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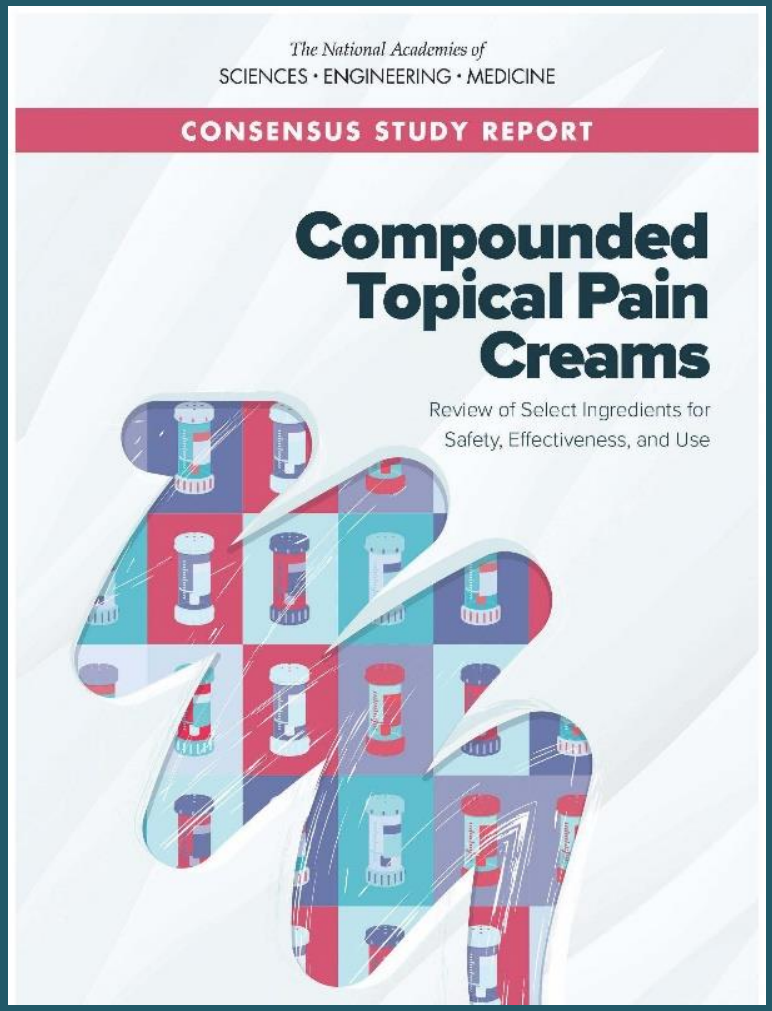
Compounded Topical Pain Creams:

Review of Select Ingredients for Safety, Effectiveness, and Use

Report Release
May 13, 2020
11:00 am (ET)



Report available for free download: https://nap.edu/25689

Study Sponsors

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

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Outline of Presentation

- Overview of study timeline, research approach, and methods
- Review of report's key messages and recommendations
- Question and comment period

Charge to the Committee

An ad hoc committee of the National Academies of Sciences, Engineering, and Medicine will conduct a study of the ingredients used in compounded topical pain creams. The committee will identify and analyze the available scientific data relating to the ingredients used in compounded topical pain creams and evaluate how that data translates to the safety and effectiveness of compounded topical pain creams 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 regarding the treatment of patients with compounded topical pain creams.

Study Timeline and Data Collection

- **March 2019**: Committee Meeting
- **April 2019:** Committee Meeting (virtual)
- **May 2019**: Committee Meeting and Public Workshop
- **July 2019**: Committee Meeting
- **September 2019**: Committee Meeting
- **February 2020**: Committee Meeting (virtual)

- **May 11, 2020**: Sponsor Briefing
- **May 13, 2020**: Public Release of Pre-publication Report

Additional Data Collection Efforts

- Review of Literature
- Stakeholder-Submitted Resources
  - American Association of Poison Control Centers
  - American Chronic Pain
  - Oral testimony
  - National Association of Boards of Pharmacy
  - U.S. Food and Drug Administration
  - Professional Compounding Centers of America

Study Background

Pain Care – Vital to the Nation

- Pain
  - Both a symptom and a disease.
  - Manifests in multiple forms, impacts all aspects of life.
  - CDC estimates that 50 million US adults live with chronic pain.
  - 1 in 5 adults across the world live with pain.
  - 1 in 10 adults are newly diagnosed with chronic pain each year.

