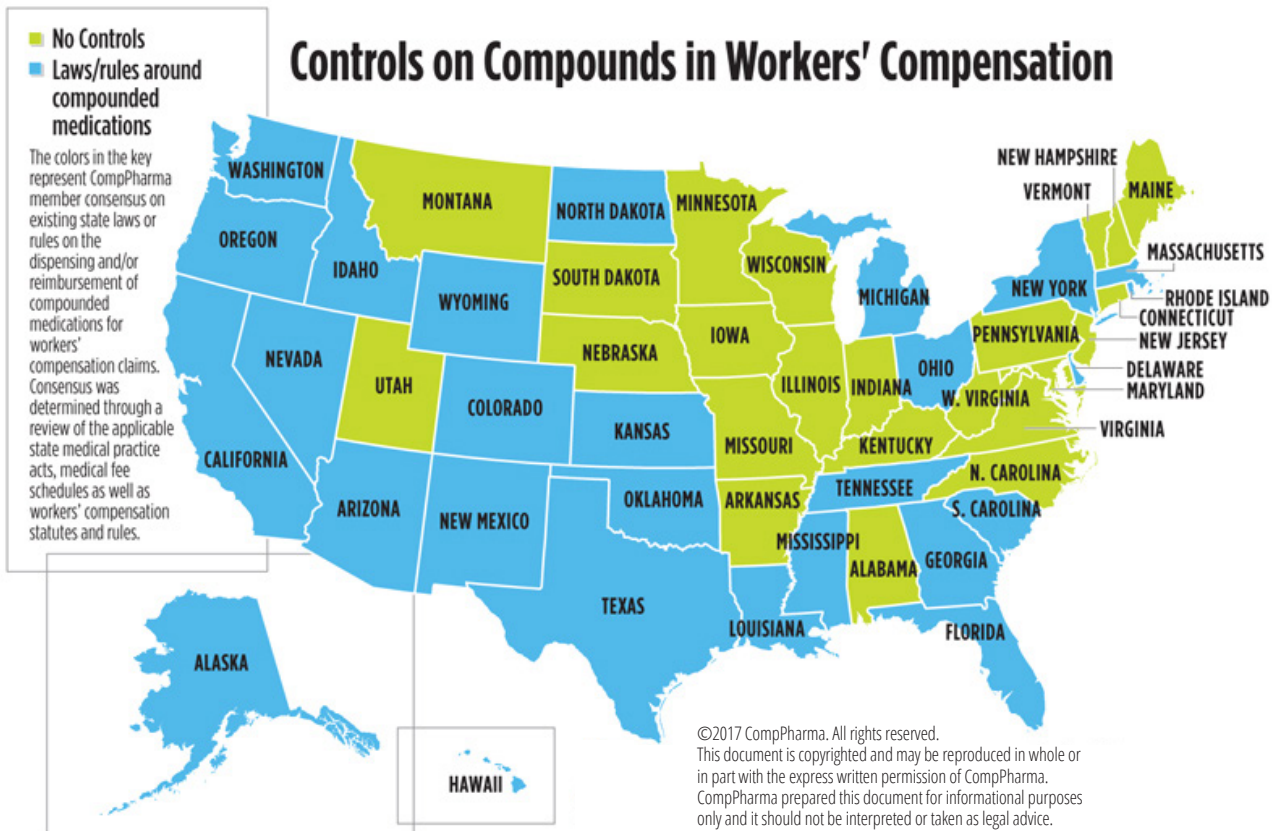
Compound kits may be difficult to identify as some products may have only the name of the ingredients such as Ibuprofen, Cyclobenzaprine or DexLido in the kit name.

In addition to lack of evidence for use of many of these kits, the AWP ranges from ~\$600 to more than \$1,700. Typically, the dispensing pharmacy submits these products for processing through the PBM using a single-ingredient NDC, rather than as a compound. This may bypass the requirements of PBMs and many states to review compounds for appropriateness. Physician use of compound kits likewise bypasses compound and other safety edits in place at the pharmacy.

Review of workers' compensation PBMs' data reveals patterns of geographic usage of topical compound kits among physicians and pharmacies. This, along with their high costs, calls into question the necessity and appropriateness of these kits. In fact, First Data Bank removed a subset of unapproved compounding kits from the MedKnowledge database, effective the week of June 8, 2015, citing concerns with safety, efficacy and concerns for marketing outside any FDA-sanctioned pathway.⁴²

Controls on Drug Compounding

Only half the states have any type of controls in place with regard to workers' compensation drug compounding and pricing. Of those, the vast majority still tie reimbursement to AWP. As stated previously, the AWP for APIs is significantly inflated, rendering these controls ineffective. CompPharma encourages state policymakers to model their statutes or regulations after those states that cap the reimbursement at a reasonable level, such as Colorado, Ohio and Michigan.



States that have some rules and regulations governing the use of and/or reimbursement of compounded prescriptions are shown in blue.

As the cost and utilization of compounded medications to treat workers' compensation injuries began to spiral upward in many jurisdictions, several states looked to novel ideas for controlling reimbursement and utilization without blocking those treatments that were medically necessary. Reimbursement tools focused on transparency in the billing process, e.g., identifying the individual component ingredients and, at a minimum, pricing at that level and/or capping the total cost of a single compound. The latter addressed inflated ingredient reimbursement values and the incentive for providers to include more ingredients to increase reimbursement.

Utilization-related tools, including prior-authorization, prospective review and proof of medical necessity, acted as front-line or pre-dispense controls, which put the prescribing practitioner under focus. These tools work to control the usage of compounded medications at the source. They are not focused on costs, they require the prescriber to justify the usage, and they provide logical safety checks to ensure the injured worker is receiving the right treatment at the right time.

Some states enacted regulations or statutes that require prior authorization for all compounds prior to dispensing. These requirements often drive communication between the payer and the prescriber as to why the compound is truly necessary. One such example is found in the implementation of the closed formulary in Tennessee. All compounds under the formulary require prior approval. If the adjuster should object, the determination of medical necessity would require prospective utilization review (UR), which would engage the physician in justifying the use of a compound.

Other states require prescribing physicians to use evidence-based medicine to clearly justify the medical need for a compound over a similar non-compounded or commercially available medication. For example, Florida regulations clearly state that compounds should only be permitted when the prescribed formulation is not commercially available. Policymakers in states with requirements for prior-authorization, justification of medical necessity and prospective UR hope that these up-front checks will cause prescribers to move away from using compounds as their medical necessity remains questionable.

Workers' Compensation Rules Addressing Compounds

State	Rules
AK	Compounds "shall be limited to medical necessity" and reimbursed at manufacturer's AWP for each drug included in the compound (listed separately by NDC) plus a \$10 compounding fee
AZ	Bill for compounds shall include NDC for each underlying ingredient used and reimbursement based upon AWP of underlying drug.
CA	Compounds billed using NDC of each ingredient (ingredients w/no NDC not separately reimbursable). Physician-dispensed compounds reimbursed based on a mark-up of documented paid cost.
CO	Reimbursement for prescription compounds categorized per 4 state-specific DoWC "Z" codes (Z0790 through Z0793) by 30-day supply (fees represent max reimbursable amount, inclusive of time, shipping, etc.) and all compound ingredients must be listed by quantity used. If state treatment guidelines approve some but not all of the active ingredients for a particular diagnosis, insurer shall count only number of approved ingredients to determine applicable category. Automatic refilling not allowed. Over-the-counter topicals (muscle relaxants, analgesics, etc.) are limited to \$30 for a 30-day supply.
DE	Compounds billed by listing each drug included in compound and separately calculating charge for each drug, using NDC. A single compounding fee of \$10 per prescription added to calculated total.

