CompPharma

Compounding is Confounding Workers' Compensation

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Table of Contents

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Introduction

Workers' compensation has seen a steady increase in prescriptions for topical compounded preparations, and prescriptions for sterile compounded drugs are appearing as well. In fact, the use of compounded drugs in workers' compensation has increased nearly five-fold in the past five years. Along with increased use, the prices charged for compounds have risen dramatically.

The quality of the preparation and the safety and efficacy of these "custom" compounds are largely unknown. Usually formulated with four to six different ingredients, compounded medications can come with staggeringly high costs, running into thousands of dollars per prescription. Compound pharmacy marketing materials tout numerous benefits of topical compounds, which boil down to:

- Applying topical drugs to the site of the injury theoretically avoids systemic absorption and subsequent side effects
- Combining multiple agents into a single preparation reduces the number of tablets or capsules needed and helps patients who have trouble swallowing oral preparations
- Compounds can omit ingredients that cause an allergic or other adverse reaction in the patient

Workers' compensation payers are questioning the cost of compounds and struggling with how to assess their efficacy and appropriateness and determine appropriate reimbursement. At the request of payers, clinical pharmacists and government relations professionals from CompPharma's pharmacy benefit managers (PBMs) sought answers to questions regarding compounded drugs. The following questions are addressed:

- **Are compounded medications more effective than manufactured drugs?**
- **Are compounded drugs safe?**
- **When should compounded medications be used?**
- **How should compounds be priced and reimbursed? Is compounding an unnecessary cost driver in workers' compensation pharmacy?**
- **Is bulk production of compounds really compounding, or should it be subject to drug manufacturing regulations?**
- **What scientific studies should be required to support the use of a compounded drug?**

This research paper examines clinical research on the safety and efficacy of compounds, reviews state and federal regulations surrounding compounding pharmacies, and discusses pricing and reimbursement methodologies. It also looks at the issue of pharmacies preparing compounds in large quantities. The paper is designed to equip payers with the information needed to make informed decisions regarding their approval of and reimbursement policies for compounds.

Executive Summary

- **Compounds have not been proven to be more effective than commercially available, manufactured drugs that have been approved by the U.S. Food and Drug Administration (FDA) in similar classes. In fact, efficacy data in general are non-existent for the types of compounds seen in workers' compensation claims.**
- **Using compounds poses risks to patients**
- **Compounds are often not medically necessary**
- **The regulation of compounding pharmacies varies from state to state**
- **Compounds are expensive**

History of Compounding

The practice of pharmaceutical compounding has ancient roots. There is evidence that hunter-gatherer societies and even ancient civilizations had some knowledge of the medicinal properties of various plants, animals, molds, and inorganic elements. Ancient civilizations found many uses for pharmaceutical compounding, including treating ill patients, keeping the healthy well, and for religious and cosmetic purposes. The first compounders extracted oils from plants and animals, discovered poisons and antidotes, and prepared ointments for wounded patients.

The combining of different agents was considered an art form historically practiced by priests and physicians. The earliest chemists studied various natural substances and their potential uses. Physicians often prepared the medications they would prescribe to patients. It was not until the 19th century that the role of pharmacists in compounding was generally accepted.

Compounding pharmacies began appearing in the United States in the early 1800s. Before mass production of medications became the mainstay, compounding was the only source of medicines and was a routine activity among pharmacists. By the end of the 20th century, compounding occurred in numerous practice settings, including hospitals, home healthcare pharmacies and retail drugstores.

Today compounding has evolved into a specialty practice intended to help individual patients obtain certain medications in dosage forms, specialized strengths, or delivery routes that are not commercially available. For example, an adult dosage of a medication might be diluted and formulated into a solution for pediatric use, or a medication may be reformulated without filler ingredients that cause a patient's allergic reaction. Patients who have difficulty swallowing oral medications that are not available in liquid dosage forms or who have allergies to ingredients in marketed products have traditionally received compounded liquid preparations when no other options are appropriate. However, the incidence of a true allergy to an inactive component of a marketed product is quite low.[1]

Patients who need a medication that is not commercially available, but is not prohibited by the FDA and for which no other medication is appropriate, may also receive a compounded version of the drug. In such cases, there is a clear and verifiable rationale for compounding. While no data exists on the percentage of patients who meet these conditions, it is likely exceptionally rare for commonly prescribed medications. It is important to note that compounding pharmacies are not allowed to make anything that can be supplied by a manufacturer.

In recent years however, some compounding pharmacies have begun pushing the boundaries by marketing new uses for existing medications. The Internet abounds with compounding companies making "therapeutic" claims for their special topical formulations. These claims have no supporting evidence of safety and efficacy. Some feature anecdotes and testimonials, but none provide suitable references.[2, 3, 4] This is especially true of compounded topical pain medications. Specific formulations are claimed to be effective for neuropathic pain, inflammation, and so on. In this respect, compounding pharmacies are acting more like manufacturers without the burden of having to conduct clinical drug trials to provide evidence to back their claims.

The determination of whether a compounded medication is being appropriately used requires a comprehensive understanding of information that needs to be gathered from a variety of stakeholders. Cooperation and input from prescribers, patients, pharmacists, and claims handlers are often necessary when determining the appropriateness of compounds.

Topical Compounds

The most common compounds in workers' compensation are "topicals" — creams, gels or ointments that are applied to the skin and are intended to manage pain. Despite their prevalence, there is very limited evidence to support the use of these preparations.

Examples of compounds processed by workers' compensation PBMs include:

- ketamine HCl 15%; ketoprofen 10%; gabapentin 6%; baclofen 2%; cyclobenzaprine HCl 2%; ethoxy diglycol; Lipopen Plus
- flurbiprofen 20%, diclofenac 10% in a cream base
- ketamine HCl 10%; gabapentin 6%; lidocaine 10%; bupivacaine HCl 3%; amitriptyline HCl 10%; diclofenac sodium 5%; cyclobenzaprine HCl 2%
- amantadine 10%; diclofenac 3%; cyclobenzaprine 2%; gabapentin 8%; tramadol 5%; lidocaine 5%; diethylene glycol monoeth; PCCA Emulsifix-205 base; PCCA Lipoderm base
- diclofenac 30%; cyclobenzaprine 2%; gabapentin 8%; tramadol 5%; lidocaine 5%; capsaicin 0.05%, menthol 10%, camphor 5% PCCA Lipoderm Base
- Lidocaine 5%, bupivacaine 2%, prilocaine 2% in cream base

Any prescription for a custom compound needs to take into account patient safety, the clinical rationale for the combinations, medical necessity, prescriber liability, and the data to support the efficacy of each drug used topically as well as the combination in the mixture. For the benefit of prescribers, payers and other stakeholders, studies related to each of these topics are presented in this document.

There is another point prescribers should consider before prescribing a compounded formulation. If these products demonstrated benefit with a lower incidence of side effects, why are pharmaceutical manufacturers not interested in developing them?

Before Prescribing or Approving Compounded Drugs

Before prescribing compounds, the prescriber should vet the credentials of the compounding pharmacy by searching the FDA web site and the State Board of Pharmacy for warning letters or actions taken against a particular compounding pharmacy.[5] It is also crucial for prescribers to know exactly what is in the compounds and to critically review data related to the safety and efficacy of the drugs they contain. Many of the compounds seen in workers' compensation transactions contain four or more drugs and are often dosed well above the FDA-approved topical product. This is commonly seen with compounds using diclofenac as an ingredient. The combinations used are questionable from a medical rationale as well as from physical and chemical stability standpoints.

Compounder websites also tout the benefits and clinical evidence for use of compounded topical formulations.[6,7,8] Some marketers even provide preprinted prescription forms to prescribers indicating the compounds are effective for specific conditions.

Compound Script

Fax:

PLEASE INCLUDE PATIENT DEMO SHEET AND FRONT/BACK OF PATIENT INSURANCE CARD WITH THIS SCRIPT

Patient Full Name _____ DOB _____/_____/_____

Address: _____ Best Contact Phone (_____ -)_____

City: _____ State: _____ Zip: _____ Allergies:

Workers Compensation? Y_____ N _____ HMO / PPO? Y_____ N_____ Diagnosis Code: _____

Claims of efficacy

INFLAMMATION

2 high potency NSAIDS

1. Musculoskeletal/Myofascial Pain-Tendonitis-Plantar Fasciitis-Arthritis-Epicondylitis
   Flurbiprofen 10%, Diclofenac 10%, Gabapentin 10%, Lidocaine 5%
2. Tendinosis-Strictures-Scarring
   Flurbiprofen 10%, Baclofen 2%, Verapamil 10%

NEUROPATHIC

2 muscle relaxants

3. General Neuropathy
   Ketamine 10%, Baclofen 2% Cyclobenzaprine 2% Flurbiprofen 10%, Gabapentin 6%, Lidocaine 2%
4. RSD/CRPS-Trigeminal Neuralgia-Phantom Limb Pain-Developing Neuropathy
   Ketamine 10%, Clonidine 0.2%, Gabapentin 6%, Imipramine 3%, Mefenamic Acid 3%, Lidocaine 2%
5. ☐ Chemotherapy Induced Peripheral Neuropathy-Diabetic Peripheral Neuropathy
   Ketamine 10%, Baclofen 2%, Gabapentin 6%, Imipramine 3%, Nifedipine(?) 2%, Lidocaine 2%

FOR OFFICE USE RXS

*Indicate cream(s) by checking box(es)

Quantity:

_____ 30 GM ____ 60 GM

_____ 90 GM ____ 120 GM

_____ 240 GM

Number or Units: _____

*Please remember prescriber information below with signature.

