

FDA Executive Summary

Prepared for the
February 21, 2014 meeting of the
Orthopedic and Rehabilitation Devices Panel

Classification of Iontophoresis Devices Not
Labeled for Use with a Specific Drug
(21 CFR 890.5525(b))

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1. Introduction

Per Section 513(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Food and Drug Administration (FDA) is convening the Orthopedic and Rehabilitation Devices Advisory Panel (the panel) for the purpose of obtaining recommendations regarding Class III uses of iontophoresis devices that were subject to orders under Section 515(i) of the FD&C Act. Iontophoresis devices are one of the remaining preamendment Class III medical devices currently cleared for marketing through the 510(k) pathway.

The purpose of this panel meeting is to discuss and make recommendations regarding the regulatory classification of iontophoresis devices not labeled for use with a specific drug [as defined under the classification regulation 21 CFR Section 890.5525(b)].

FDA is holding this panel meeting to obtain input on the risks to health and benefits of these iontophoresis devices. The Panel will also be asked to discuss and make recommendations regarding a classification strategy for iontophoresis devices currently within this classification regulation. The Panel will discuss whether iontophoresis devices not labeled for use with a specific drug should remain in Class III (and be subject to premarket approval [PMA] applications) or be reclassified to Class II (subject to General and Special Controls) or Class I (subject only to General Controls). If the Panel believes that a lower classification is appropriate for these devices than Class III, the Panel will also be asked to discuss appropriate controls that would be necessary to mitigate the risks to health.

1.1. Background on the Reclassification Process

FDA regulates medical devices and categorizes them into one of three classes (I, II, or III).

1.1.1. Class I [21 CFR 860.3(c)(1)]

Class I devices are subject to the least regulatory control. They usually present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. A device is Class I if general controls are sufficient to provide a reasonable assurance of the safety and effectiveness of the device. Examples of general controls include registration and listing, medical device reporting, good manufacturing practices (GMPs), prohibitions against adulteration and misbranding, and labeling. Devices may also be considered Class I if the device “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 does not present a potential unreasonable risk of illness or injury.”¹ Examples of Class I devices include elastic bandages, examination gloves, and hand-held manual surgical instruments. Most Class I devices are exempt from premarket review

¹ See Section 513(a)(1)(A) of the Food, Drug and Cosmetic (FD&C) Act.

requirements (e.g., 510(k)) and can be marketed without a premarket submission; most Class I devices are also exempt from GMPs.

1.1.2. Class II [21 CFR 860.3(c)(2)]

Class II devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are also subject to special controls. Special controls may include requirements for specific labeling or performance testing, including clinical testing. Most Class II devices must obtain marketing clearance through premarket notification submissions [510(k)s]. Sponsors are required to submit valid scientific evidence in their 510(k) demonstrating that the device is as safe and effective as a predicate device. Companies submitting a 510(k) for a device must demonstrate how any specified special controls have been met in order to receive marketing clearance. Examples of Class II devices include transcutaneous electrical nerve stimulation (TENS) devices, powered wheelchairs, infusion pumps, and surgical drapes.

1.1.3. Class III [21 CFR 860.3(c)(3)]

Class III is the most stringent regulatory category for devices. Class III devices are typically higher risk devices, but also include devices for which insufficient information exists to assure safety and effectiveness solely through general or special controls. All devices that are not substantially equivalent to any existing devices in Class I or II are automatically classified in Class III. Class III devices typically require marketing approval through a premarket approval (PMA) application. Examples of Class III devices include endovascular grafts, total artificial disc replacements, and implanted neuromuscular stimulators.

Class III refers to the class of devices for which premarket approval is or will be required in accordance with section 513 of the FD&C Act. A device is in 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
- 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.

Medical devices that require 510(k) submissions are required to demonstrate substantial equivalence to a legally marketed device(s) (i.e., *as safe and as effective as*). A legally marketed device may be either another device that has already been cleared through the 510(k) process or a “preamendments” device, i.e., a device that was on the market in the United States prior to May 28, 1976

(the date of the enactment of the Medical Device Amendments to the FD&C Act). Devices that require PMA applications are required to independently demonstrate safety and effectiveness and to demonstrate that the probable benefit to health from the use of the device outweighs any probable risk of injury or illness from such use.

Although most Class III devices require PMA approval, when FDA began regulating medical devices in 1976, FDA categorized over 170 devices in Class III, but did not establish an effective date for the requirement for premarket approval. The intent was that this regulation would be temporary and that, over time, FDA would decide to either reclassify those devices into Class I or II, or to sustain the classification in Class III and call for PMA applications. Iontophoresis devices not labeled for use with a specific drug are one of these device types; they are currently classified as Class III devices, but are cleared for marketing authorization through a 510(k) submission. These devices were classified as Class III because the original classification panel did not believe there was sufficient evidence to support safety and effectiveness for general drug delivery through Class I or II. At the time, FDA agreed and formally classified these devices in Class III in 1983.

The present panel meeting is the result of FDA's ongoing 515 Program Initiative to facilitate the final adjudication of the remaining Class III devices that are regulated through the 510(k) program. FDA is required to hold a meeting of a device classification panel prior to finalizing the reclassification of a device type; this panel will focus on iontophoresis devices not labeled for use with a specific drug (21 CFR 890.5525(b)).

1.2. Indications for Use

The indication for use (IFU) statement identifies the condition and patient population for which a device should be appropriately used, and for which the device has demonstrated a reasonable assurance of safety and effectiveness.

Paragraph (a) of 21 CFR 890.5525 defines an iontophoresis device for 'certain specified uses' and states, "*An iontophoresis device is a device that is intended to use a direct current to introduce ions of soluble salts or other drugs into the body and induce sweating for use in the diagnosis of cystic fibrosis or for other uses if the labeling of the drug intended for use with the device bears adequate directions for the device's use with that drug. When used in the diagnosis of cystic fibrosis, the sweat is collected and its composition and weight are determined.*" These devices are classified into Class II and are not the subject of this meeting.

21 CFR 890.5525(b) defines iontophoresis devices 'for any other purposes' as "*An iontophoresis device is a device that is intended to use a direct current to introduce ions of soluble salts or other drugs into the body for medical purposes other than those specified in paragraph (a) of this section.*" Therefore, an iontophoresis device

that is not indicated for use in the diagnosis of cystic fibrosis or for use with a specific drug that has been approved for delivery by iontophoresis would be regulated under 21 CFR 890.5525(b). However, this does not imply that iontophoresis devices under paragraph (b) of the regulation may be indicated or labeled for use with specific drugs that have not been approved for iontophoretic delivery. Any device indication or labeling that references a drug must be consistent with the approved route of administration of such drug, and FDA cannot clear a new route of administration for a drug through the 510(k) process. Rather, this would require approval in an application for Premarket Approval (PMA) or a New Drug Application (NDA). Paragraph (b) of the regulation acknowledges the use of iontophoresis as a general drug delivery tool (such as a syringe) that does not identify a specific drug, but may be used in an on-label manner with one or more drugs that are labeled for iontophoretic delivery. It also acknowledges use of iontophoresis with solutions that do not include a regulated drug, such as tap water. Devices under paragraph (b) are the subject of this meeting.

There are slight variations in the indications for use of the iontophoresis devices that have been found substantially equivalent through the 510(k) process under paragraph (b) of the regulation. Since 1977, FDA has cleared 63 devices under paragraph (b) of the regulation through the 510(k) process.² The indications for which the devices in this regulation were cleared are summarized below (note that some devices are in multiple categories).³

- All iontophoresis devices have been cleared for ‘prescription use only.’
- 40 devices were cleared for general transdermal drug delivery, usually for delivery of “ions of soluble salts or other drugs into the body for medical purposes” and as an “alternative to hypodermic injection.”
 - 4 of these devices specifically mention use with Iontocaine (Lidocaine HCl 2% and Epinephrine 1:100,000 Topical Solution), which was approved in an NDA and is therefore part of the Class II designation (according to 890.5525(a)). However, these are considered Class III devices because they also mention general administration of ions of soluble salts or other drugs as an alternative to hypodermic injections.
- 6 devices were cleared “for the administration of drug solution, salts, or ions into the ear, including the tympanic membrane, for medical purposes,” which was a preamendments indication for iontophoresis devices.
- 3 devices were cleared for use in the treatment of hyperhidrosis (excessive sweating) using tap-water iontophoresis, which was also a preamendments indication for iontophoresis devices.

² FDA recently discovered that 14 of these devices are incorrectly listed in our public 510(k) database as Class II devices under paragraph (a), even though they were correctly identified as Class III devices on the original decision letters from FDA. We are in the process of rectifying this error, but at this time our public database incorrectly lists only 49 devices in paragraph (b) under product code EGJ.

³ One device meets the definition of a Class II device under 21 CFR 890.5525(a) and appears to have been assigned the incorrect product code. Therefore, it is not included in the discussion of indications for use.

In addition to these indications, some devices were submitted to FDA for review with labeling or indications that mentioned use with specific drugs that had not been approved for use with iontophoresis. At the time, CDRH's practice was to clear the device if the device technology was substantially equivalent, while also notifying the manufacturer that the determination applied to the device only and that they could not market their device for use with a specific drug. The following indications were included in 510(k) submissions that were found substantially equivalent prior to 1994:

- 11 devices had indications or labeling that identified a specific drug that was not approved for iontophoresis (dexamethasone, fluoride, and lidocaine and/or epinephrine prior to NDA approval).
- 9 devices identified a class of drugs (corticosteroids, anesthetics), although no specific drugs were mentioned.
- 3 devices were cleared for the delivery of fluoride or sodium chloride to the teeth for dental use.

However, for the last 20 years, CDRH has not cleared any iontophoresis devices if unapproved drugs (or classes of drugs) are identified in the indications or labeling.

The panel discussion will be limited to iontophoresis devices with indications for general drug delivery (without identifying a specific drug or class of drugs) and tap water iontophoresis for the treatment of hyperhidrosis. All other uses are beyond the scope of this classification proceeding.

1.3. Device Description

Iontophoresis is the non-invasive transdermal delivery method in which a substance is introduced into the body by an electric current. There are three different mechanisms that may be present in iontophoretic transport:

1. Electromigration: movement of ions under influence of the electric field through repulsion of like charges and attraction of opposite charges.
2. Electro-osmosis: movement of the bulk of the solution driven by a layer of ions adsorbed at the surface of the skin pores and crevices. Keratin, a surface protein of epidermis cells, is negatively charged at pH greater than 4, which means that positive ions adjacent to the surface move the bulk of the solution from anode to cathode and carry drug molecules in this direction independent of their charge.
3. Facilitated passive diffusion: application of electrical current leads to increased permeability, which enables the penetration of drug molecules through the skin by diffusion.

However, for the charged species that are typically delivered by iontophoresis (*e.g.*, lidocaine), transport is dominated by electromigration [1]. In iontophoretic electromigration, the current produces a net charge at the electrode that repels ions with like charges. As depicted in Figure 1, two electrodes are employed: the anode

(positive electrode) and the cathode (negative electrode). If the substance intended to be delivered is a positively charged species (cation), it is placed at the site of the anode and is driven away from the electrode and into the body. The cathode is then usually placed at an alternate site on the skin with no drug in order to complete the circuit. If the substance intended to be delivered is a negatively charged species (anion), it is placed at the site of the cathode and is driven away from the electrode and into the body. Again, the anode is then usually placed at an alternate site on the skin to complete the circuit.

How quickly and how far the charged particle moves through the skin is determined by the electric field applied, the polarity and charge of the molecule, the molecular weight, the pH of the solution, and the permeability of the skin (or tympanic membrane when used in the ear).

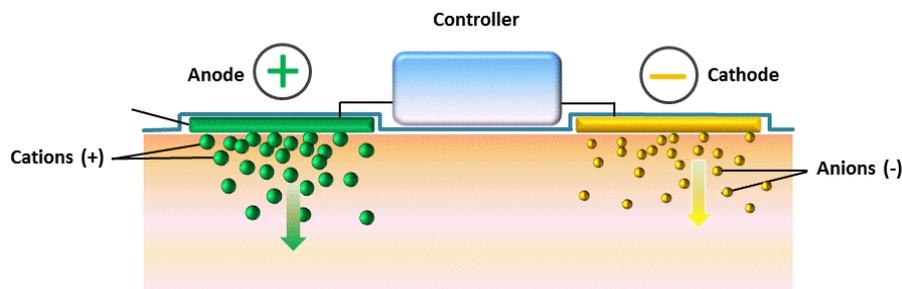


Figure 1: Diagram of Iontophoresis

Iontophoresis systems consist of the iontophoresis device and the drug or other solution to be administered. If the system is marketed as a complete product that includes both a device and drug component, then it would be considered a drug delivery system, regulated as a drug-device combination product⁴, and the Center for Drug Evaluation and Research (CDER) would have the lead jurisdictional authority. Alternatively, if the device component is marketed separately from a drug, or as a complete system with a non-drug solution, then it would be regulated as a medical device by the Center for Devices and Radiological Health (CDRH).

⁴ As defined in 21 CFR 3.2(e), a combination product includes: (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity; (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products; (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Iontophoresis devices generally include a controller, active electrode(s) (for drug/solution delivery), return electrode(s), and a power supply used to deliver currents. While these components need to be used together for the device to function, they may currently be marketed and cleared through the 510(k) process separately. For instance, some companies only manufacture the electrodes, which may be used with different controllers.

There are four general types of iontophoresis devices that FDA has organized by the type of active/return electrode design and intended use: (1) adhesive electrodes; (2) handpiece electrodes; (3) ear electrodes; and (4) palmar/plantar electrodes. All four types have the same general operating principle.

- Electrodes:

1. Adhesive Electrodes - Devices that utilize adhesive electrodes have both anode and cathode electrodes that adhere to the skin. The electrodes may either be connected by leads (wires) to a separate controller or the electrodes and controller may all be contained on a single adhesive patch powered by a battery. The portion of the active electrode that contacts the skin also has a drug/solution reservoir. End users saturate the reservoir with the ionic solution to be delivered. The reservoir contacts the electrode and the drug/solution is delivered to the patient transdermally. Examples of iontophoresis devices that include adhesive electrodes are presented in Figure 2 and Figure 3.

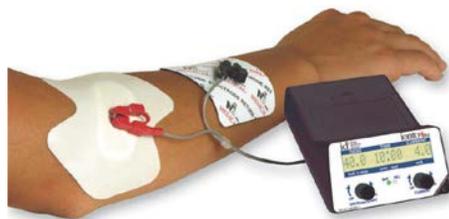


Figure 2: Adhesive Electrode (machine type)⁵



Figure 3: Adhesive Electrode (patch type)⁶

2. Handpiece Electrodes - Devices that utilize this design typically have a single active electrode handpiece with either a conductive roller-ball electrode, a stylus pen electrode, or a multi-electrode handpiece used

⁵ <http://e-current.com/richmar-id3-iontophoresis-unit.aspx>

⁶ <http://www.wisdomking.com/product/companion-80-wireless-drug-delivery-system>

on the skin (as seen in Figure 4). End users either apply the drug/solution to be delivered transdermally directly to the skin, or the handpiece may have a reservoir with a port that releases the solution during use. These type of devices usually also employ the use of a separate return electrode which adheres to the skin at another location to complete the circuit of current flow.



Figure 4: Handpiece Electrode⁷

3. Ear Electrode– Devices that utilize the ear electrode design contain a small conductive electrode on a plug that is inserted into the external ear. These devices are intended to transport ions into the ear, including the tympanic membrane, rather than into the skin. End users fill the ear with the drug/solution to be delivered and insert the active electrode ear plug as depicted in Figure 5. An adhesive return electrode is placed on the skin in another location to complete the circuit (*e.g.*, on the arm).

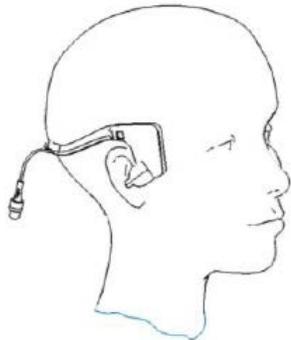


Figure 5: Ear Electrode⁸

⁷ <http://www.matteng.com/ionto2.jpg>

⁸ https://www.jnjgatewayifu.com/eLabelingContent/Acc/USENG/IFU005066_Rev_D_Tula_Iontophoresis_System_IFU_71831.pdf

4. Palmar/Plantar Electrode– Devices that utilize this design contain electrodes applied to the palms of the hands and/or soles of the feet and are indicated for the treatment of hyperhidrosis. End users place two plate electrodes in separate tubs of tap water and each hand or foot is placed on an electrode as shown in Figure 6. Alternatively, the electrodes may utilize water-soaked sponges instead of tubs. In both of these setups, the anode is placed under one hand or foot and the cathode under the other. The polarity of the electrodes may also be alternated during treatment.