FL	Compounding permitted when prescribed formulation not commercially available. Compound billed under NDC of each individual ingredient. Reimbursement is lessor of contract or AWP of each ingredient plus a \$4.18 dispensing fee.
GA	Compounds shall be reimbursed at sum of AWP for each active ingredient, minus 50%, plus a single \$20 compounding fee. Reimbursement shall only be considered for preparations that contain not more than three FDA active ingredient(s).
HI	Reimbursed by gram weight of each AWP of the underlying drug set by the original manufacturer.
ID	Reimbursed at sum of AWP of each drug included plus \$5 dispensing fee and \$2 compounding fee. All components of compounds require NDC of original manufacturer. Components without NDCs may require medical necessity confirmation by treating physician prior to reimbursement.
KS	Reimbursed same as pharmacy fee schedule - based on original manufacturer NDC - and require prior approval of employer/carrier.
LA	Reimbursed utilizing same reimbursement formula as generics.
MA	Reimbursed similar to non-compounded drugs, but additional dispense fee amounts depending on type of ingredients.
MI	Reimbursed based upon original manufacturer's NDC. Topical compounds billed using specific amount of each component drug and original manufacturer's NDC. Components w/out NDCs not reimbursed. Single dispense fee for non-sterile compound = \$12.50. Reimbursement limited to a max of \$600. Additional reimbursement eligibility standards adopted for topical compounds, including (among others), that there is no readily available commercially manufactured product and the prescriber is able to demonstrate to the payer that the compound is clinically appropriate for the intended use.
MS	Reimbursed at sum of AWP of each underlying NDC drug product plus single \$5 dispense fee. Bills must include each individual drug and NDC. Compound creams limited to max of \$300 for a quantity of 120 grams per month (any additional quantity requires further documentation and prior-authorization).
ND	WSI has specific reimbursement (including a compounding fee based on level of effort), quantity and product restrictions and limitations.
NM	Compounds reimbursed at ingredient level (based on manufacturer's AWP), w/ each ingredient identified using NDC and quantity and bills must include NDC of original manufacturer.
NV	All bills for compounds shall list each ingredient at the ingredient level and, where applicable, include a valid NDC. Insurer and dispensing provider shall agree upon the quantity as well as the reimbursement for a compound before dispensed. Insurer not required to reimburse any compound ingredient which lacks a valid NDC. Prior authorization required for compounds, request for which must include prescriber's justification of medical necessity and efficacy.
NY	Compounds reimbursed at ingredient level, with each ingredient identified using NDC and corresponding quantity. Payment based on sum of allowable fee for each ingredient plus a single dispense fee per compound. Ingredients lacking an NDC are not reimbursable.
OH	Reimbursed based on ingredient NDCs (no reimbursement for ingredients w/no NDC), and maximum product cost component reimbursement for any 1 compounded Rx = \$400. Separate dispense fees depending on if compound is sterile or non-sterile. Bureau of Workers' Compensation (for state fund claims) may approve reimbursement for a non-sterile compound for topical use only after the injured worker has been prescribed and tried for at least 30 days, a commercially available topical prescription or OTC with documentation that intended therapeutic benefit was not achieved or an unacceptable adverse event or allergic reaction occurred.

OK	Bills require listing each ingredient, corresponding NDC and quantity and reimbursed at sum of allowable fee for each ingredient plus single \$5 dispense fee per Rx (ingredients w/o NDC not reimbursed). State formulary requires preauthorization for compounds.
OR	Compounds must be billed by ingredient, listing each ingredient's NDC (ingredients w/o NDC not reimbursable). Max fee for compound = AWP minus 16.5% for each individual ingredient plus a single \$10 compounding fee (compounding fee includes the dispense fee).
RI	Reimbursement for compounds is based upon sum of each individual ingredient at existing pharmacy fee schedule. Any ingredient lacking a valid and recognized NDC shall not be reimbursed; in no instances should reimbursement for topical compounds exceed \$500 per prescription (\$500 fee provides 30-day supply). All compounds shall be billed on a single bill at ingredient level with a separate line item for each ingredient, corresponding quantity and charge amount. Any ingredient in a topical compound shall be FDA-approved for topical use in order to be reimbursable.
SC	Billed by listing each ingredient NDC and reimbursed at sum of each NDC's amount plus a single \$5 dispense fee for compound. No payment required for ingredient w/no NDC.
TN	Compounding fee not to exceed \$25 per compound may be charged if two or more prescriptive drugs require compound preparation when sold by a hospital, pharmacy or provider of service other than physician. All bills must include NDC of original manufacturer registered w/ FDA or its authorized distributor's stock package used in compounding. State formulary requires prior approval for compounds.
TX	Billed by listing each drug included and calculating charge for each drug separately plus a \$15 compounding fee. State formulary requires preauthorization for compounds containing ODG-designated "N" drugs.
WA	Reimbursed at cost of ingredients plus \$4.50 professional fee plus \$4 compounding time fee (per 15 minutes). Must be billed with NDC for each ingredient. Requires prior-authorization.
WY	Paid per fee schedule and reimbursed per line item if each ingredient is determined to be coverable. Division allows a professional fee for compounding services. Physicians billing for compounds must provide pharmacy invoice, and the Division pays 130% of the supplier's/ manufacturer's invoice price.

Chart cites states' workers' compensation rules and regulations for compounded medications. States may also have adopted treatment guidelines that discuss compound utilization in greater detail.

Summary and Recommendations

In CompPharma's 2014 research paper "Compounding is Confounding Workers' Compensation," the authors made several distinct recommendations for claims professionals to consider when confronted with an authorization request for a prescription compound. These recommendations included:

- Approval should be limited to those situations with a unique patient-specific requirement, e.g., documented allergy or inability to swallow.
- Obtain a letter of medical necessity to obtain proof that conventional therapy has been tried and failed.
- Request evidence of effectiveness and safety for topical compounds, such as an article published in a peer-reviewed medical journal with a randomized controlled trial that demonstrates effectiveness.
- Avoid approval of topical compounds that contain multiple active ingredients.
- In the absence of FDA approval or satisfactory evidence of effectiveness and safety, require a signed informed consent by the patient if a decision is made to authorize the compounded medication.

The authors of this paper stand by these recommendations.

We also support pharmaceutical compounding in modern medicine when it is restricted to patients with specific needs not served by a commercial product, is used for the preparation of certain radioactive pharmaceuticals or is used in situations where a manufacturer cannot possibly provide the medication in a timely manner. However, when FDA-approved medications for the condition are available, the widespread use of topical, non-sterile compounding or sterile compounding cannot be justified. There have been numerous instances of patient harm and death linked directly to compounded prescription products, and there is a lack of evidence-based data or stability data to support the use of multi-ingredient compounds.

