U.S. FOOD & DRUG ADMINISTRATION

Assessment of the Available Scientific Data Regarding the Safety and Effectiveness of Ingredients Used in Compounded Topical Pain Products

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Overview

Compounded Drugs and Their Use

- Drug compounding is often regarded as the process of combining, mixing, or altering a drug or its ingredients to create a sterile or non-sterile medication tailored to the needs of a patient.
- Compounded drugs can be important for patients whose medical needs cannot be met by an approved drug, such as for patients who:
  - Have an allergy to an ingredient of an approved drug
  - Cannot swallow a tablet or capsule and need a medicine in a liquid dosage form that is not otherwise available
- Compounded drugs are not reviewed by FDA for safety, efficacy, or manufacturing quality before marketing.
- Most compounders do not report adverse events to FDA.

Compounding Under Section 503A

- Section 503A of the Federal Food, Drug and Cosmetic Act (FD&C Act) describes the conditions under which drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, can qualify for exemptions from three sections of the FD&C Act:
  - FDA premarket approval requirements (section 505)
  - Current Good Manufacturing Practice (CGMP) requirements (section 501(a)(2)(B))
  - Labeling with adequate directions for use (section 502(f)(1))

- Generally, state boards of pharmacy have primary responsibility for the day-to-day oversight of state-licensed pharmacies that are not registered with FDA as outsourcing facilities. These compounders generally do not register with FDA.

Conditions of Section 503A Include:

- Drug is compounded for an identified individual patient based on the receipt of a valid prescription order
- If the drug is compounded from a bulk drug substance, it must:
  - be a component of an approved drug product, or
  - comply with the standards of an applicable USP or NF monograph and the USP chapter on pharmacy compounding, or
  - be on a list established by FDA.
- Compounders do not compound, regularly or in inordinate amounts, drug products that are “essentially copies” of a commercially available drug product.

Compounding Under Section 503B

- Section 503B of the FD&C Act describes the conditions under which drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility can qualify for exemptions from three sections of the FD&C Act:
  - FDA premarket approval requirements (section 505)
  - Labeling with adequate directions for use (section 502(f)(1))
  - Drug supply chain security requirements (section 582)

- Outsourcing facilities are not exempt from CGMP requirements
- Outsourcing facilities must register with FDA and are subject to risk-based FDA inspections.

Conditions of Section 503B Include

- Outsourcing facilities may or may not receive prescriptions for identified individual patients.
- Drug is compounded in an outsourcing facility that does not compound using a bulk drug substance unless it appears on a list established by FDA of bulk drug substances for which there is a "clinical need" or unless the drug compounded appears on the drug shortage list
  - FDA is reviewing nominated bulk drug substances for the "503B bulks list"
- The compounded drug is not "essentially a copy" of one or more approved drugs

