

# Anti-Spasmodic Agents

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# Global Topical Pain Relief Market

- The Global Topical Pain Relief Market: \$7,481 million in 2017, and projected to reach \$13,276 million by 2025 at a CAGR of 7.4% from 2018 to 2025\*
- Non-steroidal anti-inflammatory drugs (NSAIDs), narcotic analgesics (transdermal opioids), anesthetics and thermal agents continue to be the mainstays of topical pain management.
- Topical pain relief market is divided into prescription pain and over-the-counter (OTC) pain relief.
- The OTC pain relief segment accounts for the largest market share due to easy availability and high demand of topical pain relief products.



# Localized Muscle Spasm: Unmet Medical Need

- Muscle spasm that arise from acute trauma, muscle strain or stress is one of the leading cause of localized pain.
- Oral centrally acting muscle relaxants (Baclofen, Tizanidine, Cyclobenzaprine, Methocarbamol, Metaxalone etc) in combination with NSAIDs are frequently prescribed for localized muscular pain
- The most common side effects associated with all oral muscle relaxants are drowsiness and dizziness, which limits their use to short term therapy
- Oral muscle relaxants can be addictive and may result in drug abuse.
- Topical analgesic products are helpful in relieving associated pain but ineffective to relieve muscle spasm



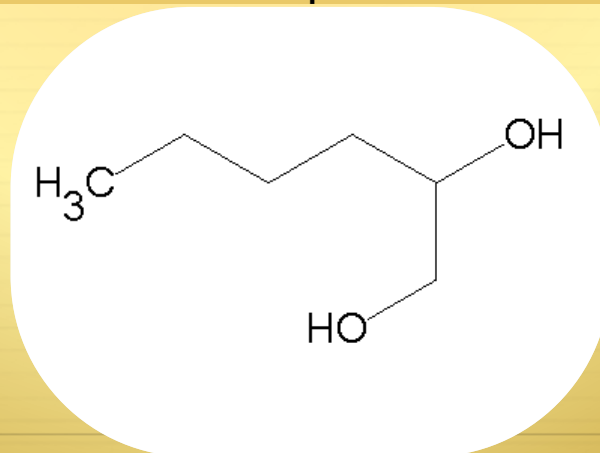
**No approved topical combination product comprising a muscle relaxant and analgesic together**

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# Invention: New Use of a Known Molecule

## 1,2-Hexanediol:

- A synthetic preservative and moisture-binding agent belonging to a class of agents known as glycols.
- Used as a preservative in multiple leading cosmetic brands – established safety profile through topical route
- **New Indication:** At concentrations more than 5%, 1,2-Hexanediol shows a strong anti-spasmodic (muscle relaxant) activity
- Stable and small molecular size with mild surfactant nature of 1,2-Hexanediol favors development of topical dosage form
- Potential combination of 1,2-Hexanediol with or without topical NSAIDs (Diclofenac) will be a highly differentiated product offering



# Current Invention



- ✦ The inventors accidentally discovered the anti-spasmodic (muscle relaxant) property of a common preservative, 1, 2 –Hexanediol (HD) when used in concentration of 5% or above.
- ✦ The inventors discovered that when common moisturizing lotions like Lubriderm or Gold Bond lotions are spiked with 5% HD, they relax the muscles, thus relieving pain associated with spasms.
- ✦ When HD is combined with an anti-inflammatory agent, like diclofenac, the results are nothing short of being miraculous.
- ✦ HD reduces the muscle spasm and the anti-inflammatory agent reduces the actual pain. Thus the beneficial effect starts almost instantly and the benefit lasts longer, as antispasmodic properties remove root cause of the pain, which is muscle spasm.

