



Life-Tech, Inc
Life-Tech International, Inc

Dockets Management Branch (HFA-305) 1 3 7 0 '00 DEC 19 AM 11:21
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

December 12, 2000

Re: Docket No. 00N-1409

Dear Sirs,

The following represents comments in response to the proposed rule that appeared in the Federal Register of August 22, 2000 (pp. 50949-50951), as Docket No. 00N-1409.

Comment 1.

The proposed rule states that, as of the date of the final rule, class III designation will be revoked for iontophoresis devices. Those devices which have not been deemed substantially equivalent to a class II device at that time would be classified into class III, and would require an approved premarket approval application (PMA). These devices will remain class III; their class designation will be unchanged. This is for all intents and purposes no more than a call for PMA for a Class III device, albeit achieved in a manner not set forth in the Food, Drug and Cosmetic Act.

However, the rule then offers manufacturers the following option to PMA submission: Submit revised labeling to FDA. Upon "satisfactory review" of this revised labeling, FDA will issue a revised order that will establish the device's equivalency to a legally marketed predicate within class II - in essence the order will reclassify the device into Class II.

Reclassification of a medical device in such a manner is contrary to statutory law. Sections 513(e) and (f), 514(b), 515(b), and 520(l) of the Food, Drug and Cosmetic Act (the "Act") provide for reclassification of a device and prescribe the procedures to be followed to effect reclassification. According to these sections of the Act, a change in classification may be effected "based on new information respecting a device" [21 USC 513(e)]. Clearly, the revised labeling requested in this proposed rule discloses no "new information respecting a device."

Further conflicting with statutory law, this proposed rule offers device reclassification on a company-by-company basis. While the agency is within its regulatory authority to reclassify a device on its own initiative, the Act allows only for industry-wide product reclassification, and makes no allowance for the more isolated type of reclassification offered in this proposed rule. To underscore the agency's understanding of the Act, it has been the former reclassification scheme that has always been practiced by the agency in the past.

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If FDA wishes to reclassify iontophoresis devices into Class II, it must do so in accordance with statutory law. This proposed rule offers no modification to any section of the Act that would permit otherwise.

It would be inappropriate for the agency to rely on the momentary revocation of class III designation to claim exception from reclassification practices. The duration of such revocation will in actuality be nonexistent for those devices that would retain class III designation.

Comment 2.

The proposed rule is very unclear as to its target audience. In the proposed rule, the agency proposes to notify (and has notified) **device** manufacturers (emphasis mine) that they can “revise the labeling of **their devices** to meet the class II identification and submit such revised labeling to the agency...” to effect a change in classification of their device. The regulation the rule proposes to modify is 21 CFR 890.5525 - Iontophoresis **device**.

However, the proposed modification to 21 CFR 890.5525 reads:

“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...if the labeling of the **drug** intended for use with the device bears adequate directions for the device’s use with that drug.”

The inconsistencies present in the Federal Register notice make it impossible to determine the agency’s intent. First, the agency sets forth its intention to notify device manufacturers of their ability to change their **device’s** labeling to meet class II identification. However, the governing regulation is rewritten to explicitly impose a requirement upon the **drug** labeling.

It appears that the agency intends to require device manufacturers to either obtain their own drug approval, or to obtain drug approval through another company. The former would require the device manufacturer to implement drug manufacturing, while the latter would require the device manufacturer to enter into a financial arrangement with a drug manufacturer. This requirement clearly favors companies with greater financial resources that would be able to implement these options. This will have the effect of driving companies with fewer financial resources out of the iontophoresis market.

Comment 3.

Neither the proposed rule nor the letter sent to manufacturers notifying them of the proposed rule contains any information about the specific text of the modified labeling. To increase the likelihood of continued availability of iontophoresis devices after the final rule becomes effective, hence the likelihood of patient care remaining at the same level, it would be helpful if the manufacturer had more specific information about the type of wording the agency requires for class II designation. The agency should provide examples, suggestions, or recommendations, for labeling that they would be more likely to approve.

Comment 4.

The wording of the proposed rule implies an assumption about iontophoresis devices that is in error. The wording requires that “the labeling of the drug... bear adequate directions for the device’s use with that drug.” This choice of words can be reasonably interpreted to require that each drug sold for use in iontophoresis contain instructions for use of that drug with a specifically named iontophoresis device on its labeling. (My issue with the imposition of this requirement is discussed in detail in comment 2, above.) This assumes that there are differences between iontophoresis devices that would significantly impact safety or efficacy to such an extent as to require differentiation between different models and/or manufacturers. This is untrue.

Function

All iontophoretic applicators function in the same manner. All iontophoresis does is drive an ionic drug through the skin into the underlying tissue by means of a direct electrical current (DC). There is nothing special about a DC current. Early research on iontophoretic drug delivery successfully used commercial power supplies. There must be an appropriate electrical current generator, but it only need generate ample DC current to accomplish iontophoresis. A particular iontophoresis device has no impact on the efficacy of a drug. An iontophoresis instrument cannot potentially cause an alteration of the drug and/or its effective delivery into the tissue. It may cause the drug to absorb at a different rate, but this would be dependent upon the current dose, which is set by the user (see below). Treatment may be administered in different ways, but the end result is always the same--the drug is driven through the skin by means of a DC current.

Operation

All commercially available iontophoretic applicators operate in the same manner.

