

Classification Discussion: Iontophoresis Devices Not Labeled for Use with a Specific Drug

21 CFR 890.5525 (b)

February 21, 2014



Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
U.S. Food and Drug Administration

Outline

- **Regulatory Definition & Purpose of Meeting**
 - Brian Pullin, M.S.
- **Description of Iontophoresis**
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- **Literature Review**
 - Xianghua Yin, M.D.
- **Clinical Review**
 - Sung Yoon, M.D.
- **Concluding Remarks**
 - Brian Pullin, M.S.

Purpose of This Meeting

Preamendments devices subject to 515(i) of FD&C Act. Iontophoresis devices not labeled for use with a specific drug are Class III, but marketed through the 510(k) process

Sufficient information to establish special controls to provide a reasonable assurance of safety and effectiveness?

Yes

No

Re-classify to Class II
[510(k)]

Remain as Class III
[PMA]

Regulatory Definition

21 CFR 890.5525 (a)

(a) *Iontophoresis device intended for certain specified uses -*

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. Class II

In other words...

- indicated for use in the diagnosis of cystic fibrosis, or
- indicated for use with a specific drug that has been approved for delivery by iontophoresis

Regulatory Definition

21 CFR 890.5525 (b)

Focus of Today's Meeting

(b) *Iontophoresis device intended for any other purposes -*

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.** Class III

In other words...

- NOT indicated for use in the diagnosis of cystic fibrosis, and
- NOT indicated for use with a specific drug.
- Also includes devices indicated for use with a specific non-drug solution (e.g., tap water).

Regulatory Definition

21 CFR 890.5525 (b)

(b) *Iontophoresis device intended for any other purposes -*

- Regulated as a general drug delivery tool, analogous to a syringe
- Hereinafter: “***part(b) iontophoresis devices***”

Regulatory Definition

21 CFR 890.5525 (b)

(b) *Iontophoresis device intended for any other purposes -*

Note:

- Any device labeling that references a drug must be consistent with the approved route of administration of that drug product (dosage, formulation, etc.).
- Iontophoresis devices under part (b) may be indicated for general drug delivery without identifying a specific drug, but they can **NOT** be indicated or labeled for use with a specific drug or class of drugs not approved for iontophoresis.

Combination Products

- Iontophoresis devices may also be regulated as combination products if:
 - a drug and device are packaged together (such as a device that is pre-loaded with the drug)
 - the drug was approved for use with only a specific device model
- CDER has reviewed all iontophoresis combination products in NDAs
- These are not the subject of today's meeting

Current Regulatory Pathway

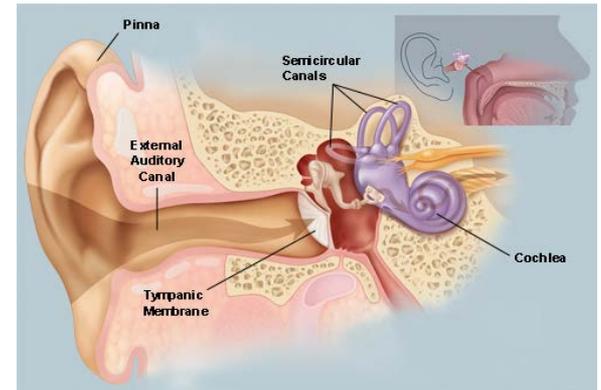
- Devices on the market prior to May 1976 are considered preamendments
- Class III, 510(k): Intended use and technological characteristics are “substantially equivalent” as compared to a predicate
- The earliest part (b) iontophoresis devices relied on comparison to preamendments devices
- 63 devices cleared under part (b)

Cleared Indications for Use

- All 'prescription use only'
- The majority (40) were cleared for general transdermal drug delivery, such as:
 - delivery of “ions of soluble salts or other drugs into the body for medical purposes”
 - and as an “alternative to hypodermic injection.”

Cleared Indications for Use (cont.)

- 6 devices for the administration of drug solution, salts, or ions into the ear and/or the tympanic membrane
- 3 devices for use in the treatment of hyperhidrosis (excessive sweating) using tap-water iontophoresis



Other Indications for Use

- 11 devices had indications or labeling that identified a specific drug that was not approved for iontophoresis
- 9 devices identified a class of drugs, e.g., corticosteroids
- 3 devices for the delivery of fluoride or sodium chloride to the teeth for dental use

Note: CDRH's practice until 1994 was to clear the device only. The sponsor was notified that they could not market their iontophoresis device for use with a specific drug.

CDRH no longer clears devices if unapproved drugs are identified.

Other Uses

- Iontophoresis devices have been investigated and used clinically for a variety of other specific uses. However, FDA does not regulate the practice of medicine.
- The Panel will be asked for their input on the classification of part (b) iontophoresis devices only for general drug delivery (no specific drug) or the treatment of hyperhidrosis.