COMBINATION

2 or 3 muscle relaxants

6. ☐ Musculoskeletal Pain-Inflammation
   Ketamine 10%, Gabapentin 6%, Baclofen 2%, Cyclobenzaprine 2%, Lidocaine 2%, Flurbiprofen 10%
7. ☐ Radiculopathy-Fibromyalgia
   Ketamine 10%, Baclofen 2%, Cyclobenzaprine 2%, Diclofenac 3%, Gabapentin 6%, Lidocaine 2%
8. ☐ Myofascial Pain Pyndromes - TMJ
   Flurbiprofen 10%, Baclofen 2%, Cyclobenzaprine 2%, Gabapentin 6%, Orphenadrine 5%, Tetracaine 2%
9. ☐ Myofasscial Pain-Post Laminectomy-Greater Neuropathic Components
   Ketamine 10%, Baclofen 2%, Cyclobenzaprine 2%, Flurbiprofen 10%, Gabapentin 6%, Lidocaine 2%

Quantity: 180 GM_____ 240 GM _____ OTHER:_____

SIG: Apply 1-2 GRAMS to affected area 3-4 times daily ALT SIG: _____

REFILLS: 1 2 3 OTHER: _____

Prescriber: _____ DEA: _____ NPI: _____

Address: _____ Office Phone: (_____) _____-_____

City: _____ State: _____ Zip: _____ Office Fax: (_____) _____-_____

Person Faxing Form: _____ Specialty: _____

Signature: _____ Date: _____

Dispense as written

Patent Insurance Information (or you may provide a copy of the patient's card front and back)

Insurance Carrier: _____ Adjuster: _____ Phone: (_____) _____-_____

Claim # _____ BIN # _____

Group # _____ Patient ID# _____

Please fax Patient demographics on first order: insurance, medications & allergies

Prescribers should question the claims made about compounds being marketed to them. The compounding pharmacist should be able to provide clinical evidence of safety and efficacy for the topical use of the individual drugs. The pharmacist should also provide the chemical and physical stability of the cocktail of drugs mixed together.

Due Diligence

Due diligence is the responsibility of the prescriber. The compounders may have hundreds of documents supposedly supporting their claims, but critical evaluation of these documents reveals that the information does not support the uses touted in marketing materials for compounds. Examples of information contained within compounders' documentation are detailed in the efficacy section of this report.

Manufactured pharmaceutical medications seeking FDA approval must conform to strict Chemistry, Manufacturing and Controls (CMC) standards for analytical, synthetic and formulation chemistry content.[9] Among other things, the CMC process requires of manufacturers a thorough physical, chemical, and biological (as necessary) understanding of all components of the dosage form and a complete analysis and knowledge of all critical manufacturing processes. Another FDA quality control initiative, Process Analytical Technologies, requires "at-line, on-line, off-line, and in-line testing of in-process materials at critical stages of manufacturing."[10] Given the stringent controls in place for FDA-approved drugs, prescribers have a responsibility to question the availability of supporting information related to quality control and safety of compounds.

At minimum, data supporting the use of a compound should include:

- Well-designed, randomized, double-blind, placebo-controlled clinical trials in humans who require treatment for the condition of interest[11]
- Physical and chemical stability data for the compounded formulation
- Animal and human safety studies for the compounded formulation
- References from recognized sources of evidence-based clinical information, such as the Official Disability Guidelines (ODG) published by the Work Loss Data Institute, the Cochrane Database of Systematic Reviews, Agency for Healthcare Research and Quality (AHRQ), and UpToDate

Patient Safety

The primary concern about compounds is that they have not been tested for safety.[12] The compounds frequently prescribed in workers' compensation and listed on page five present a number of potential risks to patients.

These include:

- There is no FDA requirement for stability testing of custom compounds
    - Therefore, it is unknown if the creams, gels or ointments prepared are physically or chemically stable in the short-term or long-term
    - Stability data for inclusion of more than four ingredients in a particular cream/ointment base were not found through extensive searches conducted for this white paper[13]
    - Some random sample testing indicates the possibility that sub- or super potent ingredients are present in compounds[14, 15, 16, 17]
- There is no requirement for providing patient information on appropriate use or side effects of compounds as there is with prescription medications
- There is no FDA requirement for reporting adverse events related to the use of compounds
    - It is often unknown what adverse events have occurred or to what extent with the exception of the hundreds of deaths caused by adulterated sterile compounds, discussed in the following section[18]
    - Non-sterile compounding processes have little to no regulatory oversight compared to the requirements for sterile compound preparation
    - Results of an FDA survey reinforce concerns about poor compound quality, purity and integrity[19]
- Specific concerns related to the compounds listed previously include the high NSAID concentrations seen such as 10% ketoprofen, 20% flurbiprofen and 3% to 30% diclofenac compared to products that have undergone regulatory approval processes. There is concern that higher concentrations may present a greater adverse medical risk to the patient.[20, 21, 22, 23]
    - A gel approved in Europe contains only 2.5% ketoprofen
    - A gel marketed internationally contains only 5% flurbiprofen
    - In the United States, only 1% and 2% diclofenac are approved for osteoarthritis
    - Inclusion of counter-irritants/rubefacients with high concentrations of NSAIDs may increase absorption and result in greater risk for adverse events
    - There are no combination NSAID/counterirritant products approved in the United States or other countries
- Pharmacies have received FDA warnings regarding topical lidocaine in concentrations greater that 5% and other topical anesthetics[24, 25]
- Skin burns have occurred with topical agents containing more than 3% menthol or more than 3% menthol and 10% methylsalicylate[26]

Duplication of Therapy

Frequently, topical custom compounds contain two muscle relaxants (baclofen and cyclobenzaprine are the most common) and at times there are two NSAIDs included (flurbiprofen and diclofenac) in the examples provided.

- There is no clinical rationale for these duplications
- Risks for adverse events may be increased with therapeutic duplications

Medical Necessity

The FDA stipulates that a compounded product must be "necessary for the identified patient."[27, 28]

- Documentation of demonstrated medical necessity is important if a compound is prescribed when FDA-approved products are available for topical or oral administration
- The FDA notes that appropriate reasons to provide a patient with a compound include:
    - A need for a medication because patient has an allergy to a certain dye in the commercially available product
    - Inability to swallow a marketed dosage form and requirement for a liquid form that is not otherwise available

Since custom compounds are created without specific clinical testing they should be considered investigational. If the medication is "investigational" the patient should be required to sign an informed consent document.

Prescriber Liability

A prescriber has the authority to prescribe medications for off-label use. However, according to the FDA, they are expected to use "their best knowledge and judgment" when using a product outside of the approved labeling.[29]

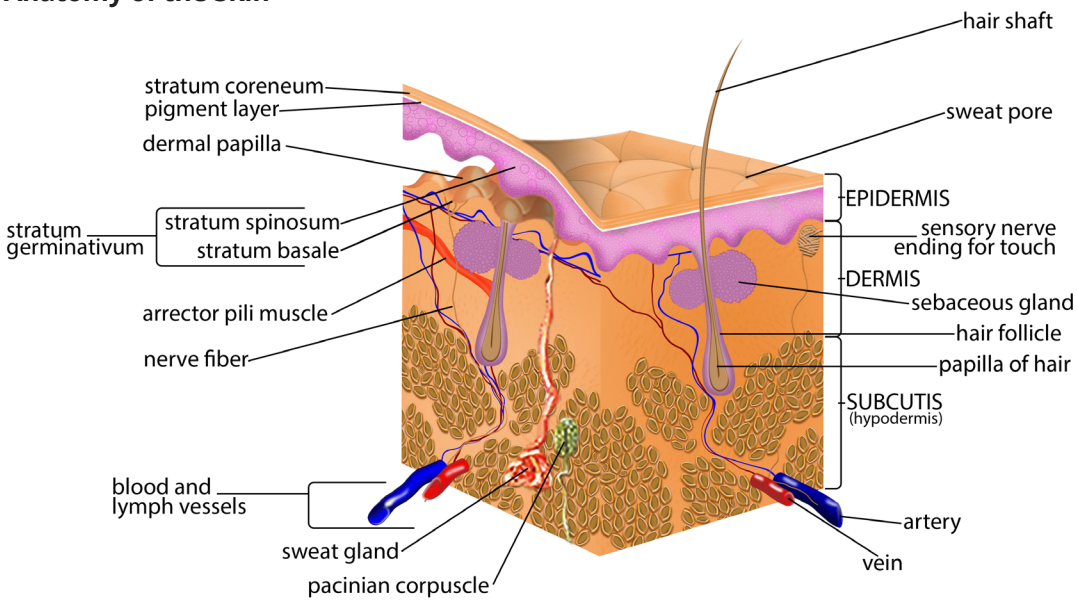
- Physicians may not be protected by malpractice insurance as in the case of injury or death of patients who received contaminated products that were labeled as sterile[30]
- Prescribers are urged to consider the following questions and document their responses:
    - Is there an FDA-approved product that can be used? If not, why not?[31]
    - Does the compound contain active and inactive ingredients contained in marketed products? Although the FDA does not approve bulk drugs, any active ingredient present in a compound needs to be one that is present in an FDA-approved product.[32]
    - How can you ensure the compound is safe and chemically and physically stable?
    - What documentation supports the clinical safety and efficacy of the compound and all the active ingredients?