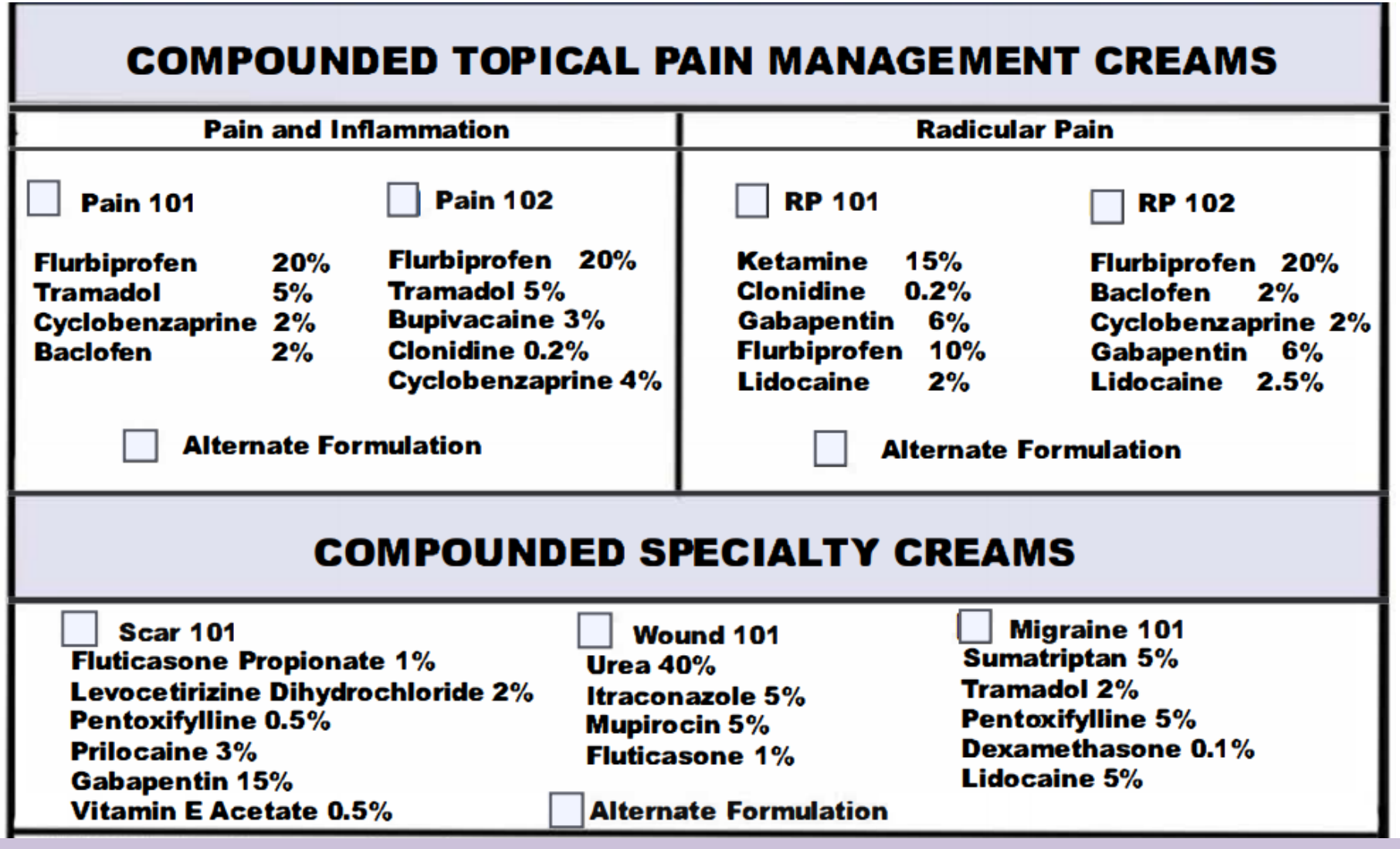
Compounded Topical Pain Products

- Many pharmacies compound topical pain products.
- Such products may contain multiple active ingredients, sometimes up to 7 or 8.
  - Some ingredients are active ingredients in FDA-approved topical pain products (e.g., lidocaine).
  - Other ingredients may be in FDA-approved non-topical pain medications (e.g., oral).
  - Still others may be found in drugs approved for non-pain indications.

Compounded Topical Pain Products

- Examples of current practice
  - A prescriber writes a prescription listing specific ingredients for a pharmacy to include in a compounded drug
  - A pharmacy provides prescribers with paper or web-based order / prescription forms that provide options for
    - Ingredient combinations for treatment of a specific pain condition/disease
    - Combinations of ingredients at set or variable concentrations

Example of order form



COMPOUNDED TOPICAL PAIN MANAGEMENT CREAMS

Pain and Inflammation

☐ **Pain 101**

Flurbiprofen	20%
Tramadol	5%
Cyclobenzaprine	2%
Baclofen	2%

☐ **Pain 102**

Flurbiprofen	20%
Tramadol	5%
Bupivacaine	3%
Clonidine	0.2%
Cyclobenzaprine	4%

☐ **Alternate Formulation**

Radicular Pain

☐ **RP 101**

Ketamine	15%
Clonidine	0.2%
Gabapentin	6%
Flurbiprofen	10%
Lidocaine	2%

☐ **RP 102**

Flurbiprofen	20%
Baclofen	2%
Cyclobenzaprine	2%
Gabapentin	6%
Lidocaine	2.5%

☐ **Alternate Formulation**

COMPOUNDED SPECIALTY CREAMS

☐ **Scar 101**
Fluticasone Propionate 1%
Levocetirizine Dihydrochloride 2%
Pentoxifylline 0.5%
Prilocaine 3%
Gabapentin 15%
Vitamin E Acetate 0.5%