Focus of Meeting

- Subject of discussion:
 - The classification of part (b) iontophoresis devices for the cleared indications, i.e., ‘Rx only’ for general drug delivery or for the treatment of hyperhidrosis
- Meeting is not about:
 - Individual devices
 - OTC use
 - Uses with specific drugs
 - Combination products
 - Other clinical uses that have not been cleared
 - Classification or definition of part (a) devices

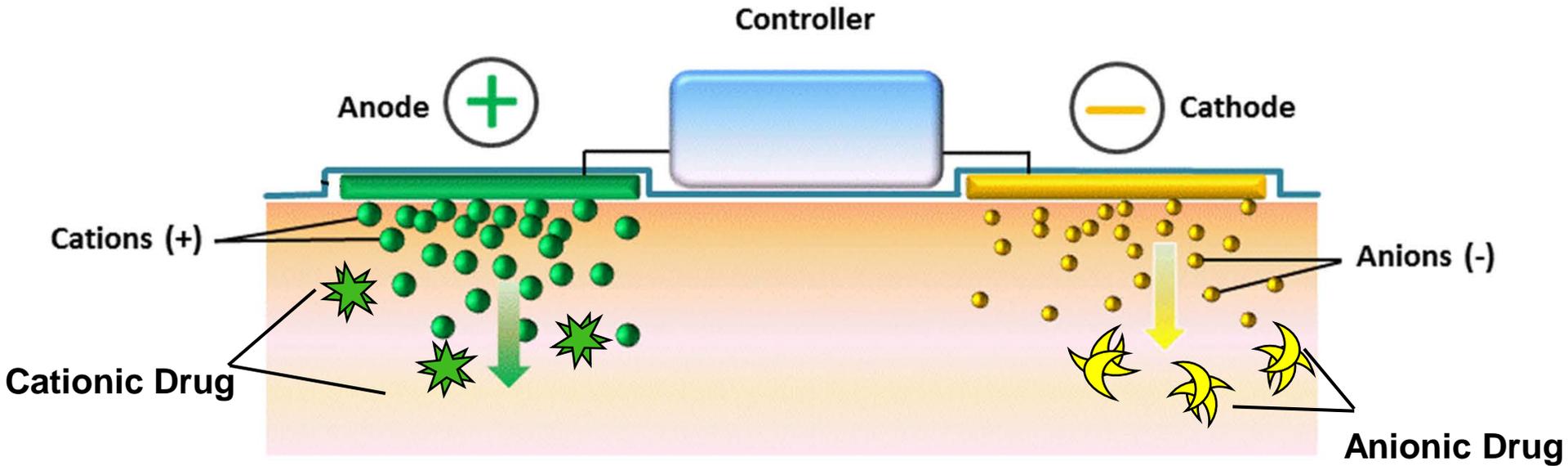
Description of Iontophoresis

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Office of Science and Engineering Laboratories
U.S. Food and Drug Administration

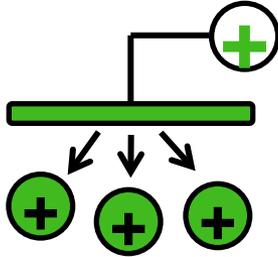


Principle of Iontophoresis

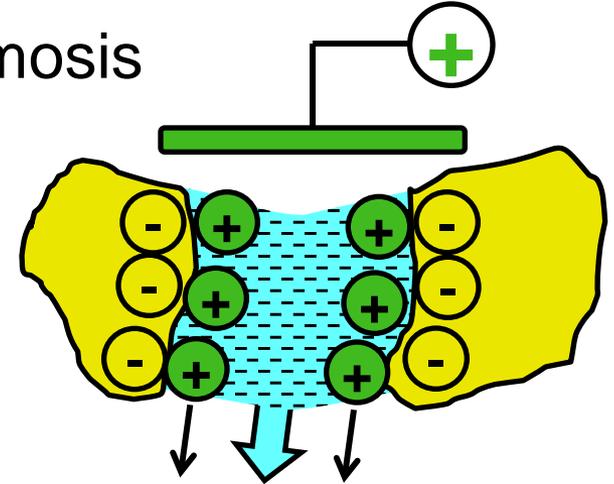


Principle of Iontophoresis

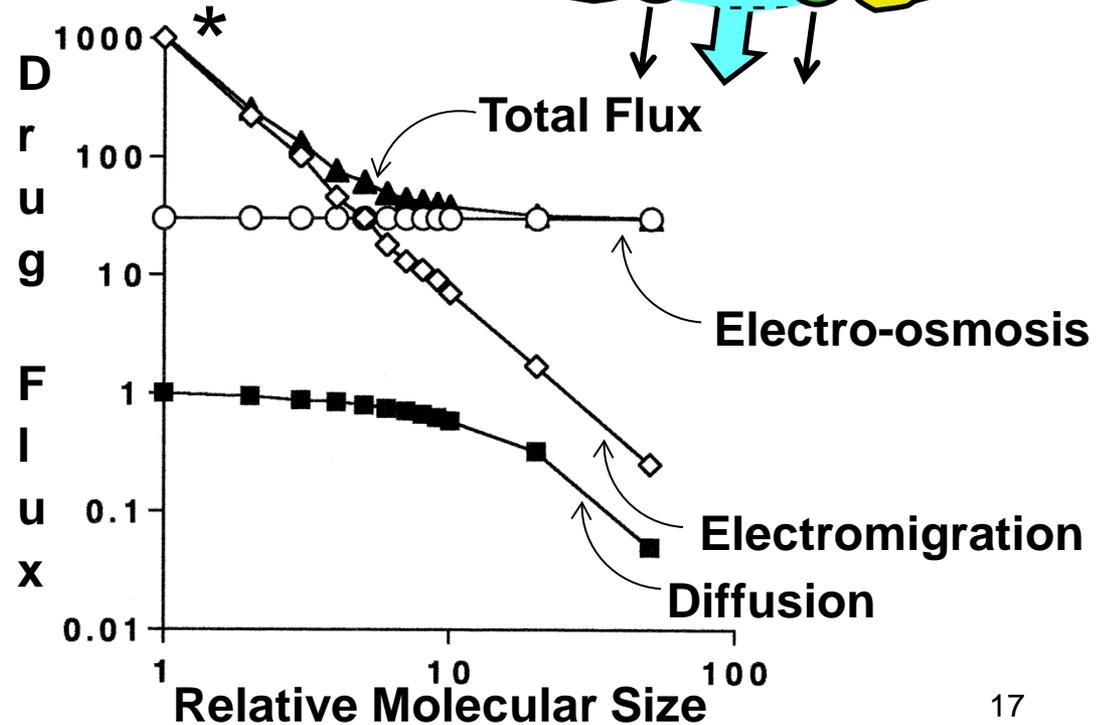
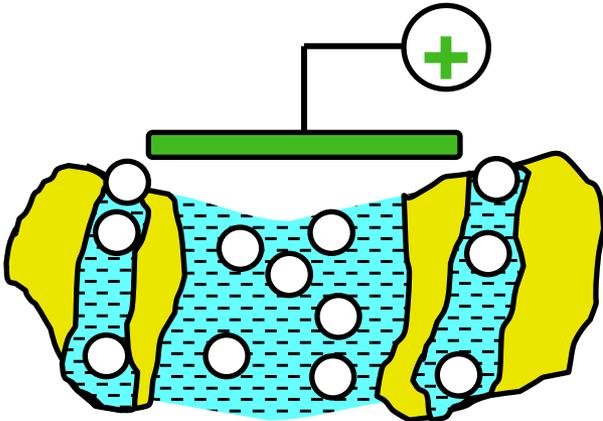
1. Electromigration



