FDA Executive Summary

Prepared for the June 3-4, 2021 Meeting of the Neurological Devices Advisory Panel

Classification of Vapocoolant Devices

Product Code: MLY

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1. Introduction

Per Section 513(b) of the Food, Drug, and Cosmetic Act (the Act), the Food and Drug Administration (FDA) is convening the Neurological Devices Advisory Panel (the Panel) for the purpose of obtaining recommendations regarding the classification of vapocoolant devices, a pre-amendments device type which remains unclassified. Specifically, the FDA will ask the Panel to provide recommendations regarding the regulatory classification of vapocoolant devices, under product code "MLY". The device names and associated product codes are developed by the Center for Devices and Radiological Health (CDRH) in order to identify the generic category of a device for FDA. While most of these product codes are associated with a device classification regulation, some product codes, including "MLY" remain unclassified.

FDA is holding this Panel meeting to obtain input on the risks to health and benefits of the vapocoolant devices under product code "MLY". The Panel will discuss whether the vapocoolant devices under product code "MLY" should be classified into Class II (subject to General and Special Controls). If the Panel believes that classification into Class II is appropriate for the vapocoolant devices under product code "MLY," the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health.

1.1 Current Regulatory Pathways

Vapocoolant devices (formerly known as "refrigerant, topical (vapocoolant)" in FDA's product classification database, and renamed "vapocoolant devices" for ease of reading and consistency with the proposed regulation) is a pre-amendments, unclassified device type. This means that this device type was marketed prior to the Medical Device Amendments of 1976 but was not classified by the original classification panels. Currently these devices are being regulated through the 510(k) pathway and are cleared for marketing if their intended use and technological characteristics are "substantially equivalent" to a legally marketed predicate device. Since these devices are unclassified, there is no regulation associated with the product code.

1.2 Device Description

Vapocoolant devices have been widely used for many years (Ethyl Chloride dates back to the second half of the nineteenth century) to induce the rapid decrease of skin temperature. Vapocoolant devices encompass a family of devices used to rapidly apply a chemical to the skin which rapidly evaporates, subsequently inducing transient cooling of the skin. The mechanism for chemical ejection and the formulation of these chemicals varies between specific products. For example, many devices are metal aerosol containers filled with one or more liquids (such as ethyl chloride), existing at low vapor pressure at room temperature sealed into a metal cannister under high pressure. When pressure is applied to the nozzle, it releases the seal and the liquid(s) escape this high pressure cannister and the droplets vaporize

rapidly. Other devices incorporate more advanced delivery methods that involve temperature-monitoring via lasers and automated/controlled release of the gas mixture. Some devices spread the droplets out or focus them into concentrated streams in order to modulate the size of the targeted surface area.

2. Regulatory History

The first product cleared under product code "MLY" was the Gebauer Company Fluori-Methane SS (K930915) cleared September 29, 1994. This product was found substantially equivalent to the pre-amendments device, Gebauer's Fluori-Methane.

To date, a total of twenty-two (22) 510(k)s were cleared under the vapocoolant devices product code (MLY). All these devices are intended to induce rapid topical cooling, with the most common intended use being some form of local anesthetic. The vapocoolants and skin refrigerant products cleared under this product code have varying formulations, and induce topical cooling by spraying a pressurized chemical onto the skin, which evaporates or sublimates upon skin contact, transiently inducing a rapid reduction in skin temperature.

Table 1: 510(k) Clearances for Vapocoolant Devices Under Product Code "MLY"

510(k) Number	Trade Name	Sponsor
K930915	Fluori-Methane@SS	Gebauer Company
K984564	Ethyl Chloride Dispenser	Dukal Corporation
K991514	Gebauer's Chloride Fine Nozzle	Gebauer Company
K992286	DermaFreeze	Rhealm Pharmaceuticals, Inc.
K001624	Gebauer's Fluori-Methane Model P/N 0386-0003-04	Gebauer Company
K002596	Gebauer's Fluoro-Ethyl Model P/N 0386-0002-09	Gebauer Company
K011666	CHILLIT	Heatshield, Inc Bottom of Form
K021726	Gebauer's Instant Ice	Gebauer Company
K030281	CRYOTRON 2" Cryotherapy Device	Cyonic Medical North America
K031036	Gebauer's Skin Refrigerant (Mist Spray) Model P/N 0386-0010-07, and Gebauer's Skin Refrigerant (Medium Spray) Model P/N 0386-0010-03	Gebauer Company
K032671	Gebauer's Skin Refrigerant (Mist Stream), and Gebauer's Skin Refrigerant (Stream Spray) Models P/N 0386-0010-07	Gebauer Company
K033720	ARI Cold Spray	ARI
K093951	Ouchless Model P/N 10114	OCCAM Design
K162218	Pain Freeze™ Mist Spray Model 2102, and Pain Freeze™ Medium Stream Spray Model 2101	Nuance Medical, LLC
K170810	CRYOFOS	CRYOFOS Medical Gmbh

K172028	Gebauer's Pain Ease Topical Anesthetic Skin Refigerant (Mist Spray and Medium Spray)	Gebauer Company
K172203	CryoDose TA OTC, Mist Spray, and CryoDose TA OTC, Stream Spray	Nuance Medical, LLC
K172598	Coventry Topical Anesthetic Mist Spray HAZMAT FREE, Coventry Topical Anesthetic Stream Spray HAZMAT FREE	ITW Contamination Control Electronics
K182392	FROZEN C	B.M. Tech. Worldwide Co., Ltd.
K190161	Ethyl Chloride Medium Jet Stream, Ethyl Chloride Fine Pinpoint Spray, Ethyl Chloride Mist, Ethyl Chloride Accustream 360* Medium Spray, Ethyl Chloride Accustream 360* Fine Spray	Gebauer Company
K193349	Vapocoolshot Mist	Vapocoolshot, Inc.
K193665	Frozen N	Yozma Bm Tech Company, Ltd.

3. Indications for Use

The Indications for Use (IFU) statement identifies the conditions and patient populations for which a device should be appropriately used.

Vapocoolant devices are intended for the temporary relief and reduction of minor topical pain and swelling from sprains, strains, bruising, contusions and minor injuries and in the management of myofascial pain, restricted motion and muscle tension. In addition, it is used for pain reduction associated with hypodermic injections including venipuncture and vaccinations, and for minor surgical procedures such as incisions, sutures and drainage of small abscesses. It is also used to reduce pain by topical application to intact mucous membranes in the oral cavity, the lips and to minor open wounds. Most, but not all, of these devices are cleared for prescription use.

The IFU statements for the cleared devices under product code MLY are specified in Table 2 below.

Table 2: Indications for Use (IFUs) for Vapocoolant Devices Under Product Code "MLY":

510(k) Submission #	Indications for Use
K930915	A vapocoolant intended for topical application in management of myofacial pain, restricted motion, and muscle spasm, and for the control of pain associated with injections
K984564	A vapocoolant intended for topical application in management of myofacial pain, restricted motion, and muscle spasm, and for the control of pain associated with injections, minor surgical procedures and the temporary relief of minor sports injuries.

K991514	Gabauer's ethyl chloride (fine and medium nozzles): Gebauer's ethyl chloride is a vapocoolant (skin refrigerant) intended for topical application to control pain associated with minor surgical procedures (such as lancing boils, incisions and drainage of small abscesses), injections and the temporary relief of minor sports injuries. it is also intended for the treatment of restricted motion associated with myofascial pain caused by trigger points.
K992286	Dermafreeze is a vapocoolant intended for topical application for the control of pain associated with minor surgical procedures (such as lancing boils, or incision and drainage of small abscesses), injections, and contusions.
K001624	Gebauer's fluori-methane: Gebauer's fluori-methane is a topical anesthetic intended to treat restricted motion associated with myofasical pain caused by trigger points. it will also control pain associated with injections and provide temporary relief from the pain of minor sports injuries.
K002596	Gebauer's fluro-ethyl: Gebauer's fluro-ethyl is a topical anesthetic intended to control the pain associated with minor surgical procedures dermabrasion and injections it is also effective in providing temporary relief from the pain associated with minor sports injuries.
K011666	1. cooling heat sensitive orthodontic wires 2. topical anesthetic 3. pulp test the vitality of teeth
K021726	Gebauer's instant ice (mist spray) use like ice for the temporary relief and reduction of minor pain and swelling from sprains, strains, bruising, contusions or minor sports injuries. Gebauer's instant ice (stream spray) use like ice for the temporary relief and reduction of minor pain and swelling from sprains, strains, bruising, contusions or minor sports injuries and muscle spasms.
K030281	The cryotron 2 cryotherapy device is for use when cold therapy is indicated for the temporary reduction of pain, swelling, inflammation, and hematoma from minor surgical procedures, minor sprains or other minor sports injuries, and as an adjunct to rehabilitative treatment (e.g., intermittent cold with stretch).
K031036	Gebauer's skin refrigerant (mist spray and medium spray) topical anesthetic: a vapocoolant (skin refrigerant) intended for topical application to control pain associated with minor surgical procedures (such as lancing boils, incisions and drainage of small abscesses), injections (venipuncture, iv starts) and the temporary relief of minor sports injuries. the medium spray is also intended for the treatment of restricted motion associated with myofascial pain caused by trigger points.
K032671	Gebauer's skin refrigerant (mist spray and medium spray) topical anesthetic: a vapocoolant (skin refrigerant) intended for topical application to control pain associated with minor surgical procedures (such as lancing boils, incisions and drainage of small abscesses), injections (venipuncture, iv starts) and the temporary relief of minor sports injuries. the medium spray is also intended for the treatment of restricted motion associated with myofascial pain caused by trigger points, restricted motion and muscle tension.