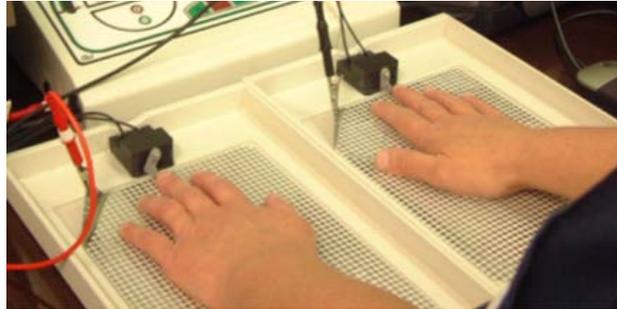


Figure 6: Palmar/Plantar Electrode⁹

- **Controller:** The controller typically consists of a microprocessor, circuitry, and software/firmware. The controller delivers and regulates the current amplitude and waveform, if applicable. Devices may have a pre-programmed, fixed DC output or have different electrical output programs and/or user specified parameters. The controller unit often has a visual display or feedback to the user to indicate if the device is in use, treatment time has expired, or there is an error in the electrical output.
- **Power Supply:** Single use devices (such as the patch design) are typically battery powered. These devices often use 3V coin cell lithium (Li) batteries. Reusable devices (such as the handpiece design) are often powered through a transformer from a wall outlet (AC mains).

1.3.1. Critical Device Parameters for Iontophoresis Devices

1.3.1.1. Current and Dose

The typical output of an iontophoresis device is a constant direct current (DC) output, which produces a steady current at a single value (see Figure 7, red line). This differs from an alternating current (AC), which changes

⁹ <http://hyperhidrosisnetwork.com/wp-content/uploads/Iontophoresis-03.jpg>

its value over time and typically alternates between a positive and negative amplitude (see Figure 7, blue line).

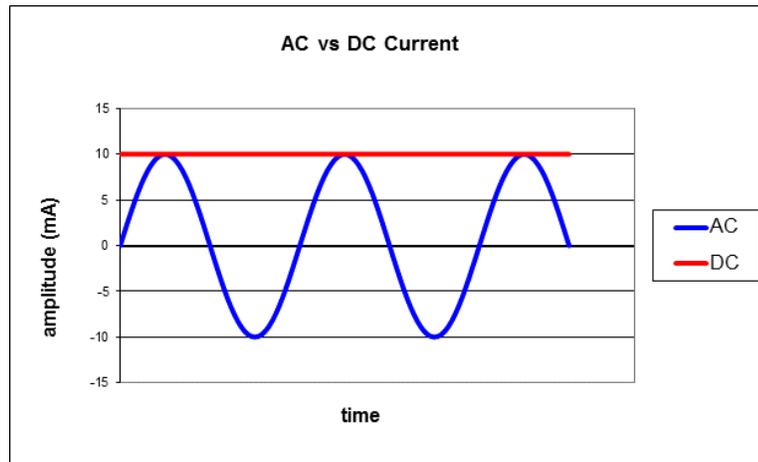


Figure 7: AC and DC Currents

The unit for current is amperes or “amps” (which is denoted with the symbol ‘A’) and represents the amount of electric charge per unit time. Therefore, the total amount of charge produced by a DC iontophoresis device is the current multiplied by the amount of time it is delivered. **For iontophoresis devices, the electric charge is called the dose** and is usually provided in units of milliamp-minutes (mA-min).

$$\text{Dose (mA-min)} = \text{DC current (mA)} \times \text{Time (min)}$$

Therefore, the **same amount of charge may be delivered using a higher current for a shorter period of time or a lower current for a longer period of time**. Except for patch electrodes, iontophoresis devices typically have adjustable current outputs and a clinician may increase the current to the highest setting tolerable by the patient to minimize the treatment time.

Some iontophoresis devices have more complex outputs and do not deliver constant DC outputs. For instance, some designs may use a pulsed DC output. For these devices, the calculation of the total charge delivered also needs to take into consideration the output waveform and the duty cycle.

1.3.1.2. pH

Applying electrical current to an aqueous solution can impact safety and effectiveness by decreasing the pH at the positive anode and increasing the pH at the negative cathode. This can potentially lead to chemical burns or reduce the efficiency of drug delivery. Therefore, it is generally considered important that the solution in an iontophoresis system is adequately buffered to keep the pH of the drug solution relatively

constant. Alternatively, changes in pH can be limited by using silver / silver-chloride (Ag/AgCl) coated electrodes, which prevent the electrolysis of water.

1.3.1.3. Current Density

Current density is the amount of current delivered per unit of surface area of the electrode. A high current density (large current relative to a small surface area) can result in burns from the resistive heating of the skin. On the other hand, a larger current may be used safely with an electrode that has a large surface area. For instance, when tap water iontophoresis is used to treat palmar or plantar hyperhidrosis, the electrode contacts the entire surface of the palm of the hand or sole of the foot. As a result, these devices typically employ currents of 10-25 mA and doses up to 400 mA-min, whereas smaller transdermal drug delivery iontophoresis devices typically deliver currents less than 5 mA and doses up to 80 mA-min.

1.3.1.4. Non-device Parameters that Impact Iontophoresis

In addition to aspects of the device design, the formulation of the drug/solution being delivered may also impact the safety and effectiveness of iontophoresis devices. As noted above, pH is one important factor. Additionally, the charge of the delivered species will dictate how much of it is introduced by electromigration. Physical size limitations such as the molecular weight of the species and the permeability of the part of the body where it is delivered will also impact the delivery. Regardless of the electric charge, species with large molecular weights are more difficult to deliver, while low molecular weight species may pass more easily. The presence of other ions (such as sodium chloride) in the solution may also decrease delivery by ionic competition with the drug.

2. Regulatory History

A brief summary of the regulatory history for iontophoresis devices is provided below.

2.1. Device Classification Panel Meetings

Since iontophoresis devices have been used in different clinical specialties, they have been discussed over a series of meetings by the Physical Medicine Device Classification Panel, the Ear, Nose, and Throat Device Classification Panel, and the Dental Device Classification Panel.

2.1.1. Physical Medicine Device Classification Panel Meetings

The Physical Medicine Device Classification Panel, hereinafter referred to as “the Physical Medicine Panel,” made preliminary classification recommendations for physical medicine devices during a series of meetings in

the late 1970's and early 1980's. Iontophoresis devices were discussed during a meeting on July 7, 1978.¹⁰ The Panel recommended Class II for iontophoresis devices, considering the device only and not the safety and efficacy of the numerous therapeutic uses of the device. The Panel believed that the devices were of theoretical and practical value, but that there was insufficient clinical data available for most of the drugs used with an iontophoresis device. They also stated that drug doses delivered by iontophoresis were much less accurate than other methods, such as injection, and uncontrolled drug delivery could result in potentially severe adverse effects. The Panel decided to separate the device from the therapeutic uses and, based on electrical safety considerations, recommended Class II for all iontophoresis devices. The Panel also identified the following risks to health for iontophoresis devices:

1. *Electrical shock: Excessive leakage current could result in injury, or a malfunction of the device could result in electrical shock.*
2. *Burns: High current densities in tissue over time could result in burns.*
3. *Cardiac arrest: Cardiac arrest may be caused by an excessive electrical current passing through the heart.*
4. *Inappropriate therapy: Inappropriate therapy could result from inaccurate current measurement function.*

2.1.2. Ear, Nose, and Throat Device Classification Panel Meetings

Although iontophoresis devices were classified under the Physical Medicine regulation, they were also initially discussed by the Ear, Nose, and Throat Device Classification Panel (hereinafter referred to as “the ENT Panel”) on November 6, 1978 because of their use in delivering topical anesthetic to the tympanic membrane.¹⁰ The ENT Panel recommended that iontophoresis devices for this use be classified into Class II. The panel based this decision, in part, on a presentation of the literature that concluded that iontophoresis for anesthetizing the intact tympanic membrane is safe and effective. However, they believed that the design and materials of the electrode needed to be regulated to prevent trauma to the patient and that general controls would not provide sufficient control over the electrode design. The Panel also believed that a performance standard would provide reasonable assurance of the safety and effectiveness of the device and that there was sufficient information to establish a standard to provide such assurance.

¹⁰ A summary of the panel discussions may be found in the August 28, 1979 issue of the Federal Register (44 FR 50520)

The ENT Panel identified the following risks to health for iontophoresis devices intended for use on the tympanic membrane:

1. *Trauma: Trauma to the ear may be caused by the use of an improperly designed electrode.*
2. *Bodily injury: Bodily injury may be caused by the use of an inappropriate drug or use of the procedure with a perforated tympanic membrane.*

2.1.3. Dental Device Classification Panel Meetings

Iontophoresis devices were also initially discussed by the Dental Device Classification Panel (hereinafter referred to as “the Dental Panel”) because of their use in accelerating the delivery of fluoride to the teeth.¹⁰ The Dental Panel recommended iontophoresis devices for this use be classified into Class I and that manufacturers of this device not be required to comply with premarket notifications [510(k)s], records and reports, or Good Manufacturing Practice (GMP) regulations because the Panel believed that the electrical voltage was low and the direct current involved was sufficiently small to not be a danger to the patient. The Dental Panel acknowledged that published reports showed an equal reduction in hypersensitivity with both fluoride and the placebo and that the reduction may be due to technique rather than the introduction of fluoride. However, they believed that the safety and effectiveness of these devices would not be appreciably altered if a minimum level of performance was not maintained. The Dental Panel concluded that general controls were sufficient to provide reasonable assurance of the safety and effectiveness of the device.

The Dental Panel identified no risks to health for use in delivering fluoride to the teeth.

2.2. 1979 Classification Proposed Rules, 1978-1979 Meetings of Device Classification Panels

Following the initial classification panel meetings, FDA published a proposed rule on August 28, 1979 (44 FR 50520), proposing classification of iontophoresis devices “for the diagnosis of cystic fibrosis”, “for the local anesthetizing of the intact tympanic membrane”, and “for dental application of fluoride”, as Class II. FDA proposed classifying iontophoresis devices “for all other purposes” as Class III (premarket approval).

FDA wrote the following reasons for the recommendation:

- *The agency recognizes that the Physical Medicine Device Classification Panel members recommended a classification for the device only and did not*

consider the specific uses of the device. The agency believes, however, that the intended use of the device and the device itself cannot be separated.

- *Limited uses (for the diagnosis of cystic fibrosis, for fluoride uptake acceleration in dentistry and for the local anesthesia of the intact tympanic membrane) of iontophoresis have been studied, documented, and accepted as being safe and effective.*
- *There is a lack of scientific data supporting the use of iontophoresis for many of the claims being made [other than the 3 uses identified above].*
- *The therapeutic value of iontophoresis is limited, and the disadvantages include the difficulty of estimating the dosage of the drug and particularly of estimating how much of the drug may act systemically.*
- *The agency believes that iontophoresis devices, when used for purposes other than those specifically considered, present a potential unreasonable risk of injury without benefit to the patient because substantial data and clinical investigations do not exist to support the claims made for the devices.*

FDA received three comments on this proposed rule, all of which objected to Class III for other uses. The treatment of hyperhidrosis (excessive sweating), the delivery of general medications and the delivery of steroids were identified in the comments as additional uses that should be Class II. When comments regarding the scope of the identifications for iontophoresis devices in this proposed rule were received, the Agency asked the Physical Medicine Device Section of the Surgical and Rehabilitation Devices Panel, hereinafter referred to as “the Panel,” to review these devices again on December 12, 1979.

The Physical Medicine Panel agreed with FDA’s recommendation to split the classification for iontophoresis devices. The Panel recommended Class II for iontophoresis devices intended for the three specific uses: to induce sweating for use in the diagnosis of cystic fibrosis, to accelerate introduction of fluoride into tooth structures, and for local anesthetizing of the intact tympanic membrane. Iontophoresis devices for any other uses, however, were recommended to be Class III. Some of the Panel members discussed the literature available at the time. They believed that safety and effectiveness for the three specific uses identified above had been established. However, the Panel felt that there was insufficient information on safety and effectiveness for other uses and they were concerned that the amount of medications delivered transdermally could not be quantified. The Panel also summarized the literature on the treatment of hyperhidrosis and concluded there was insufficient evidence to determine if it was safe and effective. For this indication, they also felt that the mechanism of action had not been established and that further clinical trials were necessary. The Panel recommended that iontophoresis devices for the treatment of hyperhidrosis be classified as Class III requiring a PMA.

2.3. 1982 Reclassification Petition and 1983 Classification Panel Meeting

On November 8, 1978, General Medical Co. submitted to FDA a 510(k) stating that it intended to market an iontophoresis device with the brand name Drionic Iontophoretic Sweat Inhibition Device (Drionic). After reviewing the information in the 510(k), FDA determined that the device was not substantially equivalent to any device that was in commercial distribution before May 28, 1976, nor was the device substantially equivalent to a device that has been placed in commercial distribution since that date and subsequently reclassified. Accordingly, this device was automatically classified into Class III under section 513(f)(1) of the FD&C Act (21 U.S.C. 360(f)(1)). On October 18, 1982, General Medical Co. submitted to FDA, under section 513(f)(2) of the act, a petition to reclassify the Drionic device from Class III into Class I.

FDA referred the petition to the General and Plastic Surgery Device Section of the Surgical and Rehabilitation Devices Panel, hereinafter referred to as the "Surgery Panel." On January 26, 1983, the Surgery Panel reviewed the petition at an open public meeting.¹¹ As part of their petition, General Medical Co. submitted data specific to the Drionic device. After considering the information in the petition and the presentations made at the January 26, 1983 meeting, the Surgery Panel unanimously recommended that the petition to reclassify the device from Class III into Class I be denied. The Panel expressed as its principal reason for opposing reclassification of the device its conclusion that there was a lack of evidence that the device was effective for its claimed use, sweat inhibition. In addition, the Panel stated that the data did not establish the safety of long-term use of the device and concluded that long-term follow-up was needed to determine whether or not there may be other safety problems.

In addition to the risks to health identified by the Physical Medicine Classification Panel in 1978, the Surgery Panel identified a number of additional potential safety concerns about the use of the petitioner's device, including the unknown consequences of chronic use of the device, particularly when no control on the number of treatments, duration of treatments, or strength of the application was available at the time.

FDA agreed with the safety concerns of the Surgery Panel and concluded that the Drionic device presented a potentially unreasonable risk of illness or injury and that there was insufficient evidence to support reclassification into a class other than Class III. Therefore, FDA denied the petition.

¹¹ A summary of the panel discussion and FDA's decision on the petition may be found in the June 3, 1983 issue of the Federal Register (48 FR 24981).

2.4. 1983 Classification Final Rule

The Agency agreed with the December 12, 1979 Physical Medicine Panel that insufficient information existed to determine that general controls would provide reasonable assurance of the safety and effectiveness and that insufficient information existed to establish a performance standard to provide this assurance when the device was used for any purpose other than (1) to induce sweating for use in the diagnosis of cystic fibrosis, (2) to accelerate introduction of fluoride into tooth structures, and (3) for local anesthetizing of the intact tympanic membrane. However, FDA also regulates drugs for safety and effectiveness and, at the time, the Agency was unaware of any drug that had labeling providing adequate directions for its use with an iontophoresis device for the dental application of fluoride or the anesthetizing of the intact tympanic membrane. Therefore, in order to prevent conflicting regulatory requirements between the Center for Devices and Radiological Health (CDRH) and the Center for Drug Evaluation and Research (CDER), CDRH determined that iontophoresis devices for the dental application of fluoride or the anesthetizing of the intact tympanic membrane should be classified into Class III.

On November 23, 1983, FDA published a final rule classifying iontophoresis devices with a split classification (48 FR 53045). The final rule revised the information that had been presented in the proposed rule to omit the dental application of fluoride and anesthetizing the intact tympanic membrane from the Class II uses. The rule classified iontophoresis devices into Class II when intended to induce sweating for use in the diagnosis of cystic fibrosis or for other uses if the labeling of the drug intended for use with the device bears adequate directions for the device's use with that drug. The rule classified iontophoresis devices into Class III for any other purposes. Accordingly, the following codified language was published in Part 890 of the Code of Federal Regulations:

890.5525 Iontophoresis device.

- (a) Iontophoresis device intended for certain specified uses
 - (1) *Identification.* An iontophoresis device is a device that is intended to use a direct current to introduce ions of soluble salts or other drugs into the body and induce sweating for use in the diagnosis of cystic fibrosis or for other uses if the labeling of the drug intended for use with the device bears adequate directions for the device's use with that drug. When used in the diagnosis of cystic fibrosis, the sweat is collected and its composition and weight are determined.
 - (2) *Classification.* Class II (performance standards).
- (b) Iontophoresis device intended for any other purposes
 - (1) *Identification.* An iontophoresis device is a device that is intended to use a direct current to introduce ions of soluble salts or other drugs into the body for medical purposes other than those specified in paragraph (a) of this section.
 - (2) *Classification.* Class III (premarket approval).

In order to require premarket approval, FDA is obligated to issue a notice calling for PMAs and establishing the effective date of that requirement. FDA published a clarification in 1987 that no effective date had been established for the requirement for premarket approval for iontophoresis devices “for any other purposes” as identified above (52 FR 17742, May 11, 1987). Therefore, these devices continued to be reviewed through the 510(k) process.