- Pain management is complex
  - Complexity of pain management can increase for special populations

- Patients and providers seeking alternative or adjunct therapies to non-oral medications
  - The supply and demand for compounded topical pain creams has increased

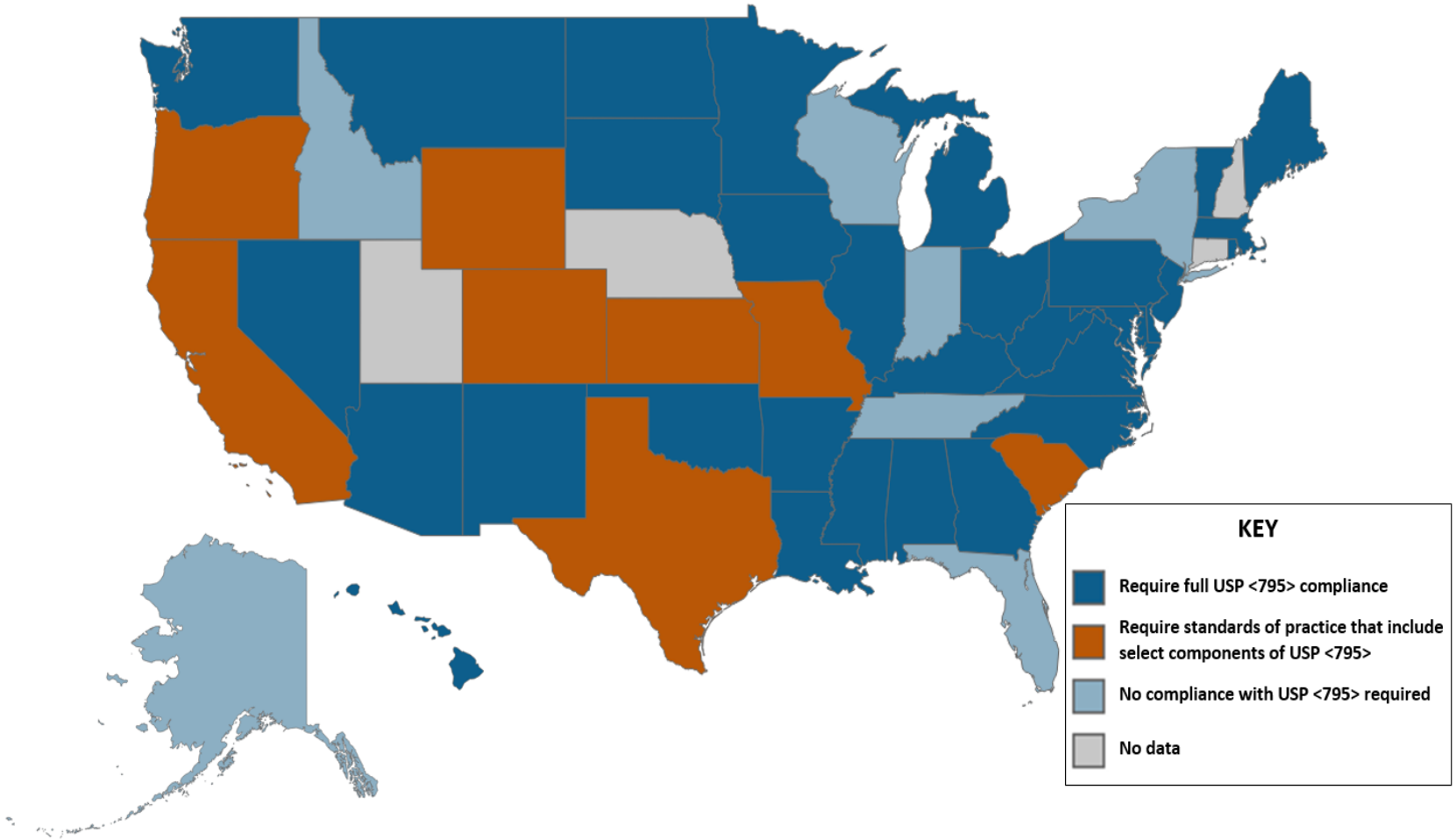
Compounded Drugs– History and Importance