K033720	The ari cold spray is intended to be used as a topical skin refrigerant to be used like ice for the temporary relief and reduction of minor pain and swelling from sprains, bruising, contusions and minor sports injuries.
K093951	Use like ice for the temporary relief of minor localized pain
K162218	Pain Freeze™ Mist Spray and Medium Stream Spray are vapocoolants (skin refrigerants) intended for topical application to skin, intact mucous membranes (oral cavity, nasal passage ways and the lips) and minor open wounds. Pain Freeze™ controls pain associated with injections (venipuncture, IV starts, cosmetic procedures), minor surgical procedures (such as lancing boils, incisions, drainage of small abscesses and sutures) and the temporary relief of minor sports injuries (sprains, bruising, cuts and abrasions). Pain Freeze™ Medium Stream Spray is also intended for the management of myofascial pain, restricted motion and muscle tension.
K170810	The CRYOFOS and Accessories indicated for use when cold therapy is indicated for the temporary reduction of pain, swelling, inflammation, and hematoma from minor surgical procedures, minor sprains or other minor sports injuries, and as an adjunct to rehabilitative treatment (e.g., intermittent cold with stretch).
K172028	Gebauer's Pain Ease Topical Anesthetic Skin Refrigerant (Mist Spray and Medium Spray): a vapocoolant (skin refrigerant) intended for topical application to skin, mucous membranes and minor open wounds. Gebauer's Pain Ease controls pain associated with minor surgical procedures (such as lancing boils, incisions, drainage of small abscesses, and sutures), injections (venipuncture, IV starts, cosmetic procedures) and the temporary relief of minor sports injuries (sprains, bruising, cuts and abrasions). The Medium Spray is also intended for the treatment of myofascial pain caused by trigger points, restricted motion and muscle tension.
K172203	Mist Spray: CryoDose TA OTC is used like ice for the temporary relief and reduction of minor pain and swelling from sprains, strains, bruising, contusions and minor sports injuries. Stream Spray: CryoDose TA OTC is used like ice for muscle spasm and for the temporary relief and reduction of minor pain and swelling from sprains, strains, bruising, contusions and minor sports injuries.
K172598	Coventry ™ Mist Spray and Medium Stream Spray are vapocoolants (skin refrigerants) intended for topical application to skin, intact mucous membranes (oral cavity, nasal passage ways and the lips) and minor open wounds. Coventry ™ controls pain associated with injections (venipuncture, IV starts, cosmetic procedures), minor surgical procedures (such as lancing boils, incisions, drainage of small abscesses and sutures) and the temporary relief of minor sports injuries (sprains, bruising, cuts and abrasions). Coventry ™ Medium Stream Spray is also intended for use the management of myofascial pain, restricted motion and muscle tension.
K182392	The FROZEN C, hyperbaric CO2 cryotherapy device, is for use when cold therapy is indicated for the temporary reduction of pain, swelling, inflammation, and hematoma from minor surgical procedures, minor sprains or other minor sports injuries, and as an adjunct to rehabilitative treatment (e.g., intermittent cold with stretch).

K190161	Gebauer's Ethyl Chloride Topical Anesthetic Spray (Mist Spray, Fine Spray and Medium Spray): A vapocoolant (skin refrigerant) intended for topical application to control pain associated with injections (starting IV's and venipuncture), minor surgical procedures (such as lancing boils, or incision and drainage of small abscesses), and the temporary relief of minor sports injuries. The Fine and Medium Sprays are also intended for the treatment of myofascial pain caused by trigger points, restricted motion and muscle tension.
K193349	The Vapocoolshot Mist is intended for topical application to skin, intact mucous membrane (oral cavity, nasal passageways, lips) and minor open wounds. The Vapocoolshot Mist is used to target and minimize cooling area for lessening pain associated with injections (venipuncture, IV starts, cosmetic procedures), minor surgical procedures (such as lancing boils, incision, drainage of small abscesses and sutures) and the temporary relief of minor sports injuries (sprains, bruising, cuts, and abrasions).
K193665	The FROZEN N, cryotherapy device using liquid nitrogen vapor, is for use when cold therapy is indicated for the temporary reduction of pain, swelling, inflammation, and hematoma from minor surgical procedures, minor sprains or other minor sports injuries, and as an adjunct to rehabilitative treatment (e.g., intermittent cold with stretch).

4. Clinical Background

4.1 Disease Characteristics

Mechanical and thermal stimuli activate nociceptors in the skin and subcutaneous tissues that stimulate A delta and C neural fibers that transmit neural signals via multiple pathways to the central nervous system where these stimuli are further processed and perceived as pain. Vapocoolant sprays rapidly reduce the temperature of the skin and impede the stimulation of nociceptors to temporarily reduce the perception of painful stimuli.

4.2 Patient Outcomes

Choice of pain control depends on the location and nature of the injury or procedure, patient characteristics, and clinician preference. With appropriate use, vapocoolant sprays can reduce pain temporarily and can be used with passive stretching techniques to improve restrictions in motion. While rare, adverse events have been reported with the use of vapocoolant sprays including local skin damage and blistering and in more severe situations, frostbite. Reports made to the FDA regarding such events note misuse of the product related to prolonged skin contact time with the vapocoolant and risk factors such as diabetes that caused a predisposition to the injuries.

4.3 Currently Available Treatment

Pain from minor injuries, injections, minor surgical procedures, minor wounds and myofascial pain can be mitigated with ice, cool compresses and topical analgesics.

Oral medication options include non-steroidal anti-inflammatory medications and acetaminophen. Pain control for minor routine procedures is not necessary in all situations. Pain secondary to myofascial and mild muscle pathology can be managed with heat-conveying modalities, injection of local anesthetics, active or passive stretching, therapeutic exercise, and the application of direct or indirect pressure via manual techniques.

4.4 Risks

FDA has identified the following risks to health associated with vapocoolant devices:

Table 3: Risks to Health and Descriptions/Examples for Vapocoolant Devices

Identified Risk	Description/Examples
Pain or discomfort	This can result from burns and/or blistering.
Skin irritation	This can result from burns and/or blistering.
Thermal injury	This can result from frostbite or burns particularly when used in combination with electrical cautery leading to ignition, leading to redness, blistering and edema.
Electrical shock or burn	This can result from electrical failure or malfunction.
Interference with other devices	Electromagnetic disturbances that may cause unacceptable degradation in device performance, leading to delayed or ineffective treatment.
Device failure/malfunction leading to ineffective treatment	Device malfunction can cause spray to contact unintended areas of the body which can lead to burns and minor injury.
Asthma	This can result from an allergic response to the product or aerosol delivery system.
Hallucination	This can result from improper use of the device and subsequent inhalation toxicity.

The Panel will be asked whether this list is a complete and accurate list of the risks to health presented by vapocoolant devices under product code "MLY" and whether any other risks should be included in the overall risk assessment of the device type.

5. Literature Review

5.1 Methods

A systematic literature review was conducted to gather and assess published literature regarding the safety and effectiveness of vapocoolant devices that are regulated under the product code "MLY". Online literature searches were performed in two electronic databases (Embase and PubMed) using the following search terms (for a complete list of terms and filters, see Appendix A):

(topical or spray or mist) AND ('norflurane' OR '1 1 1 3 3 pentafluoropropane' OR '1 1 1 2-Tetrafluoroethane' OR '1, 1, 1, 3, 3-pentafluoropropane' OR '1,1,1,2-Tetrafluoroethane' OR 'ethyl chloride' OR 'compressed medical-grade carbon dioxide gas' OR propane, isobutane, n-butane OR dichlorotetrafluoroethane OR trichloromonofluoromethane OR 'ethylene oxide' OR vapocoolant OR 'refrigerant')

The search was limited to human clinical studies published in the English language, with publication dates between January 1, 2010 and December 31, 2020. Database filters were used to exclude non-original human clinical studies such as conference abstracts, commentaries, and editorials. Due to extensive research on vapocoolant devices, many randomized controlled trials (RCTs) were conducted and published in the last decade. Therefore, this literature review is limited to RCTs wherein at least one treatment arm used a vapocoolant device in the trial. Other non-experimental studies such as cohort studies, case-control studies and case series reports were excluded from this review.