2.5. 2000 Proposed Rule to Revoke 21 CFR 890.5525(b)

On August 22, 2000, FDA published a proposed rule (65 FR 50949) to amend 21 CFR 890.5525 to remove paragraph (b) of the regulation (the Class III identification), such that only paragraph (a) of the regulation (the Class II identification) would remain. In this rule, FDA stated that it believed it had made an error in the original classification and that there were no iontophoresis devices on the market prior to the Medical Device Amendments of 1976 (generally referred to as “preamendments devices”) that met the Class III identification. Although several devices had been cleared under this regulation between 1976 and the publication of the proposed rule, FDA believed that those devices could meet the definition of a Class II iontophoresis device with modifications to their labeling. Any device that could not meet the Class II definition (i.e., for any other use than the diagnosis of cystic fibrosis or with a specific drug approved for iontophoretic delivery) would require submission of a PMA. FDA requested that comments to this proposed rule be submitted by November 20, 2000.¹²

FDA received seven comments in response to this proposed rule. Several comments disagreed with FDA’s assertion that no Class III preamendments iontophoresis devices existed. Two comments asserted that the assumption that there are differences between different iontophoresis devices that would warrant linking a particular device to a particular drug is in error, and suggested that FDA should consider reclassification of iontophoresis devices into either Class I or Class II as drug delivery systems comparable to syringes and pumps. In contrast, another comment rejected what it perceived as the implication that all iontophoresis drug delivery systems were the same and that any iontophoresis device could be relabeled to reference any drug approved for iontophoretic administration, whether or not the drug had actually been tested for use with that particular device.

As a result of these comments, on November 4, 2004, FDA withdrew (69 FR 64266) the August 2000 proposed rule that proposed to revoke paragraph (b) of the regulation. In that same issue of the Federal Register, FDA also published a notice of its intent (69 FR 64313) to initiate a proceeding to reclassify Class III iontophoresis devices into Class II (special controls).

¹² See docket [FDA-2000-N-0158] available at: <http://www.regulations.gov/#!docketDetail;D=FDA-2000-N-0158>.

2.6. 2009 515(i) Order for Remaining Class III Preamendments Devices

On April 9, 2009, pursuant to Section 515(i) of the FD&C Act, FDA issued an order in the Federal Register (74 FR 16214) to call for information on the remaining Class III 510(k) devices. Included in this group of devices were iontophoresis devices, as defined under 21 CFR 890.5525(b). Manufacturers were required to submit a summary of “...*information known or otherwise available to them respecting such devices, including adverse safety or effectiveness information concerning the devices...to determine...whether the classification of the device should be revised to require the submission of a PMA...or whether the device should be reclassified into Class I or II.*”

Letters were sent out to every manufacturer of a preamendments device registered with FDA, notifying them of this request; each was given until August 7, 2009 to respond. FDA received ten submissions regarding iontophoresis devices in response to this call for information.¹³

One response stated that the company was only a repackager/relabeler of the device and did not have a recommended classification or information on safety and effectiveness. The remaining 9 responses were all from manufactures of iontophoresis devices. Eight of the manufacturers recommended that the devices be reclassified into Class II with special controls. The other manufacturer provided only safety and effectiveness information and did not recommend a classification. The risks to health identified by the manufacturers are included as part of the discussion in Section 4 below.

Because this call for information was specifically for device manufacturers, there were no responses from patients, consumers, healthcare practitioners, or other members of the public. Before issuing a final classification for iontophoresis devices not labeled for use with a specific drug, in addition to seeking feedback by convening this Panel meeting, FDA will also issue a proposed order in the Federal Register and solicit comments from both industry and the public.

2.7. Rationale for the Panel Meeting

On July 9, 2012, enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) made changes to sections 513 and 515 of the FD&C Act. FDASIA changed the process for taking final administrative action for these remaining devices, requiring that FDA use an administrative order process instead of using rulemaking. Under the new requirements, FDA must issue proposed and final orders to call for PMAs or reclassify into Class II or Class I and hold a device classification panel meeting to consider the classification of each of these devices. FDA would like to request the Panel to comment on whether iontophoresis devices

¹³ The redacted versions of these responses are available at the following address: <http://www.regulations.gov/#!docketDetail;D=FDA-2009-M-0101> (the responses related to iontophoresis are numbered FDA-2009-M-0101-0100 through 2009-M-0101-0109).

not labeled for use with a specific drug should remain in Class III or whether they should be reclassified to Class II with special controls, in combination with general controls, or Class I with general controls only.

FDA has conducted additional review of the scientific literature and has carefully reviewed the information received in response to the August 22, 2000 proposed rule and the April 9, 2009 call for information.

As previously discussed, devices are 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
- 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.

FDA does not believe that iontophoresis devices not labeled for use with a specific drug are life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health. FDA does believe these devices present a potential unreasonable risk of illness or injury, yet believes that special controls would provide reasonable assurance of safety and effectiveness. As a result, FDA is considering reclassification to Class II for iontophoresis devices not labeled for use with a specific drug, with appropriate special controls, in combination with general controls.

3. Summary of Clinical Evidence

3.1. Clinical Background

Although Class III iontophoresis devices are not labeled for use with specific drugs, there are a number of drugs approved for iontophoretic delivery for a variety of indications that may be used with these devices. FDA has approved five NDAs for three different drugs or drug combinations:

- lidocaine and epinephrine for local dermal analgesia,
- fentanyl for short-term management of post-operative pain, and
- sumatriptan for acute treatment of migraines.

Additionally, FDA has cleared Class III iontophoresis devices for tap water iontophoresis to treat palmar and plantar hyperhidrosis. Each of these uses is discussed further below.

FDA is also aware that iontophoresis devices are being investigated and used clinically with drugs and other solutions that have not been approved for delivery by iontophoresis, or for indications that have not been cleared or approved by FDA. While the Agency does regulate the labeling and marketing of drugs and devices, we

do not regulate the practice of medicine. Because iontophoresis devices have not been cleared or approved for these drugs or indications, a discussion of the safety and effectiveness of each of these specific uses are outside the scope of this proceeding. However, based on information gathered from scientific literature and studies on clinicaltrials.gov, FDA has noted the following examples of clinical and/or investigational uses of iontophoresis in addition to the approved uses noted above. Note this list is just a small sampling and is not intended to be exhaustive: dexamethasone and salicylates for inflammation, vitamin C and sodium nitroprusside for systemic sclerosis, acyclovir for herpes, acetylcholine for Raynaud disease, verapamil for Peyronie's disease, terbinafine for onychomycosis, tretinoin for acne, botulinum toxin for hyperhidrosis, and treprostinil for vasodilation.

One of the most common uses for iontophoresis devices not labeled for use with a specific drug is in the practice of physical therapy. There are numerous clinical conditions in physical therapy for which iontophoresis has been investigated or used clinically. Although not an exhaustive list, some of the common conditions are for managing pain associated with tendinitis (including epicondylitis and Achilles tendinitis), bursitis, plantar fasciitis, and arthritis. Medications used include lidocaine, dexamethasone, and acetic acid.

3.2. Safety Data

3.2.1. FDA Adverse Event Databases

FDA reviewed adverse events associated with iontophoresis devices that were reported to the Agency. Because iontophoresis devices are not differentiated by technology and because devices not labeled for use with a specific drug may also be used with approved drugs, FDA expects that the risks associated with all iontophoresis devices (both Class II and Class III) are applicable to Class III iontophoresis devices not labeled for use with a specific drug. Therefore, FDA evaluated the adverse event reports in both our medical device and drug databases and for both Class II and Class III iontophoresis devices.

3.2.1.1. CDRH's Manufacturer and User Facility Device Experience (MAUDE) Database for Medical Devices

The MAUDE database is maintained by the Office of Surveillance and Biometrics (OSB) in CDRH at FDA. This database contains adverse events and reportable product problems with medical devices. The database was fully implemented in August 1996, and contains individual adverse event reports submitted by manufacturers, user facilities, importers, and voluntary reporters. Medical device manufacturers are required to report known adverse events as part of the general controls that most medical devices are subject to; patients and consumers are also encouraged to voluntarily report adverse events.

FDA/CDRH has received a total of 150 adverse events reports associated

with iontophoresis devices between the dates of January 1, 1996 to November 1, 2013. Iontophoresis devices for “certain specified uses” are classified as Class II devices and are designated under product code KTB. Thirty-four adverse events were associated with 36 MAUDE reports for iontophoresis devices classified under this product code. Iontophoresis devices “for any other purposes” are classified as Class III devices and are designated under product code EGJ. One hundred sixteen (116) adverse events were associated with 120 MAUDE reports for iontophoresis devices classified under this product code.

Serious Injury Reports

Eighty-two serious injury reports (no death reports) were identified under product code EGJ. Individual review of these reports found that the chief patient problem was burns ranging from first to third degree burns (80), with second degree burns (33) being the most common. There was one report of chest pain and shortness of breath and another report of a hole in an arm. Twenty-nine (29) serious injury reports (no death reports) were identified under product code KTB, all of which were burns. Individual review of these reports found that they ranged from unspecified (9) to third degree burns (1), with the majority identified as second degree burns (19). A review of all injury reports found no reports associated with any complications with a particular drug.

Device Malfunctions

Thirty-four (34) malfunction reports were identified under product code EGJ. Individual review of these reports found that 29% (10/34) of the malfunction reports were attributed to the device and 12% (4/34) of the malfunctions were attributed to use error. Device malfunctions attributed to the device included defective electrodes (3), electric shock (3), electrodes used without gel (2), electrode break in flexible circuit (2), and a defective transistor in the electrode (1). Device malfunctions attributed to use error included that the treatment dose exceeded the maximum recommended dosage, an electrode wore out, and a battery detached from the electrode as the electrode was placed on the incorrect side of the release liner. All of these device malfunctions were associated with burns, aside from 3 that were associated with shock. In 59% (20) of malfunction reports, a malfunction code was reported by the author of the report; however, no further information was provided on the nature of malfunction. Furthermore, the cause of injury was unknown so the device could not be ruled out. This was primarily because the device was not evaluated or returned to the manufacturer. All of these reports identified skin burns.

Five malfunction reports were identified under product code KTB. Individual review of these reports found that 20% (1/5) of the malfunction reports were attributed to the device and no malfunctions were attributed

to use error. This device malfunction included a defective electrode contact. In 80% (4/5) of malfunction reports, a malfunction code was reported by the author of the report; however, the cause was unknown so the device could not be ruled out. No further information was provided on the nature of the malfunction. This was primarily because the device was not evaluated or returned to the manufacturer. All of these reports identified skin burns.

Recalls

The Recall Enterprise System (RES) is owned and maintained by the Office of Regulatory Affairs (ORA) at the FDA. RES is an electronic data system used by FDA recall personnel to submit, update, classify, and terminate recalls. The RES database was searched for all recalls associated with product codes EGJ and KTB from January 1, 1996 to November 1, 2013. There were no recalls with product code KTB and one recall with product code EGJ. This recall occurred in 2005 for a specific lot, in which the conductor portion of the electrode was installed backwards with the plastic and silver portions of the electrode reversed. One adverse event was associated with this manufacturing mistake in which the patient incurred a second degree burn.

Summary

In summary, the primary patient problem is burns (109 adverse events) ranging from first to third degree. The largest numbers of burns associated with the use of this device were reported as second degree burns (52 adverse events). The causes of use error associated with serious injuries were attributed to the treatment exceeding the recommendations in either treatment time or dosage of medication. There were no drug complications to the patient that could be identified from these reports. A corrective action was initiated in March 2005 by one firm for the issue of defective electrodes. However, this issue is noted to be a problem across many manufacturers.

There are limitations to MAUDE reporting, including the fact that not all events are captured since this is a voluntary reporting system and that the total number of devices used during the time frame evaluated is unknown. Given the low number of reports, substantial conclusions are difficult to make.

Table 1: Adverse Events & Recalls Reported to CDRH

Event Information	Events Reported	
	EGJ	KTB
Product Code	EGJ	KTB
Total Adverse Events	116	34
Deaths	0	0
Serious Injury	82	29
Burns	80	29
1 st Degree	0	0
2 nd Degree	33	19
3 rd Degree	12	1
Unspecified Degree	35	9
Chest Pain & Shortness of breath	1	0
Hole in arm	1	0
Malfunction	34	5
Caused Burns	31	5
Caused Electric Shock	3	0
Attributed to Device	10	1
Defective Electrodes	3	1
Electrodes without gel	2	0
Break in circuit	2	0
Defective Transistor	1	0
Attributed to Use Error	4	0
Unknown Cause	20	4
Recalls	1	0

3.2.1.2. FDA Adverse Event Reporting System (FAERS) Database for Drugs and Biologics

Because iontophoresis devices are used to deliver drugs, CDRH also worked with CDER staff to identify adverse events related to iontophoresis that have been reported to CDER. The FAERS database contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD). FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous adverse event reporting system (AERS) to FAERS.

FDA/CDER has received a total of 86 adverse events reports from 1996 through September 23, 2013 related to iontophoretic drug delivery. Sixteen (16) adverse event reports identified an approved iontophoresis

drug in the report, fentanyl hydrochloride (13 cases), epinephrine/lidocaine hydrochloride (2 cases), and pilocarpine (1 case).

Death Reports

Five (5) death reports were reported among the 86 adverse event reports. Individual review of these reports found that one (1) patient was in a study comparing intravenous morphine to iontophoretic administration of fentanyl. The patient was in the morphine control group and, therefore, did not receive iontophoresis. The remaining 4 deaths are listed below.

- 1 patient with a history of abdominal aortic aneurysm and multiple vessel disease died of a myocardial infarction. The approved iontophoresis drug fentanyl was identified, but the reporting facility stated that the patient had comorbidities and did not consider the drug or device related to the death.
- 1 patient died of an unknown cause. The patient was participating in a study of bevacizumab and capecitabine for metastatic colorectal cancer in which iontophoresis with pilocarpine was used to assess endothelial cell function. No further information on this death was available.
- 1 patient died of central nervous system (CNS) depression caused by encephalopathy. The patient had ongoing chronic respiratory failure, post herpetic neuralgia, chronic obstructive pulmonary disease, and ischemic heart disease. Iontophoresis was identified as concomitant therapy to pregabalin for neuralgia, but the drug was not identified. The reporting facility did not identify iontophoresis as a potential contributor to the death.
- 1 patient with multiple myeloma died of multi-organ failure associated with aggravated renal function and blood dyscrasias. The patient had received iontophoresis with an unknown drug for herpes zoster (shingles) within the month prior to death. However, the reporting facility attributed the death to disease progression.

Serious Injury

Seventy-nine (79) injury reports were reported among the 86 adverse events. Twelve (12) of these reports identified an approved iontophoresis drug in the report. Individual review of these reports found five (5) reports of skin burns, two (2) reports of skin necrosis, two (2) reports of skin peeling, one (1) report of electrical shock, one (1) report of disorientation, and one (1) accidental exposure. Device-related injury could not be ruled out for cases reporting skin necrosis, skin burns, and peeling skin. Sixty-seven (67) of the 79 injury reports did not identify the associated iontophoretic drug delivered to the patient. Individual review of these reports found two (2) reports of skin burns/reactions, one (1) report of discoloration at the treatment site, and two (2) reports of pain at the treatment site. Device-related injury could not be ruled out in these reports. Individual review of the remaining 62 reports found no

association with the reported patient problem and the iontophoretic device component of the treatment. These included various musculoskeletal diseases and disorders such as ligament sprains, tendon strains, and epicondylitis, Peyronie's disease, amnesia, arthralgia, tendon ruptures, blood disorders, diarrhea, convulsion, hypertension, asthma, among many other diseases and disorders.

Device Malfunctions

Two (2) device malfunctions were reported among the 86 adverse events. Individual review of these reports could not identify the specific device malfunctions. The approved iontophoresis drug, fentanyl, was identified within these two reports.

Summary

In summary, in 17 of the 86 adverse events, device-related injury could not be ruled out. Among these reports, the primary patient injury was skin burns (7). Some of the injuries were as severe as to involve skin peeling (2).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Table 2: Adverse Events Reported to CDER

Event Information	Events Reported
Total Adverse Events	86
Deaths	5
Myocardial Infarction	1
CNS Depression	1
Multiple Myeloma	1
Unknown Cause	1
Unrelated (did not receive iontophoresis)	1
Serious Injury	79
Possibly Device Related	17
Burns	7
Skin Necrosis	2
Skin Peeling	2
Electric Shock	1
Disorientation	1
Accidental Exposure	1
Discoloration at treatment site	1
Pain at treatment site	2
Associated Drug	--
Fentanyl	13
Lidocaine	2
Pilocarpine	1
Not identified	70

3.2.2. Systematic Literature Review

FDA conducted a systematic literature review to assess the safety of iontophoresis devices by analyzing the existing clinical literature from 2003 to the present. While this did exclude some pre-2003 references, FDA believed a search covering a 10-year span would capture the most relevant research and be sufficient to provide comprehensive safety information on iontophoresis devices. A wide range of drugs and uses have been studied for iontophoresis. However, because Class III iontophoresis devices have not been cleared for use with specific drugs or for specific clinical conditions (other than the treatment of hyperhidrosis, which is addressed in Section 3.3.2), FDA did not attempt to evaluate the effectiveness of each of these uses. Therefore, the systematic literature review was limited to evaluating the safety of iontophoresis devices by reviewing potentially device-related adverse events. Although drug-related adverse events may be caused by insufficient or excessive drug delivery with an iontophoresis device, the adverse effects will vary based on the delivered drug. As a result, a focus was placed on application site reactions as potential device-related adverse events.