- **The Basics of Compounding**
  - Long and important history in the field of pharmacy
  - Can be defined as the process of altering or combining ingredients to create medications that are tailored to meet the specific clinical needs of an individual patient
  - Compounded medications represent therapeutic alternatives for people with clinical needs not met by FDA-approved products

- **Current Relevance**
  - Historically small-scale, patient-specific, and ad hoc practice
  - Limited testing and regulatory oversight as compared to FDA-approved products
  - Emergence of compounding that is not patient specific with greater volumes sold across state lines
  - Potential patient population widened

Comparative Processes for FDA-Approved Products vs Compounded Preparations

Variability in State Required Compliance with USP <795> Non-Sterile Compounding Standards



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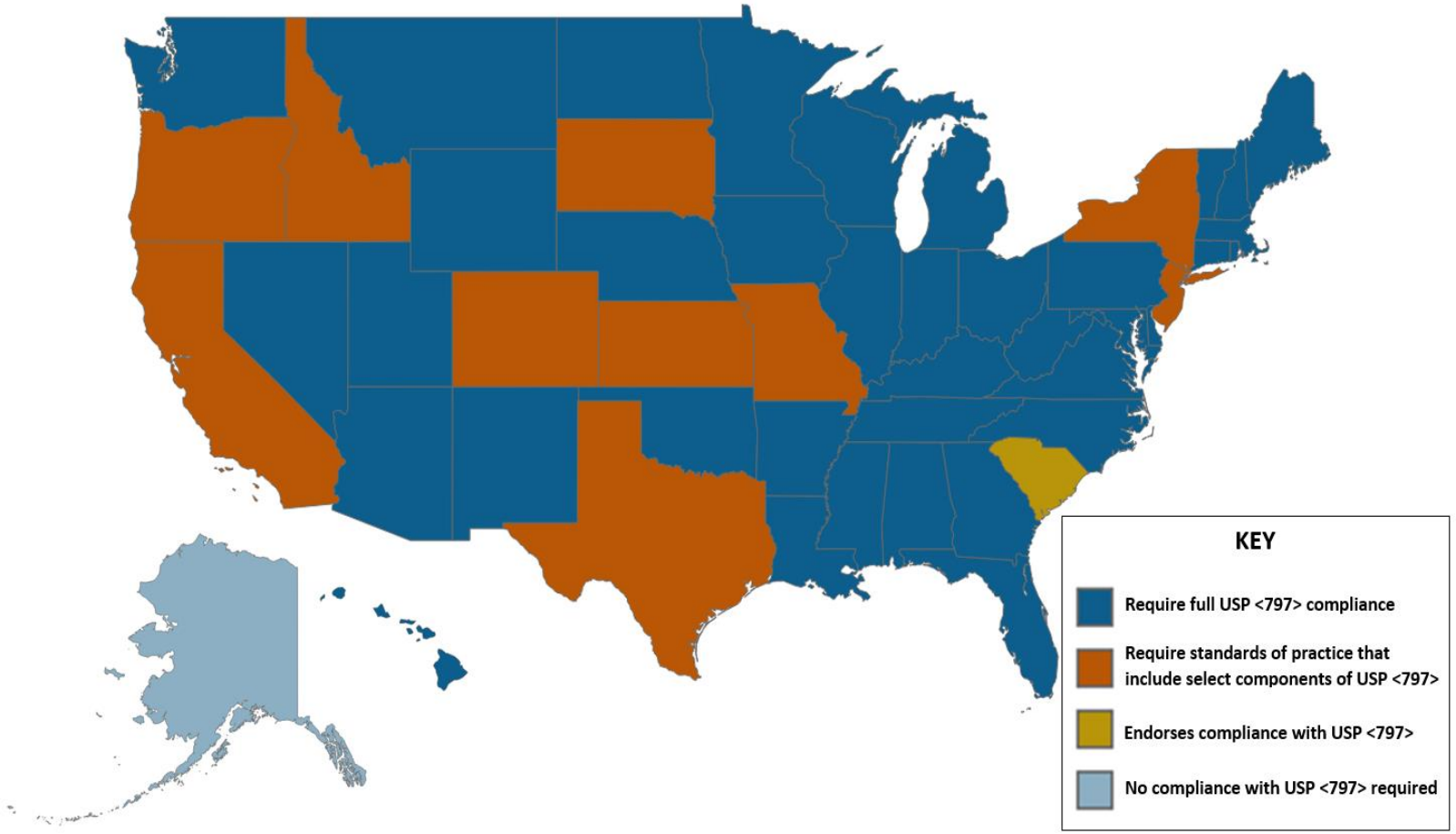
Variability in State Required Compliance with USP <797> Sterile Compounding Standards