# IP Status



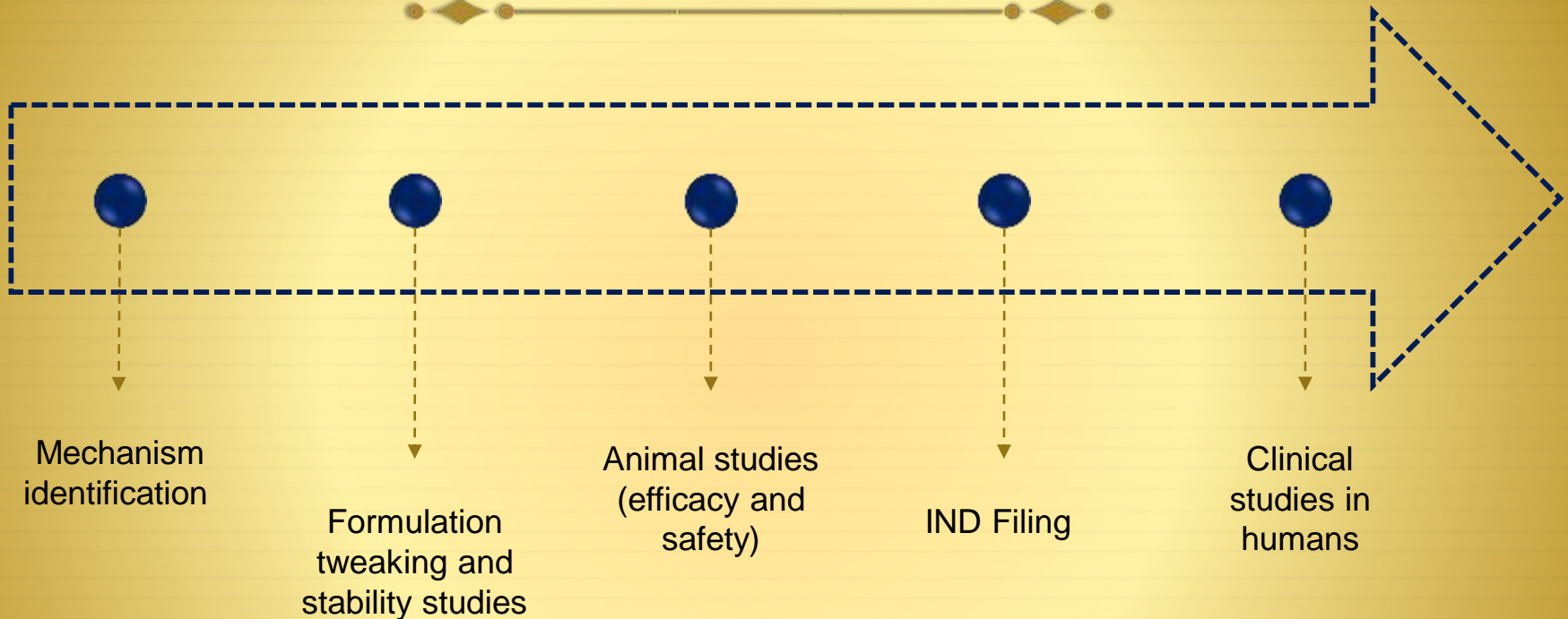
## **Current Status**

- The inventors of the present invention have set up a company in the name of Prima Innovations and have managed to get a patent granted for therapeutic use of HD for relief of muscle spasms. The US patent no. is 8,853,189 B2. Additionally, patent has been granted in Japan, 5 major EU countries, Mexico, Russia, Canada and India.
- The original application was filed in 2012. For most countries, validity will be till 2032.
- Additionally, the inventors have also filed patent applications in Canada, which is under prosecution.

## **Future filings:**

- Additional patents on formulation, PK profile, clinical data can be filed globally

# Global Development Strategy



## Other Studies:

- Genotox and mutagenicity (not required because literature on safety and human use is available),
- Skin irritation to be done on the formulation

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# Global **Development** Strategy



## **28 Days Toxicity Studies:**

- To be done on the formulation
- **Two species:** Rat and Dog (Global) or Rat and Rabbit (developing markets)
- Multiple CRO options available in India
- **Cost of Development:** ~US\$ 140k

## **Pharmacology Studies:**

- To be done on the formulation
- Established animal models for topical analgesic products
- Option to conduct at leading institutions or CRO in India
- **Cost of Development:** ~US\$ 50K
- Some work already done and additional work planned in India.



# Safety (Tox study)




- ✦ In a repeat insult patch containing 15% HD and 5% octanediol, safety of HD has been established by Revlon in a carbomer gel and a cosmetic formulation at an actual use concentration. No delayed Type IV hypersensitivity reactions were observed.
  - ✦ Reference: Cutan Ocul Toxicol. 2009;28(1):23-4
- ✦ The purpose of this study was to understand HD toxicity in cosmetic products. Since the plan was not there, no muscle relaxant property was discovered.