3.2.2.1. Methods

On December 31, 2013 FDA searched the published literature in PubMed. In order to identify studies with safety evaluations, FDA's search focused on key safety terms and known adverse events of iontophoresis devices. The primary strategy employed the following search terms:

- ("iontophoretic" OR "iontophoresis" OR "electromotive drug administration" OR "electrically-assisted transdermal delivery" OR "transdermal electromotive administration")
- AND (transdermal OR skin OR "stratum corneum" OR ear OR "tympanic membrane")
- AND ("electrical Shock" OR "chemical burn" OR "chemical burns" OR "electrical burn" OR "electrical burns" OR "cardiac arrest" OR "inappropriate therapy" OR blister OR rash OR "rupture of dermis" OR scarring OR shock OR "chest pain" OR infection OR adverse OR "adverse events" OR "side effect" OR "side effects" OR risk OR risks OR death OR mortality OR complication OR complications)

The above search yielded 440 articles. The search was further limited to studies published after January 1, 2003 and those published in English, resulting in a total of 230 articles. These titles and abstracts were further screened and articles were excluded if they were studies with small sample size ($n < 10$ patients), non-clinical research (e.g., non-systematic review, letter to the editor, protocol, non-clinical methods paper, editorial, conference abstract without full text report), article without human data, article not containing any data on iontophoresis devices, non-English article, no safety endpoints related to the use of iontophoresis devices, published before January 1, 2003, devices not FDA approved or cleared (to eliminate prototype devices or others that would not have any public health impact), or duplicate article. This screening resulted in the exclusion of 183 articles for the following reasons:

- no safety endpoint ($n=88$),
- non-clinical research ($n=56$),
- non-human data ($n=29$),
- sample size < 10 ($n=7$),
- not iontophoresis devices ($n=2$), and
- duplicate ($n=1$).

The full-texts of the remaining 47 articles were examined for eligibility using the same criteria as above, of which 22 were excluded for the following reasons:

- no safety endpoint (n= 11),
- not FDA approved or cleared devices (n=6),
- non-clinical research (n= 3),
- non-English (n=1), and
- sample size < 10 (n=1).

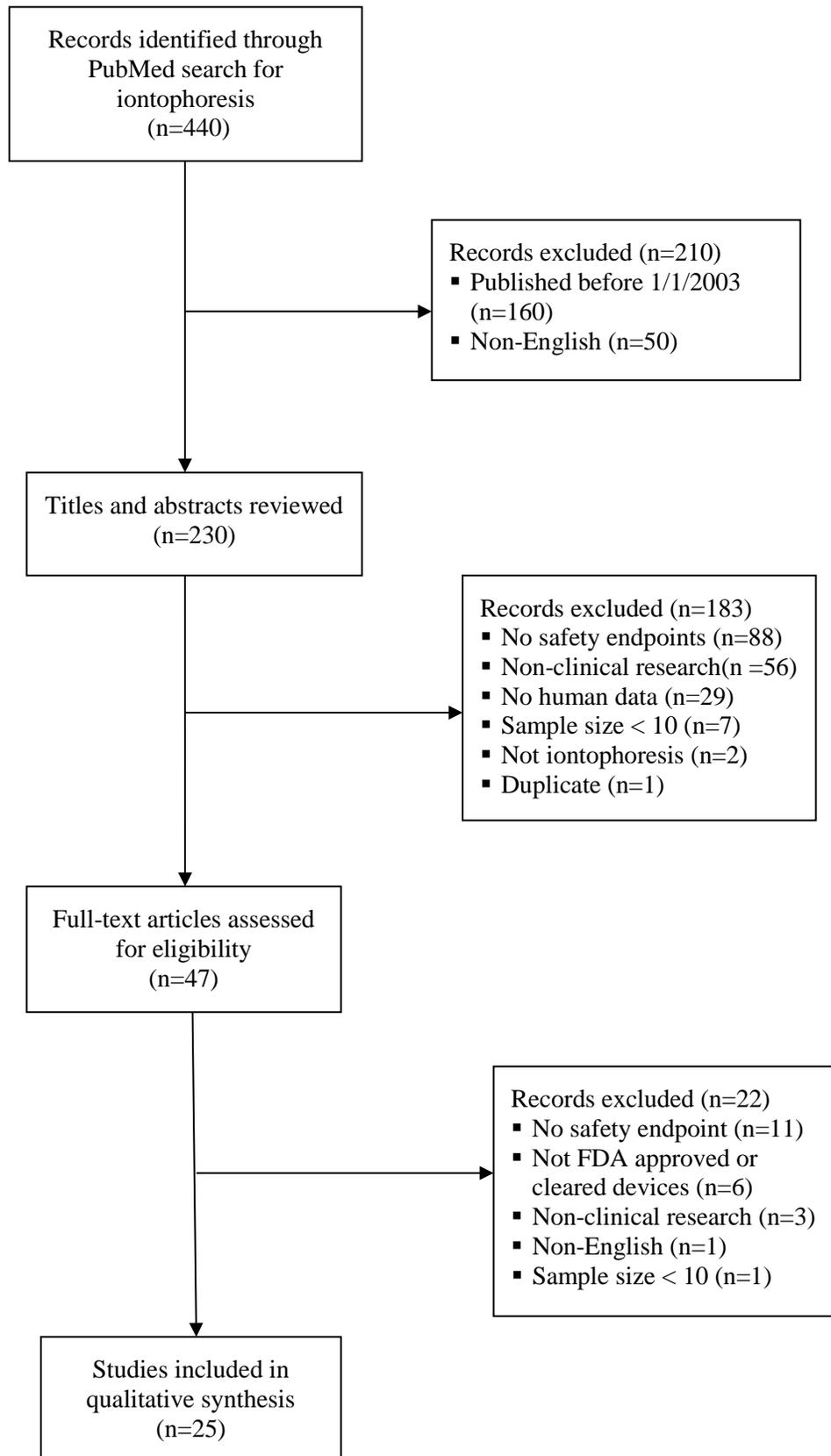
Therefore, as summarized in Figure 8, 25 articles were identified for iontophoresis devices in the current systematic epidemiological review for qualitative synthesis.

3.2.2.2. Summary of Results

Twenty-five articles were found that examined the safety of iontophoresis devices in human populations. There were thirteen randomized controlled trials (RCT) [10,11,13-16,21-24], five secondary analyses [3,4,8,9,12], five crossover studies [5-7,20,26], one single arm trial [25], and one cohort study [2]. Articles were published between the years 2003 and 2011, with no new literature published between 2011 and 2013. Studies were conducted in various locations, including sixteen in the US and Canada, eight in Europe, and one in Thailand.

The articles evaluated the safety of iontophoresis devices for eight indications, including 1 for central neuropathic pain [16], 1 for migraine [6], 1 for juvenile idiopathic arthritis [2], 1 for Parkinson's disease [17], 2 for Peyronie's disease [21,26], 1 for Raynaud's phenomenon [5], 6 for topical anesthesia [7,18,20,23-25], and 12 for postoperative pain control [3,4,8-15,19,22]. Overall, adverse events reported included delivered medication-related events and application site reactions (ASR). Delivered

Figure 8: Diagram of Article Retrieval and Selection



medication-related events varied by indications for use. Regardless of the study design, the types of ASR reported were similar, but frequency of ASR varied in these studies and included erythema, blanching, pruritus, tingling and itching, local skin irritation, burning sensation, vasoconstriction, burn, urticaria, edema, and vesicles.

3.2.2.3. Indications for Central Neuropathic Pain, Migraine, Juvenile Idiopathic Arthritis, Parkinson's Disease, Peyronie's Disease and Raynaud's phenomenon

No adverse events that required medical intervention were reported for these indications in 7 eligible articles (3 RCTs [16,17,21], 3 crossover studies [5,6,26], and 1 retrospective cohort study [2]).

Regardless of the study design, drugs or placebos were all administered by iontophoresis devices in these studies except Pierce's 2009 study [6]. This crossover study tested multiple types of administration such as subcutaneous, oral, and nasal spray administration. ASR were commonly reported, of which, the overall incidence of mild transient erythema at site of electrodes regardless drug treatment assignment was 2 (6.1%) in Vranken's 2005 RCT (n=33), 24 (86%) in Mina's 2011 retrospective cohort study (n=28), 1 (6.3%) in Li's 2005 RCT (n=16), 96 (100%) in Di Stasi's 2004 RCT (n=96), and 1 (2%) in Di Stasi's 2003 crossover study (n=49). Other reported ASR included pruritus in Pierce's 2009 crossover study (7/17 patients, 41%), skin blister in Mina's 2011 study (1/28 patients, 4%), and tingling and itching in Li's 2005 study (16/16 patients, 100%). All these events were self-limited.

Delivered medication-related adverse events varied by study. These included sedation, dizziness, vivid dreams, headache, confusion, nausea and vomiting reported in Vranken's 2005 study (drug studied: S(+)-ketamine), headache reported in Pierce's 2009 study (drug studied: sumatriptan), metallic taste reported in Mina's 2011 study (drug studied: dexamethasone), pallor and dizziness reported in Blaise's 2010 crossover study (n=10, drug studied: sodium nitroprusside). The frequencies of these adverse events are presented in Table 5.

Summary

Overall, there were few studies that reported adverse events for indications of central neuropathic pain, migraine, juvenile idiopathic arthritis, Parkinson's disease and Peyronie's disease. Sample sizes of the seven eligible studies were small ranging from 10 to 96. Variation of the proportions of ASR was large, ranging from 6.1% to 100%. Although the incidence of the reported ASR may be as high as 100%, all these events were mild in severity and did not require treatment. In addition, no adverse events that required medical intervention were reported for these

indications. Use of iontophoresis for these indications may be safe based on these findings. However, due to small sample size, the safety findings may not be extrapolated to broader populations with the same indications.

3.2.2.4. Indication for Topical Anesthesia

Three RCTs [18,23,24], two crossover studies [7,20], and one single arm study [25] reported adverse events of iontophoresis devices indicated for topical anesthesia within the patients in the treatment arm.

There were no adverse events that required medical intervention reported in these six studies. Reported adverse events included blanching, erythema, tingling, edema, pain at application site, burning sensation, vasoconstriction, a partial thickness burn, itching, and urticaria. Incidences of adverse events varied in these studies such as the most frequently reported ASR, erythema, which ranged from 3% [7] to 97% [23].

Three placebo-controlled RCTs conducted by Zempsky et al. in 2003 and 2004 enrolled 649 patients (317 adults and 332 children) to compare lidocaine to placebo delivered by an iontophoresis device for topical anesthesia. Burning sensation, vasoconstriction, partial thickness burn, itching, and urticaria were reported (incidence ranging 0.4% to 1.8%), whereas blanching and/or erythema were reported with much higher incidences (ranging 90% to 97%) [18,23,24]. All these events resolved within 24 hours.

Three studies (n= 12 ~ 30) without control groups (2 crossover studies [7,20] and 1 single arm trial [25]) reported adverse events of iontophoresis devices indicated for topical anesthesia including blanching, erythema and tingling. The incidences of these events (Table 5) varied in a wide range, such as erythema (0% [20] to ~ 93% [7]). All these adverse events did not require treatment and resolved within 48 hours.

Summary

For the indication of topical anesthesia, there were six eligible articles. One RCT (Zempsky, 2004 [18]) enrolled both adult and pediatric patients and did not find a statistical difference in the 5-point Draize scale for erythema/edema in both adult and pediatric arms. A partial thickness burn was reported in 1 (0.4%) child in the same study. Blanching/erythema were the most frequently reported ASR with a wide range of incidence such as 0% in Phahonthep's 2004 study (0/16) [20] and 97% (58/60) in Zempsky 2003 [23]. All these events resolved within 48 hours. No AEs requiring medical intervention were reported. Iontophoresis devices indicated for topical anesthesia appear safe based on these findings. However, the small sample sizes (n=12-276) limits the generalizability of these findings. Also, the lack of a placebo control group (3 out of 6 articles

had no control group) hinders causal inference of the relation of AEs to device use. For instance, the observed AEs might be due to specific participant's characteristics in these studies, such as sensitive skin that is prone to develop an ASR.

3.2.2.5. Indication for Postoperative Pain Management

There are seven RCTs and five secondary analysis studies that reported adverse events of iontophoresis devices used for postoperative pain management. Fentanyl was used for iontophoresis in all of these studies, compared with active control morphine used for intravenous (IV) patient-controlled analgesia (PCA) or placebo. The most frequently reported adverse events included those relevant to the use of opioids and ASR. The frequency of adverse events varied in these studies with a range of 9.4% [13] to 53.8% [19].

The adverse events relevant to use of opioids that were reported in at least 2% of patients included nausea, vomiting, dizziness, headache, respiratory depression, paralytic ileus, hypoxia, hypotension, constipation, insomnia, urinary retention, hypokalemia, hypoventilation, atrial fibrillation, tachycardia, somnolence, fever, abdominal pain, pharyngitis, confusion, chills generalized spasm, and extremity pain in these studies. The type and frequency of these adverse events varied depending on surgical procedures as presented in Table 5. As all studies were not powered to detect a statistical difference in the incidences of adverse events between treatment groups, the results are only presented in number and percentage of patients in each group.

Of twelve eligible articles, seven articles are original research (5 active-controlled RCTs, 2 placebo-controlled RCTs) and the other five are secondary analysis studies. Application site reactions including erythema, itching, vesicles, and edema were reported in these studies, with incidences ranging from 4.5% [14] to 44.8% [22]. Most events were mild and did not require treatment. However, Grond et al. (2007) reported 11 events in 7 patients requiring treatment. All patients recovered from these severe application-site reactions during the study, except for one patient who had not yet recovered at trial termination. Two placebo-controlled RCTs [14,22] showed that the proportions of ASRs were numerically higher in the fentanyl iontophoresis group than control groups. Secondary analysis studies examined these events among subgroups and found that the incidence of AEs was generally lower for elderly patients than for patients 65 years or younger [2]. Only one study examined the occurrence of device malfunction or failure of 1183 fentanyl iontophoresis units, but did not report ASR [8] (details in Table 5).

Summary

For the indication of postoperative pain management, there were twelve eligible articles that reported adverse events, including seven original research studies (5 active-controlled RCTs, 2 placebo-controlled RCTs) and five secondary analysis studies. Most adverse events (i.e., application site reactions) reported were mild in nature and did not require treatment [3,4,8-10,12-15,19,22], except one case that had not recovered after treatment at trial termination [11]. It is of note that all of these RCTs and secondary analysis studies were not powered to detect any statistical difference between treatment groups (e.g., fentanyl iontophoresis vs. morphine IV PCA) or among subgroups such as age, gender, or race. Also, even fewer studies investigated device malfunction or failure and its relation to ASR. All findings from RCTs may only be applicable to highly selected participants in these studies, who are different from those in observational studies (e.g., registries) in the distribution of patients' age, gender, and race. This limitation becomes more important given that rare events may be detectable only in large observational studies such as registry studies.

3.2.2.6. Overall Literature Review Conclusions

Adverse events related to drugs used in the eligible studies were considered as part of the safety profile of medications rather than the iontophoresis devices. Except in the case of a potential overdose caused by a device problem, drug-related adverse events are not iontophoresis device specific and, therefore, were not the focus of this assessment of the safety profile of iontophoresis devices in the current literature. However, FDA does acknowledge the potential for inappropriate doses as a risk with iontophoresis devices, although the actual adverse effect would depend on the drug delivered.

There are 25 articles evaluating the safety of iontophoresis devices for 8 indications, including central neuropathic pain, migraine, juvenile idiopathic arthritis, Parkinson's disease, Peyronie's disease, Raynaud's phenomenon, topical anesthesia, and postoperative pain management. Application site reactions including erythema, itching, edema, and vesicles were the most frequently reported adverse events related to the use of iontophoresis devices. Incidences of these adverse events varied in studies from low to high regardless of study design and indication. Most adverse events were mild and did not require treatment. These studies support the safety of iontophoresis devices for these indications. However, all of the studies were not powered to detect safety endpoints, which may result in an imprecise estimate of the incidence of ASR with wide confidence intervals. Study participants were also highly selected in these studies. Thus, the findings may not be generalized to broader populations.

3.3. Effectiveness Data

Class III iontophoresis devices have been cleared for indications for both general drug delivery and for the treatment of hyperhidrosis using tap water iontophoresis. The available data on effectiveness for each of these uses is summarized below.

3.3.1. Drug Delivery

As explained in Section 1.3.1, the effectiveness of iontophoretic delivery can be impacted by both the device (e.g., electric current, electrode size) and the drug being delivered to the body (e.g., charge, molecular weight). Therefore, any evaluation of the effectiveness of an iontophoresis device must include an evaluation with a drug or other agent to be delivered. Although Class III iontophoresis devices are not labeled for use with a specific drug, as a class of devices, they are not technologically distinct from iontophoresis devices and the approved iontophoresis combination products¹⁴ that are labeled for use with specific drugs.¹⁵ Additionally, iontophoresis devices not labeled for use with a specific drug are expected to be used clinically with drugs that have been approved for delivery by iontophoresis, since new routes of administration for drugs cannot be cleared through the 510(k) process. Therefore, from a device standpoint, FDA believes that effectiveness information on specific iontophoresis drug-device systems can be used to evaluate the general effectiveness of this class of iontophoresis devices not labeled for use with a specific drug.