An initial search was performed on May 1, 2020 using publication dates between January 1, 2010 and May 1, 2020. Supplementary searches was performed on September 1, 2020 and March 17, 2021 to capture any additional articles published between May 1, 2020 and December 31, 2020. The flow diagram in Appendix B represents the total number of articles and exclusion criteria obtained from all three searches.

5.2 Results

The search yielded 277 initial literature references. After duplicate articles were removed between databases, a total of 215 articles remained. The screening process for the publications is presented in Appendix B. Following a review of the titles and abstracts, a total of 103 articles remained for full-text review. Of these, 35 RCTs were determined to be relevant to the safety and efficacy of vapocoolant devices. Characteristics of the included RCTs are described in Appendix C.

Sample sizes of the included RCTs range from 30 to 450 patients, with a median of 124 patients. Studies were conducted in both pediatric and adult populations. One RCT evaluated vapocoolant device use among infants from newborn up to three months. Four pediatric studies included patients from 1 to 18 years of age[2-6]. The rest of the RCTs were focused on adult populations. Fifteen of the 35 RCTs were conducted in the United States. Other RCTs were conducted in Australia, Canada, China, Germany, India, Indonesia, Iran, Israel, Korea, Spain and Turkey.

5.3 Adverse Events Associated with Vapocoolant Devices

Systematic review of the medical literature demonstrated that adverse effects from vapocoolant device use were largely mild to moderate in severity. No cases of patient mortality were reported from any of the studies reviewed. Adverse events from vapocoolant use in the RCTs reviewed were typified by the study of Page and Taylor

who reported that unexpected events were rare and minor from vapocoolant use in the study. The authors reported 4 (4.4%) events of mild pruritus, 1 (1.1%) event of mild pain, and 1 (1.1%) event of transient erythema. No patient required treatment for these events[7]. Lunoe et al. evaluated venipuncture pain reduction in young children (aged 1 to 6 years) comparing Jet-injected lidocaine with vapocoolant spray and a sham control. Patients were randomized into three groups: intervention (J-Tip), control (vapocoolant spray), and sham (vapocoolant spray and pop of an empty J-Tip). The authors reported 8.6% of patients experienced bruising and 4.3% of patients exhibited other mild skin reactions in the vapocoolant arm compared to 14.4% of patients exhibiting bruising and 1.2% of patients exhibiting other skin reactions in the Jet-injected lidocaine arm and 6.5% of patients exhibiting bruising and 4.3% of patients exhibiting other skin reactions in the sham control arm[3]. Gupta reported 20% of patients exhibited erythema and swelling in the vapocoolant plus breast feeding arm in a randomized study of 90 infants up to three months of age during whole cell diphtheria, pertussis, and tetanus (wDPT) vaccination compared to 17% and 15% in the Eutectic Mixture of Local Anesthetics (EMLA) cream with breast feeding arms and breast feeding only arm, respectively[1]. Taddio et al. reported lower skin reactions (either blanching or reddening; edema and bleeding) for vapocoolant compared to lidocaine (13.6% vs. 26.1%, respectively) in a RCT of 352 adult patients who underwent immunization[8]. Wiswall et al. reported that when vapocoolant was used in the mouth, 81% of patients reported a sore on the palate in the vapocoolant group compared with 0% from other options such as no concurrent stimulation, pressure, or pressure and topical anesthetic (20% benzocaine)[6]. The author concluded that the vapocoolant material – 1,1,1,2-tetrafluoroethane – placed with pressure for ten seconds appeared injurious to the oral mucosa.

From these published studies, the reported complication rates from vapocoolant device use have been associated with complication definition, patient age, and specific conditions or procedures for which that pain management is required. All reported complications were considered mild and resolved without intervention after discontinuation of using the vapocoolant. Review of the literature revealed one case report of vapocoolant device abuse, the deliberate inhalation of the topical refrigerant[9].

5.4 Effectiveness Associated with Vapocoolant Devices

The results of studies of the effectiveness of vapocoolant devices in reducing the pain associated with needlestick procedures, such as intravenous line initiation, were mixed. Among 32 RCTs, 22 studies reported effective decreases in pain with the administration of vapocoolant devices prior to the needlestick procedure. A double-blind study by Barbour et al. exemplified this group of randomized controlled trials[10]. A total of 100 adult patients were randomized to sterile water (placebo) or vapocoolant spray (1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane) before venipuncture. A total of 76% of the vapocoolant group reported significantly less pain compared to previous venipunctures. The results were statistically significant (76% for the vapocoolant group vs. 14% for the placebo group, $p < 0.001$).

Patient reported satisfaction also heavily favored the vapocoolant group. Patients in the vapocoolant group were 32% very satisfied and 40% satisfied. This was in sharp contrast to the placebo group, where only 2% were very satisfied and 18% were satisfied ($p < 0.001$).

Barbour et al. recently published a second randomized controlled trial using 300 adult patients who were randomized to sterile water (placebo) or vapocoolant spray (1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane) before peripheral intravenous (IV) placement[11]. A total of 77% of the vapocoolant group reported significantly less pain compared to previous IVs. The results were statistically significant (77% for the vapocoolant group vs. 32.4% for the placebo group, $p < 0.001$). Patient reported satisfaction also heavily favored the vapocoolant group. Patients in the vapocoolant group were 42% very satisfied and 44% satisfied. This was in sharp contrast to the placebo group, where only 11.3% were very satisfied and 40.7% were satisfied ($p < 0.001$).

Fossum et al. performed a randomized, double-blind, placebo controlled cross-over trial that enrolled 38 health care provider volunteers[12]. The study compared ethyl chloride treatment to sterile water to reduce pain during intravenous line initiation with an 11-point ordinal pain verbal numeric rating scale (VNRS). The study found that median pain scores were 4 for placebo and 2 for ethyl chloride. The effect size for pain reduction with ethyl chloride compared with placebo was 2 (95% confidence interval, 0.5-2; $p = 0.001$).

DiMarco and Wetmer conducted a randomized, cross-over trial which compared the effectiveness of reducing pain during anterior middle superior alveolar injection dentistry[13]. A total of 30 adult patients received either 20% benzocaine gel for 2 minutes or a topical refrigerant, 1,1,13,3-pentafluoropropane, 1,1,1,2-tetrafluoroethane, for 5 seconds. The study found no statistically significant difference in pain reduction between the benzocaine and topical refrigerant groups ($p = 0.283$).

In 2016, Mace reported the results of a randomized, double-blind, placebo-controlled trial of the effectiveness of vapocoolant in reducing the pain of venipuncture[14]. A total of 100 adults were randomized to the vapocoolant or placebo groups. The median (interquartile range) pain of venipuncture was 3 (1.2 - 5) for the placebo group and 1 (0 – 3) in the vapocoolant group ($p < 0.001$) on a 10-point numerical rating scale.

A second RCT performed by Mace et al. examined the effect of vapocoolant spray in reducing the pain of intravenous line initiation[15]. A total of 300 adults participated in the study. The median Numeric Rating Scale interquartile pain score for peripheral intravenous cannulation was 4 (2 - 7) for the placebo spray group vs. 2 (0 - 4) for the vapocoolant spray group ($p < 0.001$).

Rusch et al. conducted a RCT that included 160 adult patients who underwent arterial cannulation[16]. Prior to the procedure, patients were randomized to either vapocoolant or lidocaine groups. The mean pain score in the vapocoolant group was significantly lower compared with the lidocaine group (difference of 1.1, $p = 0.032$).

A second RCT performed by Rusch et al. examined the ability of vapocoolants or lidocaine to reduce pain during venipuncture[17]. A total of 450 adult patients were enrolled in the study. For a 17-gauge cannula, both the vapocoolant spray (Numerical Rating Scale (NRS) = 2.6) and lidocaine (NRS =3.5) lessened the pain during venipuncture compared to the control group (NRS = 5.0).