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Key Concerns with Safety and Effectiveness

- **Safety**
  - The rate and extent of the drug's absorption into the skin and beyond is often unknown
  - No clear clinical rationale for specific combinations of APIs and dosages used
  - Inadequate labeling requirements for compounded preparations
    - detailed description of the formulation
    - clear guidance for use
    - caution for potential adverse effects
  - Limited and variable oversight of the development of compounded preparations
  - Documented cases of harm and, in some cases, death of patients using compounded topical pain creams
  - Nonstandardized surveillance procedures and protocols for reporting of adverse events, in most cases.
  - Few well-designed studies of compound safety

Key Concerns with Safety and Effectiveness

- **Effectiveness**
  - Little to no publicly available information on formulations and compounding protocols
  - Little to no justification available for formulations, doses, and whether skin penetration enhancers are being used and why
  - Little to no publicly available information on mechanisms of action of multiple APIs in a single formulations and with inactive elements of a compounded product
  - Few well-designed studies of formulation effectiveness

ACTIVE PHARMACEUTICAL INGREDIENTS (API) SELECTION AND EVALUATION PROCESS

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API Selection Process

- Selected 10 APIs identified by FDA as high priority
- Selected additional 10 ingredients commonly used in compounded topical pain creams

- APIs were selected based on
  - mechanism of action or drug class,
  - representation between and within relevant drug classes,
  - widespread use or relevance in clinical pain management, and
  - safety concerns or reported adverse events.

The omission of a category, or mechanism, does not imply safety or effectiveness, or potential usefulness of drugs in that category used in compounded topical pain creams.

APIs Identified by FDA

- **Muscle relaxant drugs**
  - baclofen
  - cyclobenzaprine
  - orphenadrine
- **Opioid agonists**
  - tramadol
- **NMDA receptor antagonists**
  - memantine
- **Alpha-2-adrenergic receptor agonists**
  - clonidine
- **Antiepileptics**
  - gabapentin
  - topiramate
- **Nonsteroidal anti-inflammatory drugs (NSAIDs)**
  - meloxicam
- **Antidepressants**
  - amitriptyline

APIs Identified by Committee

- **Anesthetics**
  - ketamine
  - bupivacaine
  - lidocaine
- **Antiepileptic**
  - carbamazepine
- **NSAIDs**
  - naproxen
- **Cannabinoid**
  - cannabidiol
- **Steroid**
  - dexamethasone
- **Calcium channel antagonist**
  - nifedipine
- **Antidepressant**
  - doxepin
- **Phosphodiesterase inhibitor**
  - pentoxifylline