☐ **Wound 101**
Urea 40%
Itraconazole 5%
Mupirocin 5%
Fluticasone 1%

☐ **Alternate Formulation**

☐ **Migraine 101**
Sumatriptan 5%
Tramadol 2%
Pentoxifylline 5%
Dexamethasone 0.1%
Lidocaine 5%

Source: https://www.newportbeachortho.com/wp-content/themes/ypo-theme/pdf/transdermal-prescription-order-form.pdf

Examples of Potential Benefits Stakeholders Associate with Compounded Topical Pain Products

- Some practitioners view compounded topical pain products as an effective alternative to highly addictive oral pain medications.
- Some clinicians report that compounded topical pain products selectively deliver drugs to peripheral sites of action or may be associated with improved tolerability because they avoid contact with the gastrointestinal system.
- Some compounders claim that they provide customizable dosages and formulations that permit combining multiple drugs with various mechanisms of action, allowing a single product to target multiple receptors of pain.
- Some compounders claim that compounded topical pain products provide for less systemic absorption and fewer side effects, less potential for abuse, and are more convenient than oral pain medications.

Examples of Concerns Associated with Compounded Topical Pain Products

- Compounded drugs are not reviewed by FDA for safety, effectiveness, or quality before they are marketed.
- Unknown effectiveness of certain ingredients used in topical formulations.
- Unknown safety of certain ingredients used in topical formulations, either alone or in combination.
- Unknown potential for systemic absorption and toxicity, particularly if there is excessive application or enhanced absorption of an ingredient.
  - For example, in 2015, a patient died after using a compounded topical anesthetic cream. A court heard evidence that the cause of death was ketamine and/or cyclobenzaprine toxicity.

Examples of Concerns Associated with Compounded Topical Pain Products

- Examples of healthcare fraud
  - In June 2016, the HHS OIG reported significant increases in Medicare Part D spending and questionable billing practices for compounded topical pain products.
  - Department of Justice has brought enforcement actions against hundreds of defendants across the country, targeting schemes involving billing Medicare, Medicaid, and TRICARE (a health insurance program for members and veterans of the armed forces and their families) for compounded topical products.

Statement of Task

The committee will:

- Identify and analyze the available scientific data relating to the ingredients used in compounded topical pain medications and
- Evaluate how those data translate to the safety and effectiveness of such products with various combinations of those ingredients.

Based on this assessment, the committee will develop a report that summarizes its findings, including addressing the following specific items:

- Identify the ingredients that the available scientific data suggest may not be safe and/or effective to treat pain topically,
- Describe the concentrations and combinations of ingredients that may raise significant safety issues, and
- Comment on the level of benefit expected for the various ingredients given their likelihood of absorption through the skin.

Based on these findings, the report will offer recommendations with respect to how the available evidence of safety and effectiveness should inform the use of compounded topical pain creams to treat patients.

Proposed Ingredients for Review

Ingredients identified in examples of compounded topical pain medication formulas and that are either:	
Found in approved drug with a pain indication, but not for topical use	**Found in approved drug without a pain indication, but some evidence exists to suggest the ingredient was used in compounding for properties to treat pain**
BACLOFEN BUPIVACAINE CAFFEINE CARBAMAZEPINE CLONIDINE CYCLOBENZAPRINE GABAPENTIN ORPHENADRINE PROMETHAZINE TIZANIDINE TOPIRAMATE TRAMADOL **Nonsteroidal Anti-inflammatory Drugs (NSAIDS)**: FLURBIPROFEN IBUPROFEN INDOMETHACIN KETOPROFEN MELOXICAM NAPROXEN PIROXICAM	AMANTADINE AMITRIPTYLINE ARIPIPRAZOLE CLOMIPRAMINE DALFAMPRIDINE DEXAMETHASONE DEXTROMETHORPHAN DILTIAZEM DOXEPIN GUAIFENESIN HALOPERIDOL KETAMINE KETOTIFEN LOPERAMIDE MEMANTINE NIFEDIPINE PENTOXIFYLLINE PHENYTOIN