Aside from the workers' compensation PBM efforts to educate their clients regarding the risks associated with compounding and to provide strategies to mitigate these risks, the unnecessary and over-prescribing of compounds continued largely unabated until both the excessive expense and overutilization of compounding was recognized by other payers, including TRICARE, Medicare, and Medicaid. Investigation into the compounding issues facing these payers led to allegations of healthcare fraud, ultimately leading to scrutiny from both the DOJ and GAO for reasons related to excessive use, prohibitive costs and violations of the Stark Act. As a result, numerous healthcare providers, including pharmacists, physicians and others, have been prosecuted for various schemes to defraud, which have included:

- Mislabeling prescriptions
- Collusion between pharmacists and prescribers to illegally distribute controlled substances via a compounded drug
- Fraudulent reimbursement claims for prescription compounds
- Illegal kickbacks and bribes to generate prescriptions that were not based on legitimate provider/patient relationships
- Misuse of patient information
- Money laundering
- Other schemes including excessive charges.

One of the goals of this paper was to alert providers to the risks involved in prescribing compounds despite the lure of significant profits. The details in the Cases Against Providers section should serve as a warning to conduct one's own due diligence before prescribing any drug product.

In the second half of this paper, we encourage insurance professionals and policymakers alike to become educated in the complexities of pharmaceutical pricing especially as it relates to compounds, and we offer these recommendations:

- Payers should work with a PBM to develop a strategy to identify all compounds, including those masquerading as a traditional pharmaceutical or compounding kit.
- Payers should utilize a formulary or other clinical tool(s) in conjunction with PBMs to make sure that a compound cannot be processed without receiving oversight and due diligence.
- Policymakers should examine any applicable workers' compensation state fee schedules to eliminate any loopholes that might exist for compounds and implement such controls as:
 - Requiring individual ingredient billing data.
 - Not allowing reimbursement for components that lack an NDC.
 - Capping reimbursement for topical compounds.
 - Requiring pre-authorization or medical justification for all topical compounds.
- Policymakers in states that are implementing a state-mandated formulary should consider making all compounds non-formulary and allow for authorization only if the exceptions identified in the 2014 paper, and outlined above, are met.

Lastly, we encourage pharmacy providers actively engaged in the practice of compounding to become an accredited provider so that in those appropriate instances when a compound should be authorized the patient, prescriber and payer alike will be able to evaluate your services in relation to your peers.



CompPharma, LLC is a consortium of pharmacy benefit management (PBM) firms that provide services for the workers' compensation marketplace. CompPharma gives member PBMs a platform for researching solutions to issues that affect the entire workers' compensation industry, including quality pharmacy care, technology for protecting patient safety and reducing administrative costs, uniform national standardization formats and advocacy for positive change. CompPharma's member PBMs are:

*Coventry Workers' Comp Services' First Script
Express Scripts
Mitchell Pharmacy Solutions
myMatrixx
OptumRx*

Please direct inquiries to hpatterson@comp-pharma.com or jpaduda@comp-pharma.com, 813-690-4787

Appendix A: Accreditation

Pharmacy Compounding Accreditation Web Sites

Accreditation Commission for Health Care (ACHC) <http://achc.org/pcab>

United Compounding Credentialing and Accreditation Program (UCAP)

UCM website, <http://www.focusscript.com/pharmacy-locator/>,

<http://www.focusscript.com/pharmacy-locator/>

The Joint Commission www.jointcommission.org/accreditation/home_care.aspx

The Center for Pharmacy Practice Accreditation (CPPA) www.pharmacypracticeaccredit.org/our-programs/community-pharmacy-practice-accreditation-program/standards

URAC <https://www.urac.org/accreditation-and-measurement/accreditation-programs/all-programs/community-pharmacy/>

Related Resources

ACHC Inspection Services (AIS)

<http://www.aisinspections.org/assets/ais-policies-and-procedures.pdf>

Policies & Procedures, Sterile Compounding Inspection AIS website, www.aisinspections.org/assets/506-florida-state-board-of-pharmacy-policies-and-procedures.pdf, accessed 9/6/2015.

American Pharmacists Association, "Pharmacy Compounding Accreditation: A How-To Manual." 2007.

Appendix B: FDA Warning Letters

Warning Letter to Custom Scripts Pharmacy (Tampa, FL)

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076194.htm>

WARNING LETTER FLA-07-05

December 4, 2006

James G. Castillo, President
Tiberius Inc.
Custom Scripts Pharmacy
4600 North Habana Ave., Suite 16A
Tampa, Florida 33614

Dear Mr. Castillo:

On April 21, 2005, investigators from the U.S. Department Food and Drug Administration (FDA) and Florida of Health, Division of Medical Quality Assurance, inspected Custom Scripts Pharmacy, 4600 North Habana Ave., Suite 16A, Tampa, Florida. This inspection revealed that your firm compounds a drug product called Betacaine LA ointment, which contains 15% fido-caine, 5% prilocaine, and phenylephrine, and a similar drug called Betacaine Plus ointment, which contains 15% lidocaine and 5% prilocaine. The inspection also revealed that your firm offers to compound polidocanol and dinitrochlorobenzene (DNCB).

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective;" is supported by substantial judicial authority. See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"); *Prof'l's & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 n.3 (5th Cir. 1995) (the FDCA does not expressly exempt pharmacies or compounded drugs from its new drug provisions); *In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd*, *Wedgewood Village Pharmacy v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.

The drugs that pharmacists compound are not FDA-approved and lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. See *Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA actions historically has not taken enforcement against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (see Notice of Availability, 67 Fed. Reg. 39,409 (June 7, 2002)).¹ The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. They further address compounding practices that result in significant violations of the new

drug, adulteration, or misbranding provisions of the FDCA. These factors include considering whether a firm compounds finished drugs from bulk active ingredients that are not components of FDA-approved drugs, without an FDA sanctioned investigational new drug application (IND). The factors in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

1. Betacaine Ointments

Like a manufacturer, you have developed a standardized line of topical anesthetic drug products called Betacaine LA and Betacaine Plus. Moreover, you have patented the formulation for both Betacaine LA and Betacaine Plus. These actions are not consistent with the traditional practice of pharmacy compounding, in which pharmacists have extemporaneously compounded reasonable quantities of drugs upon receipt of valid prescriptions from licensed practitioners to meet the unique medical needs of individual patients.

Moreover, the agency is concerned with the public health risks associated with the compounding of Betacaine ointments. There have been at least two non-fatal reactions and two deaths attributed to the use of compounded topical local anesthetic creams containing high doses of local anesthetics. Local anesthetics, like your firm's Betacaine ointments, may be toxic at high dosages, and this toxicity can be additive. Further, there is a narrow difference between the optimal therapeutic doses of these products and the doses at which they become toxic, i.e. they have low therapeutic index.

Adverse events consistent with high systemic exposures to these products include seizures and cardiac arrhythmias. The risk of systemic toxicity with pre-existing is greatest in small children and in patients heart disease. Factors that may increase systemic exposure are the time and surface area of exposure, particularly when the area of application is covered by an occlusive dressing. Prilocaine has an additional toxicity not seen with lidocaine. This toxicity, which is known as methemoglobinemia, is an acquired decrease in the oxygen-carrying capacity of the red blood cells. It is related to the use of large doses of prilocaine. Further, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations of local anesthetics because of their inability to metabolize them. Phenylephrine is a vasoconstrictor agent that can cause serious adverse events related to hypertension and vasoconstriction at the significant dose present in your firm's Betacaine LA ointment.