In 2020, Moon et al. conducted a randomized clinical trial that examined the effects of vapocoolant spray and Eutectic Mixture of Local Anesthetics (EMLA) cream on decreasing pain during intra-articular injections of the shoulder[18]. A total of 63 adult patients who underwent intra-articular injections of the shoulder were randomized into vapocoolant spray, EMLA and placebo groups. The visual analog scale (VAS) scores for pain during intra-articular injection were 30.0 (95% CI = 19.7 - 41.2) in the vapocoolant spray group, 50.0 (95% CI = 37.7 - 63.0) in the EMLA group and 53.8 (95% CI = 40.6 -65.0) in the placebo group ($p < 0.01$). In addition, the vapocoolant spray group had significantly better Likert scale scores than the placebo group for participant satisfaction ($p = 0.003$) and preference for repeated use ($p < 0.001$).

Moon et al. performed a RCT of the prevention of pain associated with propofol injection[19]. A total of 90 adult patients were randomized to vapocoolant, lidocaine, and placebo groups. Propofol induced pain was significantly lower in the vapocoolant and lidocaine groups than in the control group ($p < 0.0001$). There was no statistically significant difference in reported pain between the vapocoolant and lidocaine groups.

In 2014, Moon et al. published the results of a study that randomized 60 adult patients into ethyl chloride or placebo spray groups prior to needle electromyography[19]. The VAS for pain was significantly lower in the ethyl chloride spray group. Patient satisfaction and preference were statistically and clinically significantly greater in the ethyl chloride group ($p < 0.05$).

In 2013, Moon et al. conducted a randomized trial where patients before electromyography were randomized to one of three groups: vapocoolant spray, EMLA, or control[21]. The VAS scores for pain intensity were significantly ($p < 0.05$) lower in the vapocoolant group (31.9; 95% CI = 22.0 – 41.7) compared to the control group (52.9; 95% CI = 34.2 – 50.7).

A RCT of the reduction of pain during infant vaccination was conducted in India by Gupta et al[1]. A total of 90 infants up to three months of age were randomized to vapocoolant and breastfeeding, EMLA and breastfeeding, and breastfeeding only groups. The modified Facial Coding Score and Neonatal Infant Pain Score at 1 minute and 3 minutes were significantly lower in the EMLA and vapocoolant groups, compared to the breastfeeding alone group ($p < 0.05$).

Taddio et al. performed a RCT of various measures to reduce pain during adult vaccinations[8]. Each of the 352 adult participants were randomized to one of four groups: 1) topical anesthesia with lidocaine, 2) vapocoolant spray, 3) tactile stimulation, and 4) distraction. The results of the study revealed that vapocoolant spray was statistically as effective as lidocaine ($p = 0.97$) and more effective than distraction ($p = 0.02$) between lidocaine and distraction) from both statistical and clinical perspectives.

A RCT of the reduction of pain during spinal injection procedures was conducted in Indonesia by Firdaus et al[22]. The study sample size was 94 adult patients who were randomized to either vapocoolant or EMLA groups. There was no statistically significant difference in the reduction of pain between the two study groups.

Waterhouse et al. performed a RCT in 95 pediatric patients[5]. Patients were randomized to vapocoolant spray (Painease) or ice pack groups before intravenous line initiation. More study subjects in the vapocoolant spray group (76%) thought their treatment worked well than in the ice group (49%).

A RCT of the reduction of pain during radial arterial puncture (AP) was conducted in India by Dhami et al[23]. The study sample size was 60 adult patients who were randomized to either vapocoolant (ethyl chloride) or ice pack application groups. There was no statistically significant difference in the mean pain score between the two study groups ($p = 0.113$). Meanwhile, the secondary outcome measure, incidence of haematoma, was significantly ($p = 0.01$) reduced in the vapocoolant group (6.66%) compared to the ice pack application group (33.3%).

Zugasti et al. studied 70 adults who received a dry needling application over the upper trapezius muscle[24]. The intervention group received vapocoolant spray and stretch. The control group did not receive any intervention. The spray and stretch group experienced a short-term (< 6 hours) effect in reducing post-needling soreness.

Rui et al. conducted a RCT that studied an intervention for pain after total knee arthroplasty[25]. A total of 306 adult patients were randomized to the ethyl chloride spray group or the control group. There was a statistically significant improvement and clinically meaningful decrease in pain in the ethyl chloride group compared to the control group at all time points after surgery ($p < 0.05$).

A RCT conducted by Irkoren et al. assessed the efficiency of ethyl chloride spray application for pain alleviation before botulinum toxin injection[26]. The study found that skin cooling with ethyl chloride spray significantly decreased the pain associated with forehead botulinum toxin injection. The average score was 6.80 ± 1.37 for the EMLA side and 2.93 ± 1.03 for the ethyl chloride sprayed side ($p < 0.05$).

Gal-Oz et al. performed a RCT that examined the use of topical refrigerants as an anti-pruritic agent[27]. A significant improvement in pruritus was observed following

treatment with ethyl chloride compared to placebo (42/50 vs. 8/50, 84% vs. 16%, $p < 0.0001$).

RCTs that failed to detect a decrease in pain with topical refrigerant use were also noted. For example, Edwards and Noah performed a randomized, double-blind, placebo controlled, single-center trial that included 72 adult patients who were randomized to either vapocoolant or placebo groups before peripheral intravenous line initiation[28]. The patient perception of pain did not vary significantly between the vapocoolant and placebo groups ($p = 0.33$).

Rekawek et al. performed a study of 120 women undergoing transabdominal chorionic villus sampling who were randomized to either a 1% lidocaine group or a topical ethyl chloride group[29]. Patients in the ethyl chloride group demonstrated statistically significantly higher pain scores than the lidocaine group ($p = 0.03$). Page and Taylor performed a non-blinded, randomized controlled trial of pain during IV cannulation in Australia with alkane spray and lidocaine groups[7]. A total of 220 adult patients participated in the study, evenly divided between the vapocoolant and lidocaine groups. The study found that vapocoolant IV cannulation pain scores were significantly greater in the vapocoolant group ($p < 0.05$).

Luthy et al. conducted a RCT of measures intended to reduce pain during vaccination[2]. A total of 68 children were enrolled in the study and randomized to one of three groups: a vapocoolant spray group, a DVD distraction group, and a control group. No significant difference in the parents' perception of their child's pain was found between the two treatment groups and the control group.

Franko and Stern conducted a RCT of the effect of ethyl chloride on perceived pain during routine hand injections[30]. A total of 151 adult patients were included in the study. No statistically significant difference in perceived pain was observed between the ethyl chloride and no spray groups.

Farahmand et al. conducted a RCT in Iran that assessed the effect of vapocoolants in reducing pain during arterial blood gas procedures[31]. The study was comprised of 80 adult patients who were randomized to vapocoolant or water spray placebo groups. The pain score was not statistically significantly lower in the vapocoolant group ($p = 0.945$).

Kose et al. conducted a RCT to assess the effectiveness of alkane vapocoolant in reducing the pain of a digital nerve block for ingrown toenail surgery[32]. A total of 62 adult patients participated in the study, which was conducted in Turkey. The authors reported that in their study alkane vapocoolant had no noticeable clinical benefit in decreasing the pain intensity during digital nerve block in patients undergoing toenail surgery.

Baxter et al. conducted a RCT of the reduction in pain associated with venous access or venipuncture related to the use of the "buzzy device" that combined vibration and

cold compared to the standard of care, the use of vapocoolants[4]. A total of 81 pediatric patients were included in the study. The authors found that children in the buzzy device group had significantly lower pain or distress based on their self-report ($p < 0.05$).

Celik et al. performed a randomized, placebo-controlled crossover study that examined the effectiveness of EMLA and vapocoolants in the prevention of pain from arteriovenous fistula cannulation[33]. A total of 41 dialysis patients participated in the study. The study found that EMLA is more effective in preventing pain from these procedures than vapocoolant spray. However, vapocoolant spray was reported to be as effective as EMLA in the prevention of mild to moderate pain.

Fung et al. conducted a placebo-controlled, single-blinded study where each patient served as their own control to examine pain perception compared using three anesthetics: EMLA, vapocoolant spray and ice, compared to a no anesthetic control during botulinum toxin A injection for lower limb spasticity[34]. The sample size of the study was relatively small at 30 adult patients. The authors reported that vapocoolant spray had little effect on patient perceived pain. In contrast, ice and EMLA were found to be effective preprocedural anesthetic agents.

A study of the effect of a range of measures to decrease pain during the injection and anesthetic deposition for greater palatine nerve block was performed by Wiswall et al.[6] Study groups were comprised of control, pressure, benzocaine and Endo-Ice vapocoolant. There was no significant difference in perceived pain response among the four study groups.

Lunoe et al. performed a RCT that examined the use of jet-injected lidocaine for venipuncture pain in children[3]. Patients were randomized to one of three study groups. The study groups were: intervention (J-tip), control (vapocoolant spray), and sham (vapocoolant spray accompanied by the pop of an empty J-tip). The authors concluded that the use of the J-tip reduced venipuncture pain compared to the control and sham groups.