Use of this Research

- FDA has sought NASEM's evaluation of available evidence of the safety and effectiveness of the ingredients used in compounded topical pain medications to:
  - Inform FDA's compounding work, including evaluation of which bulk drug substances may be used in compounding by outsourcing facilities.
  - Inform healthcare providers' prescribing decisions and patients' choices about pain medications.
  - Provide valuable information to other federal entities that may reimburse for these products, such as the Centers for Medicare and Medicaid Services and the Department of Defense.
- NASEM's findings may relate to the safety and effectiveness of individual ingredients used in compounded topical pain medications, or groups or classes of ingredients used in compounded topical pain medications.
- FDA is also interested in NASEM's impressions of whether there are significant scientific or public health issues related to the compounding and use of these products generally.

Scientific Background

Scientific background

- Pain pathways and pharmacologic targets
- Systemic and local delivery in topical formulations
- Products containing multiple active ingredients

Understanding Pain

- Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”
- We experience pain as a defensive and adaptive mechanism to protect ourselves from harm
- The ability to diagnose and treat pain depends on our understanding of the various processes involved in experiencing pain

From http://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Pain

Origin of Pain

- Pain can be subdivided by origin of the pain - *nociceptive, neuropathic, or of mixed nociceptive/neuropathic origin.*
- *Nociceptive pain* is defined as pain arising from stimulation of somatic or visceral nociceptors
  - Visceral pain affects internal organs (e.g., pancreatitis, renal colic)
  - Nonvisceral pain affects skin or musculoskeletal sites (e.g., postoperative orthopedic surgery, fractures, and other musculoskeletal pain)
- *Neuropathic pain* is defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system.
  - Peripheral neuropathic pain syndromes (e.g., painful diabetic peripheral neuropathy, postherpetic neuralgia, complex regional pain syndrome, and HIV-associated neuropathy)
  - Central neuropathic (e.g., postspinal injury pain, poststroke pain, multiple sclerosis)

From FDA **Guidance for Industry Analgesic Indications:** Developing Drug and Biological Products

Pathway of Nociceptive Pain

The process of pain can be divided into four general steps:

1. Transduction
2. Transmission
3. Perception
4. Modulation

Reference: Loveridge, R. and Patel, S. (2014). Systemic non-opioid adjuvant analgesics: Their role in acute postoperative pain in adults. *Trends in Anaesthesia and Critical Care*, [online] 4(1), pp.10-18. Available at: https://www.sciencedirect.com/science/article/pii/S2210844013001305 [Accessed 5 Nov. 2018].

Pharmacologic Targets of Transduction

Drug classes that include FDA approved pain medications which target substances active at or adjacent to the site of transduction:

- Local Anesthetics
- NSAIDs
- Counterirritants
- Alcohols and Ketones
- Aspirin
- APAP

Reference: Nba.uth.tmc.edu. (2018). *Pain Principles (Section 2, Chapter 6) Neuroscience Online: An Electronic Textbook for the Neurosciences | Department of Neurobiology and Anatomy - The University of Texas Medical School at Houston*. [online] Available at: https://nba.uth.tmc.edu/neuroscience/m/s2/chapter06.html [Accessed 5 Nov. 2018].

Pharmacologic Targets of Modulation

Drug classes that include FDA approved pain medications which target neurotransmitters active at the site of modulation:

- Opioids
- GABA derivatives
- Antidepressants
- Alpha-2 Agonists
- Systemic Anesthetics

Reference: Rnceus.com. (2018). *Nociceptive Pain*. [online] Available at: http://www.rnceus.com/ages/nociceptive.htm

Systemic and Local Delivery in Topically-Applied Formulations

- Topically-applied products can have either or both systemic and local effect
  - **Systemic effect**– the drug is absorbed through the skin for distribution throughout the body by the systemic circulation. The drug does not have to be applied on the skin at the site of pain.
  - **Local effect** – the drug is applied and absorbed into the skin at the site of pain.
- Compounded pain drugs applied topically at the site of pain may be intended to have a local effect, but also may have a systemic effect.

