4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 890

[Docket No. FDA-2000-N-0158]

Physical Medicine Devices; Reclassification of Iontophoresis Device Intended for Any Other Purposes

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final order to reclassify iontophoresis devices intended for any other purposes, which are preamendments class III devices (regulated under product code EGJ), into class II (special controls) and to amend the device identification to clarify that devices intended to deliver specific drugs are not considered part of this regulatory classification.

DATES: This order is effective on [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER].

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SUPPLEMENTARY INFORMATION:

I. Background--Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Pub. L. 94-295), the Safe Medical

Devices Act of 1990 (Pub. L. 101-629), the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115), the Medical Device User Fee and Modernization Act of 2002 (Pub. L. 107-250), the Medical Devices Technical Corrections Act (Pub. L. 108-214), the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85), and the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), among other amendments, established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513(d) of the FD&C Act, devices that were in commercial distribution before the enactment of the 1976 amendments, May 28, 1976 (generally referred to as preamendments devices), are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

A preamendments device that has been classified into class III and devices found substantially equivalent by means of premarket notification procedures (510(k)) to such a preamendments device or to a device within that type (both the preamendments and substantially equivalent devices are referred to as preamendments class III devices) may be marketed without submission of a premarket approval application (PMA) until FDA issues a final order under

section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval or until the device is subsequently reclassified into class I or class II.

Devices that were not in commercial distribution prior to May 28, 1976 (generally referred to as postamendments devices) are automatically classified by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval unless, and until, the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

On July 9, 2012, FDASIA was enacted. Section 608(a) of FDASIA amended section 513(e) of the FD&C Act, changing the mechanism for reclassifying a device under that section from rulemaking to an administrative order.

Section 513(e) of the FD&C Act governs reclassification of classified devices. This section provides that FDA may, by administrative order, reclassify a device based on "new information." FDA can initiate a reclassification under section 513(e) of the FD&C Act or an interested person may petition FDA to reclassify a preamendments device. The term "new information," as used in section 513(e), includes information developed as a result of a reevaluation of the data before the Agency when the device was originally classified, as well as information not presented, not available, or not developed at that time. (See, e.g., Holland-Rantos Co. v. United States Department of Health, Education, and Welfare, 587 F.2d 1173, 1174

n.1 (D.C. Cir. 1978); Upjohn v. Finch, 422 F.2d 944 (6th Cir. 1970); Bell v. Goddard, 366 F.2d 177 (7th Cir. 1966).)

Reevaluation of the data previously before the Agency is an appropriate basis for subsequent action where the reevaluation is made in light of newly available authority (see Bell, 366 F.2d at 181; Ethicon, Inc. v. FDA, 762 F.Supp. 382, 388-391 (D.D.C. 1991)), or in light of changes in "medical science" (Upjohn, 422 F.2d at 951). Whether data before the Agency are old or new data, the "new information" to support reclassification under section 513(e) must be "valid scientific evidence," as defined in section 513(a)(3) of the FD&C Act and 21 CFR 860.7(c)(2). (See, e.g., General Medical Co. v. FDA, 770 F.2d 214 (D.C. Cir. 1985); Contact Lens Association v. FDA, 766 F.2d 592 (D.C. Cir. 1985), cert. denied, 474 U.S. 1062 (1986).)

FDA relies upon "valid scientific evidence" in the classification process to determine the level of regulation for devices. To be considered in the reclassification process, the "valid scientific evidence" upon which the Agency relies must be publicly available. Publicly available information excludes trade secret and/or confidential commercial information, e.g., the contents of a pending PMA. (See section 520(c) of the FD&C Act (21 U.S.C. 360j(c)).)

Section 513(e)(1) of the FD&C Act sets forth the process for issuing a final order to reclassify a device under that section. Specifically, prior to the issuance of a final order reclassifying a device, the following must occur: (1) Publication of a proposed order in the Federal Register; (2) a meeting of a device classification panel described in section 513(b) of the FD&C Act; and (3) consideration of comments to a public docket.