Efficacy

Once the question of safety has been fully addressed, the efficacy of a product becomes paramount. Topical delivery of drugs is a complex matter, and it is important to understand the skin and dermal absorption.

The skin is an organ intended to prevent systemic exposure to toxic substances, such as chemicals, disease, ultraviolet light, and physical or mechanical damage. It is composed of multiple layers that differ in thickness and composition, including aqueous and lipid sections. The stratum corneum is considered the greatest barrier to drug absorption, and the science of dermal absorption, penetration, and distribution remain an area of intense study.[33]

Anatomy of the Skin



Accessed on March 2014. http://training.seer.cancer.gov/melanoma/anatomy

Dermatology has been practiced for millennia with documentation of ancient Egyptian dermatologic treatments in 1500 BC.[34] In the United States, the first formal lectures on dermatology took place in New York in 1837 at the Broome Street Infirmary for Diseases of the Skin.[35]

The pharmacokinetics of dermal absorption is also an area of continuing research. Early models differentiated the kinetics into compartments, skin surface, stratum corneum, viable cutaneous tissue and dermal capillaries.[36] More recent research has expanded on the compartmental models to include the role that enzymes play in dermal drug metabolism and pharmacokinetics.[37]

Drug absorption into and through the skin into muscle depends on the physical and chemical characteristics of the drug. These include molecular size, lipophilicity, permeability, and fraction unbound in viable skin.[38] Additionally, the concentration of the drug, duration of contact, and use of an occlusive barrier over a topical agent can all alter drug absorption and penetration.

Once a drug is absorbed into the skin, transdermal penetration into underlying tissue is needed for joint or muscle pain to be relieved. It is believed that the most important factor for flux and drug distribution is the molecular size of the drug.[39] Other important drug characteristics are:

- A more lipid soluble drug is expected to have a greater depth of penetration
- A higher fraction of unionized drug (permeability) may also play a role in absorption
  The pH of the vehicle has a strong influence on drug ionization
- A higher unbound fraction of drug is also correlated with drug clearance from viable skin to the muscle
- Studies have demonstrated that the fraction of unbound drug is the most important factor for clearance from the skin to muscle[40]

A third critical component of topical drug efficacy is the vehicle. The composition of the vehicle (cream, gel or ointment), pH, lipid characteristics and drug solubility in the vehicle, all influence the amount and depth of absorption of a drug into the skin and underlying tissues.[41] Various vehicles have been tested to optimize formulations and to determine the tissue concentrations present following topical application. Most of the research over the past several decades has involved NSAIDs. A few of the more recent studies are summarized here to provide a better sense of the complexities and variables involved in topical drug delivery.

In 2001, an in vitro study to determine the theoretical topical efficacy of six NSAIDs was conducted.[42] The study attempted to determine an "index of topical anti-inflammatory activity" (ITAA). This index is the ratio of drug concentration at the site of activity to the concentration that is assumed to produce anti-inflammatory activity, specifically COX-2 inhibition. A ratio greater than one suggests topical efficacy.

Each study drug was dissolved in dimethyl sulfoxide (DMSO) and diluted further with Dulbecco's modified Eagles' medium (DMEM). The authors indicate that the DMSO/DMEM vehicle did not affect activity. Human dermal fibroblasts were used to determine COX-2 activity as determined by high performance liquid chromatography (HPLC) analysis. Table 1 summarizes several key results.

Table 1

Drug	MWa	Jmb	ITAA (I=50%)c	ITAA (I=75%)c	ITAA (I=90%)c	Results
Ketorolac	255.3	13	37.2	19.0	9.7	Most dermally active
Diclofenac	296.2	1.4	43.8	18.8	8.1	2nd dermally active
Ketoprofen	254.3	16	23.6	4.1	0.7	3rd dermally active
Indomethacin	357.8	0.7	3.4	1.6	0.8	4th dermally active
Piroxicam	331.4	0.08	0.0019	0.0006	0.0002	Least dermally active
Tenoxicam	337.4	0.7	0.0104	0.0034	0.0011	Least dermally active

a = MW – molecular weight; b = maximum flux; c = Theoretical concentration needed to inhibit COX-2 by 50%, 75% or 90%, respectively; it is assumed that 75% or 90% is needed for clinically significant benefit.

Keeping in mind that this was an in vitro study and that the effective concentration needed for efficacy is theoretical, the results suggest that ketorolac and diclofenac may be effective topically. It also appears that ketoprofen may be effective if a lower concentration is used, but may not be effective if a higher concentration at the site is needed.

Other studies evaluating the effect of vehicles on NSAID skin penetration are summarized in Table 2.

Table 2

Citation	Key Points
Wenkers BP, Lippold BC. Skin penetration of nonsteroidal anti-inflammatory drugs out of a lipophilic vehicle influence of the viable dermis. J Pharm Sci. 1999;88(12):1326-31.	+Permeability through the skin depends on the drug solubility in the vehicle +Viable epidermis is a barrier to drug transport
Jaekle E, Schaefer UF, Loth H. Comparison of effects of different ointment bases on the penetration of ketoprofen through heat-separated human epidermis and artificial lipid barriers. J Pharm Sci. 2003;92(7):1396-1406.	+Compare results of an artificial membrane to human skin samples
Penzes T, Blazso G, Aigner A, Eros I. Topical absorption of piroxicam from organogels – in vitro and in vivo correlations. Int J Pharmaceutics. 2005;298:47-54.	+In vitro skin penetration predictions differed from in vivo effect. +Care is advised when attempting to draw conclusions concerning in vivo skin penetration based on studies using synthetic barriers.
Chang J-S, Huang Y-B, Hou S-S, Wang R-J, Wu P-C, Tsai Y-H. Formulation optimization of meloxicam sodium gel using response surface methodology. Int J Pharmaceutics. 2007;338:48-54.	+The bioavailability of meloxicam via transdermal absorption appeared to be approximately 50%.
Herkenne C, Naik A, Kalia YN, Hadgraft J, Guy RH. Effect of propylene glycol on ibuprofen absorption in human skin in vivo. J Pharm Sci. 2008;97(1):185-97.	+Higher percent propylene glycol (PG) in the vehicle resulted in significantly increased drug in the skin.
Jaksic I, Lukic M, Malenovic A, Reichl S, Hoffmann C, et. al. Compounding of a topical drug with prospective natural surfactant-stabilized pharmaceutical bases: physicochemical and invitro/invivo characterization – a ketoprofen case study. Eur J Pharm Biopharm. 2012;80:164-75.	+Study topical vehicles containing alkyl polyglucoside type surfactant for safety and effect on drug delivery
Gratieri T, Pujol-Bello E, Gelfuso GM, de Souza JG, Lopez RFV, Kalia YN. Iontophoteric transport kinetics of ketorolac in vitro and in vivo: demonstrating local enhanced topical drug delivery to muscle. Eur J Pharm Biopharm. 2013; available online at: http://dx.doi.org/10.1016/j.ejpb.2013.06.009.	+Stability of the drug did not appear to significantly impacted by electrical current +Drug accumulation in muscle tissue was higher with iontophoretic application as compared to passive absorption and oral administration.

After reviewing the studies summarized in Table 2, it is impossible to conclude that any of the studied compound drugs are efficacious. The wide range of dependent and independent variables, vehicles and concentrations tested, and differences in methodologies and barriers used (animal, human skin, artificial) all confound the ability to pool information and make sound decisions about the optimum vehicle for topical application of any particular NSAID.

Further, these studies primarily focused on a single active ingredient in the test samples. In the workers' compensation patient population, it is relatively common to see compounds that contain four or more drugs in addition to NSAIDs. Unless randomized controlled clinical studies are performed on the exact mix of active and inactive ingredients, it is impossible to determine the skin penetration, bioavailability, and clinical effect of drugs in the mix. Physical and chemical stability after mixing and expiration dating are also unknown.

Moreover, despite the research conducted to date on topical NSAIDs, only one NSAID, diclofenac, has been approved for topical use in the United States. Diclofenac is FDA approved as a 1% gel for osteoarthritis of the knee, hand and other "amenable joints;" and as 1.5% and 2% solutions for osteoarthritis of the knee, and as a 1.3% topical patch for acute treatment of strains, sprains and contusions.

In an attempt to find information on other drug ingredients in the topical compounds prescribed in workers' compensation, scientific literature searches were conducted to determine what, if any, clinical support exists for their topical use.