Systemic versus Local Drug Delivery

- Drug that penetrates the subcutaneous tissue and enters the blood can elicit a systemic effect, while drug that remains in the skin can elicit a local effect.
- Certain characteristics may make a drug more likely to be systemically absorbed, such as drugs with moderate lipophilicity.
- Semisolid formulations such as creams or gels are often used to deliver drugs locally, but can also deliver drugs systemically.
- In other cases, drugs intended for systemic absorption are placed in more complex transdermal delivery systems to better control their release. Such systems are not the focus of this study.

Reference:
http://www.newdirectionsaromatics.com/blog/20110323/detoxifying-with-essential-oils/151/skin-layers_istock_000013091643xsmall

Systemic v. Local Drug Delivery

- Semisolid dosage form can deliver a drug both locally and systemically.
- Topically-applied drugs approved by FDA for systemic absorption are often in more complex transdermal delivery systems, rather than in semisolid dosage forms, to better control their release.
- FDA is considering whether to propose to add drug products that employ matrix or reservoir type transdermal or topical delivery systems to the list of products that present demonstrable difficulties for compounding.

Reference: Adapted from Kathe K and Kathpalia H. Asian Journal of Pharmaceutical Sciences. 12 (2017) 487– 497

Examples of Prescription Topical Pain Products Approved by FDA

- **Systemic Effect**
  - Fentanyl transdermal system 12.5-100mcg/hr
  - Buprenorphine transdermal system 5-20mcg/hr
- **Local Effect**
  - Diclofenac 1% and 2% (solution, gel, cream)
  - Diclofenac epolamine topical system 1.3%
  - Lidocaine topical system 1.8% and 5%
  - Lidocaine 2.5% with prilocaine 2.5% cream (EMLA)
  - Capsaicin topical system 8%
  - Nitroglycerin ointment (Rectiv) 0.4%

FDA-Approved Products with Multiple Active Ingredients

- FDA regulation on fixed combination prescription drugs, 21 CFR 300.50, provides
  - Two or more drugs may be combined in a single dosage form **when each component makes a contribution to the claimed effects,** and
  - the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.
- Generally the benefit of each ingredient in the product is established through clinical data.

FDA-Approved Products with Multiple Active Ingredients

- **FDA Draft Guidance for Industry** Analgesic Indications: Developing Drug and Biologic Products
  - "a new combination of two or more analgesic drug substances must provide data that demonstrate that that 'each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug'"
  - studies that **compare** the fixed-combination drug product to individual component treatment arms (+/- placebo) over multiple doses is expected

Considerations in Support of Research Goals

Does the ingredient have a mechanism of action to treat pain?

- Does an FDA-approved drug exist that contains the ingredient for treatment of pain in a topical formulation or other formulation?
- Is there other evidence of a mechanism of action to treat pain, and what is the strength of that evidence?
- Is topical administration at the site of pain consistent with the ingredient's mechanism of action and intended effect?

Examples of Ingredients in Compounded Topical Pain Medications and Whether They Are Present in FDA Approved Formulations

Ingredient (Brand Drug Example)	Generic Drug Available	Approved Topical Formulation	Approved Pain Indication
Baclofen (Lioresal)	Yes	No. Intrathecal injection and oral.	Yes
Gabapentin (Neurontin)	Yes	No. Oral tablet, capsule, and solution.	Yes
Cyclobenzaprine (Amrix)	Yes	No. Oral tablet and capsule.	Yes
Clonidine (Catapres, Duraclon)	Yes	Yes. Oral, injectable, ophthalmic, transdermal (ER film)	Yes
Orphenadrine (Norflex)	Yes	No. Injection and oral.	Yes
Topiramate (Topimax, Qsymia)	Yes	No. Capsule (IR, ER) and tablet.	Yes
Meloxicam	Yes	No. Oral tablet, capsule, and suspension.	Yes
Tramadol (Ultram)	Yes	No. Oral tablet and capsule (IR, ER).	Yes
Amitriptyline (Elavil)	Yes	No. Oral, injectable.	No
Memantine (Namenda)	Yes	No. Oral tablet and capsule (IR, ER).	No
Aripiprazole (Abilify)	Yes	No. Oral, intra-muscular	No