Among to 30 RCTs that evaluated pain reduction, two RCTs also assessed the anxiety reduction impact from vapocoolant devices[2, 28]. Neither of these studies reported effectiveness of vapocoolant devices on reduction of pain or anxiety.

Vapocoolant devices were also evaluated for impacts other than pain reduction. Gal-Oz et al. studied the antipruritic effect from ethyl chloride. The study recruited 51 healthy volunteers. Patients were randomly assigned to ethyl chloride and placebo control arm. The authors found significant improvement in pruritus (Ethyl chloride vs. placebo: 84% vs. 16%; $p < 0.0001$)[27].

Im et al. studied the change in facial temperature caused by the application of various coolants[35]. Cold gel packing demonstrated the greatest reduction in facial surface

temperature, 10.6 degrees Celsius, compared to reductions of 4.3 degrees Celsius for ethyl chloride and 3.7 degrees Celsius for ice pack rubbing ($p < 0.001$).

Gur et al. studied the impact of vapocoolant device use on quality of radiographic imaging in patients experiencing acute ankle trauma. The authors found the mean scores for image quality were statistically significantly better in patients treated with vapocoolant than placebo control (8.13 ± 1.8 vs. 6.58 ± 2.2; mean difference: -1.56, 95% CI:-2.20 to -0.92; $p < 0.05$).

5.5 Overall Literature Review Conclusions

A total of 35 RCTs were determined to be relevant to assess the safety and effectiveness of vapocoolant devices, of which three RCTs studied the impact of vapocoolant devices other than for topical anesthesia such as skin cooling effect, imaging quality, and antipruritic effect. The majority (71.4%) of publications reported no complications or did not report on adverse events or safety risks with the use of the device. Ten RCT studies reported adverse events, which include numbness, erythema, swelling, blanching, sores, and other minor local skin reactions, were mild in scope and severity. There is no evidence of a mortality risk from the use of the device. The adverse events were transient or temporary, and resolved soon after the cooling effect expired without the need for additional treatments. The effectiveness of the device in the reduction of pain from routine procedures involving needlesticks such as vaccination, cannulation, and venipuncture is supported by 22 out of 32 RCTs in comparison with placebo control or alternative treatments. However, ten RCTs did not show effectiveness of vapocoolant devices in such comparisons. Therefore, based on the clinical evidence derived from this systematic literature review, the benefit/risk profile of vapocoolant device use for the reduction of pain from routine procedures involving needlesticks is favorable, with no adverse events or only minor transient skin reactions.

6. Risks to Health Identified through Medical Device Reports (MDRS)

6.1 Overview of the MDR System

The MDR system provides FDA with information on medical device performance from patients, health care professionals, consumers and mandatory reporters (manufacturers, importers and device user facilities). The FDA receives MDRs of suspected device-associated deaths, serious injuries, and certain malfunctions. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDRs can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a “real world” setting/environment

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the submission of incomplete, inaccurate, untimely, unverified, duplicated or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about the frequency of device use. Finally, the existence of an adverse event report does not definitely establish a causal link between the device and the reported event. Because of these limitations, MDRs comprise only one of the FDA's tools for assessing device performance. As such, MDR numbers and data should be taken in the context of the other available scientific information.

6.2 MDR Data: Vapocoolant Devices (Product Code MLY)

Individual MDRs for vapocoolant devices are reported through FDA's Manufacturer and User Facility Device Experience (MAUDE) Database, which houses mandatory reports from medical device manufacturers, importers and user facilities, as well as voluntary reports from entities such as health care professionals, patients and consumers.

The Agency searched the MDR database on March 9, 2021 to identify adverse events related to the use of vapocoolant devices (product code MLY) entered between November 1, 1989 and December 31, 2020. The search identified 15 relevant MDRs.

The 15 reported adverse events were entered into the System for Uniform Surveillance (SUS) database between October 22, 1997 and December 20, 2018 and included Injury (n = 10), Malfunction (n = 4), and Death (n = 1) reports. The majority of the reports originated from the United States (n = 10) and the remaining originated from an unknown reporting country (n = 4) and outside of the United States (n = 1). Patient age was reported in nine MDRs and ranged from 10 to 60 years of age, of which three were pediatric age (age less than 22 years old). (See Appendix D for pediatric MDR descriptions).

- The Injury MDRs (n = 10) were reported by manufacturer (n = 7), voluntary reporter (n = 2), and user facility (n = 1). The noted injuries were burns /frostbite (n = 6), seizure (n = 1), asthma reaction (n = 1), hallucination (n = 1), and skin irritation (n = 1). Concomitant use with cautery and resultant open flame was reported in three reports of burns. One report of frostbite noted that the diabetic condition of the patient may have caused the adverse reaction to the product due to poor circulation. Two reports of frostbite mention that it is typically associated with prolonged application of the product. The report of skin irritation also noted concomitant use of a lidocaine patch.

- The Malfunction MDRs (n = 4) were voluntary reports (n = 3). One described inadequate spray and a separation of the spray apparatus causing a portion to hit the patient on the forehead, but no injury was noted (n = 2). Another identified concomitant use of cautery that ignited an absorbent pad in use underneath the treatment area (n = 1). The flame was extinguished and did not result in patient injury. The manufacturer in one Malfunction MDR (n = 1) noted spraying out of the side of the valve rather than the actuator.

- The Death MDR (n = 1) was a manufacturer report entered into the SUS database on October 4, 2006 that noted use of the device at home and death due to intoxication from chloroethane (ethyl alcohol), the active ingredient in the device.

7. Recall History

7.1 Overview of Recall Database

The Medical Device Recall database contains Medical Device Recalls classified since November 2002. Since January 2017, it may also include correction or removal actions initiated by a firm prior to review by the FDA. The status is updated if the FDA identifies a violation and classifies the action as a recall and again when the recall is terminated. FDA recall classification may occur after the firm recalling the medical device product conducts and communicates with its customers about the recall. Therefore, the recall information posting date ("create date") identified on the database indicates the date FDA classified the recall, it does not necessarily mean that the recall is new.

7.2 Recall Results: Vapocoolant Devices

Two Class II recall[b]s have been identified in the Medical Recall Database with the product code MLY. Both of these recalls were voluntarily initiated by the Gebauer Company during 2007-2008.

The first recall was initiated on April 17, 2007 for six prescription-only vapocoolant devices including Gebauer's Spray and Stretch Fine- Stream Topical Anesthetic Skin Refrigerant, Gebauer's Instant Ice Mist, Gebauer's Pain Ease Medium Stream - Topical Anesthetic Skin Refrigerant, Gebauer's Pain Ease Sample Spray -Topical Anesthtic Skin Refrigerant, Gebauer's Pain Ease Mist Spray- Topical Anesthetic Skin Refrigerant, and Gebauer's Instant Ice Medium Stream. The nationwide recall was made due to Aspergillus fumigatus mold contamination identified during internal

[b] Recalls are classified into a numerical designation (I, II, or III) by the FDA to indicate the relative degree of health hazard presented by the product being recalled. A Class II recall is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

quality control sampling, specifically, during the six month stability testing of the microbial limits for total aerobic count. The recall was completed February 2, 2008.

The second recall was initiated on September 3, 2008 in response to a customer complaint which led to a CAPA investigation (CAPA (b)(4)) that revealed some lots of Gebauer's Fluro-Ethyl had a defective gasket. Gebauer's Fluro-Ethyl Nonflammable Topical Anesthetic Skin Refrigerant (Aerosol Can) P/N 0386-0020-20 lot Numbers: (b)(4), (b)(4), and (b)(4) were all recalled as a result of this complaint. This defective gasket led to a valve malfunction wherein the valve sprayed refrigerant out from the side of the valve in addition to or instead of spraying in the normal inverted position from the product's actuator. Specifically, the product was intended to be sprayed on the patient's upper arm prior to an injection, but the malfunctioning valve caused spray to contact the patient's neck and ear. No injury was reported as a result of the malfunctioning unit.

Gebauer reviewed other complaints of inadvertent spraying in the eyes with functioning product and no serious injuries were reported. The recalled product was discontinued because the valve supplier was unable to correct the issue without a major re-design of the valve, which the Gebauer Company contended was not feasible from a business standpoint. Six FDA recall audit checks were conducted, and all were effective.

8. Summary

In light of the information available, the Panel will be asked to comment on whether vapocoolant devices under product codes "MLY":

meet the statutory definition of a Class III device:

- insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness, and

- the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury

or would be more appropriately regulated as Class II, in which:

- general and special controls, which may include performance standards, postmarket surveillance, patient registries and/or development of guidelines, are sufficient to provide reasonable assurance of safety and effectiveness;

or as Class I, in which:

- the device is subject only to general controls, which include registration and listing, good manufacturing practices (GMPs), prohibition against adulteration and misbranding, and labeling devices according to FDA regulations.