Search results found little to no clinically appropriate information for topical use of many of the ingredients in the compounds listed. Table 3 and the Appendices at the end of this report provide summary and detail of search results.

Table 3

Drug name	Peer-Reviewed* Publication	# of Articles Found	Observation
Amitriptyline	Yes	9	Little to no effectiveness
Baclofen	Yes	2	Need more studies - may be effective in chemotherapy-induced neuropathy
Clonidine	Yes	1	Need more studies - some diabetic neuropathy
Cyclobenzaprine	None found	0	
Gabapentin	Yes	1	Not applicable to workers' compensation injuries
Guiafenesin	None found	0	
Imipramine	None found	0	
Ketamine	Yes	10	Not conclusive
Nifedipine	Yes	4	Not applicable to workers' compensation injuries
NSAIDs	Yes	4	Refer to Table 1 and discussion for details
Orphenadrine	None found	0	
Pentoxifylline	None found	0	
Tramadol	Yes	1	Not applicable to workers' compensation injuries
Verapamil	Yes	1	Not applicable to workers' compensation injuries

Topical Summary

CompPharma's research has not revealed any evidence that topical compounds are safe or effective. In fact, the evidence indicates that there is significant variation between the stated potency of a compounded product and the actual ingredients. As long as there are no regulatory requirements related to testing and post-dispensing safety surveillance, the procurement of compounded medications is indeed a situation where the prescriber must beware.

While a lack of information does not prove a lack of efficacy, the lack of research suggests that ineffective topical compounded drugs are being used instead of FDA-approved drugs that have been shown to be safe and effective.

The data presented also begs the question: if no strong clinical research supports the use of compounded medications, is a custom compound the right thing to do for the patient? A policy of requiring the injured worker to sign an "informed consent" may be a way to

ensure that the patient is aware that the compounded product is not FDA approved and carries direct and indirect risks.

With compounded medications we face two significant issues. First, has the prescriber exercised appropriate caution in assessing the safety and efficacy of the prescribed compound and employed appropriate patient informed consent? Second, has the payer put appropriate processes in place to challenge the compounded medication to protect the patient?

Sterile Compounding

Compounds which require sterile preparation, such as injectable medicines and eye drops, have come under intense scrutiny from regulators and the mainstream media in the past year. While not used in workers' compensation as frequently as topical, non-sterile preparations, sterile compounding does occur in the preparation of solutions such as morphine and baclofen, intended for intrathecal (spinal pump) use, as well as injectable corticosteroids used to decrease inflammation. Their presence cannot be ignored in light of the relatively frequent use of epidural steroid injections in workers' compensation and the high risk these products potentially pose to injured workers.

In addition to the federal and state level regulations that dictate the volume of drug which can be pre-made at a compounding pharmacy, accurate preparation is tremendously important when considering sterile products. It is one thing when a product is simply ineffective, but quite another when the product can inflict fatal harm if prepared inappropriately.

Regulations surrounding the facility and environment in which sterile compounds can be made have been a state-level function until recently. The recent Federal Drug Quality and Security Act will impact state laws, but most states still retain some degree of expressed regulation pertaining to sterile compounding. The rate and thoroughness of inspections to ensure compliance varies from state to state.

For example, Arizona regulations spell out detailed requirements for sterile pharmaceutical preparation, including square footage designation, environmental and equipment requirements, policy and procedure guidelines, and quality control regulations.[43] The enforcement of these regulations, however, is not expressly implied in the code; and the procedures for and frequency of the inspections are not specifically outlined for sterile compounding. Some states require separate licensing for pharmacies that produce sterile

products. California, for example, requires additional licensing and performs annual reviews before the license can be renewed.[44]

A survey completed in 2007 asked 117 compounding pharmacies to report their processes for personnel training, existence of compounding policies and procedures (P&P) documents, expiration dating, storage, labeling, and sterile technique, among others. While 92% of pharmacies reported the capability to compound, almost one-third of the pharmacies did not have a P&P document in place and did not provide specific compounding training to their staff. Just 17% reported that they use a quantitative analytical measurement to verify the active ingredient content in each prescription. Finally, only 46% responded that they would be willing to send their products to an external laboratory to verify dosing and sterility.[45] In short, it is the responsibility of the pharmacist in charge to ensure that the pharmaceuticals they produce are in compliance with law and are safe for human use.

Numerous studies report a higher level of contamination within compounded products as compared to commercially manufactured products. A meta-analysis of 19 studies reported contaminated products in more than 5% of individually prepared doses, whereas the manufactured batches contained 0% contaminants.[46]

While the obvious concern with compounded sterile products is whether or not the product is truly sterile and is free of contaminants, dosing accuracy is also important. A study completed in 2012 compared the quality of a compounded baclofen (intrathecal) sterile product with that of a manufactured product. The results show a clear difference. All of the manufactured product was within 5% of the expected dose. However, 82% of the compounded products tested had more than a 5% difference from the labeled, expected dose. An additional 30% showed more than a 10% difference.

The safety outcome of a 10% dosage variability is largely dependent upon the drug or drugs that are in the product. Baclofen has a very narrow therapeutic index when administered intrathecally (into the spine). "Variable clinical efficacy, or life-threatening overdose or withdrawal may occur in patients who are sensitive to slight dose fluctuations."[47]

Another study completed in 2009 (Moberg-Wolff E.)[48] collected samples from six compounding pharmacies and from a commercial manufacturer. Forty percent of the compounded samples had greater than a 5% difference in concentration, and 22% had

greater than a 10% difference in concentration. The only samples with no difference in the labeled concentration were commercially prepared.

While compounders are required to use only FDA-approved ingredients in their products, occasionally cases occur in which non-FDA approved drugs are used. Arthritis injections are not without sterility issues as well. A pharmacy in Fort Smith, Arkansas was found to be making an arthritis pain-relief injection in 2002 which was contaminated with a potentially lethal fungus, penicillum rugulosum.

The FDA inspects both pharmacies and pharmaceutical manufacturers, however large-scale drug manufacturers undergo more frequent, and potentially more thorough inspection than retail pharmacies, as outlined on the FDA's website.[49] Manufacturers receive stringent examination every time they submit an application to market a new product and for routine inspections as well as "for cause" inspections to identify a specific problem.[50] Inspection of pharmacies, however, tends to fall under the purview of various state boards of pharmacy, therefore allowing greater variability of quality in the United States.

Drug manufacturers produce such a large volume of product that they are able to test and validate that each batch, or lot, of their product meets dosing, quality and sterility requirements. Compounds do not undergo this verification, in part because of the impracticality of doing so (ideally each drug is made on a per-prescription, per-patient basis). Also compounders are not required to complete such testing by the FDA as the compounds do not need to be FDA approved in order to be dispensed.

The issue of compromising quality and sterility at the expense of creating more volume of product (and sales) then enters the picture. At what point should a compounding pharmacy be expected to fall under a manufacturer's regulations in order to assure safety and sterility? This is a question that has come to light in response to the New England Compounding Center (NECC) contamination crisis discussed below.

Several national organizations have attempted to standardize the regulation and quality of compounding, particularly for sterile compounds. These include the United States Pharmacopeia Convention (USP) and the American Society of Health-System Pharmacists (ASHP).[51]

The USP 797 is a regulation that governs many different avenues of pharmacy policy and procedures. While largely associated with sterile preparations in hospitals, such as

intravenous fluid preparation and parenteral nutrition, it does apply to outpatient, retail compounding pharmacies as well. For example, sterile compounds should be prepared in designated "clean rooms" that are engineered to have certain air flow in order to reduce the number of particulates in the air. Additionally, regulations discuss the use of vertical and horizontal hoods (laminar flow workbenches), aseptic hygiene, clothing, HEPA filtration, and cleaning agents.[52] Accreditation by the Joint Commission (formerly The Joint Commission on Accreditation of Healthcare Organizations or JCAHO) is also available for pharmacies that follow USP 797, and those that gain this certification and maintain those standards exemplify the ethics and good faith that are desired and expected by the receiving public. To find out if a local compounding pharmacy has Joint Commission accreditation, go to www.qualitycheck.org.

What Went Wrong at NECC?

In mid-2012, NECC shipped 17,000-plus vials of injectable methylprednisolone to clinics and hospitals in 23 different states. The batches of steroid were contaminated with several types of molds, such as Aspergillus fumigatus, which can cause lethal fungal meningitis. Over 50 people have died and over 700 others have recurrent fungal infections. Treating fungal infections is a complicated and arduous task and the condition is not easily eradicated. NECC was also traced as the originator of contaminated triamcinolone and heart surgery medications several months later. NECC has since ceased its operations and filed for bankruptcy.[53]

The debate which followed sought to determine the root cause of such a contamination. The outbreak is said to be "one of the worst public health crises associated with contaminated drugs in the history of the United States, and exposed a fundamental failure in drug safety oversight."[54] Numerous complaints about the pharmacy had been filed with both state and federal agencies as early as 11 years prior to the outbreak, many of them questioning its quality controls. Had the FDA taken additional action on these complaints, could the deadly occurrence have been prevented? Who holds greater responsibility: the Massachusetts Board of Registration in Pharmacy or the FDA? These questions are still under investigation and remain to be answered.