Compounded Topical Products with Multiple Active Ingredients

ACTIVE INGREDIENTS USED IN COMPOUNDED MIGRAINE CREAMS

Sumatriptan
Apomorphine
Cyclobenzaprine
Diclofenac
Lidocaine
Prilocaine
Promethazine
Tizanidine
Tramadol

"Compounded migraine creams combine multiple therapeutic ingredients designed to reduce the duration and severity of migraine headaches."

Pharmacy website example
Source: https://starkpharmacy.com/specialty-creams/

Drug	Mechanism of Action	Indications for Approved Drug
Sumatriptan	$5HT_{1B/1D}$ agonist	Acute treatment of migraine with or without aura
Apomorphine	Precise MOA is unknown; believed to be due to stimulation of post-synaptic dopamine D_2 receptors	Acute, intermittent treatment of hypomobility, "off" episodes associated with advanced Parkinson's
Cyclobenzaprine	Structurally related to TCAs; Influences gamma and alpha motor systems by anticholinergic effects; acts primarily at the brain stem	Adjunct treatment for skeletal muscle spasm

Can the drug be effectively and safely delivered in a topical formulation?

- Is the drug delivered to the site of action in sufficient amounts to achieve an effect?
- Is a topical formulation appropriate to achieve effectiveness for drugs that have a systemic mechanism of action (e.g., drugs that are approved for oral use or, in some cases, controlled release via a transdermal system)?
- Is a topical formulation appropriate to safely deliver drugs to their site of action, whether local or systemic?
  - For example, is a semisolid dosage form appropriate to safely deliver a systemically absorbed ingredient in a safe and controlled manner?

Adverse Events Associated With Compounded Topical Pain Products

- 23 year man presents with altered mental status, slow heart rate, and hypertension
- Diagnosed with subarachnoid hemorrhage (stroke) and hypertensive emergency
- That day, he applied a compounded pain cream to large area of skin containing clonidine, gabapentin, imipramine, ketamine, lidocaine, and mefenamic acid
- Clonidine blood level was 5,200 ng/ml (reference range 0.5 – 4.5 ng/ml)

Table 1 Toxicological testing of the patient's initial serum specimen

Test	Result	Reference range
Clonidine[a]	5,200 ng/ml	0.5–4.5 ng/ml[b]
Lidocaine[c]	Not detected	1 μg/ml[d]
Monoethylglycinexylidide (MEG-X)[c]	Not detected	0.5 μg/ml[d]
Imipramine[a]	13 ng/ml	150–300 ng/ml[b]
Desipramine[a]	<10 ng/ml	150–300 ng/ml[b]

(J. Med. Toxicol. (2014) 10:61-64)

Adverse Events Associated With Compounded Topical Pain Products

- An 18-month-old healthy child had an ointment applied topically to a diaper rash, consisting of a single pump of a prescription ointment that his father received from a compounding pharmacy for neck pain.
- The ointment contained ketamine 100 mg, clonidine 2 mg, gabapentin 60 mg, mefenamic acid 10 mg, imipramine 30 mg, and lidocaine 10 mg per application.
- Approximately 20 minutes later, he had gasping respiration but was otherwise unresponsive.
- In the ED, physical examination was significant for unresponsiveness, pinpoint pupils, and hyporeflexia. The patient's mental status continued to deteriorate with depressed respirations, and he was intubated and placed on a ventilator.
- He did well over the next several hours with supportive care and had return to normal vital signs over the following 12 hours and eventually extubated.
- Blood taken at the time of ED presentation had a serum clonidine level of 9.2 ng/mL (reference range, 0.5-4.5 ng/mL) and a norketamine level of 41 ng/mL (reporting limit, >20 ng/mL).