II. Regulatory History of the Device

FDA presented the complete regulatory history of these devices in the proposed order to reclassify iontophoresis devices for any other purposes, published in the Federal Register of

September 22, 2014 (79 FR 56532) (the "proposed order"). The following are the most relevant pieces of the regulatory history of these devices. On August 28, 1979, the Agency published a proposed rule (44 FR 50520) for classification of all iontophoresis devices. On November 23, 1983, FDA issued a final rule in the Federal Register (48 FR 53032 at 53045) classifying iontophoresis devices into two different classes based on the device's intended use. Specifically, 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 only when the labeling of the drug intended for use with the device bears adequate directions for the device's use with that drug (§ 890.5525(a) (21 CFR 890.5525(a))). These devices are currently under product code KTB. The rule classified iontophoresis devices into class III when intended for any other purposes (§ 890.5525(b)), but did not establish an effective date of requirement for premarket approval. These devices are currently under product code EGJ. In 2009, FDA published an order under section 515(i) of the FD&C Act (the "515(i) Order") requiring manufacturers of remaining class III devices for which regulations requiring PMAs had not been issued, including iontophoresis devices (§ 890.5525(b)), to submit a summary of information concerning those devices by August 7, 2009 (74 FR 16214, April 9, 2009).

As discussed in the proposed order, FDA considered the available information on iontophoresis devices intended for any other purposes and concluded that these devices, which are prescription devices, could be reclassified to class II, subject to the special controls identified in the proposed order, because there was sufficient information that these special controls, along with general controls, would provide reasonable assurance of safety and effectiveness. As required by section 513(e)(1) of the of the FD&C Act, FDA convened a meeting of a device classification panel described in section 513(b) of the FD&C Act, specifically the Orthopaedic

and Rehabilitation Devices Panel (the 2014 Panel), to discuss whether iontophoresis devices intended for any other purposes should be reclassified or remain in class III on February 21, 2014 (Ref. 1). Please see the proposed order for additional information on the 2014 Panel. Ultimately, the panel concluded that sufficient information exists to establish special controls for these devices, and that special controls in combination with general controls could provide a reasonable assurance of safety and effectiveness; and thus, iontophoresis devices for any other purposes could be classified in class II.

FDA received and has considered three sets of comments on this proposed order, as discussed in section III of this document. Therefore, FDA has met the requirements for issuing a final order under section 513(e)(1) of the FD&C Act. FDA is not aware of new information since the 2014 Panel meeting that would provide a basis for a different recommendation or finding.

III. Public Comments in Response to the Proposed Order

In response to the proposed order, FDA received three sets of comments from various stakeholders. The comments and FDA's responses to the comments are summarized as follows.

(Comment 1) One comment requested that iontophoresis devices intended for any other purposes remain classified in class III, and that FDA call for PMAs for these products. The commenter disagreed that general controls and special controls are sufficient to provide a reasonable assurance of safety and effectiveness because of, among other reasons, the commenter located, at the time of the 2014 Panel meeting, 40 adverse event reports for a 5-year period that implicated device malfunction, 12 of which include burns, in a search of the Manufacturer and User Facility Device Experience (MAUDE) database for iontophoresis devices intended for any other purposes. The commenter stated that manufacturing inspections during

the PMA process would help ensure that iontophoresis devices are constructed properly and, therefore, be less likely to cause third degree burns and other injuries.

(Response) FDA disagrees that iontophoresis devices intended for any other purposes should remain in class III and require PMA approval. As discussed in section V, "Risks to Health," of the proposed order, these devices have certain risks to health; however, the Agency believes that those risks can be mitigated by the special controls. For example, the special controls include performance testing that will mitigate the risks of burns, insufficient or excessive drug delivery, and/or infection. Performance testing using a drug approved for iontophoretic delivery, or a solution, identified in the labeling, will ensure that device malfunction or use error is minimized. Additionally, performance testing will ensure that iontophoresis devices intended for any other purposes maintain a safe pH level to minimize burns from a large electrical current density or highly acidic solution. Based on FDA's review of the MAUDE database, the number of adverse event reports identified for iontophoresis devices intended for any other purposes has decreased over the last several years, supporting that the risk of injury is low. Furthermore, in the past decade, there have been no recalls for iontophoresis devices intended for any other purposes.

(Comment 2) In addition, the commenter expressed concern that the special control requiring a labeling warning about adverse systemic effects was an insufficient safeguard because clinicians and patients may not see or read the label.