1. The appropriate drug polarity is set
The software code or circuit determines which polarity will be used based on the action of the user. If the instrument's polarity selection is a manual switch, the user need only flip the switch from the positive position to the negative position. If the instrument is programmable, the user selects the appropriate polarity via the software. If the instrument does not have either, the lead wires are switched around (usually at the electrode connection) to apply correct polarity.
2. The current dose is set
3. The applied current is set
The applied current is dependent upon patient comfort and the current density rating of the electrode in use. Different individuals have different sensitivities to varying degrees of applied current. Each electrode is labeled with its own current density rating.
4. Delivery time is calculated, based on current and dose
The delivery time calculation is $\text{Current} \times \text{Time} = \text{Dose}$ (in mA minutes) [example: 4 mA for 10 minutes = 40 mA minute dose]
The instrument calculates the total time of delivery based on dose and current, both of which have been set by the user. The delivery time is dependent on the applied

current, which is usually between 1 and 4 mA, depending on electrode size and patient comfort. A 40 mA minute dose can be delivered in as little as 10 minutes or as long as 40 minutes.

Variables Affecting Safety and Efficacy

As is readily apparent, the virtually identical design of iontophoresis instruments is such that there are no instrument-design variables that could affect safety or efficacy of the procedure. Those variables that exist are only in the way the delivery parameters are controlled by the user. These user-controlled variables are negligible in comparison to those variables that are introduced elsewhere in the delivery of iontophoresis, and are unrelated to the device.

The components of an iontophoresis treatment are as follows: Iontophoretic applicator; Electrodes; Drug; Protocol; Clinician; and Patient.

Variables contributed by each of these are as follows.

- The Iontophoretic applicator has already been discussed.
- Electrodes vary from model to model among the physical variables of size and material, and the functional variables of current density rating and hydration mechanism. These variations are inconsequential, due to the fact that all electrodes function the same if used properly. Even if there were electrode design differences that affected safety and efficacy, there is no conceivable effect that drug formulation could have, in relation to electrode design, on safety and efficacy of drug delivery.
- The Drug – This discussion is moot, since the topic at issue is the variables present in the procedure in the iontophoretic delivery of the same drug.
- The Protocol – There are a finite number of established protocols for iontophoretic delivery of drugs. Significant deviation from these recognized protocols, for example the use of current higher than that recommended for electrode size, might result in patient injury in the form of third-degree burns underneath one of the electrodes. All iontophoresis instruments are designed around clinical protocols that require operation in the same manner, as described above. Instruction manuals of the three largest iontophoresis companies indicate they all function in a similar manner to achieve protocol requirements (dose in mA minutes).
- Clinician – The clinician must screen each patient prior to the performance of iontophoresis. Iontophoresis is contraindicated for patients with heart conditions, pacemakers, diabetes, and pregnancy. Failure of the clinician to inspect the delivery site for an area that can cause high resistance such as moles, scars, new wounds, newly shaved or abraded skin, or dry skin conditions, may result in patient injury in the form of third-degree burns underneath one of the electrodes.
- Patient - Since ionized medications are pH dependent, changes in skin pH may alter drug performance. In most cases, the change in skin pH would have to deionize the drug in order for the performance to be altered. Some people have high sensitivity to applied electrical current, which could cause irritation or burn. Young children and geriatric patients may have very thin skin.

Labeling drugs for use with particular devices is not an effective manner to maximize the consistency of drug delivery. As described above, there are many variables innate to the iontophoresis procedure that can cause patient injury and/or questionable efficacy of the

procedure, even with the use of the same drug with the same device. The previous discussion illustrates the fact that there are many variables (such as clinical protocol and patient skin condition) that affect iontophoretic drug delivery to a significantly greater degree than those that are device-based. All of these variables are under the direct control of the user. There are no material differences between iontophoresis devices, and thus no rationale behind linking approval of a particular device to a specific device-associated drug.

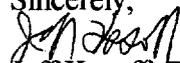
Comment 5.

The proposed rule contains the phrase "...if the labeling of the drug intended for use with the device bears adequate directions..." This would require submission and approval of an NDA for each drug that has not been approved for use in iontophoresis. Since all iontophoretic applicators function the same (see comment 4), it makes no sense that all manufacturers would have to receive separate NDAs for the use of the same drug with their instruments. If the agency decides to establish precedent and require such a "device-specific" NDA, the effective date of a final rule requiring such an NDA cannot be earlier than the timeframe in which an NDA could be submitted and approved. Only one of the many drugs routinely used in iontophoresis has an approved NDA. The other drugs commonly delivered by iontophoresis in clinical practice would require preparation, submission, and approval of NDAs, which could certainly not be completed by the effective date of the final rule. If the agency takes the position of requiring a device- and drug-specific NDA for each instrument, an allowance must be made in the final rule for a device to be continued to be marketed pending approval of its NDA. To not do so would result in shortage in the marketplace of iontophoretic devices during the NDA evaluation process.

Comment 6.

The proposed rule demonstrates the agency's apparent intention to eliminate the use of unapproved (i.e., off-label) drugs in iontophoresis. Passage of the proposed rule would not have that affect. Practitioners have been using dexamethasone in iontophoresis for at least the past two decades. This drug is used in approximately 80-90% of iontophoresis procedures. It is naïve of the agency to believe that this rule will in any way modify this statistic. Independent of regulatory action by FDA, medical practitioners will continue to practice medicine as they see fit. Thus, the rule will not accomplish what it was intended to.

Sincerely,



Jeff Kasoff, RAC

Director of Regulatory Affairs