# Possible Mechanism of Action



- ✦ HD due to its small molecular size and mild surfactant nature, penetrates the skin rather easily.
- ✦ Once it crosses the skin, it likely works similar to succinyl choline, which is responsible for muscle relaxation. Thus it relieves muscle contraction.
- ✦ Relieving muscle spasm releases lactic acid and some cytokines, which in turn relieves pain.

# Objective Evaluation in Rats (animal study)



Measurement of length of time to fall down from rotating rod  
If the muscles are relaxed, rats will fall down quickly.

# Rats Rota Rod Model



Efficacy of orally administered 1,2-Hexandiol was compared to a known muscle relaxant, Chandonium Iodide.

Intraperitoneal Injection	Time to Reduced Muscle Movement*	Time to recover
2.5% HD solution 10mL/Kg	5 to 6 min	2 min
5.0% HD solution 10mL/Kg	5 min	15 min
7.5% HD solution 10mL/Kg	3-4 min	15 min
10.0% HD solution 10mL/Kg	2-3 min	18 min
Chandonium Iodide 5 mg/Kg	3-4 min	Animals died

## Interpretation:

Quick onset and short duration of muscle relaxant action, with excellent safety.

\*Hind limbs relaxed, so animals showed difficulty in holding on to the rotating rod.

# Animal Efficacy models

## ✦ *In Vitro Muscle Testing Model*

*In Vitro* muscle testing typically requires a servomotor, which can both control and detect changes in force and length. One end of the sample tissue is anchored in place, while the other is attached to the motor, and the entire muscle is bathed in Ringer Solution with oxygen bubbling through in order to keep the tissue alive and metabolically active. Muscles are stimulated to contract by applying electric current to either nerve which innervates the muscle or the entire muscle and the servomotor detects the changes in force and/or length due to muscle contraction.

- ✦ When pennate muscles are used, sonomicrometry is often used to accurately determine fiber length during the test.
- ✦ Similarly *In Situ* muscle testing model can also be used, where muscles is not removed from the animal body.
- ✦ *In Vivo* models like Morphine-induced Straub tail for potency comparison model can also be used.

# Subjective Evaluation in Humans



Informal clinical evaluation done by an occupational therapist

# Testimonials



For my back pain I use custom blended topical cream consisting of Ketamine, Ketoprofen, Flexeril, Elavil and Lidocaine. One day I forgot my custom blended cream and Ms. Shah suggested I try her formulation. I did and found it to be at least as effective as my custom blended cream, if not more so.

I found it to be highly effective and strongly believe that this new formulation is a winner.

Dr. Amalia Kelly, MD  
Associate Professor, Columbia University, NY

# Testimonials, cont.



I sustained a hand injury while subduing a combative person at work. The injury required me to have three separate surgeries over the course of three years. The combination of injury and surgery led to chronic pain, for which I was placed in pain management in 2014.

The topical ointment that Priti Shah concocted to this day is the only thing that effectively managed my pain and level of comfort.

Sean Higgins  
Sheriff Officer, SWAT Team



# Testimonials, cont.



I want to express how magical the 'Wonder Cream' is. I was having pain from arthritis in my hand for an extensive time. During one of my sessions, the cream applied to my area of pain. At first, I did not feel any difference but within 15 minutes of application, the pain disappeared. I could not believe, how well, it worked.

I have tried over the counter creams and have also had cortisone shots. The shots have not worked and are painful to get. The cream takes away the pain without the needles. If this cream was available for purchase, I will highly recommend it.

Kristine Muller  
Businesswoman

# Testimonials, cont.



I have been Priti for approximately 4 weeks for therapy of both shoulders, due to arthritis. It was so bad, it affected my sleep. After my first visit of Priti manipulating my shoulder and muscles, using what I call wonder cream, I found I was actually able to sleep through the night, for the first time, in a long time.

Joseph Melone  
Limo Driver

# Testimonials, cont.



In November, 2014, I seriously, injured, four fingers, of my right hand. Multiple fractures and crushing injuries, caused, considerable swelling in my hand. Significant swelling lasted for more than two months.

My therapist, Priti Shah, applied cream on my hand. To my amazement, the swelling was noticeably, lessen within 24 hours. This results continued as Ms. Shah, gae me a small amount to use at home. I usually apply the cream at bedtime. I have a history of cronic lower back problems. I admit to using some of this cream on my back. It gave me relief in a relatively short time.

David Passafaro  
Retired Banker