Your sheet entitled "The Recommended Procedures for Usage of Lidocaine Compounds" does not identify the risks that can reasonably be anticipated with the use of prescription preparations containing lidocaine and/or prilocaine. The sheet states "Apply the ointment to intact skin only. Once the skin surface is removed, do not apply." This sentence is not clear as there is no warning to the patient that the product should not be applied over raw surfaces or blistered areas. Further, when using a topical local anesthetic, patients should be made aware that the production of dermal analgesia may be accompanied by the block of all sensations in the treated skin. For this reason, the patient should avoid inadvertent trauma to the treated area by scratching, rubbing or extreme hot or cold temperatures until full sensation has returned. Also, no warning is given that this product should only be applied externally. Even though the sheet states that "due to possible side effects and allergic reactions, apply in the physician's office if possible or have someone with you at all times. Do not drive or operate heavy machinery," it does not state what should be done if an allergic reaction is suspected. The sheet also does not contain any warnings regarding the use of the product in certain special populations such as the elderly.

The Betacaine LA and Betacaine Plus ointments compounded by your firm are drugs within the meaning of section 201(g)(1) of the FDCA (21 U.S.C § 321(g)(1)). These products are misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. These products are not exempt from this requirement under 21 CFR § 201.115 because they are new drugs within the meaning of section 201(p) of the FDCA (21 U.S.C. § 321(p)) that lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

The Betacaine LA and Betacaine Plus ointments compounded by your firm are also misbranded within the meaning of section 502(a) of the FDCA (21 U.S.C. § 352(a)) because their labeling is false and misleading in that they fail to reveal facts material with respects to the consequences that may result from the use of the article under such conditions of use described in their labeling.

2. Polidocanol and DNCB

Your firm's promotional materials indicate that it also offers to compound polidocanol for sclerotherapy and DNCB for treatment of warts. Polidocanol and DNCB are not active ingredients contained in any FDA-approved drug product. FDA does not sanction their use in pharmacy compounding and will not exercise its enforcement discretion for compounded products containing polidocanol or DNCB.

The agency is seriously concerned about the public health risks associated with the compounding of polidocanol injection. Known adverse events include deep venous thromboses, necrosis, and ulceration at the treated site. Reversible cardiac arrest after polidocanol sclerotherapy has been reported. DNCB is highly toxic and may be fatal if inhaled, swallowed, or absorbed through skin. High concentrations of DNCB are also extremely destructive to tissues of the mucous membranes and upper respiratory tract, eyes, and skin.

If your firm is compounding products containing polidocanol or DNCB, then those products would be drugs within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). Those products would be misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling would fail to bear adequate directions for their use. Further, the products would not be exempt from this requirement under 21 CFR § 201.115, because they would be new drugs within the meaning of section 201(p) of the FDCA (21 U.S.C. § 321(p)) which lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

Finally, please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited. Under section 301(d) of the FDCA (21 U.S.C. § 331(d)), the introduction or delivery for introduction into interstate commerce of a new drug that under has not been approved section 505 is also prohibited.

The above violations regarding topical anesthetics, polidocanol, and DNCB are not intended to be an all-inclusive list of deficiencies. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice. These actions include, but are not limited to, seizure of your products or injunction against you or your firm. Federal agencies are routinely advised of the issuance of warning letters so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter, of any steps you will take to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, please state the reason for the delay and the time frame within which the correction will be completed.

You should address your reply to this letter to the U.S. Food and Drug Administration, Florida District Office, 555 Winderley Place, Suite 200, Maitland, FL 32751. Attn: Compliance Branch. If you have any further questions, please feel free to contact our Director of Compliance, Jimmy E. Walthall at (407) 475-4734.

Sincerely,

/S/

Emma R. Singleton
Director, Florida District

Public Health Service, Food and Drug Administration
555 Winderley Pl., Ste. 200
Maitland, FL 32751

1. Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Supreme Court's ruling in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), that Section 503A included unconstitutional restrictions on commercial speech. And those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

Warning Letter to Hal's Compounding Pharmacy, Inc. (San Diego, CA)

<http://wayback.archive-it.org/7993/20161023104720/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076195.htm>

WARNING LETTER

DEC 4 2006

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

Mr. Harold Keller
Hal's Compounding Pharmacy, Inc.
3825 32nd Street
San Diego, CA 92104

Dear Mr. Keller:

On January 24, 2005, investigators from the U.S. Food and Drug Administration (FDA) began an inspection of your firm, located at 3825 32nd Street, San Diego, California. On March 3, 2005, the investigators completed the inspection. This inspection revealed that your firm compounds human prescription drugs in various dosage forms and strengths.

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective," is supported by substantial judicial authority. See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"); *Prof'l's & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 n.3 (5th Cir. 1995) (the FDCA does not expressly exempt pharmacies or compounded drugs from its new drug provisions); *In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd*, *Wedgewood Village Pharmacy v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.

The drugs that pharmacists compound are not FDA-approved and lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. See *Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (see Notice of Availability, 67 Fed. Reg. 39,409 (June 7, 2002)).¹ The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. These factors include considering whether a firm compounds

drugs that are copies or essentially copies of commercially available FDA-approved drug products without an FDA sanctioned investigational new drug application (IND). The factors in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

1. Topical Anesthetics

During the inspection, FDA investigators documented that your firm compounds and distributes several products that contain high concentrations of lidocaine and/or tetracaine, alone or in combination with other active ingredients (such as prilocaine and benzocaine). These products include: Anesthetic Skin Lotion (lidocaine 10%, prilocaine 2%); Tetracaine 6% in DMSO Gel; and Triple Kwick Anesthetic Gel (benzocaine, lidocaine, and tetracaine). We also note that your firm offers to compound N*E*W* topical anesthetic (lidocaine 30%, prilocaine 2%, tetracaine 4%); Kwick Anesthetic Gel (benzocaine, lidocaine, tetracaine, DMSO); Lidocaine and Tetracaine Demi Gel; and Anesthetic Skin Gel 3+ (lidocaine, prilocaine, tetracaine). Like a manufacturer, you have developed a standardized line of anesthetic drug products, extolling their effectiveness for all patients. This action is not consistent with the traditional practice of pharmacy compounding, in which pharmacists extemporaneously compound reasonable quantities of drugs upon receipt of valid prescriptions from licensed practitioners to meet the unique medical needs of individual patients. Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Supreme Court's ruling in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), that Section 503A included unconstitutional restrictions on commercial speech. And those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

Moreover, the agency is concerned with the public health risks associated with the compounding and sale of products that contain high doses of lidocaine and/or tetracaine. There have been at least two non-fatal reactions and two deaths attributed to the use of compounded topical local anesthetic creams containing high doses of local anesthetics. Local anesthetics may be toxic at high doses, and this toxicity can be additive. Further, there is a narrow difference between the optimal therapeutic dose of these products and the doses at which they become toxic, i.e., they have low therapeutic index.

Adverse events consistent with high systemic exposures to these products include seizures and cardiac arrhythmias. Specifically, risk of systemic adverse events from tetracaine products includes (1) a systemic allergic response to p-aminobenzoic acid (PABA) which, at worst, could lead to cardiac arrest; or (2) excessive systemic absorption following repetitive or extensive application, especially for 4 and 6% products, which could ultimately lead to convulsions. Tetracaine is associated with a higher incidence of allergic reactions than other anesthetics, such as lidocaine. The risk of systemic toxicity is greatest in small children and in patients with pre-existing heart disease. Factors that may increase systemic exposure are time and surface area of exposure, particularly when the area of application is covered by an occlusive dressing. Benzocaine and prilocaine have an additional toxicity not seen with lidocaine. This toxicity, which is called methemoglobinemia, is an acquired disease in the oxygen-carrying capacity of the red blood cells. Further, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations of local anesthetics because of their inability to metabolize them.