2. Electro-osmosis

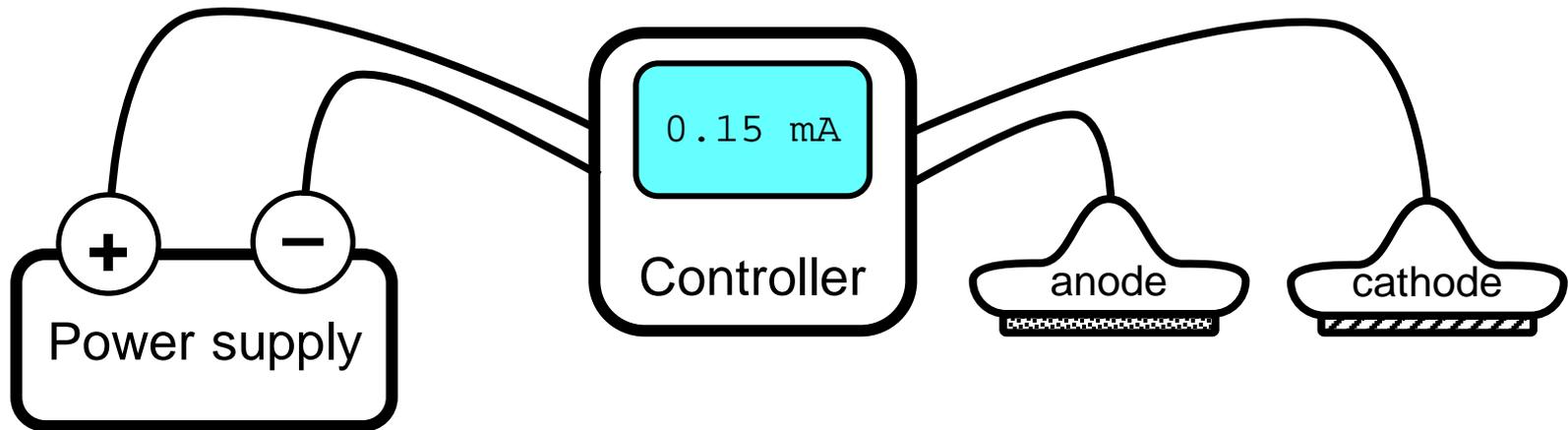


3. Passive diffusion



*adapted from Guy et al, J Control Rel, 2000

Design of Iontophoretic Devices



Design of Iontophoretic Electrodes

Adhesive Electrodes



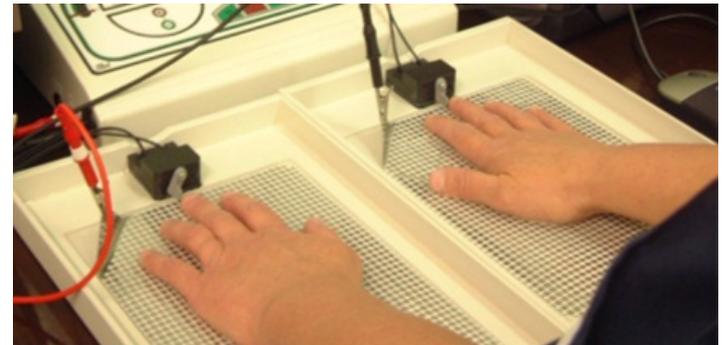
Ear Electrodes



Handpiece Electrodes

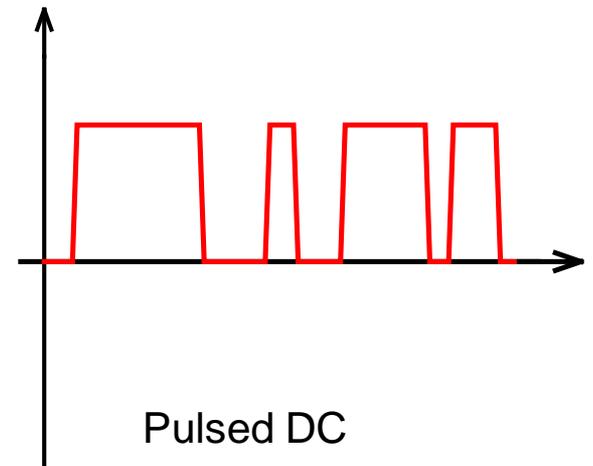
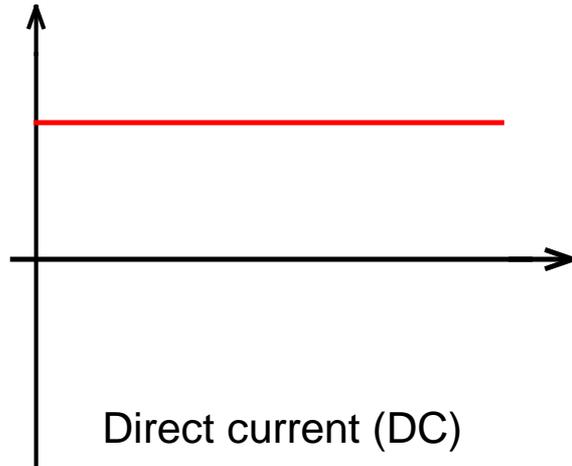


Palmar/Plantar Electrodes



Critical Parameters for Iontophoretic Devices

- Current profile

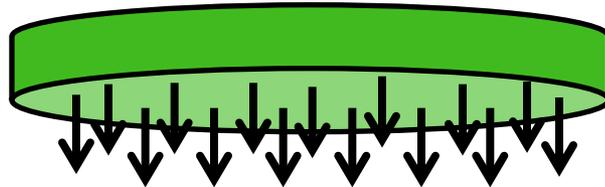


- Dosing

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

Critical Parameters for Iontophoretic Devices (cont.)

- Current density



$$\text{Current density (mA/cm}^2\text{)} = \text{Current(mA)} / \text{Area(cm}^2\text{)}$$

Critical Parameters for Iontophoretic Devices (cont.)

- pH

Drop in pH on the anode: $2\text{H}_2\text{O} \rightarrow \text{O}_2 + 4\text{e}^- + 4\text{H}^+$

Increase in pH on the cathode: $2\text{H}_2\text{O} + 2\text{e}^- \rightarrow \text{H}_2 + 2\text{OH}^-$

- Non-device Parameters

- charge of the species
- molecular weight of the species
- point of application and local skin permeability
- formulation

Regulatory History

Brian Pullin, M.S.

Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
U.S. Food and Drug Administration



Regulatory History

- FDA began regulating medical devices in 1976
- Devices on the market prior to May 1976 referred to as “preamendments”
- Classification meetings with 3 different panels for iontophoresis devices held in 1978
 - Physical Medicine Panel
 - Ear, Nose, and Throat (ENT) Panel
 - Dental Panel

1978 Classification Panels

- Physical Medicine
 - Discussion focused on use as an “alternative to hypodermic injections”
 - Drug doses delivered by iontophoresis were much less accurate than other methods
 - Iontophoresis devices were of value, but insufficient clinical data available for most of the drugs
 - Uncontrolled drug delivery could result in potentially severe adverse effects
 - Recommended Class II for device only
 - Risks identified: electric shock, burns, cardiac arrest, inappropriate therapy

1978 Classification Panels

- ENT Panel