For the purposes of classification, FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;

2. The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. The reliability of the device.

8.1 Special Controls

FDA believes that special controls, in addition to general controls, can be established to mitigate the risks to health identified, and provide a reasonable assurance of the safety and effectiveness of vapocoolant devices. The following is a risk/mitigation table, which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks:

Table 4: Summary of Risks to Health and Proposed Special Controls for Vapocoolant Devices

Identified Risk	**Recommended Mitigation Measure**
Pain or discomfort	Labeling
Skin irritation, including: • Bruising • Numbness • Erythema • Swelling	Labeling
Thermal injury, including: • Skin blanching • Sores • Frostbite • Burns	Non-clinical performance testing Labeling
Electrical shock or burn	Electrical safety testing
Interference with other devices	Electromagnetic compatibility (EMC) testing
Device failure/malfunction leading to ineffective treatment	Non-clinical performance testing Labeling
Asthma	Labeling
Hallucination	Labeling

The Panel will be asked whether this list is a complete and accurate list of the risks to health presented for vapocoolant devices and whether any other risks should be included in the overall risk assessment of the device type.

Based on the identified risks and recommended mitigation measures, FDA believes that the following special controls would provide reasonable assurance of safety and effectiveness for the vapocoolant devices under product code "MLY":

1. Non-clinical performance testing must characterize the change in skin surface temperature control when the device is used as intended.

2. Non-clinical performance testing must demonstrate electrical safety and electromagnetic compatibility for powered devices.

3. Healthcare provider and patient labeling must include:
   a. Information on how the device operates and the typical course of treatment.
   b. A warning that the device should not be used near an open flame, high heat or electric cautery devices.
   c. A warning regarding the risk of frostbite or burns if device is not used as directed.
   d. A warning that if skin irritation persists, discontinue use of the product.
   e. A warning that the device should not be used by individuals with known allergies to product ingredients, as use by such individuals may lead to an allergic response including difficulty breathing.
   f. A warning that the device should not be directly inhaled, as this may be harmful or fatal.

If the Panel believes that Class II is appropriate for the vapocoolant devices under product code "MLY," the Panel will be asked whether the identified special controls appropriately mitigate the identified risks to health and whether additional or different special controls are recommended.

8.2 Overview of Proposed Classification/FDA Recommendation

Based on the safety and effectiveness information gathered by the FDA, the identified risks to health and recommended mitigation measures, we recommend that vapocoolant devices indicated for the temporary relief and reduction of minor topical pain and swelling be regulated as Class II devices.

890.5871 Vapocoolant device.

(a) *Identification.*

A vapocoolant device is a cold therapy device intended for the temporary relief and reduction of minor topical pain and swelling. The device consists of a compressed low-vapor pressure liquid, which is rapidly sprayed onto the skin, whereupon the contacted skin is transiently cooled through rapid evaporation.

(b) *Classification.*

Class II (special controls). The special controls for this device are:

1. Non-clinical performance testing must characterize the change in skin surface temperature control when the device is used as intended.

2. Non-clinical performance testing must demonstrate electrical safety and electromagnetic compatibility for powered devices.

3. Healthcare provider and patient labeling must include:
   a. Information on how the device operates and the typical course of treatment.
   b. A warning that the device should not be directly inhaled, as this may be harmful or fatal.
   c. A warning that the device should not be used near an open flame, high heat or electric cautery devices.
   d. A warning regarding the risk of frostbite or burns if device is not used as directed.
   e. A warning that if skin irritation persists, discontinue use of the product.
   f. A warning that the device should not be directly inhaled, as this may be harmful or fatal.

Based on the available scientific evidence, the FDA will ask the Panel for their recommendation on the appropriate classification of vapocoolant devices under product code "MLY."

Appendix A: Literature Search Terms and Filters for Vapocoolant Devices

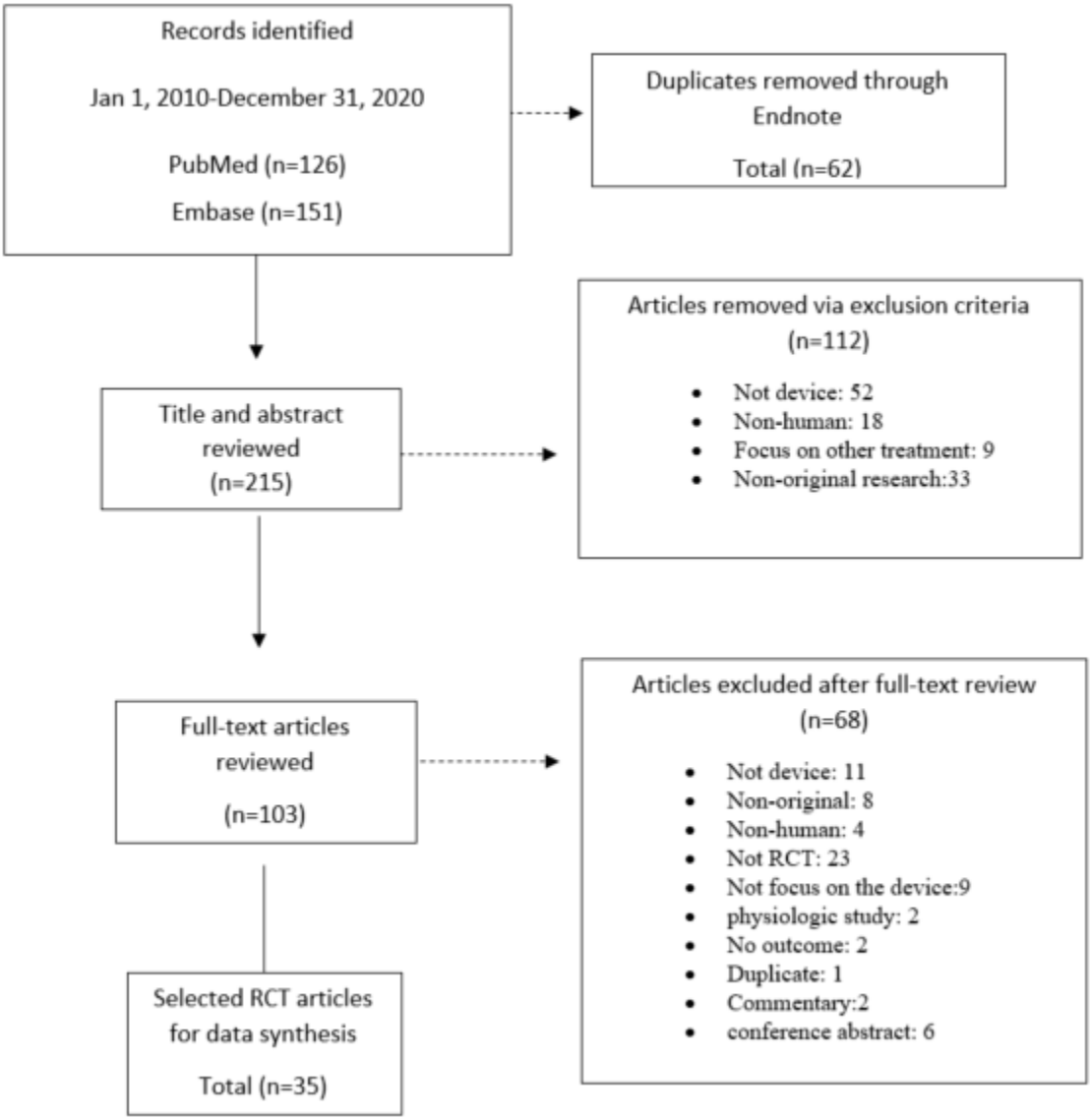
Table 4: Search Terms for Embase and PubMed

AND	OR
Topical	Spray
	Mist
Norflurane	1 1 1 3 3 pentafluoropropane
	1 1 1 2 tetrafluoroethane
	1, 1, 1, 3, 3 - Pentafluoropropane
	1, 1, 1, 2 - Tetrafluoroethane
	ethyl chloride
	compressed medical-grade carbon dioxide gas
	propane, isobutane, n-butane
	dichlorotetrafluoroethane
	trichloromonofluoromethane
	ethylene oxide
	vapocoolant
	refrigerant

Table 5: Search Filters for Embase and PubMed

AND	OR
Publication year 2010-2020	
Humans	
English	
Case reports	Clinical trial
	Controlled clinical trial
	Journal article
	Meta-Analysis
	Observational study
	Pragmatic clinical trial
	Randomized controlled trial
	Review
	Systematic reviews