(Pediatr Emerg Care. 2013 Nov;29(11):1220-2)

Considerations related to chemistry, including availability of scientific evidence to support that:

- The formulation, including inactive ingredients, does not adversely impact bioavailability of the active ingredient
- The active ingredients are physically and chemically compatible with each-other (if more than one in a formulation)
- The active ingredients do not physically or chemically interact with the product base (e.g., cream) or excipients (e.g., preservatives)
- The product is stable and does not degrade
- The product does not crystallize
- The product is of appropriate viscosity
- The product does not cause hypersensitivity or irritation, or other tolerability or use issues

For multi-ingredient topical pain creams, is there available scientific evidence to support that:

- each component makes a contribution to the effectiveness of the compounded topical pain product?
- the dosing interval and dosage are appropriate for all components?
- potential interactions between ingredients are understood and do not have a deleterious effect?

Compounded Topical Products with Multiple Active Ingredients

PRESCRIBER'S SIGNATURE: X_____**DATE:** _____

Commonly Requested Medications: (CMPD references a Medication Compounded by Pharmacy, TC references a Topical Cream, TS references a Topical Solution, CA references a Commercially Available Medication)

1. ____ CMPD Flurbiprofen 3.5%, Amitriptyline 0.5%, Gabapentin 1%, Lidocaine 2.25%, Prilocaine 2.25% TC (1794)
2. ____ CMPD Nabumetone 2.5%, Gabapentin 2.5%, Lidocaine 2.25%, Prilocaine 2.25% TC (1742)
3. ____ CMPD Meloxicam 0.09%, Topiramate 2.5%, Lidocaine 2.15%, Prilocaine 2.15% TC (1817)
4. ____ OTHER _____
5. ____ CMPD Gabapentin 5%, Lidocaine 2.25%, Prilocaine 2.25% TC (1754)

Directions: (Directions selected below apply to all medications indicated above – please check desired dosing)

____ Apply 4 grams three to four times daily for treatment of pain – DISPENSE #480 (FOUR-HUNDRED-EIGHTY) GRAMS FOR 30 DAY SUPPLY (PAINNORM)

____ OTHER _____

I authorize pharmacy to dispense any of the checked medications below, in lieu of medication checked above, if desired by the patient for any reason

____ CA Diclofenac Sodium 1.5% Solution #300ml (2 Bottles)– Apply 40 drops (1.3ml) to each painful area (up to 2 areas) three to four times daily (max of 10.4ml daily) (DICLOF) AND DISPENSE CA Lidocaine 2.5%, Prilocaine 2.5% Cream #480 grams – Apply 4 grams three to four times daily for treatment of pain (PAINNORM)

Source: https://2z3ul13mb9752eva2g4c8796-wpengine.netdna-ssl.com/wp-content/uploads/2017/09/Topical-Pain-Focused-Order-Form-V2.1.12.17-1.pdf

Summary of Scientific Considerations

- **Mechanism of Action:** A drug's mechanism of action does not necessarily lend itself to providing a meaningful benefit in all types of pain or in all dosage forms.
- **Drug Delivery in a Topical Formulation:** To achieve a desired effect, a drug must be delivered to the site of action in a controlled and appropriate amount. Many of the drug ingredients used in compounded topical pain products are in approved drugs that are only indicated for oral administration. This means there may not be information supporting topical administration for the approved drug. Relevant considerations include:
  - Dose (e.g., concentration, amount applied)
  - Duration of effect / reapplication timing
  - Variable absorption from topical pain products which will affect effectiveness and safety
- **Combined Active Ingredients:** Compounded topical pain products may contain five or more ingredients, which may have the potential to interact. In an FDA-approved product, such ingredients should all have a demonstrated benefit.
- **Chemical considerations:** formulation of active ingredient(s) and excipients can affect bioavailability. Chemical attributes of the active ingredient(s) (e.g., solubility, molecular weight, stability) can influence whether the ingredient can be absorbed through the skin.
- **Toxicity of certain ingredients can be serious if excess absorption occurs.**

Discussion and Questions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