 - Iontophoresis safe and effective for anesthetizing the tympanic membrane
 - Electrode designs could cause injury
 - Recommended Class II
 - Risks identified: trauma, bodily injury
- Dental Panel
 - Iontophoresis safe for delivery of fluoride to the teeth due to low voltage
 - Recommended Class I
 - No risks identified

Conclusions from the Panels

- Sufficient information for
 - Diagnosis of cystic fibrosis
 - Anesthetizing the intact tympanic membrane
 - Dental application of fluoride to the teeth
- Lack of scientific data supporting safety and effectiveness for other uses because it is difficult to estimate the amount of drug delivered

1979 Proposed Rule

- FDA proposed that iontophoresis devices should have a split classification as follows
 - Class II for:
 - Diagnosis of cystic fibrosis
 - Anesthetizing the intact tympanic membrane
 - Dental application of fluoride to the teeth
 - Class III for all other purposes.

1979 Physical Medicine Panel

- The Panel agreed with FDA's proposed rule
- After reviewing the literature, the Panel found insufficient evidence on safety and effectiveness of iontophoresis, except for the 3 previous uses (cystic fibrosis, tympanic membrane, fluoride)
- Recommended Class III for general drug delivery and hyperhidrosis

1983 Final Rule

- FDA believed scientific data supported safety and effectiveness of iontophoresis for the 3 uses
- But, no drugs were labeled for anesthetizing the intact tympanic membrane or delivery of fluoride
- Therefore, iontophoresis devices classified as:
 - a) Class II for:
 - Diagnosis of cystic fibrosis
 - Use with a specific drug that has been approved for delivery by iontophoresis
 - b) Class III for any other purposes

2000 Proposed Rule

- Although Class III, FDA has not called for PMAs and part (b) iontophoresis devices continue to be reviewed through the 510(k) process
- In 2000, FDA proposed to revoke part (b) of the regulation – stating there were no such devices on the market prior to 1976
- Manufacturers could modify their labeling to meet part (a) or would require a PMA
- Comments in response argued there **were** preamendments devices and FDA withdrew the proposed rule