Your compounded local anesthetic products are drugs within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). These products are misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in their labeling fails to bear adequate directions for their use. These products are not exempt from this requirement under 21 CFR § 201.115 because they are new drugs within the meaning of section 201(p) of the FDCA (21 U.S.C. § 321(p)) and they lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355). Depending on their labeling, these products may also violate section 502(a) of the FDCA (21 U.S.C. § 352(a)). A drug or device is misbranded under section 502(a) if its labeling is false and misleading in any particular (e.g., if the labeling for your local anesthetic products fails to reveal the consequences that may result from the use of the products as local anesthetics).

2. Copies of Commercially Available Drug Products

The inspection also revealed that your firm is compounding several products that appear to be copies or essentially copies of commercially available FDA-approved drug products. These products include, but are not limited to, progesterone 100 mg capsules, retinoic acid cream (tretinoin) 0.05% cream, and retinoic acid 0.1 % cream. As stated in the CPG and noted above,

FDA typically does not exercise its enforcement discretion for the compounding of copies of commercially available FDA-approved products. We remind you of your commitment to our investigator that your firm will only compound such drugs upon written instructions and justification from the prescriber of the medical need for the particular variation of the compound for an individual patient.

Like the topical anesthetic products, the progesterone and retinoic acid products that your firm compounds are drugs within the meaning of section 201(g) of the FDCA. They, too, are misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. These products are not exempt from this requirement under 21 CFR § 201.115 because they are new drugs within the meaning of section 201(p) of the FDCA (21 U.S.C. § 321(p)) that lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355). Please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited. Under section 301(d) of the FDCA (21 U.S.C. § 331(d)), the introduction or delivery for introduction into interstate commerce of a new drug that has not been approved under section 505 is also prohibited.

The above violations are not intended to be an all-inclusive list of deficiencies. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice. These actions include, but are not limited to, seizure of your products or injunction against you and your firm. Federal agencies are routinely advised of the issuance of warning letters so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter of any steps you will take to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, please state the reason for the delay and the time frame within which the correction will be completed. You should address your reply to this letter to Samia Nasr, Team leader, Compounding team, Office of Compliance, Division of New Drugs and Labeling Compliance, HFD-317, 5600 Fishers Lane, Rockville, Maryland 20857.

Sincerely,
/s/
Mike M. Levy
Director
Division of New Drugs and Labeling Compliance
Office of Compliance
Center for Drug Evaluation and Research

Warning Letter to New England Compounding Center (Framingham, MA)

<http://wayback.archive-it.org/7993/20161023104715/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076196.htm>

NWE-06-07W
VIA FEDERAL EXPRESS

December 4, 2006

Barry J. Cadden, Director of Pharmacy and Owner
New England Compounding Center
697 Waverly Street
Framingham, MA 01702

Dear Mr. Cadden:

On September 23, 2004, investigators from the U.S. Food and Drug Administration (FDA) and the Massachusetts Board of Pharmacy inspected your firm, located at 697 Waverly Street, Framingham, Massachusetts. On January 19, 2005, the inspection was completed. This inspection revealed that your firm compounds human prescription drugs in various dosage forms and strengths. We acknowledge the receipt of your October 1, 2004, letter addressed to FDA's New England District Office, concerning questions presented during the referenced inspection.

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective," is supported by substantial judicial authority. See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"); *Prof'l s & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 n.3 (5th Cir. 1995) (the FDCA does not expressly exempt pharmacies or compounded drugs from its new drug provisions); *In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd*, *Wedgewood Village Pharmacy v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.

The drugs that pharmacists compound are not FDA-approved and lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. See *Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (see Notice of Availability, 67 Fed. Reg. 39,409 (June 7, 2002)).¹ The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manu-

facture of unapproved new drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. These factors include considering whether a firm compounds drugs that are copies or essentially copies of commercially available FDA-approved drug products without an FDA sanctioned investigational new drug application (IND). The factors in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

1. Copies of Commercially Available Drug Products;

It has come to our attention that you are compounding trypan blue ophthalmic products. During the inspection at your firm, you advised an investigator from FDA's New England District Office that the trypan blue products that your firm compounds are devices. FDA classifies trypan blue products as drugs, not devices. Further, on December 16, 2004, trypan blue ophthalmic solution was approved by FDA and it is commercially available. As stated in the CPG, FDA will not exercise its enforcement discretion for the compounding of copies of commercially available FDA-approved products, including this one.

We have also learned that your firm may be compounding 20% aminolevulinic acid solution (ALA). Please note that there is a commercially available, FDA-approved aminolevulinic acid solution 20%. Like compounded trypan blue, FDA regards compounded 20% aminolevulinic acid solution as a copy of commercially available drug.

Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Supreme Court's ruling in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), that Section 503A included unconstitutional restrictions on commercial speech. And those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment. FDA does not sanction the compounding of copies of FDA-approved, commercially available drugs and the agency will not exercise its enforcement discretion regarding the trypan blue and ALA products compounded by your firm.

All products compounded by your firm containing trypan blue or ALA are drugs within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). These products are misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. They are not exempt from this requirement under 21 CFR § 201.115 because they are new drugs within the meaning of section 201(p) of the FDCA and they lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

2. Anesthetic Drug Products

Equally serious, your firm's promotional materials reveal that it offers to compound "Extra Strength Triple Anesthetic Cream" which contains 20% benzocaine, 6% lidocaine, and 4% tetracaine. Like a manufacturer, you have developed a standardized anesthetic drug product that you sell under the name "Extra Strength Triple Anesthetic cream." Further, you generate sales by giving physicians "courtesy prescriptions" (i.e., free samples). These actions are not consistent with the traditional practice of pharmacy compounding, in which pharmacists extemporaneously compound reasonable quantities of drugs upon receipt of valid prescriptions from licensed practitioners to meet the unique medical needs of individual patients.

Moreover, the agency is concerned with the public health risks associated with the compounding of "Extra Strength Triple Anesthetic Cream." There have been at least two nonfatal reactions and two deaths attributed to the use of compounded topical local anesthetic creams containing high doses of local anesthetics. Local anesthetics, like "Extra Strength Triple Anesthetic Cream," may be toxic at high dosages, and this toxicity can be additive. Further, there is a narrow difference between the optimal therapeutic dose of these products and the doses at which they become toxic, i.e. they have low therapeutic index. Adverse events consistent with high systemic exposures to these products include seizures and cardiac arrhythmias. Specifically, risk of systemic adverse events from tetracaine products includes (1) a systemic allergic response to p-aminobenzoic acid (PABA) which, at worst, could lead to cardiac arrest; or (2) excessive systemic absorption following repetitive or extensive application, especially for a 4% product, which could ultimately lead to convulsions. Tetracaine is associated with a higher incidence of allergic reactions than other anesthetics, such as lidocaine. The risk of systemic toxicity is greatest in small children and in patients with preexisting heart disease. Factors that may increase systemic exposure are time and surface area of the exposure, particularly when the area of application is covered by an occlusive dressing. Benzocaine has an additional toxicity not seen

with (idocaine, methemoglobinemia, an acquired decrease in the oxygen-carrying capacity of the red blood cells. Further, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations of local anesthetics because of their inability to metabolize them.