Study Scope

- Topical vs transdermal
- Healthy and intact human skin
- Focus on nonsterile preparations
- Effectiveness vs efficacy

Committee Research and Evaluation Process

- Conducted a literature search to identify any publications on the 20 selected APIs applied topically
- Results were narrowed based on research questions and scope parameters
- Identified articles relevant to the committee's task were reviewed by one committee member and then discussed by the whole group
- Systematic reviews and all studies with a comparator group (RCTs, cohorts, and case control studies) were reviewed for findings on the safety and effectiveness of APIs when applied topically to treat pain on intact skin.
- For ingredients lacking in this level of evidence, case reports, case series, or preclinical studies were discussed where relevant.

Literature Results

- 22 RCTs reviewed *individual* APIs in compounded topical pain creams
  - 7 had a high risk of bias
  - 13 had a low risk of bias
  - 2 noted as having some concerns

- 11 RCTs reviewed *multiple* ingredients in compounded topical pain creams
  - 7 had high risk of bias
  - 3 had low risk of bias
  - 1 noted as having some concerns

Committee's Primary Research Conclusions

- Out of the 20 APIs reviewed, 3 individual APIs (doxepin, lidocaine, and naproxen) and 1 two-drug combination (pentoxifylline/clonidine) demonstrate potential clinical effectiveness in compounded topical pain creams.
  - Doxepin (tricyclic antidepressant) and lidocaine (local anesthetic) alone show evidence of effectiveness
  - Naproxen (nonsteroidal) alone has inconsistent evidence, but demonstrates potential effectiveness to treat certain types of pain.
  - A high dose of pentoxifylline/clonidine combination (vasodilator/nerve receptor agonist) has limited evidence of effectiveness in one pain model, possibly due to systemic absorption of its APIs, but additional studies are needed.

Committee's Primary Research Conclusions

- Data are inadequate to conclusively support conclusions regarding safety and risks related to the use of any compounded topical pain creams.
- High levels of systemic absorption of certain APIs in topical pain creams have occurred, potentially enabled by excipient selection.
- A substantial amount of high-quality research is still needed to identify effectiveness in all APIs reviewed as well as the relative risk for adverse effects in response to absorption of compounded topical pain creams.

Areas of Additional Committee Conclusions

Three additional critical areas of concern related to safety and effectiveness of compounded topical pain creams should be addressed:

1. Inadequate federal and state level regulation and oversight
2. Lack of data collection and surveillance
3. Inadequate level of training and education for health care providers and individuals who compound

Committee's Overarching Conclusions

- There is limited evidence to support the use of compounded topical pain creams to treat pain conditions in the general adult population. The few APIs that show potential effectiveness in compounded topical pain creams (doxepin (tricyclic antidepressant), lidocaine (local anesthetic), and naproxen (nonsteroidal) are either already available in FDA-approved topical products used to treat pain or in the case of naproxen, other NSAIDs (e.g., diclofenac) are in such FDA-approved products.
- In context of the recent rise in supply and demand of compounded preparations, lack of evidence regarding systemic absorption of ingredients used in compounded topical pain creams gives rise to a substantial public health concern. It is important to consider the potential effects and safety of all compounds (including APIs and excipients) that may permeate the skin.

Committee Overarching Conclusions

- There is an opportunity for the U.S. Department of Health and Human Services to provide additional oversight to ensure the safety of compounded pain creams, with prioritized focus on those containing APIs that, when applied topically, cross the skin barrier to enter the bloodstream and act systemically within the body.

RECOMMENDATION REGARDING TREATMENT

Recommendation 1

To prescribing clinicians, compounding pharmacists, and other health professionals who compound topical pain cream preparations:

Caution should be used when prescribing or dispensing compounded topical pain cream preparations.