According to documentation following a US Congress Report from April 2013,[55] primary responsibility is placed upon NECC for its lackadaisical management style and desire to expand as a company before assuring quality and safe pharmaceuticals were dispensed in every batch. However, the lack of regulatory response to the flood of complaint calls and letters about the company is also of concern. It is expected that new laws, regulations, and

licensing requirements will be developed in the coming years to prevent improper business ethics from affecting the healthcare system.

Within the acute care hospital settings, "56% of hospitals made changes or planned to make changes to compounded sterile preparation sourcing practices in response to that [NECC] meningitis outbreak."[56]

As a result of this occurrence and in light of public attention, national and state-level regulators have increased the frequency of their inspections. Seemingly all of a sudden, there are monthly, sometimes weekly, reports in mainstream media about additional contaminants found, recalls, or license restrictions due to inspection failures. The National Association of Boards of Pharmacy (NABP) has stepped forward to support states with their regulations of sterile compounds. A compounding action plan was released in December 2012 in an effort to conduct additional inspections in multiple states. Iowa and New Jersey are currently engaging NABP to conduct inspections in all of their pharmacies, and several other states have legislation in process.[57]

Sterile Compounds in Workers' Compensation

While the majority of compounds seen in the workers' compensation industry are for topical use, sterile products are occasionally prescribed for injured workers. Most medications billed through PBMs within this population are for implantable pain pumps. The most common medications used include clonidine, morphine, bupivacaine, hydromorphone, fentanyl, and baclofen.[58] Intrathecal preparations such as these may be billed through pharmacies, or submitted through a medical claim form directly from prescriber's offices.

Additionally, injectable steroids are a common treatment for work-related injuries. The offender of the NECC meningitis outbreak is a steroid, which is used to treat chronic pain, likely one of the most common and expensive compensable diagnoses in workers' compensation. Arthritis injections of many kinds have been crafted and produced by compounding pharmacies in recent years, and an increasing number are appearing as a result of drug manufacturing shortages.

Hospitals and clinics cite several reasons for using a sterile compound versus a commercially manufactured alternative. First, is the shortage of available commercial products. The need for medications exists, even if the manufacturer is unable to supply the demand for the drug. Decreased supply of initial base ingredients and reduced profitability

of a drug may reduce commercially available supply. So, compounding pharmacies step in to replace the void. Additionally some compounded products report extended shelf-life and stability as compared to similar commercial products. This can reduce costs for the hospital or clinic because they are able to use the product over a longer period of time.[59]

Regulatory Issues

Costs associated with the compounding of custom drugs have given rise to new rules and regulations across the United States. In addition, the costs associated with custom designer drugs prescribed by physicians and charged at an exorbitant rate are responsible for skyrocketing pharmaceutical costs in the workers' compensation arena. States, often playing catch-up, have passed new laws, attempting to reign in these costs. This has led to different statutory creations.

Some states have attempted to rein in costs to the workers' compensation system by addressing compound drugs in fee schedules and by limiting reimbursement. For example, Ohio caps reimbursement for compounds at $600 and sets compounding dispensing fees at $12.50 for non-sterile drugs and $25 for sterile drugs,[60] while Louisiana requires compounded drugs to be billed at the same reimbursement formula as generic drugs.[61]

The most common attempt to regulate compound drug costs is requiring compounds to be billed at the ingredient level. This type of regulation aims to lower costs by requiring prices to be based on the amount of each ingredient instead of overcharging based on a small quantity of an expensive drug included in the compound. Twelve states — California, Colorado, Delaware, Idaho, Mississippi, New York, Oklahoma, South Carolina, Tennessee, Texas, Washington, and Wyoming — currently do this.[62] Eight of the 12 states also require compound drugs be billed based on a fee schedule and cap the total cost of each prescription.[63] For example, California limits reimbursement of pharmacy-dispensed compounds to 100% of the Medi-Cal (Medicaid) system rate per ingredient. Further, California limits physician-dispensed compound drug reimbursement to the total cost for the compound drug at 300% (and no more than $20) of the documented paid costs.

It remains to be seen how effective these regulations will be. An early study of the effectiveness of California's compound billing law, that took effect on Jan. 1, 2012, reports mixed results.[64] The report says, "The changes in the utilization and cost of compound drugs associated with the implementation of AB 378 point to a mixed bag of statutory and administrative successes and remaining challenges. The successes are found in the legislative intent to curb compound drug utilization, as the data show that compound

drugs fell from 3.1 percent of California workers' compensation prescriptions prior to AB 378 to 2 percent of the prescriptions after the law took effect."

As this study indicates, it is still too early to tell what, if anything, has improved and a few more years of study are needed to determine the true impact of these regulations. Even with little evidence of effectiveness, states continue to fall in line and enact similar provisions. Michigan, for example, is currently seeking to cut unnecessary costs by enacting similar ingredient level billing regulations. Likely others will follow.

The Feds Versus the States

The battle over control and safety of compounding drugs has pitted the FDA against state boards of pharmacy. On one side, the FDA seeks to regulate the compounding of drugs that go beyond traditional compounding (individually based, specific to patient needs) into the realm of mega, non-prescription compounding. On the other, the states, spurred on by the compounding drug industry, seek to keep control by issuing new rules and passing new regulations.

States have been busy legislating in the realm of compounding drugs. These new laws mainly deal with licensing, inspection and defining of the compounding drugs. California, Georgia, Maine, Maryland, Massachusetts, Minnesota, Mississippi, Oklahoma, Oregon, Tennessee, Texas, and Virginia have recently passed or are in the process of passing new laws that require out-of-state compounding pharmacies to be licensed in those states.[65] A few of these states go further by requiring compounding pharmacies to have an initial inspection and regular inspections thereafter.[66] Texas is even seeking random inspections of out-of-state compounding pharmacies, and requiring the bill be paid for by the compounding pharmacy.[67] Oklahoma is seeking to require the compounding pharmacy to have a pharmacist-in-charge (PIC) who is licensed in Oklahoma.[68]

Another area of concern is safety standards. Several states require compounding pharmacies to follow standards for sterile and non-sterile compounding of drugs issued by the USP.[69] Oklahoma is considering requiring the Pharmacist in Charge to sign an affidavit attesting that the pharmacy will comply with non-sterile and sterile compounding standards "of the newest edition of the USP and the FDA Good Manufacturing Practices."[70]

States are also changing and adding compounding definitions to battle confusion.[71] Most new definitions define compounding as prescription based, done on an individual basis, and when no commercially available alternative dosage form exists. Some states are proposing

or enacting legislation that distinguishes compounding from manufacturing. For example, Virginia's new law defines manufacturing as "compounding of inordinate amounts" in which "there is no observed historical pattern of prescriptions and a dispensing to support an expectation of receiving a valid prescription for the preparation." [72]

Those not satisfied with state actions, are calling for the regulation of non-traditional compounded drugs by the Federal government. Congressman Ed Markey of Massachusetts introduced the Verifying Authority and Legality in Drug Compounding Act of 2013 (VALID). VALID calls for the creation of a new category of drug manufacturers called "compounding manufacturers."[73] The legislation would place this new category of compound drugs under the authority of the FDA, while leaving traditional compounding to the state boards of pharmacies.[74]

This bill has great support among pharmacy trade groups. ASHP argues that this legislation is needed to establish a "clear boundary between FDA jurisdiction and the jurisdiction of state boards of pharmacy."[75] ASHP states that "the Committee got it right with this proposed legislation."[76] They further argue that this legislation will allow health care professionals a sense of assurance as this bill requires that compounding pharmacies "have taken the necessary steps to ensure their facilities meet the most rigorous Current Good Manufacturing Practices, have been inspected by the FDA, and most importantly, do not pose a threat to our patients due to inadequate regulatory oversight." [77]

Not all industry groups share this view. Compounding drug associations, such as The International Academy of Compounding Pharmacists (IACP), disagree with the new legislation's creation of a "compounding drug manufacturer" category.[78] The "new category [will] create more confusion and further blur the jurisdictional authority of regulators," they argue.[79] IACP believes that the regulation of compounding pharmacies should be left to the states. They argue that states are already enacting laws which "strengthen and clarify appropriate and safe pharmacy practices." [80]

Recent exposure of potential safety concerns along with high costs associated with compound drugs, demonstrate that new compound drug laws are badly needed. It appears likely that more states will follow California's lead and pass strict billing guidelines in an attempt to contain rising costs associated with compound drugs. Likewise, the increased regulation of nontraditional compounding of drugs will continue across the country. In addition, it is possible that the FDA will lay claim to regulating the mega compounding of drugs. Nevertheless, it is clear that more laws and regulations addressing safety restrictions

and procedures associated with nontraditional, mega compounding of drugs, will likely be enacted swiftly across the country.

With the Drug Quality and Security Act of November 2013, the federal government has taken a small step toward regulating compounded drugs by creating a new "outsourcing facilities" class of pharmacy. The new rule allows compounding pharmacies to register themselves as outsourcing facilities. As a registered facility, the compound pharmacy must meet established guidelines and comply with reporting requirements to be exempt from the FDA's approval requirements for new drugs. The new law also requires the agency to setup a process in which to receive information regarding compounding actions by state boards of pharmacies.