(Response) FDA takes issue with this statement. As stated in the proposed order, iontophoresis devices are restricted to patient use only upon the authorization of a practitioner licensed by law to administer or use the device and the device identification in § 890.5525(b) has been revised to clarify that these are prescription devices in accordance with § 801.109 (21 CFR

801.109). Per § 801.109(c), a prescription device, including iontophoresis devices intended for any other purposes, must include labeling that describes the indications and other information for use, such as methods, frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions under which the practitioners can use the device safely. Accordingly, clinicians will have access to and be aware of the warnings and precautions in the labeling, and as such, clinicians should be adequately informed of the risks associated with these devices. The clinician can inform the patients of the relevant risks. Therefore, the warning and precaution statements are an appropriate mitigation. FDA believes, therefore, that the special controls identified in this final order, in combination with general controls, will adequately mitigate the risks identified for iontophoresis devices intended for any other purposes and will provide a reasonable assurance of safety and effectiveness. FDA believes that iontophoresis devices may benefit patients by improving the noninvasive transdermal delivery of drugs or other solutions intended to treat various medical ailments or issues. As such, it is appropriate to reclassify these devices from class III (PMA) to class II (special controls). This is also the conclusion supported by the 2014 Panel.

(Comment 3) Two comments supported the reclassification of iontophoresis from class III to class II when these devices are intended for any other purposes. One comment, although overall supportive of reclassification, disagreed with the modified identification language and special controls. This comment asserted that the special controls, by requiring testing using a drug approved for iontophoretic delivery and labeling that contains language referring the user of the device to approved drug labeling, would create different regulatory paradigms for § 890.5525(a) and (b), such that a new drug application (NDA) and 510(k) are needed for iontophoresis devices falling under paragraph (b) of the regulation, and that a 510(k) is needed

for paragraph (a), although the devices are similar. The commenter uses iontophoresis devices that deliver pilocarpine for the diagnosis of cystic fibrosis, regulated under § 890.5525(a), as an example of this inconsistency.

(Response) To the extent the commenter is raising issues related to products regulated under § 890.5525(a), such products are not the subject of this reclassification; and as such, are not addressed here. However, we do note that the commenter's statement about two different regulatory paradigms is incorrect. As stated previously in this document and in the proposed order, whether an iontophoresis device falls into § 890.5525(a) or (b), any drug that is intended to be used with these devices is required to have marketing authorization for iontophoretic administration of that drug. FDA intends to consider addressing the regulation of iontophoresis devices under § 890.5525(a) through a separate process.

In addition, iontophoresis devices intended for any other purposes regulated under § 890.5525(b) will need to comply with the applicable special controls prior to entering the market. "Any other purposes" means that these devices are neither intended for use in the diagnosis of cystic fibrosis nor for use with a specific drug. Devices for any other purposes may include those intended for general iontophoretic delivery of drugs that are approved for that route of administration or intended for use with specific solutions. One example of an iontophoretic device for "any other purposes" is one indicated for use with tap water for treatment of hyperhidrosis.

(Comment 4) The commenter also requested clarification on the identified risk of infection and the special control that states the patient-contacting elements of the device must be assessed for sterility.

(Response) FDA believes that patient-contacting elements should be assessed for sterility if the device is labeled as sterile, and has clarified the special control in question (§ 890.5525(b)(2)(vi)) to specify such.

IV. The Final Order

Based on the information discussed previously and in the preamble to the proposed order, the comments on the proposed order, a review of the MAUDE database, a review of current scientific literature, and panel deliberations (see the 2014 Panel transcript (Ref. 1)), FDA concludes that special controls, in conjunction with general controls, will provide reasonable assurance of the safety and effectiveness of iontophoresis devices intended for any other purposes. Under section 513(e) of the FD&C Act, FDA is adopting its findings as published in the preamble to the proposed order, with the modification of the special control pertaining to sterility (§ 890.5525(b)(2)(vi)) to clarify that only devices labeled as sterile must have their patient-contacting elements assessed for sterility. FDA is issuing this final order to reclassify iontophoresis devices intended for any other purposes from class III to class II and establish special controls by revising § 890.5525(b).