Appendix B: Flow Diagram of Systematic Literature Review Search Results



Appendix C: Characteristics Randomized Controlled Clinical Trials (RCTs) Included in Literature Review

Table 6: Characteristics of included RCTs

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
Luthy, K. E. et al.	2013	ethyl chloride	pain and anxiety	vaccination	68 children aged 2 to 12 years	vapocoolant vs. DVD distraction vs. usual care Parent reported outcomes: pain: no difference p=0.801 anxiety: no difference p=0.860	not reported	USA
Edwards, C. et al.	2017	1,1,1,3,3-pentafluoro pr opane and 1,1,1,2-tetrafluoroeth ane	pain and anxiety	intravenous access	72 adults	vapocoolant vs. placebo: Median scores for patient perception of pain: 2 vs.2.5; p=0.33 patient forecasted anxiety: 0.5 vs. 0; p>0.05	no AE	USA
Franko, O. I. et al.	2017	ethyl chloride	pain and anxiety	hand injection	151 adults	Likert responses for the no-spray and spray groups were similar: injection pain (3.08 vs 3.10), p=0.96 anxiety (2.46 vs 2.71), p=0.62	not reported	USA

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
Page, D. E. et al.	2010	propane, butane, and pentane blend	pain	cannulation	220 adults	Vapocoolant vs. Lidocaine Median anesthetic administration pain scores: 0 vs. 11 mm, (P<0.001) Median cannulation pain scores were 9 vs. 0 mm, (P<0.001)	lidocaine group, one (1.0%) mild transient erythema vapocoolant group, four (4.4%) reporting mild pruritus, one(1.1%) mild pain, and one (1.1%) transient erythema. No patient required treatment for these events.	Australia
Kose, O. et al.	2010	propane, butane, and pentane blend	pain	ingrown nail surgery	62 adults	Vapocoolant vs. no treatment The mean VAS pain score during needle penetration was 1.32 ± 1.14 vs. 2.43 ± 1.09, p=.001 The mean VAS pain score during infiltration of anesthetic was 5.44 ± 1.08 vs. 5.51 ± 1.14, P = .807	no AE	Turkey
Farahmand, S. et al.	2017	propane, butane, and pentane blend	pain	arterial puncture during arterial blood gas (ABG) sampling	80 adults	vapocoolant vs. placebo: pain score during ABG sampling: 4.78±1.761 vs. 4.90±1.837; P=0.945	numbness	Iran

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
Rüsch, D. et al.	2017	propane, butane, and pentane blend	pain	radial artery cannulation	160 adults	vapocoolant vs. lidocaine: Mean pain scores: 3.4 (±1.58) vs. 4.5 (±2.29), p =0.032;	not reported	Germany
Moon, Y. E. et al.	2013	not specified	pain	needle electromyography examination	97 adults	VAS for pain intensity between vapocoolant and the control group (no intervention) (31.9; 95% CI, 22.0--41.7) vs. (52.9; 95% CI, 45.9--60.0; =.002); EMLA vs. vapocoolant: Patient satisfaction (65.6% vs. 36.4%) and preference (81.3 vs. 42.4%) for repeated use, p<0.05	not reported	Korea
Lunoe, M. M. et al.	2015	not specified	pain	venipuncture	205 young children aged 1-6 years	device vs. vapocoolant cs sham control: mean change in pain scores from treatment to venipuncture: (0.26; 95% CI: 0.31 to 0.82) vs. (2.82; 95% CI: 1.91 to 3.74) vs. (1.68; 95% vs. 0.83 to 2.52).	vapocoolant: Bruise: 8.6% other 4.3%	USA

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
Rüsch, D. et al.	2017	not specified	pain	venous cannulation	450 adults	vapocoolant spray vs. placebo: numeric pain score: 2.6 ± 1.3 vs. 5.0 ± 1.5 (p<0.0001).	mild erythema	Germany
Gupta, N. K. et al.	2017	not specified	pain	vaccination	90 infants up to 3 months of age	EMLA vs. vapocoolant vs. placebo median (IQR) duration of cry: 35.86s (21.07--107.75) vs. 32.58s (21.25-106.21) vs. 67.5s (27.6-180), (P=0.147); median (IQR) latency of cry:1.26s (1.06-1.8) vs. 1.84s (1.25-2.21) vs. 1.48s (1.13-1.92) (P>0.05).	EMLA vs. vapocoolant vs. placebo erythema and swelling 17% vs. 20% vs. 15% (P>0.05).	India
Çelik, G. et al.	2011	ethyl chloride	pain	venipuncture in hemodialysis patients	41 adults	Ethyl chloride as effective as EMLA in preventing mild to moderate pain (P>0.05). Statistically significant than placebo. (p<0.05)	no AE	Turkey
Martín-Pintado Zugasti, A. et al.	2014	ethyl chloride	pain	Healthy volunteers	70 adults	Between-group differences (vapocoolant vs. no vapocoolant) were significant only immediately after intervention (P=.002).	not reported	Spain

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
Moon, Y. E. et al.	2014	ethyl chloride	pain	needle electromyography in the upper extremity	60 adults	vapocoolant vs. placebo: VAS 35.5 vs 45.0, p=0.011; satisfaction: 73.3% vs. 26.7%	not reported	Korea
Irkoren, S. et al	2015	ethyl chloride	pain	Botulinum toxin injection	45 adults	pain VAS: ethyl chloride vs. control: 3.20 ± 1.20 vs. 7.26 ± 1.94; P<0.05 ethyl chloride vs. EMLA: 2.93 ± 1.03 vs. 6.80 ± 1.37; p<0.05	no AE	Turkey
Fossum, K. et al.	2016	ethyl chloride	pain	venous catheterization	38 adults	pain reduction between vapocoolant vs. placebo: numeric rating scale: 2 95% CI: 0.5--2.0; p=0.001	no AE	USA
Moon, Y. E. et al.	2017	ethyl chloride	pain	propofol-induced pain	90 adults	vapocoolant vs. lidocaine vs. placebo: median pain score (interquartile range): [0.5 (0–2.25) vs. 0.5 (0–1) vs. 5 (1–7), p < 0.001] satisfaction scores: [5 (4–5) vs. 4 (3.75–5) vs. 2 (2–3), p < 0.001]	no AE	Korea

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
Rui, W. et al.	2017	ethyl chloride	pain	total knee arthroplasty	306 adults	VAS pain score (vapocoolant vs. no treatment) was significantly lower at all time points after surgery ($p<0.05$). Total analgesic consumption: vapocoolant vs. no treatment: 1190.5 ± 238.2 vs. 1356.2 ± 288.0, $p < 0.001$	no difference between vapocoolant vs. no treatment	China
Firdaus, R. et al.	2018	ethyl chloride	pain	Spinal Injections	94 adults	EMLA vs. vapocoolant: NPRS 0 (0–3) vs. 0 (0–4)	no AE	Indonesia
Rekawek, P. et al.	2019	ethyl chloride	pain	transabdominal chorionic villus sampling	120 adults	ethyl chloride vs. lidocaine median pain score (interquartile range): 50mm (40–65) vs 50mm (30–60);P=.03	no AE	USA
Y. E. Moon, et al.	2020	ethyl chloride	pain	intraarticular injection	63 adults	vapocoolant vs. EMLA vs. placebo: VAS: 30.0 (95% CI, 19.7- 41.2) vs. 50.0 (95% CI, 37.7-63.0) vs. 53.8 (95% CI, 41.6-65.0) (P<.01). Likert scale scores (vapocoolant vs. placebo) for participant satisfaction (P=.003) and preference for	no AE	Korea

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
						repeated use (P<.001).		
Taddio, A. et al.	2010	1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane	pain	immunization injection	352 adults	vapocoolant is as effective as Liposomal lidocaine and more effective than distraction. Pain score liposomal lidocaine vs. vapocoolant: p= 0.97; pain score liposomal lidocaine vs. distraction: p= 0.02.	vapocoolant has lower skin reactions than liposomal lidocaine (13.6% vs. 26.1%)	Canada
Baxter, A. L. et al.	2011	1,1,1,3,3-pentafluorpropane and 1,1,1,2-tetrafluoroethane	pain	pediatric venipuncture	81 aged 4 to 18 years	device vs. vapocoolant: self-report pain (4 vs. 2, p=0.029)	not reported	USA