To date, CDER has approved 5 NDAs for drug-device combination products that utilize iontophoresis as a route of drug administration. A brief summary of the clinical data on which CDER based its approvals are summarized below.

3.3.1.1. **Iontocaine (NDA 20530 Approved on December 21, 1995)**

Iontocaine contains 2% lidocaine hydrochloride (HCl) and 0.01mg/ml epinephrine and is labeled for use with the Phoresor Iontophoretic Drug Delivery system and the IOMED Iontophoretic Drug Delivery Electrodes. Prior to use, the reservoir in the drug delivery electrode is filled with Iontocaine, and the product is then applied to the skin. The duration and amount of current delivered by the device are adjustable. Iontocaine was approved “for production of local dermal analgesia by iontophoresis.”

The clinical effectiveness of Iontocaine in adults was evaluated in 5 clinical studies with 243 subjects for superficial dermal analgesia of the

¹⁴ An iontophoresis system is considered a combination product when the drug and device are marketed together or cross-labeled. To date, CDER has had the lead review authority for all iontophoresis combination products.

¹⁵ FDA is not asserting that there are no technological differences between specific iontophoresis devices. We are only highlighting that the regulations currently distinguish these groups of devices by indications for use and labeling, rather than any type of difference in technology.

pain associated with pulsed dye laser therapy, shave biopsies, curettage, and the pain associated with establishment of peripheral vascular access using 20 gauge catheters. A 40 mA-min electric current dose was applied and demonstrated significant reductions (or elimination) of pain associated with these procedures.

The clinical effectiveness of Iontocaine in children was evaluated in 60 pediatric subjects for dermal analgesia of the pain associated with shave biopsies and curettage. A 40 mA-min electric current dose was applied and demonstrated effective reductions of pain associated with these procedures.

3.3.1.2. LidoSite Topical System Kit (NDA 21504 Approved on May 6, 2004)

The LidoSite Topical System¹⁶ consists of the LidoSite Patch and the LidoSite Controller. The Patch adheres to the skin and contains the drug (10% lidocaine HCl and 0.1% epinephrine) in a reservoir at the active electrode. The Controller is a portable, microprocessor-controlled, battery-powered device that provides a 1.77 mA DC current for 10 minutes per application. The product was approved as “a topical local anesthetic delivery system indicated for use on normal intact skin to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions. LidoSite System is indicated for use on patients 5 years of age and older.”

The clinical effectiveness of Lidosite was evaluated in two separate studies, one in adults and one in pediatric patients. The study in adults was a randomized, double-blind, placebo-controlled, parallel-group, single-center study in which 48 adult subjects were evaluated for the degree of dermal analgesia upon venipuncture or intravenous (IV) cannulation. All subjects received treatment on each of their antecubital fossae prior to venipuncture, and on the dorsum of each hand prior to cannulation. The LidoSite System (Patch + Controller) was applied to 3 of the treatment locations and the 4th location was treated with placebo (topical application of the Patch with no electrical current). Effectiveness was demonstrated by lower mean pain scores in the active group, as measured by a 10-cm visual analog scale (VAS), with 0 indicating no discomfort and 10.0 indicating the worst pain imaginable. VAS scores for active and placebo treatments were 0.7 and 3.2, respectively, at the antecubital fossa, and 1.6 and 4.0, respectively, on the dorsum of the hand.

The study in children was a randomized, double-blind, placebo-controlled, single-center study with 48 pediatric patients ranging in age from 5 to 18 years old. Patients were evaluated for the degree of dermal analgesia upon

¹⁶ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021504s000_LidositeTOC.cfm

venipuncture in the antecubital fossa after treatment with either the LidoSite System (Patch + Controller) or placebo (topical application of the Patch with no electrical current). Effectiveness was demonstrated by lower mean pain scores in the active group, as measured by the Nine Face Integrated Scale (NFIS). The mean NFIS scores for all age groups were 2.8 and 4.3 for LidoSite System and placebo, respectively (with “1” through “9” equated to “A” through “I” on the scale).

3.3.1.3. Empi Lidopel (NDA 21486 Approved on October 26, 2004)

Lidopel¹⁷ contains 2% lidocaine HCl and 1:100,000 epinephrine and is labeled for use with the Empi Dupel Iontophoretic Bi-Layer Ultra Electrodes and the Dupel Iontophoretic Controller. Different device output settings are available to the user. The product was approved “for the iontophoretic production of local analgesia for superficial dermatological procedures such as venipuncture, shave removals and punch biopsies.”

The clinical effectiveness of Lidopel was evaluated in 3 separate studies for venipuncture, shave removals, and punch biopsies. In all studies, Lidopel was compared with a placebo solution (1:100,000 epinephrine without lidocaine) and electric current was delivered to both groups.

Reduction in the discomfort associated with peripheral venipuncture was assessed in a randomized, crossover study of 40 adult subjects. A 20 mA-min iontophoretic dose of Lidopel was administered to one arm and a 20 mA-min dose of the comparator treatment was administered to the contralateral arm. Effectiveness was demonstrated by statistically significantly lower mean pain scores, as measured by a 100-mm visual analogue scale (VAS). The mean VAS scores for Lidopel and comparator treatments were 10.6 and 23.7, respectively.

The primary effectiveness outcome for the evaluation of punch biopsies and shave removals was treatment failure rate. The test was conducted in three phases, and each phase had the potential for a treatment failure: iontophoretic delivery of the drug, pin prick testing to assess anesthesia, and the dermatological procedure. Subjects who could not tolerate the iontophoresis delivery, reported pain during the pin prick test, or who requested supplemental analgesia during the dermatological procedure were considered failures. For punch biopsies, there was a statistically significant reduction in failure rates for the Lidopel group (37.5% or 6/16 subjects) compared to the placebo (100% or 16/16 subjects) when subjects received a DC current dose of 80 mA-min. For shave removals, there was a statistically significant reduction in failure rates for the Lidopel group (15% or 3/20 subjects) compared to the placebo (90% or 18/20 subjects)

¹⁷ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021486s000TOC.cfm

when subjects received a DC current dose of 80 mA-min. There was also a statistically significant reduction in failure rates for the Lidopel group (12.5% or 5/40 subjects) compared to the placebo (75% or 15/20 subjects) when subjects received a DC current dose of 60 mA-min.

3.3.1.4. IONSYS Fentanyl HCl (NDA 21338 Approved on May 22, 2006)

IONSYS¹⁸ consists of a battery-powered iontophoresis patch that is pre-loaded with 10.8 mg of fentanyl HCl. The product was approved “for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization. Patients should be titrated to an acceptable level of analgesia before initiating treatment with IONSYS. IONSYS is not intended for home use and is, therefore, inappropriate for use in patients once they have been discharged from the hospital. It is not recommended for patients under the age of 18 years.” The product includes an activation button that delivers a 40 µg dose over a 10 minute period. A maximum of 6 doses per hour can be administered and a maximum of 80 doses can be administered in a 24 hour period.

The clinical effectiveness of IONSYS for treatment of short-term acute pain was evaluated in three placebo-controlled studies in 727 subjects who were enrolled while in the recovery room shortly after major surgery (predominantly lower abdominal or orthopedic) if they were expected to require at least 24 hours of parenteral opioid treatment and were not opioid tolerant. The placebo was a product that delivered no electric current. In the immediate postoperative period, patients were titrated to comfort with IV fentanyl or morphine per hospital protocol as needed to achieve comfort up to three hours post-enrollment. After 3 hours, patients were randomized and the IONSYS or matching placebo system was applied to provide analgesia. Patients were instructed to use the system for pain relief.

The primary effectiveness outcome was the number of subjects who dropped out of the study more than 3 hours after initiation of therapy due to inadequate pain control, i.e., treatment failure rate. Effectiveness was demonstrated by statistically significantly lower failure rates in the active group compared to the placebo, as shown in the table below.

¹⁸ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021338_toc.cfm

Patients who withdrew due to inadequate analgesia in hours 3 to 24			
	IONSYS n=454	Placebo n=273	p-value
Study 1	27% (64/235)	57% (116/204)	<0.0001
Study 2	25% (36/142)	40% (19/47)	0.049
Study 3	8% (6/77)	41% (9/22)	0.0001

**3.3.1.5. ZECUITY Transdermal System
(NDA 202278 Approved on January 17, 2013)**

ZECUITY Transdermal System (TDS)¹⁹ consists of a drug reservoir card and a battery-powered iontophoretic device that adheres to the skin and delivers electric current. The drug and delivery system are a completely integrated system. ZECUITY TDS is placed on the leg or arm and, once activated, delivers 6.5 mg of sumatriptan over a period of 4 hours. The product was approved “for the acute treatment of migraine with or without aura in adults.”

The clinical effectiveness of ZECUITY TDS was evaluated in a randomized, double-blind, controlled study of 454 subjects. Patients were instructed to treat a migraine headache of moderate to severe pain with a single ZECUITY TDS or matching TDS with no sumatriptan in the drug reservoir. Additional medications were allowed as rescue therapy beginning 2 hours after the initial treatment. The primary efficacy endpoint was the proportion of patients who had no headache pain at 2 hours post TDS activation. Secondary endpoints were absence of nausea, photophobia, phonophobia, and headache pain relief (reduction in pain severity from moderate or severe to mild or no pain) at 2 hours post TDS activation. Effectiveness was demonstrated by statistically significant improvements in these endpoints in the active group compared to the placebo, as shown in the table below.

Percentage of patients with relief 2 hours after TDS activation			
	ZECUITY n=226	Placebo n=228	p-value
No Headache Pain	18%	9%	0.0092
No Nausea	84%	63%	<0.0001
No Photophobia	51%	36%	0.0028
No Phonophobia	55%	39%	0.0002
Headache Pain Relief	53%	29%	<0.0001

¹⁹ http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/202278Orig1s000TOC.cfm

3.3.2. Treatment of Hyperhidrosis

Primary focal hyperhidrosis is a chronic autonomic disorder that results in the production of abnormal and excessive quantities of sweat, beyond what is required for thermal regulation. It typically occurs on the palms of the hand, soles of the feet, and armpits (axillae). Hyperhidrosis, especially when severe, can have a significant negative impact on social and professional life and psychological health. The etiology of primary focal hyperhidrosis is unknown and it occurs in otherwise healthy people (with a reported incidence rate of 0.6-1%). Increases in sweating are usually caused by mental stimuli (stress) rather than exercise or hot environments. A number of treatments are available, though the degree and duration of success vary, as do the associated adverse effects.[27,28]

In addition to iontophoresis, treatments for hyperhidrosis may target the sweat glands or the sympathetic nerves that innervate them. The treatment modality that is utilized depends on the severity of the condition and the patients' preferences, especially as they relate to adverse effects of the treatment. The first line of treatment is typically topical application of aluminum chloride (20% aluminum chloride in anhydrous ethyl alcohol or 12% aluminum chloride in sodium carbonate-water). The adverse effects are minor (e.g., skin irritation), but the effectiveness is temporary (days to weeks) and treatments must be reapplied. Systemic anti-cholinergic drugs (e.g., glycopyrrolate) have been employed because they block the neurotransmitter acetylcholine. These can produce adverse effects such as dry mouth, blurred vision, urinary retention, and constipation. Intradermal injections of botulinum toxin A may also be used locally to inhibit the release of acetylcholine and may help to manage symptoms for several months after a single treatment. Side effects include temporary weakness, pain during injection, headaches, soreness, increased facial sweating, and itching. Botulinum toxin A is FDA approved for treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents. FDA has also cleared devices for microwave heating of the sweat glands for the treatment of axillary hyperhidrosis, with adverse effects such as transient numbness, soreness, swelling, burns, and skin irritation.

Local surgical options for axillary hyperhidrosis include excision of the axillary glands, subcutaneous curettage, and liposuction, although these are associated with more significant adverse effects such as troublesome scarring and other general complications associated with surgery. Thoracic sympathectomy (sympathetic surgery at T2, T3, and/or T4 ganglia and connections) has been shown to be very effective with failure rates from 0-7%, but is also associated with more severe adverse effects such as Horner syndrome, neuralgia, phantom sweating, gustatory sweating, compensatory sweating (especially with T2-4 sympathectomy), pneumothorax, and other common surgical complications.[27,28]

Three devices have been cleared for the treatment of hyperhidrosis by tap water iontophoresis (TWI). FDA conducted a literature review to assess the safety and effectiveness of TWI for hyperhidrosis by analyzing the existing clinical literature from January 1, 1979 to January 5, 2014. While this did exclude some pre-1979 references, FDA believed a search covering 30+ years would capture the research conducted since the Panel last reviewed the literature on December 12, 1979. In addition, FDA conducted the literature review only for the cleared indications for use: treatment of hyperhidrosis using tap water iontophoresis. While applications of other drugs by iontophoresis (such as anti-cholinergic agents) for hyperhidrosis are present in the publications database, they are outside the scope of this review.

The primary goal of the literature review was to determine what evidence is available on the effectiveness of TWI for the treatment of hyperhidrosis. A secondary goal was to evaluate the reported adverse events associated with the use of TWI for the treatment of hyperhidrosis (in addition to the information on the safety of iontophoresis devices in general provided in Section 3.2).

3.3.2.1. Methods

On January 5, 2014, FDA searched the published literature in PubMed using the following search terms:

- “hyperhidrosis” AND
- “water” AND
- "iontophoretic" OR
 - "iontophoresis" OR
 - "electromotive drug administration" OR
 - "electrically-assisted transdermal delivery" OR
 - "transdermal electromotive administration"

The search was limited to studies published on or after January 1, 1979, human studies, and those published in English. We permitted randomized controlled trials (RCTs), observational studies, and case series with $n \geq 10$, but omitted articles that did not include original research (such as review articles, meta-analyses, and systematic literature reviews). This search yielded a total of 29 unique hits. A first pass of the articles was conducted by reviewing the title and abstract of each returned hit, excluding for: non-human studies, articles without original research, less than 10 subjects, papers covering an unrelated device type, articles that did not utilize only water for iontophoresis in at least one group, and papers that did not have endpoints to evaluate sweat reduction. Information on sweat reduction was important because some papers were focused on determining the mechanism of action of TWI (e.g., through histological examination of

biopsies), rather than clinical effectiveness, which was the goal of this literature review.

Of the 29 identified articles, 14 were excluded by review of titles and abstracts. Titles were excluded during this time for the following reasons:

- not original research (n=10)
- less than 10 subjects (n=4)

These exclusions left 15 articles for full epidemiological review and assessment. Seven articles were further excluded for the following reasons:

- not original research (n=1)
- less than 10 subjects (n=2)
- no sweat endpoints (n=2)
- did not utilize only water in at least one group (n=2)

At the end of the article selection process, 8 articles, listed in Section 3.3.2.4 below and summarized in Table 6, were retained for full epidemiological analysis and data synthesis [29-36].

3.3.2.2. Summary of Search Results

Eight papers were identified in this literature review, including 4 studies categorized as RCTs (where randomization was to the left or right hand and each subject received both treatments simultaneously), 2 time series, 1 crossover study, and 1 uncontrolled, retrospective audit. These studies all evaluated the effectiveness of TWI for the treatment of palmoplantar hyperhidrosis (effectiveness for axillary hyperhidrosis was not investigated) and were published between 1987 and 2013. Sample sizes ranged from 10 to 112, with 2 of the 8 studies enrolling more than 70 participants. The age range for the studies was from 8 to 57 years old. Two of the studies were conducted in Germany, two in Turkey, and one study each in the United States, United Kingdom, China, and Denmark. All 8 studies appear to have recruited patients from a single clinical site within these countries.

For one of the RCTs, tap water iontophoresis was delivered to the control hand and the experimental hand received iontophoresis with anti-cholinergic drugs. Since the goal of this review was to evaluate the effectiveness of TWI, only the time course results of the control group were included in the evaluation.

3.3.2.3. Study Designs and Methodology

The eight papers included in this review varied in study design and methodology. A number of different iontophoresis devices were evaluated,

including many devices that were custom made or ordered by the investigators. None of the identified devices appears to have been cleared through the 510(k) process for marketing in the USA. However, the devices typically consisted of galvanic (DC) generators connected to plate electrodes placed in shallow plastic pans of water, or in some cases, electrodes with water-soaked absorbent material.

During the treatment, the hands and/or feet were placed in the pans of water or on the wetted material. The current was gradually increased to the treatment level and then maintained for the prespecified time. In most studies, the current was set to the maximum that was comfortable to the patient. However, some studies used pre-determined current values.

Of the 4 RCTs, the subjects were blinded to tap water iontophoresis in 3 of them. In this case, the control was either an AC current (to maintain the tingling sensation of electric current) or the current was set below the perceptible limit and then shut off in the control.

The timing of treatments varied by study, but was generally 3-4 times a week for 3-4 weeks. Study endpoints included quantitative measurements of sweat intensity (weight of sweat absorbed), qualitative measurements of sweat intensity (colorimetric changes on iodine-starch paper), and patient-reported outcomes (degree of sweating using a 5-point scale, duration of effects).