Financial Considerations

As noted in the previous section, several states have specific fee schedules in place regarding compounded pharmaceuticals. Some of these fee schedules are very specific and relatively straightforward in that reimbursement is based on average wholesale price (AWP) or the actual cost of ingredients (ACI) plus a markup factor, dispensing fee or both as indicated in Table 4.

However, even with specific fee schedules in place, one of the challenges in reimbursing compounds at the correct rate is to identify which prescriptions are indeed compounds. If the dispensing pharmacy processes the prescription on-line via the payer's PBM, then the pharmacist uses a "compound indicator" to flag the prescription as a compound. However, many compound prescriptions are still billed on paper where the reimbursement process is not always so straightforward. In addition, many of the ingredients used in compounds have names that are very similar to conventional generic pharmaceuticals.

Table 4

State	Compound Fee Schedule
Louisiana	AWP + 40% + 5.77
Massachusetts	AWP - 16% + $3.00 + (a)or(b)
Tennessee	AWP + $25.00
Texas	AWP+25%+$15 per compound
Washington	ACI + $4.50 + $4.00 CTF

Legend: ACI = Allowed Cost of Ingredients; AWP = Average Wholesale Price; CTF = Compounding Time Fee; (a) = an additional $1.00 fee for: 1. compounding ointments or solutions, 2. preparing solutions which involve the weighing of ingredients; (b) = an additional $2.00 fee for: 1. compounding suppositories, 2. compounding capsules, tablets, triturates or powders

An age-old rule to identify compounds on paper bills is to look for phrases in the drug name that indicates something other than a tablet or capsule, e.g., "cyclobenzaprine pow" versus "cyclobenzaprine 10 mg tab" to identify a powder used in compounding. However, this process is not absolute and truncated names may cause a prescription to be incorrectly identified.

Another method of identifying compounding ingredients is to rely on the NDC number.

The vast majority of ingredients today have an NDC number. The NDC number is always 11 digits long with the first five digits identifying the manufacturer, the next four digits identifying the drug and the last two digits identifying the package size. Based on this, the first five digits may be used to identify known manufacturers of compounding supplies. A partial list appears at right.

This list does not include manufacturers that produce both compounding ingredients as well as traditional drugs, with Mallinkrodt being a prime example, but it does provide a way to help identify potential compound products for those states that specify a unique fee schedule for compounds.

NDC Example

Manufacturer	5-digit NDC
Apotheca	37803
B&B	63275
Cedarburg	64181
Fagron	51552
Freedom	52372
Hawkins	63370
Humco	00395
Letco	62991
Medisca	38779
PCCA	51927
Pharmaceutical Specialties	45334
Pharmaceutics Corp	49430
Spectrum	49452

Colorado has a somewhat more complicated fee schedule based on different categories that determine the compounding fee. All prescriptions shall be billed using the Department of Workers' Compensation's Z code corresponding with the applicable category for compounded topical products as follows:

Category I

Z0790 Fee $75.00 per 30 day supply
Any anti-inflammatory medication or any local anesthetic single agent.

Category II

Z0791 Fee $150.00 per 30 day supply
Any anti-inflammatory agent or agents in combination with any local anesthetic agent or agents.

Category III

Z0792 Fee $250.00 per 30 day supply
Any single agent other than anti-inflammatory agent or local anesthetic, either alone, or in combination with anti-inflammatory or local anesthetic agents.

Category IV

Z0793 Fee $350.00 per 30 day supply
Two (2) or more agents that are not anti-inflammatory or local anesthetic agents, either alone or in combination with other anti-inflammatory or local anesthetic agents.

All ingredient materials must be listed by quantity used per prescription. Category fees include materials, shipping and handling and time. Regardless of how many ingredients or what type, compounded drugs cannot be reimbursed higher than the Category IV fee. Although very specific, this rule may actually complicate the procedure for reimbursing compound prescription at the correct rate.

California offers an on-line utility that allows the pharmacist or others to answer a series of questions related to a compound and obtain a calculated medical fee schedule based on those entries. An example of a topical compound that contains 5% of both gabapentin and ketamine is provided below.

Topical Compound Example

NDC No	Label name	Price date (start)	Number or units	Unit price	Product
51927421300	Gabapentin Bulk Powder	1/1/2011	9.0	28.884	259.956
51927279000	ketamine hcl powder	9/2/2010	9.0	18.924	170.316
				Total of ingredients:	**$430.27**
The compouning fe for route of administration form **Topical** with a dose MDU of **180** is				$0.00	
The allowed sterility fee (lesser of the usual and customary sterility fee and the maxium sterility fee) for route of administration form **Topical** with a dose MDU of **180** is				$0.00	
The dispensing fee for a patient **Not in** a nursing home on and after 9/1/2004 is				$7.25	
Therefore the total allowed compond dispensing fee is:				7.25	
Plus the compounding fee of **$7.25** times **1** Containers: (The container count is only applied for routes of administration 4 – injection, and 15 – perfusion.)					**$7.25**
Equals subtotal:					**$437.52**
Which is **lower than** the usual and customary price of:					**$500.00**
Therefore, the **Payment price** is the Medi-Cal price minus the **$0.00** reduction for a patient **Not in** a nursing home (No reduction for dates of service on and after 9/1/2004):					**$437.52**

http://www.dir.ca.gov/dwc/pharmfeesched/pfscompound.asp; Pricing is from data as of 7/10/2013. Please note the Usual and Customary price of $500.00 is fictitious and was used for illustration only.

This on-line tool is also effective for eliminating a costly error that is sometimes made in pricing or reimbursing compound prescriptions; reimbursing for the cost of the active ingredient(s) only. The total quantity of a compound is rarely the determining factor for price, whereas the total quantity of a traditional prescription drug is always the determining factor. A traditional prescription with a quantity of 180 tablets would have a price based on the AWP of the individual tablet multiplied times the total quantity with a discount and dispensing fee applied to that total. A compound prescription with a total quantity of 180 on

the other hand must be evaluated in terms of the amount of active ingredient and not total quantity. Unfortunately, with paper billing it is not always easy to make that determination.

Today, the majority of states have remained silent on compound reimbursement. As a result, pricing is generally based on "usual and customary," which is ill defined; or an implied assumption that compounds will be reimbursed via the same fee schedule as traditional brand or generic pharmaceuticals. The latter assumption or practice is particularly problematic.

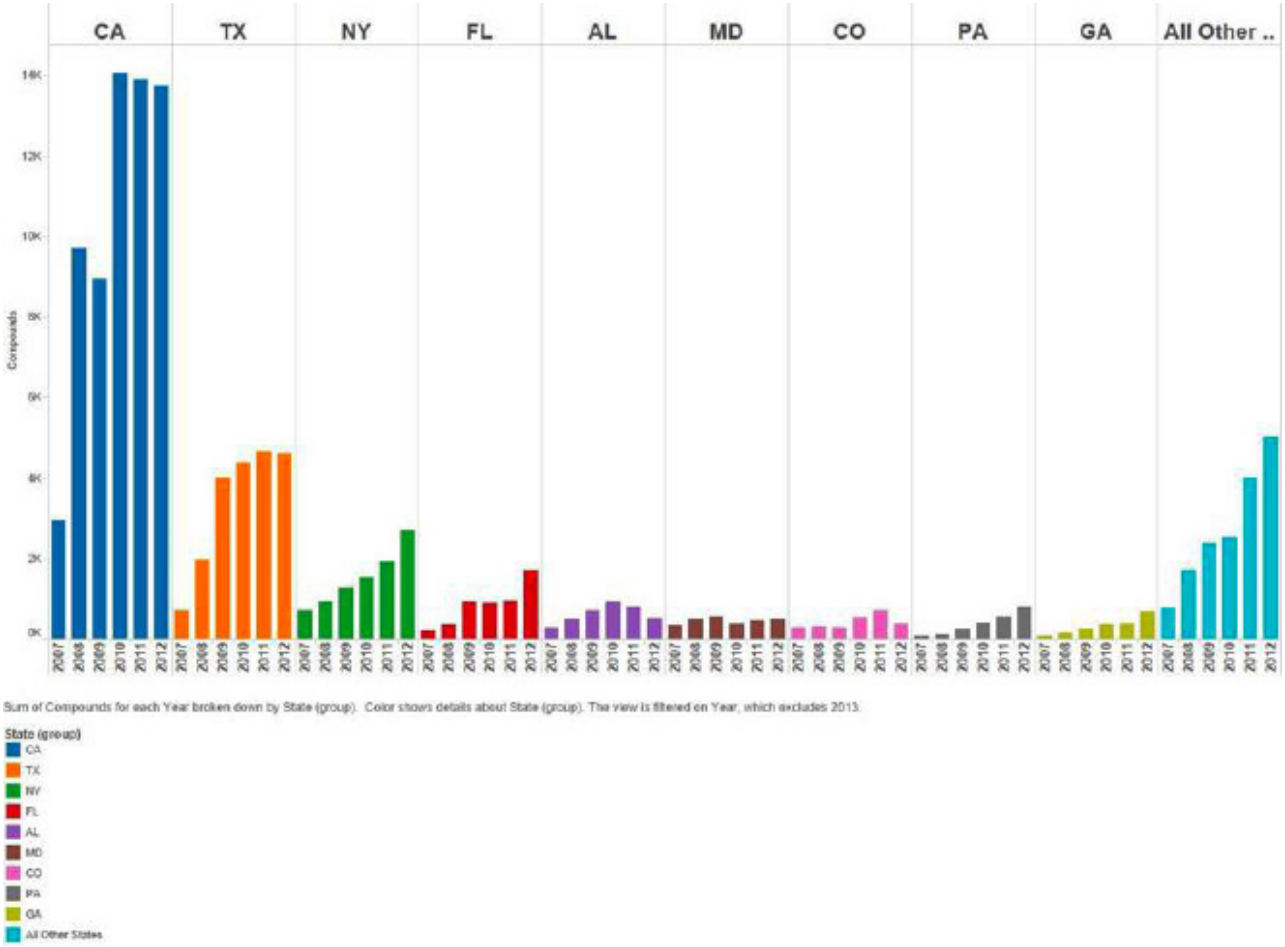
By definition, compounds are neither brand nor generic therefore neither fee schedule would apply unless the state has created a rule like Louisiana specifying that the generic rate will be used. To further complicate matters, compound ingredients are assigned a Multi-Source Code by Medispan of "N," which traditionally indicates a brand name pharmaceutical. When it applies to compounding ingredients the "N" designation actually means "Not Applicable."