Summary of Regulatory History

- Part (b) iontophoresis devices are Class III, requiring a 510(k)
- 63 cleared devices
 - most for general drug delivery
 - 3 for tap water iontophoresis for hyperhidrosis
- Although safe and effective for use in the ear and teeth, there are no drugs approved
- Despite a 2000 proposed rule, the regulation remains unchanged from 1983

2009 Notice

- Call for information on remaining Class III preamendments devices
 - Submissions were received from 9 iontophoresis device manufacturers
 - 8 recommended Class II
 - 1 made no recommendation
- FDA considered the information in each submission to inform today's discussion

Clinical Evidence

- Safety
 - Adverse Event Reports
 - Systematic Literature Review of Safety
- Effectiveness
 - Clinical Data on Approved Drugs
 - Review of Literature on Hyperhidrosis



Reported Adverse Events

MAUDE Database

- MAUDE (Manufacturer and User Facility Device Experience) maintained by Office of Surveillance and Biometrics (OSB) in CDRH
- Fully implemented in 1996
- Adverse event reports can be submitted by manufacturers, user facilities, importers and voluntary reporters
- Medical device manufacturers required to report adverse events
- Not all events are captured since this is a voluntary reporting system

MAUDE Reports

- Reported to CDRH: January 1996 – November 2013
- 150 AEs for all iontophoresis devices
- 111 Serious AEs (0 deaths)
 - 109 burns (serious)
 - 52 - 2nd degree
 - 13 - 3rd degree
 - 44 - unspecified degree
 - 1 chest pain; 1 “hole in arm”
- 39 Malfunctions
 - 36 caused burns; 3 caused electric shock

FAERS Database

- FAERS (FDA Adverse Event Reporting System) maintained by CDER
- Fully implemented in 2012, but includes data migrated from AERS dating to 1969
- Includes adverse event and medication error reports coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology
- Manufacturers required to report adverse events
- Not all events are captured since reporting is voluntary for healthcare professionals and consumers

FAERS Reports

- Reported to CDER: 1969 – September 2013
- 86 AEs from 1998 – 2013 (79 injuries, 5 deaths, 2 malfunctions)
- Associated drugs identified as fentanyl (13), lidocaine (2), and pilocarpine (1)
- 5 deaths (iontophoresis/drug not considered related):
 - myocardial infarction
 - unknown cause
 - CNS depression
 - multi-organ failure
 - (no iontophoresis used)

FAERS Reports cont.

- 17 AEs possibly device related
 - burns (7),
 - skin necrosis (2),
 - skin peeling (2),
 - pain at treatment site (2),
 - electric shock (1),
 - disorientation (1),
 - accidental exposure (1),
 - discoloration at treatment site (1)

Adverse Event Databases

- 236 total adverse event reports over 17 years
- Most common AEs reported to FDA:
 - burns, mild to serious (3rd degree)
- Limitations of AE reporting to FDA
 - voluntary reporting system for users
 - insufficient information to determine device attribution
 - number of iontophoresis devices in use unknown