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
Fung, S. et al.	2012	1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane	pain	botulinum toxin type A injections for lower limb spasticity.	30 adults	Numerical Rating Scale (NRS): Both the EMLA and ice induced significantly greater pain relief compared with vapocoolant (P=.013). Wong-Baker FACES scale: the ice condition was significantly more effective in pain relief than vapocoolant (P=.007).	not reported	USA
Waterhouse, M.R. et al.	2013	1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane	pain	intravenous catheter placement	95 aged 9 to 18 years	More subjects in the vapocoolant group (76%) felt treatment worked well, compared to 49% in the ice group (p<0.05).	not reported	USA
Mace, S. E.	2016	1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane	pain	venipuncture	100 adults	placebo vs. vapocoolant pain score median (interquartile range): 3 (1.2-5) vs. 1 (0-3), P<.001.	vapocoolant minimal blanching 4%, minimal erythema 18%	USA
Mace, S. E.	2017	1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane	pain	intravenous cannulation	300 adults	median pain score (interquartile range) between placebo and vapocoolant: 4 (2, 7) vs. 2 (0, 4), (P <0.001)	minimal erythema: 2.7% (4/150),	USA

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
Barbour, T. et al.	2018	1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethane	pain	venipuncture	100 adults	vapocoolant vs. placebo: reported less pain: 76% vs. 14%, p < .001	not reported	USA
Wiswall, A. T. et al.	2014	1,1,1,2-tetrafluoroethane	pain	posterior palatal	84 samples from 42 adult patients	no statistically significant difference in perceived pain response	sore on palate 81% in vapocoolant group vs. 0 from other options	USA
DiMarco, A. C. et al.	2016	topical refrigerant	pain	patients need dental hygiene therapy or routine restorative therapy	30 adults	pain reduction between a 5-second application of a refrigerant compared with a 2-minute application of a 20% benzocaine gel (P=.283).	no AE	USA
Gur, S. T. A., et al.	2020	not specified	image quality	acute ankle trauma	155 adults	vapocoolant vs. placebo: The mean scores for image quality were 8.13 ± 1.8 vs. 6.58 ± 2.2, (mean difference: -1.56, 95% CI: -2.20 to–0.92; p=.000)	not reported	Turkey

First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
Im, Y. G.	2012	ethyl chloride	Facial skin temperature	healthy volunteers	30 adults	ethyl chloride spraying had a limited cooling effect on the facial skin tissue and could not reduce the skin surface temperature enough for local analgesia. cold gel packing vs. ethyl chloride spray vs. ice block rubbing: reduction in surface temperature (10.6 °C) vs. (4.3 °C) vs. (3.7 °C), (P < 0001).	no AE	Korea
Gal-Oz, A. et al.	2010	ethyl chloride	Antipruritic	healthy volunteers	51 adults	Significant improvement in pruritus (Ethyl chloride vs. placebo: 84% vs. 16%; p<0.0001).	no AE	Israel
Barbour, T. et al.	2020	1,1,1,3,3-pentafluoropropane and 1,1,1,2-tetrafluoroethrane	Pain	Patients needing peripheral intravenous placement	300 adults	Significantly less pain (p < 0.001) by using the topical refrigerant spray (77%) versus the placebo spray (32.4%) compared to previous IVs	No AE	USA
Dhami, H. et al.	2020	Ethyl chloride	Pain	Patients needing radial arterial puncture	60 adults	No significant difference (p = 0.113) between the mean pain score for	Not reported	India

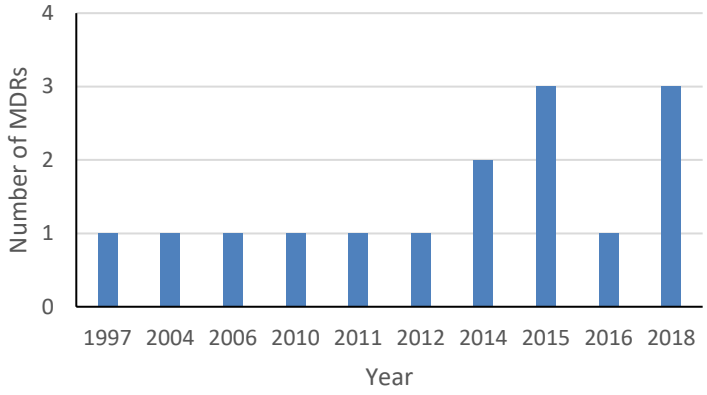
First Author	Year	Materials	Indication	Condition	sample size	Effectiveness	Safety	Country
						patients given ethyl chloride (2.5±1.2) versus ice pack (3.1±1.8). Incidence of haematoma was significantly (p=0.01) reduced with ethyl chloride (6.66%) versus ice pack (33.3%)		

Appendix D: Pediatric Medical Device Report (MDR) Descriptions for Vapocoolant Devices

Pediatric Age in MDRs (Product Code MLY)

Age in Years	Date Entered	Event Type	Event Description
13	June 4, 2004	Injury	Concomitant use of electric cautery. Patient's synthetic hair caught on fire and resulted in 1st degree burn on patient's ear.
16	February 8, 2018	Injury	Concomitant use of electric cautery resulted in 1st degree burn on patient's toe.
10	March 26, 2018	Malfunction	Concomitant use of cautery resulted in ignition of protective pad in use under the treatment area. No patient injury reported.

Chart 1. Product Code MLY Reports by Calendar Year



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Classification of Vapocoolant Devices
FDA Questions

Neurological Devices Panel of the Medical Devices Advisory Committee June 3-4, 2021

1. FDA has identified the following risks to health for vapocoolant devices:

Identified Risk	**Description/Examples**
Pain or discomfort	This can result from burns and/or blistering.
Skin irritation	This can result from burns and/or blistering.
Thermal injury	This can result from frostbite or burns particularly when used in combination with electrical cautery leading to ignition, leading to redness, blistering and edema.
Electrical shock or burn	This can result from electrical failure or malfunction.
Interference with other devices	Electromagnetic disturbances that may cause unacceptable degradation in device performance, leading to delayed or ineffective treatment.
Device failure/malfunction leading to ineffective treatment	Device malfunction can cause spray to contact unintended areas of the body which can lead to burns and minor injury.
Asthma	This can result from an allergic response to the product or aerosol delivery system.
Hallucination	This can result from improper use of the device and subsequent inhalation toxicity.

Please comment on whether you agree with inclusion of all the risks in the overall risk assessment of vapocoolant devices under product code "MLY". In addition, please comment on whether you believe that any additional risks should be included in the overall risk assessment of these vapocoolant devices.

2. Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:

    - insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, AND

    - if, in addition, the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

A device should be Class II if:

- general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness, AND

- there is sufficient information to establish special controls to provide such assurance.

A device should be Class I if:

- general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR
- insufficient information exists to:
  - determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness, OR
  - establish special controls to provide such assurance, BUT
    I. is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and
    II. does not present a potential unreasonable risk of illness or injury.

FDA believes general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness and sufficient information exists to establish special controls to adequately mitigate the risks to health and provide reasonable assurance of device safety and effectiveness for this device type. As such, FDA believes that Class II is the appropriate classification for vapocoolant devices. Following is a risk/mitigation table which outlines the identified risks to health for this device type and the recommended controls to mitigate the identified risks.

Risk/mitigation recommendations for vapocoolant devices under product code "MLY"

Identified Risk	**Recommended Mitigation Measure**
Pain or discomfort	Labeling
Skin irritation, including: • Bruising • Numbness • Erythema • Swelling	Labeling
Thermal injury, including: • Skin blanching • Sores • Frostbite • Burns	Non-clinical performance testing Labeling
Electrical shock or burn	Electrical safety testing

Identified Risk	Recommended Mitigation Measure
Interference with other devices	Electromagnetic compatibility (EMC) testing
Device failure/malfunction leading to ineffective treatment	Non-clinical performance testing Labeling
Asthma	Labeling
Hallucination	Labeling

Please discuss whether the identified special controls for vapocoolant devices appropriately mitigate the identified risks to health and whether additional or different special controls are recommended:

1. Non-clinical performance testing must characterize the change in skin surface temperature control when the device is used as intended.

2. Non-clinical performance testing must demonstrate electrical safety and electromagnetic compatibility for powered devices.

3. Healthcare provider and patient labeling must include:
   a. Information on how the device operates and the typical course of treatment.
   b. A warning that the device should not be used near an open flame, high heat or electric cautery devices.
   c. A warning regarding the risk of frostbite or burns if device is not used as directed.
   d. A warning that if skin irritation persists, discontinue use of the product.
   e. A warning that the device should not be used by individuals with known allergies to product ingredients, as use by such individuals may lead to an allergic response including difficulty breathing
   f. A warning that the device should not be directly inhaled, as this may be harmful or fatal.

3. **Please discuss whether you agree with FDA's proposed classification of Class II with special controls for vapocoolant devices. If you do not agree with FDA's proposed classification, please provide your rationale for recommending a different classification.**