RECOMMENDATIONS TO ADDRESS PUBLIC HEALTH CONCERNS

Recommendation 2

To pain researchers, public and private funding agencies, and relevant patient advocacy organizations:

Strengthen and expand the evidence base on the safety and effectiveness of APIs and excipients commonly used in compounded topical pain creams.

Recommendation 3

To state boards of pharmacy, schools of pharmacy, and nonprofit professional societies and organizations within the medical and pharmaceutical sectors:

Require continued training for clinicians who prescribe compounded pain medication, particularly pain management specialists.

Revise current educational requirements for compounding pharmacists and non-pharmacists who compound.

Recommendation 4

To National Association of Boards of Pharmacy:

Additional state-level oversight of compounded topical pain creams is needed to improve safety and effectiveness.

Recommendation 4

To FDA and global standards-setting organizations (e.g., U.S. Pharmacopeia):

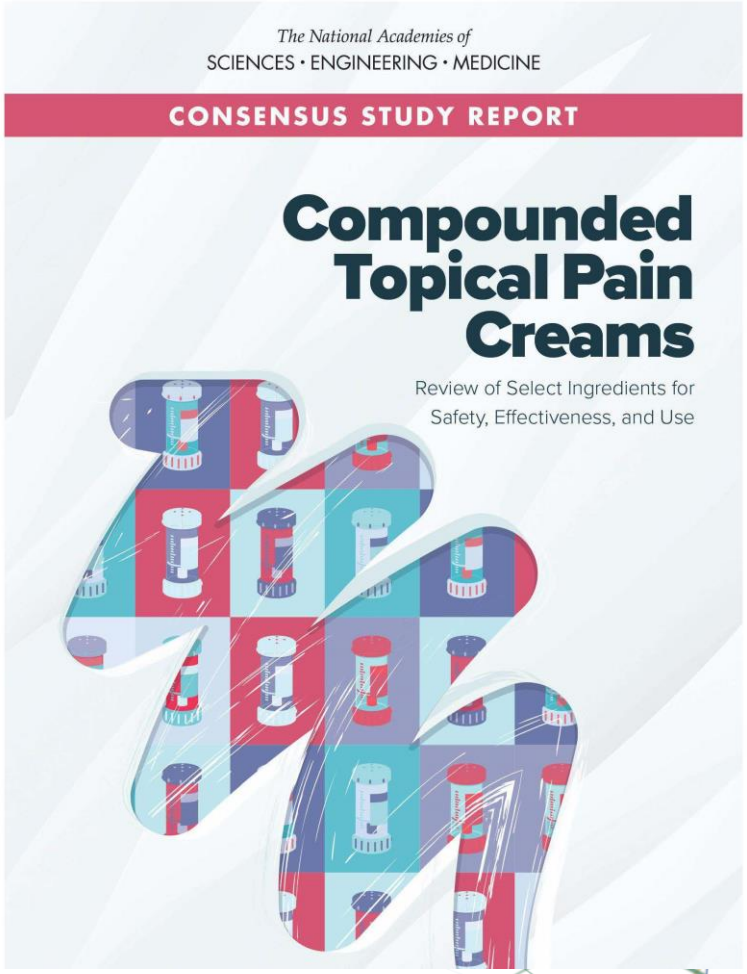
Develop standard processes for testing APIs (in solitude and combinations) and excipients commonly used in compounded topical pain creams.

Final Thoughts

- In absence of well-designed, high-quality studies on the efficacy of APIs in compounded topical pain creams, there is a public health concern for potential harms.
- Current data on safety and risks are inadequate.
- Compounded topical pain creams should be prescribed and dispensed with utmost caution.

Next Steps

- **Full Report, report highlights, and recommendation list available for free download:**
  - https://nap.edu/25689
- **Ongoing dissemination activities:**
  - Social media, seminars, conferences, etc.



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THANK YOU

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QUESTIONS?