Literature Review

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Outline

- Objective
- Methods
- Findings on safety
- Discussion of limitations
- Summary

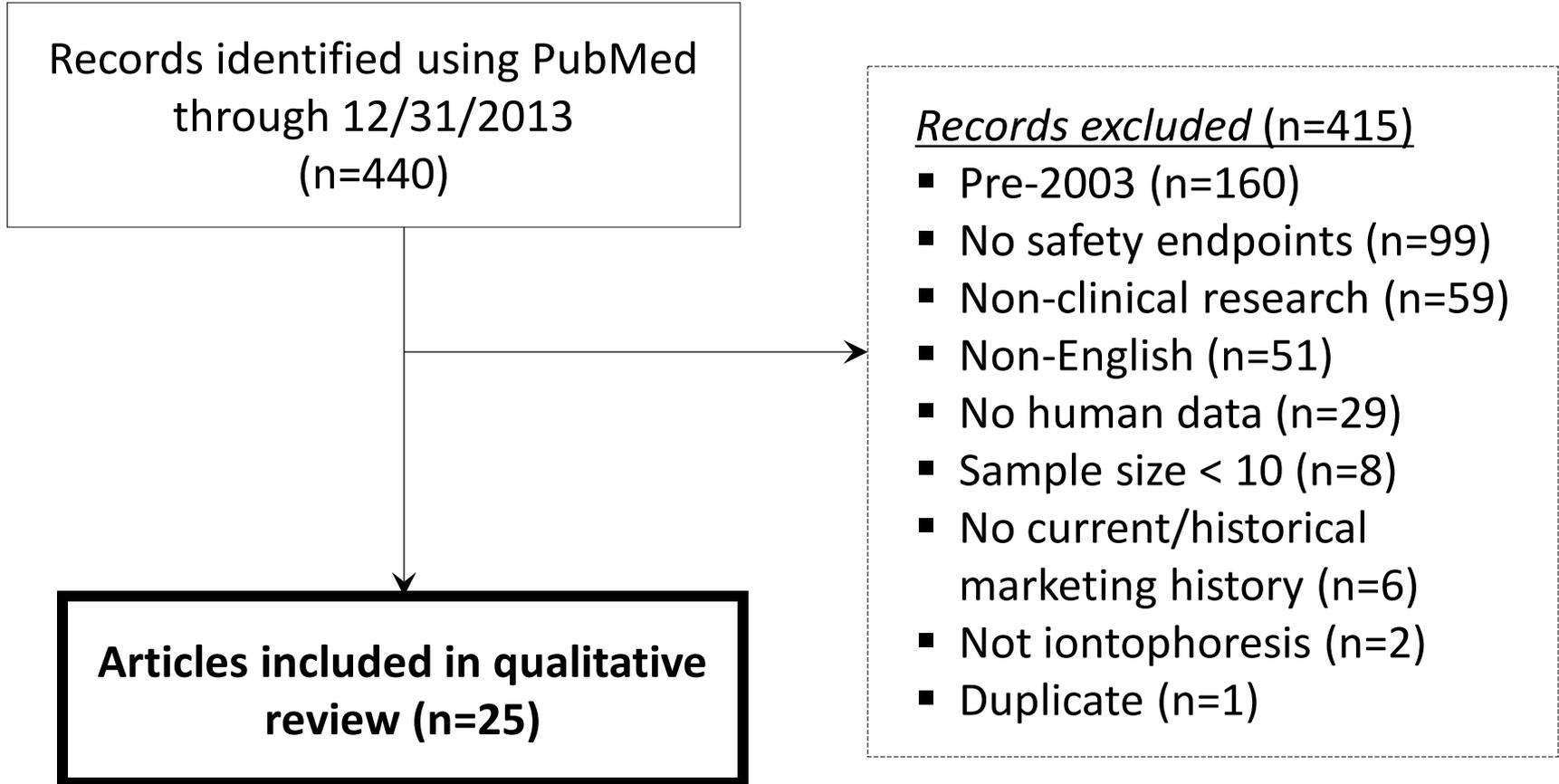
Objective

To provide safety information on the use of the iontophoresis devices for medical purposes previously specified in Part (b) of the regulation (Re: 21 CFR 890.5525).

Methods

- PubMed search limited to English (January 1, 2003 - December 31, 2013)
- Iontophoresis Devices
 - "iontophoretic", "iontophoresis", "electromotive drug administration", "electrically-assisted transdermal delivery", "transdermal electromotive administration", transdermal, skin, "stratum corneum", ear, "tympanic membrane", "electrical shock", "chemical burns", "chemical burns", "electrical burn", "electrical burns", "cardiac arrest", "Inappropriate therapy", blister, rash, "rupture of dermis", scarring, shock, "chest pain", infection, adverse, "adverse events", "side effect", "side effects", risk, risks, death, mortality, complication, complications

Article Retrieval and Selection



Systematic Literature Review

Characteristics of the Identified Studies

Study Design	Number of Articles
Randomized clinical trial (RCT)	13
Crossover study	5
Secondary analysis	5
Cohort study	1
Single arm study	1

- 16 in US & Canada, 8 in Europe, 1 in Thailand
- Publication years: 2003–2011
- No eligible articles: 2012-2013

Overview

- Medical conditions for use
 - Postoperative pain control, n=12
 - Topical anesthesia, n=6
 - Miscellaneous, n=7
 - Central neuropathic pain, migraine, juvenile idiopathic arthritis, Parkinson's disease, Peyronie's disease, Raynaud's phenomenon
- Application site reactions (ASR) as potential device-related adverse events
- Wide range of proportions reported without any trend observed over the years

Postoperative Pain Control (12 articles)

	Application Site Reaction (ASR)§				
	Erythema	Itching	Vesicles	Pruritus	Oedema
Number of articles	12	7	5	2	2
Sample size*	138-1288	316-1288	205 -1288	205 -309	309 - 325
Follow-up (day)	1 - 28			1	1 – 3
Proportion**(%)	0.15 - 48.9	0.15 - 7.1	2.2 - 12.6	2.4 – 13.0	1.6 – 6.5
Severity	Mild to moderate				
Treatment	Most cases (> 86.2%) self-resolved				
Outcome	Recovered				

§ASRs in those received treatment

*Number of patients who received treatment

**Number of patients with ASRs/ number of patients received treatment

Topical Anesthesia (6 articles)

	Application Site Reaction (ASR)				
	Blanching /Erythema	Tingling /itching	Partial thickness burn**	Urticaria	Vasoconstriction
Number of articles	5	2	1	1	1
Sample size	12-548	16 - 548	548		
Follow-up (day)	1-2	1			
Proportion *** (%)	0- 97	1.8 - 6.2	0.2	0.7	0.2
Severity	Mild		-	-	-
Treatment	Not needed	-	-	-	-
Outcome	Resolved*	-	-	-	-

*Within 48 hours or less

**Zempsky et al (2004) reported a single case due to a defect in coating wires in the pediatric arm (N=272). No follow-up data was reported for this case.

***Number of patients with ASRs/ number of patients received treatment

Miscellaneous conditions* (7 articles)

	Application Site Reaction (ASR)			
	Erythema	Pruritus	Skin blister	Tingling and itching
Number of articles	5	1	1	1
Sample size	16 – 96	17	28	16
Follow-up (day)	7 – 42	3	33	7
Proportion** (%)	2 – 100	41	4	100
Severity	Mild and transient			
Treatment	Not needed			
Outcome	Self-resolved			

*Central Neuropathic Pain, Migraine, Juvenile Idiopathic Arthritis, Parkinson’s Disease, Peyronie’s Disease and Raynaud’s phenomenon (7 articles)

**Number of patients with ASRs/ number of patients received treatment

Limitations

- The studies were not powered to detect any pre-specified safety endpoints, which may result in imprecise estimates of incidence of ASR.
- Study participants were highly selected in the clinical trials, which may restrict the generalizability of the safety findings to broader populations.

Summary

- Proportion of patients with ASRs varied across the studies and medical conditions. Erythema was most frequently reported application site reaction.
- Most ASRs were mild and did not require treatment.
- The published safety findings in this review do not raise concerns about any specific adverse events for use of iontophoresis devices for the aforementioned medical conditions.