As noted previously, the identification for § 890.5525(b) has been clarified to specify that devices intended to deliver specific drugs, including those drugs that may have adverse systemic effects, like fentanyl, are not considered part of this regulatory classification (§ 890.5525(b)(1)).

Following the effective date of this final order, firms submitting a premarket notification (510(k)) for iontophoresis devices intended for any other purposes must comply with the applicable mitigation measures set forth in the codified special controls. This includes firms who are required to submit a new 510(k) under § 807.81(a)(3) because the device is about to be significantly changed or modified. Additionally, a firm whose device was legally in commercial

distribution before May 28, 1976, or whose device has been found to be substantially equivalent to such a device, must also comply with the special controls to remain legally on the market.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the devices. FDA has determined that premarket notification is necessary to provide reasonable assurance of safety and effectiveness of iontophoresis devices intended for any other purposes, and therefore, this device type is not exempt from premarket notification requirements.

V. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Paperwork Reduction Act of 1995

This final order refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in part 807, subpart E, have been approved under OMB control number 0910-0120; and the collections of information under part 801 have been approved under OMB control number 0910-0485.

In addition, FDA concludes that the labeling statement codified in this order does not constitute a "collection of information" under the PRA. Rather, the labeling statement is a public

disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public (5 CFR 1320.3(c)(2)).

VII. Codification of Orders

Prior to the amendments by FDASIA, section 513(e) of the FD&C Act provided for FDA to issue regulations to reclassify devices. Although section 513(e) as amended requires FDA to issue final orders rather than regulations, FDASIA also provides for FDA to revoke previously promulgated regulations by order. FDA will continue to codify classifications and reclassifications in the Code of Federal Regulations (CFR). Changes resulting from final orders will appear in the CFR as changes to codified classification determinations or as newly codified orders. Therefore, under section 513(e)(1)(A)(i) of the FD&C Act, as amended by FDASIA, in this final order, we are revoking the requirements in § 890.5525(b) related to the classification of iontophoresis devices intended for any other purposes as class III devices and codifying the reclassification of iontophoresis device intended for any other purposes into class II (special controls).

VIII. Reference

The following reference is on display in the Division of Dockets Management (HFA-305) Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and is available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; it is also available electronically at http://www.regulations.gov. FDA has verified the Web site address, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. The panel transcript and other meeting materials for the February 21, 2014, Orthopedic and Rehabilitation Devices Panel are available on FDA's Web site at

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/ucm386335.htm.

List of Subjects in 21 CFR Part 890

Medical devices, Physical medicine devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, part 890 is amended as follows:

PART 890--PHYSICAL MEDICINE DEVICES

1. The authority citation for part 890 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. In § 890.5525 revise paragraph (b) and remove paragraph (c) to read as follows:

§ 890.5525 Iontophoresis device.

* * * * *

(b) Iontophoresis device intended for any other purposes--(1) Identification. An iontophoresis device intended for any other purposes is a prescription device that is intended to use a current to introduce ions of drugs or non-drug solutions into the body for medical purposes other than those specified in paragraph (a) of this section, meaning that the device is not intended for use in diagnosis of cystic fibrosis, or a specific drug is not specified in the labeling of the iontophoresis device.

(2) Classification. Class II (special controls). The device is classified as class II. The special controls for this device are:

(i) The following performance testing must be conducted:

(A) Testing using a drug approved for iontophoretic delivery, or a solution, if identified in the labeling, to demonstrate safe use of the device as intended;

(B) Testing of the ability of the device to maintain a safe pH level; and

(C) If used in the ear, testing of the device to demonstrate mechanical safety.

(ii) 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 drug labeling approved for iontophoretic delivery 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, including the following warning:

> Warning: Potential systemic adverse effects may result from use of this device. Drugs or solutions delivered with this device have the potential to reach the blood stream and cause systemic effects. Carefully read all labeling of the drug or solution used with this device to understand all potential adverse effects and to ensure appropriate dosing information. If systemic manifestations occur, refer to the drug or solution labeling for appropriate action.

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

(iv) Appropriate software verification, validation, and hazard analysis must be performed.

(v) The elements of the device that may contact the patient must be demonstrated to be biocompatible.

(vi) The elements of the device that may contact the patient must be assessed for sterility, for devices labeled as sterile.

(vii) 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.

Dated: July 20, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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