The pharmacy industry has attempted to remedy many of the concerns outlined above through the National Council for Prescription Drug Programs (NCPDP). NCPDP is an American National Standards Institute (ANSI)-based, member-driven organization that establishes standards for the on-line processing of prescription drugs. The latest version, identified as the Telecommunication Standard Version D.0, is the only HIPAA approved version available (see www.ncpdp.org/hipaa.aspx). Among other things D.0 supports the transmission of multiple ingredients included in a single prescription, which is a significant step forward in that each ingredient may be evaluated both for its exact quantity as well as for any clinical pharmacy concerns regarding all drugs that a patient may receive. In other words there will be no overstated quantities or "hidden" ingredients.

The rationale for clear and comprehensive reimbursement guidance is in part driven by the dramatic increase in the volume of compounded drug prescriptions. For decades there was little reason for a workers' compensation policy maker to be concerned with compounds. As a result, most states' regulations are silent when it comes to reimbursement of these drugs.

The following graph illustrates the proliferation of compounding for workers' compensation since 2007. The graph is based on 145,146 compounded drug prescriptions processed by four different workers' compensation PBMs, and it provides a trending analysis on which certain conclusions may be based.

Proliferation of Compounding Prescriptions Since 2007



The above graph is based on a limited sample size of data representing 145,146 prescriptions processed by four different workers' compensation PBMs.

It has long been presumed that the compounding proliferation started in California and then spread to other states. That assumption is certainly supported by this analysis, which indicates that California represents almost half of all prescriptions included in the study and still represented 44.84% of all compounding prescriptions analyzed for 2012. However, the data is insufficient to confirm another widely held belief which is that alignment of the California workers' compensation prescription fee schedule to that state's Medicaid or Medi-Cal reimbursement caused pharmacy providers to seek more lucrative reimbursement through compounding: neither profitability nor therapeutic decisions were included in the data.

Based on the available data, other trends may be observed, including the following:

- Compounding prescriptions included in the study data increased almost five-fold during the study period from 6416 in 2007 to 30,669 in 2012
- Six states – CA, TX, NY, FL, GA and PA – represent 80.10% of all compound prescriptions included in the data
- These same six states still represented 79.16% of all compound prescriptions for 2012
- Only two states had zero compounding prescriptions throughout the sample period: ND and WY
- Of the remaining 42 states, in aggregate there has been a year-over-year increase in compound prescriptions
- Only three states among the top nine – AL, MD, and CO – have experienced a decline in compounding between years during the study period

It is important to note that changes in contracts between national and state workers' compensation payers and PBMs may impact whether data was available throughout the study period. However, it is still apparent from the data that compounding is a growing trend, and as such, deserves attention from all stakeholders: workers' compensation payers, state policy makers, providers, PBMs and others involved in the provision of care or the establishment of guidelines for treatment of injured workers.

Therefore, it would behoove all states to create or re-examine their rules concerning these products, and a prudent approach would incorporate the following elements:

- Ensure that guidelines that define appropriate use of these products are in place
- Ensure that the fee schedule, if any, specifically addresses compounds and eliminates any confusion that exists in today's environment
- Ensure that compounding prescriptions are either processed on-line compliant with D.0 or, if billed on paper, utilize the Universal Claim Form

Conclusions

The compounding of drugs will, and should, remain a part of patient care. Compounding might be the only avenue available to provide medications to patients with unique needs. The time-honored physician–patient–pharmacist relationship has, until recently, ensured that a conflict of interest related to financial gain did not exist. The physician diagnoses a patient's condition and prescribes the appropriate medication, which may or may not be a compound. The patient then takes that prescription to the pharmacist of his or her choice. The pharmacist reviews the prescription for any clinical concerns and then fulfills the prescription and counsels the patient. The fact that the pharmacist makes money from the sale of the prescription has never created a conflict of interest since the pharmacist cannot prescribe medications except in very limited situations.

All that changed when pharmacists began marketing their compounding services directly to physicians. Some adopted marketing strategies used by pharmaceutical manufacturers, albeit in a less organized manner. As a result, those pharmacists have created a market for compounding that did not exist under the traditional triad relationship. Furthermore, that marketing has led to a conflict of interest in that the pharmacist is now directly influencing what is prescribed, which pharmacy to utilize, and how much to charge.

That alone should be enough to prompt reform, but unfortunately another practice began that violated the physician–patient–pharmacist relationship: the preparation and distribution of compounded sterile medications in advance of a prescription. These were not just in one or two doses, but in prepared lots of thousands of doses.

The traditional relationship is a strictly a one-to-one relationship in that the physician writes a prescription that is unique to one patient, and the pharmacist dispenses that prescription only after the patient presents that prescription to him or her. Pharmacists cannot sell prescription drugs without a prescription; that requires a wholesaler license. Likewise, pharmacists cannot compound medication in advance of a prescription except for very limited quantities; a manufacturing license is required for that.

Therefore, the preparation of compounded medications in bulk is essentially manufacturing without a license. If a manufacturing license had been obtained by these "pharmacies," then they would have been subject to FDA oversight, and the tragedy highlighted by NECC and the meningitis outbreak may have been avoided.

At this writing, it has been just over a year since a meningitis outbreak brought national attention to compounding. Prior to that event, little attention was placed on the regulation of compounding, and that lack of attention resulted in dire consequences. Although not all of the questions around oversight have been answered, it is now clear that at least some of the oversight responsibility will shift from the various state boards of pharmacy to the FDA.

That shift will most certainly impact all aspects of sterile compounding. Most significantly for the workers' compensation community, there will be more stringent controls around the preparation of sterile intrathecal products. These controls may drive up costs for these products, or on the other hand, they may remove the profitability for performing these procedures.

In addition to the impact on sterile compounding, FDA oversight will undoubtedly impact non-sterile compounding as well. At a minimum, the FDA is charged with making sure that drugs approved for use are "safe and effective." Neither statement can be proven for compounded drugs today.

One may argue that the nature of compounds necessitates a custom preparation that is not conducive to the rigorous tests imposed on drug manufacturers. Although true, this does not negate the FDA's role. One avenue the FDA could take would be to create a Risk Evaluation and Mitigation Strategy for compounds, similar to what the agency has done for opioids, chemotherapy, and other dangerous remedies.

In addition, fee schedule limitations on compounded prescriptions need to be revised and updated. At a minimum, such regulations must recognize that by definition compounds are neither brand nor generic – the fee schedule must address compounds specifically. In addition, the regulations must recognize and require the use of NCPDP D.0 standards for either on-line prescription processing, or the use of NCPDP's Workers' Compensation/ Property & Casualty Universal Claim Form (WC/PC UCF) if billed on paper. More progressive limitations would even require proof of a trial and failure of traditional prescription drugs before initiation of a compound.

Lastly, as a payer, the following considerations should be made before approval of payment for a compounded medication:

- **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, and if a decision is made to authorize the compounded medication, require a signed informed consent by the patient**

Although compounding is finally getting the attention it deserves from federal and state policy makers, but one cannot assume that these compounded preparations are all produced with the skill and attention patients expect. The decision to prescribe and approve these products puts a burden on the payer and the prescriber to ensure all of the considerations outlined above have been met and that the safety and well-being of the patient is assured.