Clinical Review

S. W. Yoon, M.D.

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Iontophoresis Use

- FDA Approved Drugs (NDAs)
- Tap Water Iontophoresis (non-drug)
- Other Clinical Uses

Approved NDAs

5 NDAs for drug/device combination products

1. Lidocaine and epinephrine for local dermal analgesia
 - Iontocaine (NDA 20530)
Approved on Dec 21, 1995
 - Empi Lidopel (NDA 21486)
Approved on October 26, 2004
 - LidoSite Topical System Kit (NDA 21504)
Approved on May 6, 2004

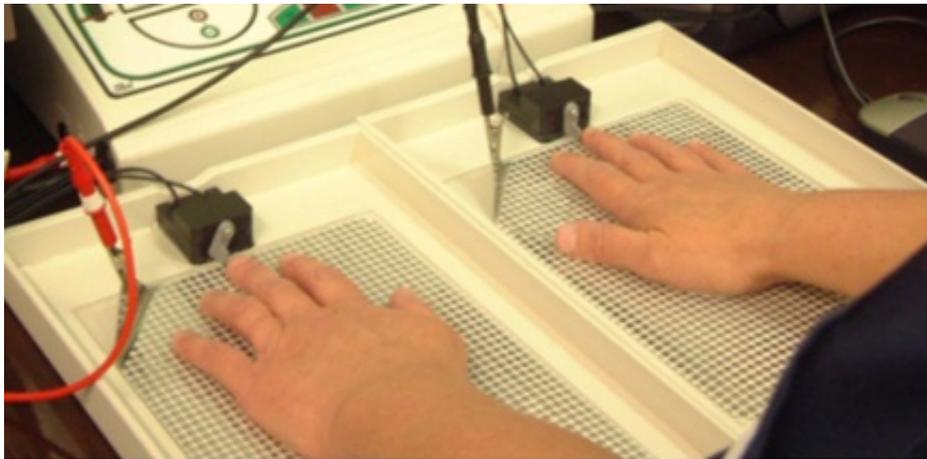
Approved NDAs

2. Fentanyl for short-term management of post-operative pain
 - IONSYS Fentanyl HCl (NDA 21338)
Approved on May 22, 2006

3. Sumatriptan for acute treatment of migraines
 - ZECUITY Transdermal System (NDA 202278)
Approved on January 17, 2013

Cleared Use: Tap Water Iontophoresis (TWI)

- Treatment of Hyperhidrosis



Primary Focal Hyperhidrosis

Only clinical condition cleared for part (b) iontophoresis devices

- Chronic autonomic disorder
- Abnormal and excessive quantities of sweat, typically occurs on the palms, soles and armpits
- Etiology – unknown (incidence rate of 0.6-1%)
- Treatments: topical aluminum chloride, anti-cholinergics, botulinum toxin injections, local surgery, thoracic sympathectomy

Literature Review of TWI

Records identified using PubMed
January 1, 1979 – January 5, 2014
(n=29)

Search Criteria: “hyperhidrosis” and “water” and
("iontophoretic" or "iontophoresis" or
"electromotive drug administration" or
"electrically-assisted transdermal delivery" or
"transdermal electromotive administration")

Records excluded (n=21)

- Not original research (n=11)
- Sample size < 10 (n=6)
- No sweat endpoints (n=2)
- Did not use tap water (n=2)

**Articles included in qualitative
review (n=8)**

Literature Review of TWI

Study	Type	n =	Effectiveness Evaluation	Results
Reinauer S et al., 1993	RCT: TWI vs. placebo	25	Mean number of treatments to normhidrosis (defined as sweat intensity < 20 mg/min weighed on paper) 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.
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 (no scoring system reported)	15 subjects showed a “marked reduction” for TWI vs. no change for placebo.
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.

Literature Review of TWI

Study	Type	n =	Effectiveness Evaluation	Results
Karakoç Y et al., 2002	Time series	112	1 hour pad glove method.	Right hand mean: 2.98 g/h to 0.84 g/h Left hand mean: 3.04 g/h to 0.97 g/h
Hölzle E and Alberti N, 1987	Time series	71	Weighted measure of sweat absorption on paper. Imprint on starch-iodine paper (5-point scale). 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
Shen JL et al., 1990	Time Series (RCT vs. drug)	10	Imprint on iodine-starch paper (scale of 0 to 4)	TWI mean score decreased by 1.5
Siaw TH and Hampton PJ, 2013	Audit	23	10-point, subjective, patient-reported outcome scale (1 = dry, 10 = extreme sweating)	Mean palmar scores (n=21): 7.6 to 1.9 Mean plantar scores (n=16): 8.47 to 3.0

Literature Review of TWI

- All 8 studies reported reduced sweating in the majority of subjects (in some cases all subjects)
- Effects typically lasted for a few weeks, and sweating always returned
- Adverse events were common, although none were serious
 - erythema, burning/tingling, mild skin irritation, vesicles, discomfort, fissures/erosions of the skin, stinging or itching, electric shock, multiple deep bullae, deep pain, soreness
- FDA concludes there is sufficient information to support safety and effectiveness of TWI.