The “pad glove method” was used in 3 studies, whereby a glove made of gauze is placed on the hand and then covered with a surgical glove for a period of time. The weight of the glove before and after application can then be quantified and reported in weight/time worn. The iodine-starch paper method was used in 3 studies, whereby the palm is placed on an iodine-treated paper. The imprint is then evaluated by the investigator and rated on a 5-point scale (0 = no print; 1 = faint dots, outline not discernible; 2 = faint print with clear outline; 3 = dark print with a ridged pattern; 4 = diffuse darkening, borders washed out).

3.3.2.4. Effectiveness Findings

Although the quality of the studies varied, all 8 studies reported reduced sweating in the majority of subjects treated with TWI, if not all. The effects typically lasted for a few weeks after the final treatment, but sweating eventually always returned to pre-treatment levels. The effectiveness findings of are summarized in Table 3 and for each study individually below.

Table 3: Summary of Hyperhidrosis Results

Study	Type	n =	Effectiveness Evaluation	Results
Siaw TH and Hampton PJ, 2013	Audit	23	10-point, subjective, patient-reported outcome scale (1 = dry, 10 = extreme sweating) for each palm or sole prior to initiation of TWI and at each treatment for the next 4 weeks.	Mean palmar scores (n=21): 7.6 to 1.9 Mean plantar scores (n=16): 8.47 to 3.0
Karakoç Y et al., 2004	Cross-over	15	1 hour pad glove method.	Right hand mean: TWI = 3.08 to 0.38 g/h; placebo = 3.12 to 3.08 g/h. Left hand mean: TWI = 3.16 to 0.39 g/h; placebo = 3.17 to 3.16 g/h.
Karakoç Y et al., 2002	Time series	112	1 hour pad glove method. Subjects were also asked to note the recurrence time of their hyperhidrosis.	Right hand mean: 2.98 g/h to 0.84 g/h Left hand mean: 3.04 g/h to 0.97 g/h
Reinauer S et al., 1993	RCT: TWI vs. placebo	25	Mean number of treatments to normhidrosis, (defined as sweat intensity < 20 mg/min) or for a maximum of 25 treatments	Mean treatments to normhidrosis: DC=11, AC/DC=11, AC = fail. Sweat intensity: DC = 45 to 19 mg/min; AC/DC = 63 to 17 mg/min.
Shen JL et al., 1990	RCT: TWI vs. drug	10	Imprint on iodine-starch paper (scale of 0 to 4)	TWI mean score decreased by 1.5
Dahl JC and Glent-Madsen L, 1989	RCT: TWI vs. placebo	11	10 minute pad glove method, while subjected to stress.	TWI median values : decreased 38%.
Stohlman LP, 1987	RCT: TWI vs. placebo	18	Imprint on starch-iodine paper (although no scoring system was reported) 5 days after the final treatment.	15 subjects showed a “marked reduction” for TWI vs. no change for placebo.
Hölzle E and Alberti N, 1987	Time series	71	Imprint on starch-iodine paper (5-point scale). Weighted measure of sweat absorption on paper. Skin temperature on the hands (subset of subjects).	Palmar mean intensity: 52 to 10 mg/min Plantar mean intensity: 43 to 15 mg/min Palmar mean imprint score: 3.5 to 1.7 Plantar mean imprint score: 3.25 to 1.1. Mean skin temp. increase: 29.7 to 33.2°C

Siaw TH and Hampton PJ, 2013 [29]

This study was a retrospective audit of 23 patients with focal hyperhidrosis who were treated with TWI to the palms of the hands and/or soles of the feet 3 times a week for 4 weeks. The treatment utilized 15-20 mA of current for 20 minutes. Effectiveness was evaluated with a 10-point, subjective, patient-reported outcome scale (1 = dry, 10 = extreme sweating) for each palm or sole prior to initiation of TWI and at each treatment for the next 4 weeks. Although no statistical analysis was reported, the numerical results showed the mean palmar scores (n=21) decreased from 7.6 to 1.9 from baseline to the last treatment. The mean plantar scores (n=16) decreased from 8.47 to 3.0.

Karakoç Y et al., 2004 [30]

This article reported a controlled “crossover” trial to evaluate if TWI was a result of placebo effect on 15 patients with idiopathic palmoplantar hyperhidrosis. Subjects first received an AC current (9-12 mA, 8-10 Hz, no DC offset, 15 min per hand) on both palms as a placebo, intended to provide the sensation of electric current. Seven treatments were applied over 3 weeks at increasing intervals (i.e., days 1, 2, 4, 7, 11, 16, and 21) and final follow-up was conducted 1 week after the final treatment. After the full course of treatment and 1-week follow-up period, the subjects then received the TWI device using DC current (18-22 mA for 15 min per hand) and the same treatment and follow-up schedule. The study was not a true crossover in that no subjects received the DC treatment first. Effectiveness was evaluated with the 1 hour pad glove method. The mean values for the right hands decreased from 3.08 to 0.38 g/h for TWI and from 3.12 to 3.08 g/h for the placebo. The mean values for the left hands decreased from 3.16 to 0.39 g/h for TWI and from 3.17 to 3.16 g/h for the placebo. Analysis demonstrated a statistically significant difference for both hands with TWI compared to placebo.

Karakoç Y et al., 2002 [31]

This study was a time series study of TWI on 112 patients with idiopathic palmoplantar hyperhidrosis. The maximum tolerable current (min 10-15 mA) was applied for 15 minutes. Treatments were administered 8 times over 3 weeks at increasing intervals (i.e., days 1, 2, 4, 7, 11, 16, 21, and 28). The final follow-up was conducted either 20 days after the final treatment or sooner (but after at least 5 days) if the subject reported ineffective treatment. Effectiveness was evaluated with the 1 hour pad glove method and subjects were also asked to note the recurrence time of their hyperhidrosis. Twenty-one (19%) of subjects reported unsatisfactory results and were deemed non-responders, while 91 subjects (81%) reported satisfactory results and were deemed responders. The authors reported the baseline mean pad glove values of all patients and the final scores of responders and non-responders separately. The mean baseline values of all subjects were 2.98 ± 1.19 g/h and 3.04 ± 1.32 g/h for the right and left hands, respectively. The mean final values for responders were 0.39 ± 0.12 g/h and 0.52 ± 0.15 g/h for the right and left hands, respectively. The mean final values for non-responders were 2.82 ± 0.98 g/h and 2.98 ± 1.02 g/h for the right and left hands, respectively. Based on the number of responders and non-responders, we can determine that the mean values of all subjects decreased from 2.98 g/h to 0.84 g/h for the right hands and from 3.04 g/h to 0.97 g/h for the left hands. The average remission period of responders was reported as 35 ± 6 days, although it is unclear what criteria were used to determine remission.

Reinauer S et al., 1993 [32]

This article reported a blinded, controlled trial with 25 subjects comparing TWI using a DC output, an AC output with no offset (centered at 0 mA), and an AC output with a DC offset (centered above 0 mA). The current was increased to the point of discomfort (8-25 mA for DC; 8-12 mA_{RMS}, 5.1kHz for AC; and 8-12 mA_{RMS}, 4.3kHz superimposed on 8 mA DC for AC/DC) for 30 minutes. Sweat intensity was measured prior to each treatment using a weighted measure of sweat absorption on paper. Treatments were applied to the palms 4 times per week until normhidrosis was achieved (defined as sweat intensity < 20 mg/min) or for a maximum of 25 treatments. Effectiveness was evaluated as the mean number of treatments to normhidrosis, which was 11 for both the DC and AC/DC groups. Subjects in the AC group never achieved normhidrosis. Sweat intensity measurements showed a reduction after 11 treatments from 45 to 19 mg/min for DC and 63 to 17 mg/min for AC/DC (all values approximate based on graphical reading). Although DC only and AC with a DC offset had comparable effectiveness, there were less adverse effects noted in the AC/DC subjects.

Shen JL et al., 1990 [33]

This study was a double-blind, randomized, controlled trial to evaluate TWI (control) vs. iontophoresis with glycopyrrolate and aluminum chloride in 10 patients. All subjects received both treatments, randomized to the left or right hand. However, because these drugs are not approved for iontophoresis, only the TWI control group will be discussed here. The maximum tolerable current was applied for 1 hour (polarity reversed after 30 minutes). Treatments were administered daily for 4 days. Effectiveness was evaluated with iodine-starch paper (scale of 0 to 4). Subjects treated with TWI had a mean decrease in score of 1.5 and an average remission period of 3.5 days.

Dahl JC and Glent-Madsen L, 1989 [34]

This article reported a double-blind, randomized, controlled trial in 11 patients with palmar hyperhidrosis. All subjects received both treatments, randomized to the left or right hand. The current was initially applied to both hands and increased to the maximum intensity that was still not perceptible to the subject (2-10 mA, median 4 mA). Then the circuit for one hand was disconnected by a regulator device. Treatments were applied for 15 minutes 1-5 times a week until patients reported “good subjective effect” (range was 6 to 12 treatments). Six patients also continued with maintenance sessions after the initial course of treatment. Effectiveness was evaluated with a pad glove method, worn for 10 minutes while subjected to stress. After patients reported success and the initial treatment regimen was completed, median pad glove values for the TWI hands decreased by 38% (1st and 3rd quartiles were 7% and 53%, respectively). There was also 32% decrease compared to the placebo hands (1st and 3rd

quartiles were 17% and 56%, respectively). Analysis demonstrated both differences to be statistically significant. For the subjects that remained on maintenance treatments (7-14 mA for 15 minutes every 2 weeks), the median reduction after 3 months was 81% (1st and 3rd quartiles were 60% and 95%, respectively), although there was no control group for comparison of this value.

Stohlman LP, 1987 [35]

This study was a non-blinded, randomized, controlled trial in 18 patients with significant palmar hyperhidrosis. All subjects received both treatments, randomized to the left or right hand. The TWI hand was placed in a pan of water with an electrode for TWI, and the other was placed in water with no electrode or current delivery. The treatment utilized 12-20 mA of current for 20 minutes, applied 3 times a week for 3 weeks. Effectiveness was evaluated with starch-iodine paper (although no scoring system was reported) 5 days after the final treatment. One of the subjects dropped out of the study due to dissatisfaction with the transient erythema. The authors reported that 15 subjects showed a “marked reduction” in sweating in the treated hand and no change evident in the untreated hands. The remaining 2 subjects showed no improvement.

Hölzle E and Alberti N, 1987 [36]

This study was a time series study of TWI on 71 patients with excessive palmoplantar hyperhidrosis. The current was increased until slight discomfort was felt (average 15 mA for palms and 20 mA for soles) for 30 minutes. Treatments were administered (sometimes by the subjects at home) “preferably once a day, 3 times a week,” although some patients treated twice daily. When sweating was sufficiently reduced, a maintenance schedule was continued on an individual basis. The final reported follow-up time for sweat reduction was after 13 to 14 treatments (week 5). Effectiveness was evaluated with starch-iodine paper (5-point scale), weighted measure of sweat absorption on paper, and by skin temperature on the hands in a subset of subjects (cold, clammy hands can be a consequence of hyperhidrosis). On the hands, the sweat reduction by weight was measured to decrease from a mean of 52 mg/min to approximately 10 mg/min. On the soles of the feet, the decrease was from a mean of 43 mg/min to approximately 15 mg/min. The authors reported that this compared favorably with the measures in healthy subjects of 0-20 mg/min and 0-15 mg/min for the palms and soles, respectively. The starch-iodine scores decreased from a mean score of 3.5 to approximately 1.7 on the palms and from 3.25 to approximately 1.1 on the soles. This compared favorably with the scores in healthy subjects of 0-1.5 (average 0.75). Finally, skin temperature was measured to increase by an average of 3.5°C (averaged over both hands of 10 subjects) from 29.7 ± 1.8°C to 33.2 ± 1.4°C.

Hölzle and Alberti also reported that their subjects continued TWI on a maintenance schedule (1-2 times per week) for an average of 14 months, including 4 patients who continued use for over 3 years. They reported that the device maintained effectiveness over that time without the need for increasing the frequency of treatments.

3.3.2.5. Adverse Events

The eight articles that were reviewed reported a number of adverse events with iontophoresis devices during treatment of hyperhidrosis. Most studies noted that they were transient and there were no serious adverse events. Not all studies provide detailed information on these events, such as the number of occurrences. However, each noted adverse event is listed below along with the applicable study reference in which it was identified:

- Erythema [29,31,32,35,36]
- Burning/tingling [31,32,35,36]
- Mild skin irritation [29,32,36]
- Vesicles [31,33,35,36]
- Discomfort [32,36]
- Fissures, erosions of the horny layer of skin [32]
- Stinging or itching [32]
- Electric shock [32]
- Multiple deep bullae [34]
- Deep pain [36]
- Soreness [36]

Hölzle and Alberti [36] also reported that there were no long-term adverse effects for their subjects who continued on long-term maintenance TWI.

Four of the 8 studies [31,33,34,35] provided information on the frequency of adverse events. Dahl and Glent-Madsen [34], who used the lowest current of all of the trials (up to 10 mA), reported no adverse events. However, they did report experience with one patient outside of the study who experienced multiple deep bullae when treated by TWI at 14 mA. The number of patients who experienced an adverse event (not the number of events) in the other 3 studies is summarized below:

- Erythema - 12/18 (67%); 12/112 (11%)
- Tingling (sometimes lasted days) - 2/18 (11%)
- Burning – 20/112 (18%)
- Vesicles - 3/18 (17%); 5/10 (50%); 8/112 (7%)

Although not noted above, Shen et al. [33] also reported one patient with transient mouth dryness in their study comparing TWI to glycopyrrolate. Dry mouth is a known side effect of glycopyrrolate and has been reported in other studies with this drug, but was not reported in the other studies using only TWI. Therefore, although the treatment group for this subject was not identified, FDA attributes this adverse effect to glycopyrrolate and not TWI.

3.3.2.6. Overall Conclusions

All 8 studies reported that tap water iontophoresis effectively reduced sweating in the majority of subjects treated with TWI. A number of the studies had limitations, such as being non-blinded, uncontrolled, using subjective and qualitative measurement methods, or eliminating non-responders from their analysis. Additionally, a range of currents, durations, and treatment regimens were used, including wide variation within many studies. However, some studies did use objective, quantitative measurements of sweat intensity and/or conducted blinded trials that support the effectiveness of TWI for the treatment of hyperhidrosis. Additionally, when all of the studies are taken cumulatively, FDA concludes that there is sufficient information to support the effectiveness of TWI. It is noted that the effects are temporary, typically lasting for only a few weeks after the final treatment. Additionally, adverse events were common, although none were serious. Nonetheless, the studies reported that most patients tolerated these adverse effects and continued to receive maintenance treatments when offered at the conclusion of the study. This indicates that patients believed the benefits of treatment outweighed the associated risks.

3.4. Summary

Based on the information in the literature and FDA's adverse event databases, the device-related risks for iontophoresis are low-to-moderate. The most common adverse events reported to FDA were burns, ranging from mild to serious third degree burns. However, the literature suggests that serious adverse events are rare and the most common adverse events reported in the literature were mild, transient skin reactions that do not require treatment, such as erythema, tingling or burning sensations, itching, edema, and vesicles.

The effectiveness of iontophoresis devices has been demonstrated for the delivery of fentanyl, sumatriptan, and lidocaine with epinephrine, which have all been evaluated in randomized controlled trials and approved by FDA. Although the iontophoresis devices that are the subject of this meeting are not labeled for use with specific drugs, FDA believes that the clinical efficacy of these specific iontophoresis drug-device systems demonstrates the general effectiveness of this class of iontophoresis devices. Additionally, the available literature, although limited, also supports the effectiveness

of tap water iontophoresis for at least the short-term management of primary palmar and plantar hyperhidrosis.

4. Discussion of Risks to Health

4.1. Original Classification Panels

As noted in Section 2.1, the classification panels identified the following specific risks in relation to iontophoresis devices:

1. Electrical shock
2. Burns
3. Cardiac Arrest
4. Inappropriate Therapy
5. Trauma
6. Bodily Injury

4.2. Risks to Health Currently Identified by FDA

Since the original classification panel meetings, more is known regarding the risk profile of iontophoresis devices. In considering risks to health, the FDA has evaluated the available clinical evidence in the published literature; the device related adverse events reported in the FDA databases; and the risks identified by the manufacturers who responded to the 2009 call for information. Therefore, FDA has updated the risks to health for iontophoresis devices not labeled for use with a specific drug and identified the following risks:

1. Electrical shock
2. Burns (due to either the electrical current or high pH)
3. Insufficient or excessive delivery of drug/solution
4. Interference with other medical devices (e.g., pacemakers)
5. Adverse tissue reactions (e.g., skin irritation, allergic reaction)
6. Infection (especially when used in the ear)
7. Ear Trauma (only when used in the ear)

The panel will be asked to discuss the risks to health that have been identified by both the FDA and the manufacturers and whether these risks are appropriate or whether there are additional risks that should be considered for iontophoresis devices not labeled for use with a specific drug.

5. FDA Recommendation

Iontophoresis devices not labeled for use with a specific drug are currently classified in Class III. In light of the information available now, the Panel will be asked to comment on whether these devices fulfill the statutory definition associated with a Class III device designation. FDA believes that these devices may be more appropriately regulated as:

- Class II, meaning general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness

As opposed to:

- Class III, meaning
 - 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 the device presents a potential unreasonable risk of illness or injury.