The Extra Strength Triple Anesthetic Cream compounded by your firm is a drug within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). This product is misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that its labeling fails to bear adequate directions for its use. It is not exempt from this requirement under 21 CFR § 201.115, because it is a new drug within the meaning of section 201(p) of the FDCA that lacks an approved application filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

Depending on its labeling, this product may also violate section 502(a) of the FDCA (21 U.S.C. § 352(a)). A drug or device is misbranded under section 502(a) if its labeling is false and misleading in any particular (e.g., if the labeling for your local anesthetic products fails to reveal the consequences that may result from the use of the product as a local anesthetic).

3. Repackaging;

Additionally, we are in receipt of a complaint alleging that you are repackaging the approved injectable drug, Avastin, into syringes for subsequent promotion and sale to health professionals. Avastin is unpreserved and is packaged and labeled in 4 and 16 ml single-use glass vials. The labeled precautions include “discard any unused portion left in a vial” Each step in the manufacture and processing of a new drug or antibiotic, from handling of raw ingredients to final packaging, must be approved by FDA, whether carried out by the original manufacturer or by some subsequent handler or repacker of the product. Pharmacists are not exempt from these statutory requirements. Generally, the agency regards mixing, packaging, and other manipulations of approved drugs by licensed pharmacists, consistent with the approved labeling of the product, as an approved use of the product if conducted within the practice of pharmacy, i.e., filling prescriptions for identified patients. However, processing and repacking (including repackaging) of approved drugs is beyond the practice of pharmacy and is thus subject to the Act’s premarket approval requirements.

The agency has an established policy, articulated in Compliance Policy Guide Sec. 446.100, Regulatory Action Regarding Approved New Drugs and Antibiotic Drug Products Subjected to Additional Processing or other Manipulations (CPG 7132c.06) (copy enclosed), concerning the manipulation of approved sterile drug products outside the scope of the FDA-approval. FDA is particularly concerned about the manipulation of sterile products when a sterile container is opened or otherwise entered to conduct manipulations. The moment a sterile container is opened and manipulated, a quality standard (sterility) is destroyed and previous studies supporting the standard are compromised and are no longer valid. We are especially concerned with the potential microbial contamination associated with splitting Avastin - a single-use, preservative-free, vial -- into multiple doses. When used intravitreally, microbes could cause endophthalmitis, which has a high probability for significant vision loss. The absence of control over storage, and delays before use after repackaging, only exacerbate these concerns.

Avastin is approved for use in the treatment of colorectal cancers. The text of your alleged promotional material offers this drug to ophthalmologists. Avastin has no approved indications for use in the eye. As such, your firm is distributing an unapproved new drug in violation of section 505 of the FDCA. Because the product lacks adequate labeling for its intended use (see 21 CFR § 201.128) your firm is also distributing a misbranded drug in violation of section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)). Also, please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited. Under section 301(d) of the FDCA (21 U.S.C. § 331(d)), the introduction or delivery for introduction into interstate commerce of a new drug that has not been approved under section 505 is also prohibited.

Further, we have been informed that, although your firm advises physicians that a prescription for an individually identified patient is necessary to receive compounded drugs, your firm has reportedly also told physicians’ offices that using a staff member’s name on the prescription would suffice. Drugs compounded in this manner are not compounded consistent with the CPG, and FDA will not exercise its enforcement discretion regarding those drugs.

The above violations are not intended to be an all-inclusive list of deficiencies. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice, including seizure or injunction against you and your firm. Federal agencies are routinely advised of the issuance of warning letters so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter of any steps that you will take to correct the noted violations, including an explanation of the steps taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, please state the reason for the delay and the time within which the correction will be complete. You should address your reply to this letter to the U.S. Food and Drug Administration, New England District Office, One Montvale Ave., 411 Floor, Stoneham, MA 02180, Attn: Ann Simoneau, Compliance Officer. If you have any further questions, please feel free to contact Ms. Simoneau at (781) 596-7732.

Sincerely,

/s/

Gail Costello

District Director

New England District Office

Warning Letter to Triangle Compounding Pharmacy (Cary, NC)

<http://wayback.archive-it.org/7993/20161023104718/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076193.htm>

December 4, 2006

Jose M. Cabaleiro, Owner
Triangle Compounding Pharmacy
550 New Waverly Place, Suite 110
Cary, North Carolina 27511

Dear Mr. Cabaleiro:

On February 17, 2005, investigators from the U.S. Food and Drug Administration (FDA) and the North Carolina Board of Pharmacy inspected Triangle Compounding Pharmacy, 550 New Waverly Place, Suite 110, Cary, NC. This inspection revealed that your firm compounds a drug product called Lasergel, which contains 10% lidocaine/10% tetracaine, and a similar drug called Lasergel Plus 10110, which contains 10% lidocaine/10% tetracaine/0.5% phenylephrine. Lasergel Plus 10/10 is associated with the death of a 22 year old female on January 5, 2005. The inspection also revealed that your firm compounds tetracaine lollipops and polidocanol drug products. FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective," is supported by substantial judicial authority. See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"); *Prof'l's & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 n.3 (5th Cir. 1995) (the FDCA does not expressly exempt pharmacies or compounded drugs from its new drug provisions); *In the Matter of Establishment Inspection of: Wedgewood Village Pharmacy*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), *aff'd*, *Wedgewood Village Pharmacy v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.

The drugs that pharmacists compound are not FDA-approved and lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. See *Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (see Notice of Availability, 67 Fed. Reg. 39,409 (June 7, 2002)).¹ The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manufacture of unapproved new drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. These factors include considering whether a firm compounds drugs that are copies or essentially copies of commercially available FDA-approved drug products without an FDA sanctioned investigational new drug application (IND). The factors in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

1. Lasergel

Like a manufacturer, you have developed a line of standardized anesthetic drug products called “Lasergel” and “Lasergel Plus 10/10.” In some instances, you provide samples of these products at no charge to encourage future sales. These actions are not consistent with the traditional practice of pharmacy compounding, in which pharmacists extemporaneously compound reasonable quantities of drugs upon receipt of valid prescriptions from licensed practitioners to meet the unique medical needs of individual patients. Moreover, the agency is concerned with the public health risks associated with the compounding and sale of Lasergel and Lasergel Plus 10/10. There have been at least two non-fatal reactions and two deaths attributed to the use of compounded topical local anesthetic creams containing high doses of local anesthetics. Local anesthetics, like Lasergel Plus 10/10, may be toxic at high dosages and this toxicity can be additive. Further, there is a narrow difference between the optimal therapeutic dose of these products and the doses at which they become toxic, i.e., they have low therapeutic index.

Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Supreme Court’s ruling in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), that Section 503A included unconstitutional restrictions on commercial speech. And those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

Adverse events consistent with high systemic exposure to these products include seizures and cardiac arrhythmias. Specifically, risk of systemic adverse events from tetracaine products includes (1) a systemic allergic response to p-aminobenzoic acid (PABA) which, at worst, could lead to cardiac arrest; or (2) excessive systemic absorption following repetitive or extensive application, especially for a 10% product, which could ultimately lead to convulsions. Tetracaine is associated with a higher incidence of allergic reactions than other anesthetics, such as lidocaine. The risk of systemic toxicity is greatest in small children and in patients with pre-existing heart disease. Factors that may increase systemic exposure are the time and surface area of exposure, particularly when the area of application is covered by an occlusive dressing, as was the case here. Further, patients with severe hepatic disease are at greater risk of developing a toxic plasma concentration of local anesthetics because of their inability to metabolize them. In addition, phenylephrine, a vasoconstrictor agent present in the Lasergel Plus 10/10, can cause serious adverse events related to hypertension and vasoconstriction.