Clinical Conclusions: Effectiveness

- Literature supports the effectiveness of tap water iontophoresis for the (short-term) management of primary palmar and plantar hyperhidrosis
- Clinical effectiveness of iontophoresis for delivery of FDA-approved drugs has been demonstrated in randomized controlled trials

Clinical Conclusions: Safety

- Most common AEs reported to FDA:
 - burns, mild to serious (3rd degree)
- Most common AEs in literature:
 - mild, transient skin reactions, such as erythema, tingling or burning sensations, itching, edema, and vesicles

FDA Recommendation

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Office of Device Evaluation
U.S. Food and Drug Administration





Classification Summary

Class III

Insufficient information exists to determine that general and special controls are sufficient to provide ***reasonable assurance of the safety and effectiveness***,

AND the device

- is 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,

OR

- presents a potential unreasonable risk of illness or injury.

Class II

General controls by themselves are insufficient to provide ***reasonable assurance of the safety and effectiveness.***

AND

There is sufficient information to establish special controls to provide such assurance.

Sec. 513 [21 USC 360c]

Class I

General controls are sufficient to provide ***reasonable assurance of the safety and effectiveness.***

OR

- Insufficient information exists to :
 - determine that general controls are sufficient to provide reasonable assurance of the safety and effectiveness or
 - establish special controls to provide such assurance,

BUT the device

- I. is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and
- II. does not present a potential unreasonable risk of illness or injury.

Reasonable Assurance of Safety

- 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.

[21 CFR 860.7(d)(1)]

Risks to Health

1. Electrical shock
2. Burns
3. Insufficient or excessive delivery of drug/solution
4. Interference with other medical devices
5. Adverse tissue reactions
6. Infection
7. Ear Trauma (only when used in the ear)

The panel will be asked to discuss the risks that should be identified for part (b) iontophoresis devices.

FDA Assessment - Safety

- Part (b) iontophoresis devices are not without risk
 - Most common AEs are mild, transient skin reactions
 - Potential for serious burns
 - Insufficient/excessive delivery could result in more serious adverse events
- Probable benefits to health outweigh the probable risks
- Special controls can provide a reasonable assurance of safety

Reasonable Assurance of Effectiveness

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.**

[21 CFR 860.7(e)(1)]

FDA Assessment – Effectiveness

- The demonstrated clinical effectiveness of approved drug-device iontophoresis systems supports the general effectiveness of part (b) iontophoresis devices when used with approved drugs
- Tap water iontophoresis provides clinically significant results for the (short-term) management of primary palmar and plantar hyperhidrosis
- Special controls can provide a reasonable assurance of effectiveness

FDA's Proposed Special Controls

If the Panel were to recommend a Class II designation, FDA believes that the following proposed special controls should be included as part of the full list of special controls:

FDA's Proposed Special Controls

1. 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.

FDA's Proposed Special Controls

2. Appropriate analysis/testing must demonstrate electromagnetic compatibility (EMC), electrical safety, thermal safety, and mechanical safety.

This typically involves testing to international consensus standards on medical device safety. For instance, part of the electrical safety testing should demonstrate proper isolation of the patient from the electric current out of a wall outlet in a fault condition.

FDA's Proposed Special Controls

3. Appropriate software verification, validation, and hazard analysis must be performed.

The manufacturer would be required to demonstrate that there are appropriate controls in place to ensure the risks associated with software errors have been minimized. For instance, verification and validation testing should demonstrate that the device performs as designed, meets user needs, and there are no “bugs” that impact safety or effectiveness. This information is outlined in FDA Guidance Documents.

FDA's Proposed Special Controls

4. The elements of the device that may contact the patient must be demonstrated to be biocompatible.

This involves either testing to international consensus standards on material biocompatibility or evidence that the material has already been demonstrated as safe when used in other products. The amount of information required depends on the type of contact with the body. For instance, new skin contacting materials must include testing for irritation, allergic sensitization, and cytotoxicity.

FDA's Proposed Special Controls

5. The elements of the device that may contact the patient must be assessed for sterility.

This typically involves testing of devices to international consensus standards to ensure an adequate Sterility Assurance Level, or the probability that all of the microorganisms have been destroyed after sterilization. Alternatively, a risk assessment may conclude that the device does not need to be sterile for use (e.g., when intended to only contact intact skin).

FDA's Proposed Special Controls

6. 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.

This involves testing to demonstrate that aging does not adversely impact the device. For instance, data should demonstrate that hydrogel electrodes do not dry out or that packaging maintains the sterile barrier.

FDA's Proposed Special Controls

7. 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.

This testing would not be to a consensus standard, but would be dependent on the device design and indications. It is likely to involve comparative testing to a predicate device.

Rationale for Performance Testing

- Even though the devices will be generally indicated for drug delivery (similar to a syringe), evaluation of device effectiveness requires consideration of the drug/solution delivered.
- A substantial equivalence evaluation includes a technological comparison to a predicate device. However, some predicates were cleared prior to the first drug approved for iontophoresis.
- Therefore, performance testing will ensure device effectiveness for use with an approved drug or non-drug solution.
- Performance testing may include validated non-clinical testing, or clinical data when necessary

Panel Question

The panel will be asked to discuss the adequacy of these proposed controls in providing a reasonable assurance of safety and effectiveness in light of the available scientific evidence.

Conclusion

- FDA does not believe that part (b) iontophoresis devices are life-supporting or life-sustaining, or “of substantial importance in preventing impairment of human health.”
- FDA does believe that part (b) iontophoresis devices may present a “potential unreasonable risk of illness or injury.”
- FDA does believe there is sufficient information to establish special controls to provide a reasonable assurance of safety and effectiveness.

Conclusion

FDA recommends that part (b) iontophoresis devices be reclassified into Class II (special controls)

The panel will be asked to comment on FDA's assessment of criteria for reclassification.



Thank you!