FDA does not believe that iontophoresis devices not labeled for use with a specific drug are life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health. FDA does believe these devices may present a potential unreasonable risk of illness or injury, yet believes that special controls, in combination with general controls, would provide reasonable assurance of safety and effectiveness. FDA is seeking the Panel's input regarding whether the available scientific evidence supports a Class III determination or a Class II determination with the establishment of appropriate special controls, in combination with general controls.

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.

Part (g)(1) of this regulation further states that it “is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls alone, or by general controls and performance standards, may support a determination that the device be classified into Class III.”

5.1. Reasonable Assurance of Safety

According to 21 CFR 860.7(d)(1), “There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.”

In plain language, the definition states that a reasonable assurance of safety exists if, when using the device properly:

- The probable benefits to health outweigh the probable risks, and
- There is an absence of unreasonable risk of illness or injury.

As the literature reviews demonstrate, iontophoresis devices not labeled for use with a specific drug are not without risk. Adverse events have been experienced with the devices according to the Manufacturer and User facility Device Experience (MAUDE) and the FDA Adverse Event Reporting System (FAERS) databases (see Section 3.2). The Panel should consider whether general and special controls can provide a reasonable assurance of safety for iontophoresis devices not labeled for use with a specific drug, or whether these devices warrant the need for a Class III designation.

5.2. Reasonable Assurance of Effectiveness

According to 21 CFR 860.7(e)(1), “There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

In plain language, the definition states that if using the device properly provides clinically significant results in a significant portion of the target population, there is a reasonable assurance of effectiveness.

While the iontophoresis devices under consideration are not labeled for use with a specific drug, they must be used in combination with a drug or other solution in order to be effective. The Center for Drug Evaluation and Research (CDER) has approved five New Drug Applications (NDAs) for drug-device combination products that utilize iontophoresis. Because these devices identify drugs whose labeling bear adequate directions for use with an iontophoresis device, these uses would fall under paragraph (a) of the existing regulation (21 CFR 890.5525(a)). However, there is no

technological distinction between the Class II devices in paragraph (a) of the regulation and the devices that are the subject of this meeting. Additionally, the outputs of iontophoresis devices are characterized in a simple description of the dose (electric charge) that the healthcare practitioner can adjust based on the drug labeling. Therefore, FDA believes that the clinical data from these drug-device combination products may be utilized to provide a reasonable assurance of effectiveness for iontophoresis devices not labeled for use with a specific drug, i.e., for general drug delivery. In accordance with this and as outlined in Section 5.3 below, FDA proposes to require manufacturers of iontophoresis devices not labeled for use with a specific drug to provide performance testing to demonstrate that their device is effective with an approved drug.

In addition to indications for general drug delivery, Class III iontophoresis devices have been cleared for use with tap water for the treatment of hyperhidrosis. After reviewing the relevant literature, FDA believes that sufficient scientific information exists to provide a reasonable assurance of effectiveness for tap water iontophoresis devices for the treatment of hyperhidrosis.

The Panel will be asked to comment on whether the available scientific evidence supports a Class III determination or a Class II determination with appropriate special controls. Based on the information discussed in this document, FDA is recommending Class II with special controls, in combination with general controls.

5.3. Special Controls

FDA believes that special controls, in combination with general controls, can be established to mitigate the identified risks and provide reasonable assurance of the safety and effectiveness of iontophoresis devices not labeled for use with a specific drug. FDA does not believe that general controls alone are sufficient to provide a reasonable assurance of the safety and effectiveness. The identified risks and recommended mitigation measures for each risk are provided in the Table 4.

Table 4: Risk/Mitigation Recommendations

Risks to Health	Mitigation Measures
Burns	Performance Testing Electrical Safety Testing Shelf Life Testing Labeling
Electrical shock	Electrical Safety Testing Shelf Life Testing Labeling
Insufficient or excessive delivery	Performance Testing Software Verification & Validation Labeling
Interference with other medical devices	Electromagnetic Compatibility Testing Labeling
Adverse tissue reactions	Biocompatibility
Infection	Sterility Shelf Life Testing
Ear Trauma (only when used in the ear)	Performance Testing Labeling

Based on these mitigation measures, FDA proposes the following special controls for iontophoresis devices not labeled for use with a specific drug. Exact language of the requirements would be based on panel feedback.

1. Performance testing must provide a reasonable assurance of safety and effectiveness of the device, including
 - a. testing using a drug approved for iontophoretic delivery, or a non-drug solution if identified in the labeling,
 - b. testing of the ability of the device to maintain a safe pH level, and
 - c. if used in the ear, testing of the mechanical safety of the device.

2. Labeling must include adequate instructions for use, including sufficient information for the health care provider to determine the device characteristics that affect delivery of the drug or solution and to select appropriate drug or solution dosing information for administration by iontophoresis. This includes the following:
 - a. a description and/or graphical representation of the electrical output,
 - b. a description of the electrode materials and pH buffer,
 - c. when intended for general drug delivery, language referring the user to approved drug labeling to determine if the drug they intend to deliver is specifically approved for use with that type of device and to obtain relevant dosing information, and
 - d. a detailed summary of the device-related and procedure-related complications pertinent to use of the device, and appropriate warnings and contraindications.

3. Appropriate analysis/testing must demonstrate electromagnetic compatibility (EMC), electrical safety, thermal safety, and mechanical safety.
4. Appropriate software verification, validation, and hazard analysis must be performed.
5. The elements of the device that may contact the patient must be demonstrated to be biocompatible.
6. The elements of the device that may contact the patient must be assessed for sterility.
7. Performance data must support the shelf life of the elements of the device that may be affected by aging by demonstrating continued package integrity and device functionality over the stated shelf life.

If the panel believes that Class II is appropriate for iontophoresis devices not labeled for use with a specific drug, the panel will be asked whether the proposed special controls can adequately mitigate the risks to health and provide a reasonable assurance of safety and effectiveness and whether additional or different special controls are recommended.

5.4. Reclassification

As previously noted, a device may be classified as Class II when general and special controls are sufficient to provide reasonable assurance of its safety and effectiveness. However, a device will be considered Class III if

- 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.

In order to change the classification of iontophoresis devices not labeled for use with a specific drug from Class III to Class II, FDA must have sufficient information to establish special controls that can provide reasonable assurance of the safety and effectiveness that, when using the device properly:

1. The probable benefits to health from using the device will outweigh the probable risks (per the definition of a reasonable assurance of safety, 21 CFR 860.7(d)(1));

2. There is an absence of unreasonable risk of illness or injury (per the definition of a reasonable assurance of safety); and
3. The device will provide clinically significant results in a significant portion of the target population (per the definition of a reasonable assurance of effectiveness, 21 CFR 860.7(e)(1))

Special controls include “the promulgation of performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents (including guidance on the submission of clinical data in premarket notification submissions in accordance with section 510(k) of the act), recommendations, and other appropriate actions as the Commissioner deems necessary to provide such assurance.”

To state that there is sufficient information to establish special controls to provide reasonable assurance of effectiveness implies two things:

1. The indications for use adequately define a target population.
2. The available evidence demonstrates that there are clinically significant results in a significant portion of that target population.

For iontophoresis devices not labeled for use with a specific drug, FDA believes that the available evidence suggests that special controls can be used to provide a reasonable assurance of safety and effectiveness. Special controls can be defined to address safety; for example, compliance with electrical safety standards, or adequate labeling. FDA also recommends that special controls include a requirement for performance data to establish effectiveness for iontophoresis devices for use with at least one drug approved for delivery by iontophoresis, or a non-drug solution if identified in the labeling.

Based on the available scientific evidence and proposed special controls, the panel will be asked whether a Class III or Class II designation is appropriate for iontophoresis devices not labeled for use with a specific drug.

6. Tables

Table 5: Publications Included in the Systematic Literature Review of the Safety of Iontophoresis Devices

Author, Year	Study Population	Study Design	Sample Size	Device Studied	Drug Studied	Adverse Events	Study Strength/Limitation
Vranken JH, 2005 [16]	Patients with central neuropathic pain	RCT(1:1)	33	Iontopatch 80, Birch Point Medical Inc.	S(+)-ketamine	K75 (n=11) vs. K50* (n=11) vs. Placebo(n=11) sedation: 0(0%), 3 (27.3%), 1 (9.1%) dizziness: 0(0%), 1 (9.1%), 3 (27.3%) vivid dream: 0(0%), 1 (9.1%), 1(9.1%), headache: 0(0%), 0(0%), 1(9.1%), confusion: 0(0%), 1(9.1%), 0(0%), nausea and vomiting: 1 (9.1%), 0(0%), 0(0%) erythema: 0(0%), 0(0%), 2(18.2%) None of the 33 patients withdrew from the study due to adverse events. All reported side effects were mild and transient in nature, resolving spontaneously. No fluctuations in blood pressure or pulse rate were observed during treatment.	Randomized, double blind trial small sample size, all study groups used the same delivery system
Pierce M, 2009 [6]	healthy volunteers participating migraine study	Crossover trial	25	Zelrix™, NuPathe Inc.	sumatriptan	Zelrix I (n=17) vs. Zelrix II (n=17) Headache: 2 (12%), 0(0%) application site pruritus: 7 (41%), 4 (24%), self resolved.	Limitations: small sample size, high drop out rate, not a RCT
Mina R, 2011 [2]	Patients with Juvenile Idiopathic Arthritis	Retrospective Cohort	28	Iontophoresis equipment: Dupel, Empi Dispersive electrode: IOGEL, IOMED, Inc	dexamethasone	single arm (n=28) non-painful erythema 86% ,transient metallic taste 4% skin blister 4%	Limitations: small sample size, inclusion/exclusion criteria not stated, not all patients underwent the same number of sessions, retrospective, lack of a control group, baseline and serial MRI not done to assess improvement

*K75:75mg ketamine treatment group, K50:50mg ketamine treatment group,

Table 5 (continued)

Author, Year	Study Population	Study Design	sample size	Device Studied	Drug Studied	Adverse Events	Study strength/Limitation
Li GL, 2005 [17]	Patients with Parkinson's disease	RCT(1:1)	16	battery-powered iontophoresis device (Central Electronics Department of the Gorlaeus Laboratories, Leiden, The Netherlands) and Modified Anodal Iomed TransQRE patches (Iomed, UT, USA)	R-apomorphine	No clinically relevant systemic adverse effects were observed. No perceptible edema was observed. tingling and itching but without pain in all patients during the current application; a transient and slight erythema (up to level 1) occurred at both the anodal and the cathodal site, which disappeared spontaneously afterwards. local skin irritation, no difference was observed between the surfactant pretreatment group and the control group.	Limitations: small sample size, underpowered to yield any statistical difference in adverse event because both groups used the same delivery system
Di Stasi SM, 2004 [21]	Patients with Peyronie's disease	RCT(1:1)	96	electrode receptacle (CT-DAS 500 Ag, Physion s.r.l) current generator (Physionizer 30, Physion s.r.l)	Verapamil+ Dexamethasone, Lidocaine	transient erythema at site of electrodes occurred in all patients, no other AE reported	Strength:prospective, randomized double blind study Limitation: Median sample size, compare two treatment regimens, both delivered by intraplaqueelectromotive administration
Di Stasi SM, 2003 [26]	Patients with Peyronie's disease	Crossover trial	49	Physionizer 30, Physion srl,	Verapamil+ Dexamethasone	No patients had a decrease in blood pressure or related cardiac effects, and no systemic, local, acute or chronic toxicity was detected, except for a transient skin erythema at the site of the penile and abdominal electrodes.	Limitation: small sample size, no control group
Blaise S, 2010 [5]	healthy volunteers participating Raynaud's phenomenon study	Crossover trial	10	Perilont System and PeriScan PIM 3 System,Perimed	sodium nitroprusside	No serious side effects occurred. One woman exhibited pallor and dizziness associated with a 10 mm Hg drop in MAP from baseline, which was possibly related to a pharmacodynamic interaction.	Limitation: no control group, small sample size, iontophoresis was not the focus of this pharmaceutical study.

Table 5 (continued)

Author, Year	Study Population	Study Design	sample size	Device Studied	Drug Studied	Adverse Events	Study strength/Limitation
Spierings EL, 2008 [7]	Patients undergoing topical anesthesia	Crossover trial	30	Numby PM900 and Phoresor PM700 devices, Iomed Inc	Iontocaine	10-minute iontophoresis (40 mA-minutes) vs. 2-minute iontophoresis (2 mA-minutes) after ultrasound vs. 2-minute iontophoresis (2 mA-minutes) after sham (immediately after iontophoresis): Blanching 6 (20%), 27 (90%), and 28 (93%); Erythema 1 (3%), 10 (33%), 9 (30%). There were no adverse events reported for up to 24–48 hours after the treatments.	Limitations: small sample size, self control crossover design.
Phahonthep R, 2004 [20]	Patients undergoing topical anesthesia	Crossover trial	16	Iomed (Model PM-850)	Lidocaine, EMLA (eutectic mixture of local anesthetics)	Iontophoresis vs. EMLA Tingling very low level: 2(12.5%), 0 Tingling low level: 1 (6.2%), 0 Tingling discomfortable very low level: 1(6.2%), 0 No severe adverse events and side effects were detected.	Limitations: crossover design, small sample size,
Zempsky WT, 2004 [18]	Patients undergoing topical anesthesia for venipuncture or venous cannulation	RCT(1:1)	276 adults (137 lidocaine, 139 placebo) 272 children (136 lidocaine, 136 placebo)	LidoSite TM (B. Braun, Bethlehem, Pennsylvania)	Lidocaine with 1:100,000 epinephrine for ITS, saline solution with 1:100,000 epinephrine. for control	Mild erythema (Draize Score 1 or 2): no patient level data reported mild edema (Draize Score 1 or 2): no patient level data reported, no statistically significant difference in the 5-point Draize scale for erythema/edema in both adult and children arms. Pain at application site leads to discontinuation in 7 (2.6%) children , burning sensation in 2 (0.7%)children, vasoconstriction in 1 (0.4%)child. a partial thickness burn: in 1 (0.4%)child in the lidocaine group caused by skin contact with a defect in the coating of the wires connecting the controller to the electrode patch. itching: 10 patients (1.8% of 548 patients) urticaria: 4 patients (0.7% of 548 patients).	Limitations: small sample size, no power to yield any statistical difference in adverse event because both groups used the same delivery system

Table 5 (continued)

Author, Year	Study Population	Study Design	Sample Size	Device Studied	Drug Studied	Adverse Events	Study strength/Limitation
Zempsky WT, 2003 [24]	Adult patients with nevi, seborrheic keratosis, or actinic keratosis undergoing topical anesthesia	RCT(1:1)	41	TransQ1 or TransQ2 Electrode (Iomed, Inc.);the iontophoresis unit (Phoresor II; Iomed, Inc.)	Lidocaine with 1:100,000 epinephrine for ITS, saline solution with 1:100,000 epinephrine. for control	blanching and/or erythema, 37 (90%)of 41 patients, both of which resolved within 24 hours	Strength: RCT Limitations: small sample size
Zempsky WT, 2003 [23]	Pediatric patients undergoing topical anesthesia for minor dermatologic procedures such as removal of a nevus or wart and/or minor incision	RCT(1:1)	60	Phoresor II; Iomed, Inc	Lidocaine with 1:100,000 epinephrine for ITS, saline solution with 1:100,000 epinephrine. for control	There were no adverse effects in either group. Blanching and/or erythema: 58 (97%)of 60 patients. All blanching and erythema resolved in less than 1 hour. No patient reported burning or stinging.	Strength: RCT Limitations: small sample size
Kearns GL, 2003 [25]	Patients undergoing topical anesthesia	Single arm trial	12	Northstar Iontophoretic Patch; Becton Dickinson Transdermal Systems, Fair Lawn	lidocaine	Any dermal abnormalities at 10 hours: 0%–28%. Most resolved within 24 hours irrespective of application site. Erythema: 4 subjects (33%). Erythema associated with the anode seemed to be more prominent when the study device was applied to either the chest or the back as compared with the antecubital fossa or dorsum of the hand. No severe adverse events were reported in association with this clinical trial.	Limitations: small sample size

Table 5 (continued)

Author, Year	Study Population	Study Design	sample size	Device Studied	Drug Studied	Adverse Events	Study strength/Limitation
Minkowitz HS, 2010 [3]	Patients need postoperative pain control	Secondary analysis on 4 RCTs (Viscusi ER, 2004 [19], Hartrick CT, 2006 [15], Minkowitz HS, 2007 [10], and Grond S, 2007 [11])	Fentanyl ITS N=1,288	IONSYS, Ortho-McNeil, Inc	fentanyl for ITS, morphine for IV PCA	Nausea 40.1% Fever 18.4% Application Site Reaction(ASR)-erythema 14.4% Vomiting 12.7% Headache 9.3% Anemia 5.7% Pruritus 5.5% Dizziness 5% Hypotension 3.7% ASR-itching 3.6% Constipation 3.5% Hypoxia 3.3% ASR-vesicles 3% Insomnia 3% Abdominal pain 2.3% Anxiety 1.9% Urinary retention 1.6% Hypokalemia 1.5% Extremity pain 1.3% Ileus 1.2% Hypoventilation 0.9% Atrial Fibrillation 0.5%	Limitations: secondary analysis, did not report on control group characteristics or outcomes, reported adverse events but they were not the focus of the paper
Mattia C, 2010 [4]	Patients need postoperative pain control	Secondary analysis on Grond S, 2007 [11]	652 for secondary subgroup analysis, fentanyl ITS: 309, morphine i.v. PCA: 310	IONSYS, Ortho-McNeil, Inc	fentanyl for ITS, morphine for IV PCA	fentanyl ITS vs. morphine i.v. PCA (incidence % range among subgroups): Nausea: 26.9-51.6 vs. 34.0-60.0%; Vomiting: 11.5-23.9% vs. 8.0-17.3%; dizziness : 3.3-8.7% vs. 5.1-24.0%; headache: 6.5-15.2% vs. 3.1-5.0%; Pruritus: 3.3-8.7% vs. 5.1-24.0%; respiratory depression:1.0% vs. 8.7%; paralytic ileus: 0% vs. 5.7%; hypoventilation (overall): 4(1.2%) vs. 11(3.3%); hypoxia (overall): 3(0.9%) vs. 8(2.4%); hypotension (overall): 7(2.2%) vs. 12(3.6%); hypotension in the upper abdominal surgery subgroup: 2 (4.4%) vs. 0. Application-site reactions (ASRs), including ASR – erythema (range among subgroups 30.8–48.9%), ASR – pruritus (range among subgroups 2.4–13.0%), ASR – edema (range among subgroups 1.6–6.5%) and ASR – vesicles (range among subgroups 2.2–12.6%), occurred in some patients who received fentanyl ITS. No relevant respiratory depression in the fentanyl ITS group.	Limitations: descriptive secondary analysis, safety endpoints were not prespecified, small size/underpowered for subgroup analyses.