CompPharma is a consortium of workers' compensation pharmacy benefit managers (PBMs) that identifies and prioritizes industry-wide problems and then develops and delivers solutions. CompPharma's member PBMs are:

Catamaran
Express Scripts
HealthCare Solutions (Cypress Care, Modern Medical & ScripNet)
Healthesystems
myMatrixx
Progressive Medical & PMSI

Appendices

Appendix A: Amitriptyline

Citation	Comments
Ho KY, Huh BK, White WD, Yeh CC, Miller EJ. Topical amitriptyline versus lidocaine in the treatment of neuropathic pain. The Clinical Journal of Pain. 2008;24(1):51-5.	Topical 5% amitriptyline was not effective
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Lynch ME, Clark AJ, Sawynok J. A pilot study examining topical amitriptyline, ketamine, and a combination of both in the treatment of neuropathic pain. The Clinical Journal of Pain. 2003;19(5):323-8.	No statistically significant difference from placebo after 2 days for any treatment during the double blind component of the trial.
Gerner P, Kao G, Srinivasa V, Narang S, Wang GK. Topical amitriptyline in healthy volunteers. Regional anesthesia and pain medicine, 2003, 28(4), 289	(N/A – various concentration of amitriptyline in 45% water/45% isopropanol/10% glycerin solution were applied to skin of 14 healthy volunteers with gauze, occluded, then pain was induced with a blunt needle.)
Dualé C, Daveau J, Cardot JM, Boyer-Grand A, Schoeffler P, Dubray C. Cutaneous amitriptyline in human volunteers: differential effects on the components of of sensory information. Anesthesiology, 2008, 108(4): 714.	(N/A -16 healthy young male volunteers were tested for mechanical (touch and nociception), and thermal (cold, warm, and heat sensation) thresholds)
Brown CS, Wan J, Bachmann G, Rosen R. Self-management, amitriptyline , and amitripyline plus triamcinolone in the management of vulvodynia. J Womens Health. 2009;18(2):163-9.	(N/A-unrelated condition - vulvodynia)
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Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD, Kugler M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy- induced peripheral neuropathy: NCCTG trial N06CA. Support Care Cancer. 2011;19(6):833-41.	Trended toward some improvement in symptoms; more study is needed
Javadzadeh A, Vatanpour H, Delavarian Z, Momajed A, Esmaeily H, VatanpoSur M. Efficacy of clobetasol, ketoconazole and amitryptiline mouthwash on Oral Lichen Planus. Iranian Journal of Pharmaceutical Research. 2008; 7(3): 171.	(N/A-oral mucosa not comparable to skin; immunologic condition unrelated to neuropathic pain)

Appendix B: Baclofen

Citation	Comments
Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD, Kugler M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy- induced peripheral neuropathy: NCCTG trial N06CA. Support Care Cancer. 2011;19(6):833-41.	Trended toward some improvement in symptoms; more study is needed
Pachman DR, Barton DL, Watson JC, et al. Chemotherapy-induced peripheral neuropathy: prevention and treatment. Clin Pharmacol Ther. 2011 Sep;90(3):377-87.)	Review of treatments; results indicate benefit for chemotherapy-induced peripheral neuropathy.

Appendix C: Clonidine

Campbell C, Kipnes MS, Stouch B, et al. Randomized controlled trial of topical clonidine for treatment of painful diabetic neuropathy. Pain. 2012 Sept;153(9):1815-23.	179 subjects; 0.1% gel; diabetic peripheral neuropathy; trend toward decreased foot pain (p=0.07).

Appendix D: Cyclobenzaprine

No citations found	

Appendix E: Gabapentin

Boardman LA, Cooper AS, Blais LR, Raker CA. Topical gabapentin in the treatment of localized and generalized vulvodynia. Obstet Gynecol. 2008 Sep;112(3):579-85.	Treatment of vulvodynia

Appendix F: Guaifenesin

No citations found	

Appendix G: Imipramine

No citations found	

Appendix H: Ketamine

Citation	Comments
Barton DL, Wos EJ, Qin R, Mattar BI, Green NB, Lanier KS, Bearden JD, Kugler M, Christensen B, Loprinzi CL. A double-blind, placebo-controlled trial of a topical treatment for chemotherapy- induced peripheral neuropathy: NCCTG trial N06CA. Support Care Cancer. 2011;19(6):833-41.	Trended toward some improvement in symptoms; more study is needed
Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. Pain. 2009;146(1-2):18-25.	20 PATIENTS; study shows promise for the use of topical ketamine
Lehman JS, Sciallis GF. Effective use of topical amitriptyline hydrochloride 2.5% and ketamine hydrochloride 0.5% for analgesia in refractory proctodynia. J Drugs Dermatol. 2008 Sep;7(9):887-9	Case report
Lynch ME, Clark AJ, Sawynok J, Sullivan MJ. Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Anesthesiology. 2005.103(1):140-6.	Small, open-label study; no difference between active and placebo groups.
Lynch ME, Clark AJ, Sawynok J. A pilot study examining topical amitriptyline, ketamine, and a combination of both in the treatment of neuropathic pain. The Clinical Journal of Pain. 2003;19(5):323-8.	No statistically significant difference from placebo after 2 days for any treatment during the double blind component of the trial.
Lynch ME, Clark AJ, Sawynok J, Sullivan MJ. Topical amitriptyline and ketamine in neuropathic pain syndromes: an open-label study. J Pain. 2005 Oct;6(10):644-9.	No significant improvement in pain scores compared to placebo.
Pöyhiä R, Vainio A. Topically administered ketamine reduces capsaicin-evoked mechanical hyperalgesia. The Clinical journal of pain. 2006;22(1):32-6.	Significant reduction of mechanical hyperalgesia was produced by topically applied ketamine in healthy patient
Shirani P, Salamone AR, Schulz PE, Edmondson EA. Ketamine treatment for intractable pain in a patient with severe refractory complex regional pain syndrome: a case report. Pain Physician. 2008 May-Jun;11(3):339-42.	Case report
Ushida T, Tani T, Kanbara T, Zinchuk VS, Kawasaki M, Yamamoto H. Analgesic effects of ketamine ointment in patients with complex regional pain syndrome type 1. Reg Anesth Pain Med. 2002 Sep-Oct;27(5):524-8.	Case report

Appendix I: Nifedipine

Citation	Comments
Appalaneni V, Fanelli RD, Sharaf RN, et al. The role of endoscopy in patients with anorectal disorders. Gastrointest Endosc. 2010 Dec-72(6):1117-23.	All 4 studies study use of nifedipine for anal fissures; pain relief was noted; extrapolation to topical use for other conditions is questioned.
Golfam F, Golfam P, Khalaj A, et al. The effect of topical nifedipine in treatment of chronic anal fissure. Acta Medica Iranica. 2010;48(5):225-299.	
Perrotti P, Bove A, Antropoli C, et al. Topical nifedipine with lidocaine ointment vs. active control for treatment of chronic anal fissure: results of a prospective, randomized, double-blind study. Dis Colon Rectum. 2002;45(11):1468-75.	
Perrotti P, Antropoli C, Molino D. et al. Conservative treatment of acute thrombosed external hemorrhoids with topical nifedipine. Dis Colon Rectum. 2001 Mar;44(3):405-9.	

Appendix J: NSAIDs

Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD007400. DOI: 10.1002/14651858.CD007400.pub2.	Topical NSAIDs can provide good levels of pain relief; topical diclofenac solution is equivalent to that of oral NSAIDs in knee and hand osteoarthritis, but there is no evidence for other chronic painful conditions. Formulation can influence efficacy. The incidence of local adverse events is increased with topical NSAIDs, but gastrointestinal adverse events are reduced compared with oral NSAIDs.
Altman RD, Barthel HR. Topical therapies for osteoarthritis. Drugs. 2011 Jul 9; 71(10):1259-79.	Topical NSAIDs demonstrate improved safety and tolerability over oral NSAIDs.
Baixauli F, Ingle´s F, Alca´ ntara P, et al. Percutaneous treatment of acute soft tissue lesions with naproxen gel and ketoprofen gel. J Int Med Res. 1990;18:372–378.	Small, single blind study; naproxen gel more effective than ketoprofen gel
Kai S, Kondo E, Kawaguchi Y, Kitamura N, Yasuda K. Flurbiprofen Concentration in the Soft Tissues Is Higher after Topical Application than after Oral Administration. Br J Clin Pharmacol. 2012 Jul 24.	16 patients; measured blood and tissue concentrations after oral or topical administration.

Appendix K: Orphenadrine

Citation	Comments
No citations found	

Appendix L: Pentoxifylline

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Appendix M: Tramadol

Akbay BK, Yildizbas S, Guclu E, et al. Analgesic efficacy of topical tramadol in the control of postoperative pain in children after tonsillectomy. J Anesthesia. 2010;24(5): 705-8. Accessed February 8, 2013.	Pediatric patients, post-tonsillectomy; topical application of 5% tramadol in saline.

Appendix N: Verapamil

Fitch WP 3rd, Easterling WJ, Talbert RL, et al. Topical verapamil HCl, topical trifluoperazine, and topical magnesium sulfate for the treatment of Peyronie's disease-a placebo-controlled pilot study. J Sex Med. 2007 Mar;4(2):477-84.	Topical gel for treatment of painful erections (Peyronie's Disease); showed benefit; extrapolation to other conditions is questioned.

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