The patient information sheet that you provide for Lasergel/Lasergel Plus 10/10 appears to be an edited version of the [redacted] (an FDA-approved drug) package insert. Apart from using Lasergel/Lasergel Plus 10/10 in place of [redacted], no changes have been made to the [redacted] package insert. But there are fundamental pharmacological differences between the two products: Lasergel/Lasergel Plus 10/10 and [redacted] are combinations of different local anesthetics: [redacted] contains lidocaine with prilocaine; Lasergel products contain lidocaine with tetracaine. In addition, Lasergel products include phenylephrine, a vasoconstrictor that is not found in [redacted]. Consequently, the Lasergel products information sheet includes warnings and other information that are not appropriate for these products.

The Lasergel/Lasergel Plus 10/10 products compounded by your firm are drugs within the meaning of section 201(g)(1) of the FDCA (21 U.S.C. § 321(g)(1)). These products are misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. They are not exempt from this requirement under 21 CFR § 201.115 because they are new drugs within the meaning of section 201(p) of the FDCA (21 U.S.C. § 321(p)) that lack approved applications filed pursuant to section 505 of the Act (21 U.S.C. § 355).

In addition, your compounded Lasergel and Lasergel Plus 10/10 products are misbranded within the meaning of section 502(a) of the FDCA (21 U.S.C. § 352(a)) because their labeling is false and misleading in that it fails to reveal the consequences that may result from the use of these articles under the conditions of use described in their labeling. Please also be aware that FDA analyzed a sample of your firm’s Lasergel Plus 10/10 Gel product, lot 36955-52. This sample was found sub-potent for both active ingredients, lidocaine and tetracaine, when compared to the amount of these two active ingredients included in your firm’s formulation. According to your firm’s label and formulation, this product should contain 10% lidocaine and 10% tetracaine: FDA laboratory analysis found that the amount of lidocaine ranged from 7.4% to 9.15%, and the amount of tetracaine ranged from 7.2% to 8.9%. Accordingly, this product was adulterated within the meaning of section 501(c) of the FDCA (21 U.S.C. § 351(c)) in that its strength differed from that which it purported or represented to possess.

2. Tetracaine lollipops

Your firm's dispensing log reports that you compound and sell tetracaine HCl [redacted] base lollipops. The agency is concerned with the public health risks associated with the compounding of tetracaine lollipops. The rapid absorption of local anesthetics through the mucous membranes of the mouth and nose may lead to convulsions. In addition to the toxicity that may accompany the rapid absorption of tetracaine, there is a concern that the local anesthetic action within the oral cavity will depress the normal reflexes that protect a patient's airway. This could result in the aspiration of secretions (vomitus or even normal feedings), especially in children. This is a particular hazard for children recovering from tonsillectomies or other intra-oral or intra-nasal ear, nose, and throat surgical procedures. Postoperative bleeding is not uncommon and swallowed blood can lead to stomach irritation and vomiting, thereby raising the hazard of aspiration and possible blockage of the airway.

Like your Lasergel products, the tetracaine lollipop products compounded by your firm are drugs within the meaning of section 201(g)(1) of the FDCA (21 U.S.C. § 321(g)(1)). These products are also misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. These products are not exempt from this requirement under 21 CFR § 201.115 because they are new drugs within the meaning of section 201(p) of the FDCA (21 U.S.C. § 321(p)) that lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

3. Polidocanol

FDA's inspection revealed that you offer to compound products containing polidocanol. The agency is very concerned about the public health risks associated with the compounding of polidocanol injection. Known adverse events include deep venous thromboses, necrosis, and ulceration at the treated site. Additionally, reversible cardiac arrest after polidocanol sclerotherapy has been reported.

Polidocanol is not an active ingredient contained in any FDA-approved drug product. FDA does not sanction its use in pharmacy compounding and will not exercise its enforcement discretion for compounded products containing polidocanol.

If your firm is compounding products containing polidocanol, then these products would be drugs within the meaning of section 201(g) of the FDCA (21 U.S.C. § 321(g)). These products would be misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling would fail to bear adequate directions for their use. These products would not be exempt from this requirement under 21 CFR § 201.115, because they would be new drugs within the meaning of section 201(p) of the FDCA (21 U.S.C. § 321(p)) that lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355).

Finally, please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited. Under section 301(d) of the FDCA (21 U.S.C. § 331(d)), the introduction or delivery for introduction into interstate commerce of a new drug that has not been approved under section 505 is also prohibited. The above violations are not intended to be an all-inclusive list of deficiencies. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice. These actions include, but are not limited to, seizure of your products or injunction against you and our firm. Federal agencies are routinely advised of the issuance of warning letters so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter of any steps you will take to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, please state the reason for the delay and the time frame within which the correction will be completed.

You should address your reply to this letter to the U.S. Food and Drug Administration, Atlanta District Office, 60 Eighth St. NE, Atlanta, GA 30309, Attn: Philip Campbell. If you have any further questions, please feel free to contact Mr. Campbell at (404) 253-1280.

Sincerely,
/s/

Dawn Todd-Murrell for Mary H. Woleske
District Director
Atlanta District Office

Warning Letter to University Pharmacy (Salt Lake City, UT)

<http://wayback.archive-it.org/7993/20161023104716/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm076192.htm>

December 4, 2006

WARNING LETTER
VIA FEDERAL EXPRESS

Mr. Richard E. Rasmuson, Owner
University Pharmacy
1320 East 200 South
Salt Lake City, UT 84102
DEN #07-02

Dear Mr. Rasmuson:

On March 21, 2005, investigators from the U.S. Food and Drug Administration (FDA) and Utah Division of Occupational and Professional Licensing inspected University Pharmacy, 1320 East 200 South, Salt Lake City, UT 84102. This inspection revealed that your firm compounds a drug product called Photocaine gel that contains [redacted] lidocaine and [redacted] tetracaine. This product is associated with the death of a 25 year old female on November 1, 2004. The inspection also revealed that your firm compounds different strengths of progesterone cream.

FDA's position is that the Federal Food, Drug, and Cosmetic Act (FDCA) establishes agency jurisdiction over "new drugs," including compounded drugs. FDA's view that compounded drugs are "new drugs" within the meaning of 21 U.S.C. § 321(p), because they are not "generally recognized, among experts . . . as safe and effective," is supported by substantial judicial authority. See *Weinberger v. Hynson, Westcott & Dunning*, 412 U.S. 609, 619, 629-30 (1973) (explaining the definition of "new drug"); *Prof'l's & Patients for Customized Care v. Shalala*, 56 F.3d 592, 593 n.3 (5th Cir. 1995) (the FDCA does not expressly exempt pharmacies or compounded drugs from its new drug provisions); In the Matter of Establishment Inspection of: *Wedgewood Village Pharmacy*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003), aff'd, *Wedgewood Village Pharmacy v. United States*, 421 F.3d 263, 269 (3d Cir. 2005) ("The FDCA contains provisions with explicit exemptions from the new drug . . . provisions. Neither pharmacies nor compounded drugs are expressly exempted."). FDA maintains that, because they are "new drugs" under the FDCA, compounded drugs may not be introduced into interstate commerce without FDA approval.