Table 5 (continued)

Author, Year	Study Population	Study Design	Sample Size	Device Studied	Drug Studied	Adverse Events	Study strength/Limitation
Viscusi ER, 2007 [8]	Patients need postoperative pain control	Secondary analysis on 3 RCTs (Viscusi ER, 2004 [19], Hartrick CT, 2006 [15], Minkowitz HS, 2007 [10])	n=1942 ITS: 963 PCA: 979	IONSYS, Ortho-McNeil, Inc	fentanyl for ITS, morphine for IV PCA	ITS / PCA Nausea 379 (39.4)/ 421 (43.0) Fever 225 (23.4) /212 (21.7) Vomiting 109 (11.3) /109 (11.1) Headache* 107 (11.1) /71 (7.3) Pruritus* 61 (6.3)/ 109 (11.1) Anemia 70 (7.3) /79 (8.1) Hypotension 41 / (4.3) 61 (6.2) Dizziness 51 (5.3)/ 42 (4.3) Hypoxia 40 (4.2) /47 (4.8) Insomnia 39 (4.0)/ 32 (3.3) Constipation 38 (3.9)/ 28 (2.9) Urinary retention 19 (2.0)/ 35 (3.6) Tachycardia 17 (1.8) /35 (3.6) Abdominal pain 23 (2.4) /17 (1.7) Pharyngitis 13 (1.3) /22 (2.2) Anxiety 20 (2.1) /19 (1.9) Somnolence 13 (1.3) /20 (2.0)	Limitations: Pooled Analysis. Contains data from the Viscusi 2004, Hartrick 2006, and Minkowitz 2007 trials
Panchal SJ, 2007 [9]	Patients need postoperative pain control	Secondary analysis 2 RCTs (Hartrick CT, 2006 [15], Minkowitz HS, 2007 [10])	Total 1305, fentanyl ITS 647, morphine IV PCA 658	IONSYS, Ortho-McNeil, Inc	fentanyl for ITS, morphine for IV PCA	Of the 1183 fentanyl ITS units used during the 2 studies, 52 (4.4%) had a device malfunction or failure. 26 of these system malfunctions or failures, 1 itching, and 1 erythema/discoloration were associated with an analgesic gap.	Limitation: only focus on system-related events that resulted in an analgesic gap
Minkowitz HS, 2007 [10]	Patients need postoperative pain control	RCT	Total 506, fentanyl ITS 252, morphine IV PCA 254	IONSYS, Ortho-McNeil, Inc	fentanyl for ITS, morphine for IV PCA	fentanyl ITS vs.morphine IV PCA: nausea (48.0% vs 44.1%, P = 0.422),headache (16.7% vs 10.6%, P = 0.053),fever (14.3% vs 11.0%, P = 0.287), pruritus (7.9% vs 13.8%,P = 0.045), and vomiting (12.7% vs 9.8%, P = 0.328). Adverse events relevant to the use of opioids, including cardiovascular system (8.3% vs 8.7%, P = 1.00), nervous system (11.5% vs 8.3%, P = 0.236), respiratory system (7.5% vs 12.2%, P = 0.101), or urogenital system-related adverse events (3.2% vs 6.7%, P = 0.099). Treatment-related adverse events (≥5%) were nausea (41.7% vs 39.4%, P = 0.651), headache (13.9% vs 9.1%, P = 0.095), vomiting (11.9% vs 9.1%, P = 0.313), and pruritus (7.1% vs 12.6%, P = 0.052) .	Strengths: RCT design, large sample size, prespecified safety endpoints. Limitation: not placebo control, no adjustment (to significance level) was applied for

Table 5 (continued)

Author, Year	Study Population	Study Design	sample size	Device Studied	Drug Studied	Adverse Events	Study strength/Limitation
						<p>fentanyl ITS(n=252) vs. morphine IV PCA (n=254): Application-site reactions (ASR) including erythema, itching, vesicles, and edema reported in 14.7% of patients treated with the fentanyl ITS, were mild-to-moderate in severity and resolved without specific treatment. ASR-erythema 24 (9.5%), ASR-itching 14(5.6%), ASR-vesicles 7(2.8%). IV insertion site reactions were 1.6%. No cases of clinically relevant respiratory depression were reported in the fentanyl ITS group. Low or high pulse: 1.6% vs 2.4%. Patients with ≥ 1 systemrelated event related to study medication and the method of pain control: 21.4% vs 22.0%. System-related events resulting in an analgesic gap: 6.0% vs 12.6%, P = 0.014.</p>	
Grond S,2007 [11]	Patients need postoperative pain control	RCT	n=660 ITS:325 PCA:335	IONSYS, Ortho-McNeil, Inc	fentanyl for ITS, morphine for IV PCA	<p>ITS (n=325) vs.PCA (n=335) Nausea: 1.5% vs 2.1%, Dizziness: 0.3% vs 1.2%, Application site reactions: 44.3% (11 cases severe. 1 patient had not yet recovered at end of study) vs. 6.6%; reported problems: 51.1% (erythaema/dyscoloration, other, device malfunction or failure, itching, oedema) vs 17.9% (other, alarm); Pain control interrupted: 4.4%(2min-4.5hr) vs 41.3%(5min-12hr)</p>	<p>Strengths: Multisite randomized controlled trial. Measured many different safety results, comparator. Large sample size. Limitations: would have liked to see more detail about 'other' problems reported.</p>

Table 5 (continued)

Author, Year	Study Population	Study Design	Sample Size	Device Studied	Drug Studied	Adverse Events	Study strength/Limitation
Eberhart L. 2007 [12]	Patients need postoperative pain control	Secondary analysis on 3 RCTs (Chelly JE, 2004 [22], Viscusi ER, 2006 [14], Viscusi ER, 2004 [19],)	1,427 patients, 791 patients received fentanyl rrs	IONSYS, Ortho-McNeil, Inc	fentanyl for ITS, morphine for IV PCA , placebo	The most frequently reported overall AEs from all controlled trials were nausea (318, 40.3%), fever (107, 13.5%), vomiting (91, 11.5%) and headache (88, 11.1%). Somnolence, confusion, hypoxia, and hypoventilation occurred in less than 3 % of patients. The most frequently reported treatment related AEs were nausea (36.9 % vs 45.9 %), vomiting (10.4% vs 8.4 %), and headache (8.7 % vs 7.5 %) for patients who received fentanyl ITS or IV PCA morphine, respectively. At least one application-site reaction occurred in 12.9 % of patients who received fentanyl ITS. The most common application-site reaction was erythema, occurring in 9.4 % (74) of patients, but cases were mostly mild and resolved without treatment. No overall differences in the incidence of AEs using fentanyl ITS were observed between the elderly population (>=65 years of age), including the subset of patients 75 years of age or older, and the adult patient population 18-64 years of age).	Limitations: results were simply pooled from four clinical trials. No statistical method was mentioned in the study.
Ahmad S, 2007 [13]	Patients need postoperative pain control	RCT	n=275 ITS: 138 PCA:137	IONSYS, Ortho-McNeil, Inc	fentanyl for ITS, morphine for IV PCA	ITS vs.PCA n (%) Nausea: 69 /(50.0) vs 78 (56.9), Headache: 26 (18.8) vs 14 (10.2), Pruritus: 15 (10.9) vs 21 (15.3), Application-site reactions: 13 (9.4) vs 0, Vomiting: 13 (9.4) vs 8 (5.8), Fever: 7 (5.1) vs 6 (4.4), Hypoxia: 7 (5.1) vs 4 (2.9), Constipation: 6 (4.3) vs 2 (1.5), Flatulence: 5 (3.6) vs 3 (2.2), Urinary retention: 4 (2.9) vs 0, Abdominal pain: 2 (1.4) vs 3 (2.2), Anxiety: 2 (1.4) vs 5 (3.6), Dizziness: 2 (1.4) vs 3 (2.2), Hypotension: 2 (1.4) vs 3 (2.2).	Strengths: RCT, large sample size, more uniform patient population Limitations: Subset of same study by Viscusi et al.

Table 5 (continued)

Author, Year	Study Population	Study Design	sample size	Device Studied	Drug Studied	Adverse Events	Study strength/Limitation
Viscusi ER, 2006 [14]	Patients need postoperative pain control	RCT	n=484 Fentanyl:244 Placebo:240	iontophoretic fentanyl HCl patient-activated transdermal system: No brand or device given	fentanyl for ITS, placebo	Fentanyl vs. Placebo n(%) Headache: 10 (4.1) vs 8 (3.3), Fever: 6 (2.5) vs 4 (1.7), Nausea: 65 (26.6) vs 35 (14.6), Vomiting: 10 (4.1) vs 10 (4.2), Flatulence: 5 (2.0) vs 2 (0.8), Insomnia: 6 (2.5) vs 8 (3.3), Dizziness: 6 (2.5) vs 2 (0.8), Pruritus: 8 (3.3) vs 1 (0.4), ASR-itching: 5 (2.0) vs 1 (0.4).	Strengths: RCT with placebo. Medium sized sample. Limitations: No information about device used.
Hartrick CT, 2006 [15]	Patients need postoperative pain control	RCT	N=799 Fentanyl ITS n=395 Morphine IV PCA n=404	IONSYS, Ortho-McNeil, Inc	fentanyl for ITS, morphine for IV PCA	ITS (n=395) vs. PCA(n=404) Adverse event (> 2% patients): Nausea: 30.1% vs 37.6%; Fever: 31.1% vs 29.5%; Anemia: 13.7% vs 12.9%; Vomiting: 10.6% vs 13.4%; Hypotension: 7.3% vs 12.1%; Pruritus: 3.8% vs 8.4%; Application Site Reaction(ASR)-erythema: 7.6% vs 0%; Hypoxia: 5.8% vs 6.9%; Dizziness: 6.8% vs 4.5%; Insomnia: 6.6% vs 5.4%; Urinary retention: 2.5% vs 5.0%; Constipation: 4.8% vs 4.0%; Headache: 4.6% vs 3.7%; Tachycardia: 2.8% vs 4.2%; generalized spasm: 3.8% vs 2.5%; Extremity pain: 3.8% vs 1.7%; Anxiety: 2.3% vs 1.7%; somnolence: 1.0% vs 2.2%; chills 2.0% vs. 1.5%; pharyngitis 0.5% vs. 2.0%; confusion: 0.3% vs 2.0%. 38 (9.6%) ITS patients had at least 1 ASR. The majority of ASRs were mild or moderate and generally self-limiting.	Strengths: reports the characteristics and outcomes of the control group Limitations: aim of the study is efficacy, not safety

Table 5 (continued)

Author, Year	Study Population	Study Design	sample size	Device Studied	Drug Studied	Adverse Events	Study strength/Limitation
Viscusi ER, 2004 [19]	Patients need postoperative pain control	RCT	Total 636, PCTS 316, IV PCA 320	fentanyl hydrochloride patient-controlled transdermal system (PCTS),E-TRANS; ALZA Corp,	fentanyl for ITS, morphine for IV PCA	Opioid-related adverse Event(> 2% patients), No. (%), Fentanyl PCTS (n = 316) vs. IV PCA Morphine (n = 320) Nausea: 129 (40.8) vs 147 (45.9); Headache: 36 (11.4) vs 24 (7.5); Vomiting: 31 (9.8) vs 27 (8.4); Pruritus: 26 (8.2) vs 40 (12.5); Application site reactions (erythema, itching, vesicles, other): 20 (6.3) vs 0; Constipation: 12 (3.8) vs 7 (2.2); Hypoxia: 12 (3.8) vs 7 (2.2); Fever: 11 (3.5) vs 13 (4.1); Dizziness: 6 (1.9) vs 12 (3.8); Somnolence: 6 (1.9) vs 7 (2.2); Anxiety: 4 (1.3) vs 9 (2.8). Scheduled skin evaluations at 24 hours after system removal revealed erythema in approximately half (53.8%) of the fentanyl PCTS patients. Most of this erythema was mild. None required treatment, and all resolved within 4 weeks.	Strengths: Prospective randomized controlled parallel-group Large sample size. Limitation: not a placebo control, blinded RCT

Table 6: Publications Included in the Literature Review of Tap Water Iontophoresis for Hyperhidrosis

Author, Year	Study Design	Sample Size	Assessment Tool	Effectiveness	Adverse Events	Study Strength/Limitation
Siah TW, 2013 [29]	retrospective audit, uncontrolled, non-blinded	23	PRO (1=dry, 10=extreme sweating)	Palmar mean score from 7.6 to 1.9; Plantar mean score from 8.47 to 3.0	mild skin irritation, erythema	- Subject to bias due to subjective, patient reported outcome and retrospective, uncontrolled, & non-blinded
Karakoc Y, 2004 [30]	“crossover”, blinded	15	1 hr pad glove method	DC Right hand: 3.08 to 0.38 g/h DC Left hand: 3.16 to 0.39 g/h AC Right hand: 3.12 to 3.08 g/h AC Left hand: 3.17 to 3.16 g/h	not reported	+ Quantitative measure, controlled, blinded; - All subjects received placebo first, no reporting of adverse events.
Karakoc Y, 2002 [31]	time series, non-blinded	112	1 hr pad glove method	91 subjects (81%) responded. Mean first remission was 35 days. Responders Right hand: 2.98 to 0.39 g/h; Left hand: 3.04 to 0.52 g/h	erythema (12 pts), local burning (20 pts), vesicular formation on palms or soles (8 pts)	+ Quantitative measure, large sample size; - Uncontrolled, non-blinded, post-hoc analysis of responders
Reinauer S, 1993 [32]	RCT (grouped by subject), blinded	25	weighed paper (1 min); subjective PRO	DC: from ~45 to ~19 mg/min, AC/DC: from ~63 to ~17 mg/min; Mean number of treatments to normhidrosis: DC=11, AC/DC=11, AC=no normhidrosis	slight discomfort; mild skin irritation; burning, tingling; transient erythema; defects of the horny layer such as fissures, erosions caused stinging, itching; electric shocks	+ Quantitative measure, controlled, blinded
Shen JL, 1990 [33]	RCT with drug (grouped by hands), double-blind	10	iodine starch paper (scored 0 to 4)	TWI had a mean -1.5 decrease; Drug had mean -3.1 decrease; Mean remission period = 3.5 days for TWI, 20 days for drug	peeling or vesiculation (5pts); transient mouth dryness (1pt)	+ Controlled, blinded - Qualitative measure, short duration (4 days), limited information published
Dahl JC, 1989 [34]	RCT (grouped by hand), double-blind	11	10 min pad glove	Median 38% reduction from baseline; Median 32% reduction vs. control	none; 1 other pt had multiple deep bullae	+ Quantitative measure, controlled, blinded - Treatment duration varied by subject
Stolman L, 1987 [35]	RCT (grouped by hand), non-blinded,	18	starch iodine imprint (subjective evaluation of whole hand)	15/18 subjects had “marked reduction”; 2/18 had no improvement; 1/18 dropped out; no change evident in control	transient erythema (caused dropout); transient vesiculation (3pts); redness for hours (12 pts); intermittent tingling sometimes lasting days (2 pts)	+ Controlled - Qualitative measure, non-blinded, subjective determination of success not defined
Hölzle E, 1987 [36]	time series, uncontrolled, non-blinded	71	gravimetric paper (1 min); colorimetric (starch iodine paper, 0 to 4)	Palmar mean gravimetric decreased from 52 to 10 mg/min (healthy subjects below 20); Plantar mean gravimetric decreased from 43 to 15 mg/min (healthy subjects below 15)	slight discomfort; mild skin irritation; burning, tingling, deep pain at high mA; transient erythema, white vesicles, slight burning, soreness	+ Quantitative measure, large sample size; - Uncontrolled, non-blinded

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