The drugs that pharmacists compound are not FDA-approved and lack an FDA finding of safety and efficacy. However, FDA has long recognized the important public health function served by traditional pharmacy compounding. FDA regards traditional compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized needs of an individual patient. See *Thompson v. Western States Medical Center*, 535 U.S. 357, 360-61 (2002). Traditional compounding typically is used to prepare medications that are not available commercially, such as a drug for a patient who is allergic to an ingredient in a mass-produced product, or diluted dosages for children.

Through the exercise of enforcement discretion, FDA historically has not taken enforcement actions against pharmacies engaged in traditional pharmacy compounding. Rather, FDA has directed its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA.

FDA's current enforcement policy with respect to pharmacy compounding is articulated in Compliance Policy Guide (CPG), section 460.200 ["Pharmacy Compounding"], issued by FDA on May 29, 2002 (see Notice of Availability, 67 Fed. Reg. 39,409 (June 7, 2002)).¹ The CPG identifies factors that the Agency considers in deciding whether to initiate enforcement action with respect to compounding. These factors help differentiate the traditional practice of pharmacy compounding from the manu-

facture of unapproved new drugs. They further address compounding practices that result in significant violations of the new drug, adulteration, or misbranding provisions of the FDCA. These factors include considering whether a firm compounds drugs that are copies or essentially copies of commercially available FDA-approved drug products without a documented patient-specific medical need. The factors in the CPG are not intended to be exhaustive and other factors may also be appropriate for consideration.

1. Photocaine Gel

Like a manufacturer, you have developed a standardized anesthetic drug product called Photocaine gel. This action is not consistent with the traditional practice of pharmacy compounding, in which pharmacists extemporaneously compound reasonable quantities- of drugs upon receipt of valid prescriptions from licensed practitioners to meet the unique medical needs of individual patients. Moreover, the agency is concerned with the public health risks associated with the compounding and sale of Photocaine gel. There have been at least two non-fatal reactions and two deaths attributed to the use of compounded topical local anesthetic creams containing high dose of local anesthetics. Local anesthetics, like Photocaine gel, may be toxic at high dosages, and this toxicity can be additive. Further, there is a narrow difference between the optimal therapeutic dose of these products and the doses at which they become toxic, i.e. they have low therapeutic index. Adverse events consistent with high systemic exposures to these products include seizures and cardiac arrhythmias. Specifically, risk of systemic adverse events from tetracaine products includes (1) a systemic allergic response to [redacted] which, at worst, could lead to cardiac arrest; or (2) excessive systemic absorption following repetitive or extensive application, especially for a [redacted] product, which could ultimately lead to convulsions. Tetracaine is associated with a higher incidence of allergic reactions than other anesthetics, such as lidocaine. The risk of systemic toxicity is greatest in small children and in patients with pre-existing heart disease. Factors that may increase systemic exposure are time and surface area of the exposure, particularly when the area of application is covered by an occlusive dressing. Further, patients with severe hepatic disease, because of their inability to metabolize local anesthetics, are at greater risk of developing a toxic plasma concentration of local anesthetics. Although Section 503A of the FDCA (21 U.S.C. § 353a) addresses pharmacy compounding, this provision was invalidated by the Supreme Court's ruling in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), that Section 503A included unconstitutional restrictions on commercial speech. And those restrictions could not be severed from the rest of 503A. In *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002), the Supreme Court affirmed the Ninth Circuit ruling that the provisions in question violated the First Amendment.

The drug information sheet you provide for Photocaine gel appears to be a locally prepared document that combines safety information with a promotional advertisement. It includes claims of effectiveness for Photocaine that have not been substantiated and cautionary advice that is inadequate. No pharmacokinetic information is included to support safe use of the product and guide prescribers to reduce the risk of systemic toxicity. In addition, the drug information sheet includes advice for use on various regions of the body skin, including sensitive areas such as eyelids and genitals. Although there is a warning to use the product with caution in denuded skin or on mucous membranes, there is no specific information to guide practitioners to avoid local toxicity such as dose reduction or time of exposure. The information sheet also does not contain any warnings regarding the use of the product in certain special populations, such as the elderly or pediatric age groups.

The Photocaine gel product compounded by your firm is a drug within the meaning of section 201(g)(1) of the FDCA (21 U.S.C. § 321(g)(1)). This product is misbranded under section 502(f)(1) of the FDCA (21 U.S.C § 352(f)(1)) in that its labeling fails to bear adequate directions for its use. This product is not exempt from this requirement under 21 CFR § 201.115 because it is a new drug within the meaning of section 201(p) of the FDCA (21 U.S.C. § 321(p)) that lacks an approved application filed pursuant to section 505 of the FDCA (21 U.S.C § 355). The Photocaine gel product compounded by your firm is also misbranded within the meaning of section 502(a) of the FDCA (21 U.S.C. § 352(a)) because its labeling is false and misleading in that it fails to reveal facts material with respects to the consequences that may result from the use of the articles under such conditions of use described in its labeling.

2. Progesterone

Your pharmacy's list of compounded biological hormones also revealed that you are compounding progesterone [redacted] and [redacted] vaginal cream, as well as progesterone, [redacted]. These formulations are copies or essentially copies of commercially available FDA-approved drug products. As stated in the CPG and noted above, FDA considers whether there

is documentation of a medical need for an individual patient for the particular variation of the compounded drug. Without proper documentation of medical need, FDA typically does not exercise its enforcement discretion for the compounding of copies of commercially available FDA-approved products.

Like Photocaine, the progesterone products that your firm compounds are drugs within the meaning of section 201(g) of the FDCA. They, too, are misbranded under section 502(f)(1) of the FDCA (21 U.S.C. § 352(f)(1)) in that their labeling fails to bear adequate directions for their use. These products are not exempt from this requirement under 21 CFR § 201.115 because they are new drugs within the meaning of section 201(p) of the FDCA (21 U.S.C. § 321(p)) that lack approved applications filed pursuant to section 505 of the FDCA (21 U.S.C. § 355). Please note that, under section 301(a) of the FDCA (21 U.S.C. § 331(a)), the introduction or delivery for introduction into interstate commerce of any drug that is misbranded is prohibited. Under section 301(d) of the FDCA (21 U.S.C. § 331(d)), the introduction or delivery for introduction into interstate commerce of a new drug that has not been approved under section 505 is also prohibited.

The above violations regarding Photocaine and progesterone are not intended to be an all-inclusive list of deficiencies. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in additional regulatory action without further notice. These actions include, but are not limited to, seizure of your products or injunction against you or your firm. Federal agencies are routinely advised of the issuance of warning letters so that they may take this information into account when considering the award of government contracts.

Please notify this office in writing within 15 working days of receipt of this letter, of any steps you will take to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, please state the reason for the delay and the time frame within which the correction will be completed. You should address your reply to this letter to the U.S. Food and Drug Administration, Denver District Office, P.O. Box 25087, Denver, CO 80225-0087, Attn: Regina Barrell.

Sincerely,

/s/

B. Belinda Collins
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Public Health Service, Food and Drug Administration
Denver District Office
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2017 Compound Paper End Notes

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Special Announcement I – FDB to Remove Unapproved Compounding Kits from the MedKnowledge Database, effective the week of June 08, 2015.