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December 15, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20850

Re: Docket No. 00N-1409
Comments – Proposed Rule (*Federal Register* 65:50949, August 22, 2000)

Dear Sir/Madam:

IOMED, Inc. is a specialty pharmaceutical company focused on satisfying unmet medical needs through the combination of ethical pharmaceuticals and our unique proprietary active transdermal drug transport technology (the Phoresor[®] Iontophoretic Drug Delivery System). As such, we are affected by issues in the subject proposed rule and believe that clarification of the rule is necessary. We welcome the opportunity to provide comments to the agency.

The Center for Devices and Radiological Health (CDRH) specifically requested comments on their proposed rule to amend the physical medicine devices regulations in order to remove the class III (premarket approval) identification for iontophoresis devices. We believe the proposed rule is unclear and depending upon one's interpretation has the potential to significantly enhance the safety and quality of medicine or to significantly diminish it.

Our concern is that the rule implies that all iontophoretic drug delivery systems (IDDS) are the same and that any IDDS may be relabeled to reference any drug that is approved for iontophoretic administration, even though no human clinical trials have been conducted with the specific drug/drug delivery system combination to ensure that it is both safe and effective.

During the last several years, the agency (ie, the Center for Drug Evaluation and Review [CDER]) has taken the position that no IDDS can reference a specific drug or clinical application unless (1) adequate human clinical studies have been conducted using the specific drug/drug delivery system and (2) a New Drug Application (NDA) has been submitted and approved. We believe that the CDER objective is to ensure safety and effectiveness by treating every pharmaceutical application of an IDDS as a unique

00N-1409

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drug/drug delivery system combination and not as a device. Therefore, it is important to note that the above-referenced interpretation of the proposed rule from CDRH would be in conflict with the CDER objective. An FDA policy statement clarifying this point is essential.

IOMED is engaged in the development of IDDS and has invested significant time and resources to conduct preclinical and clinical studies involving the administration of specific drugs with its unique and proprietary IDDS. Among other things, numerous studies were conducted to support a NDA for the iontophoretic administration of Iontocaine[®] (our brand of Lidocaine HCl 2% and Epinephrine 1:100,000 Topical Solution). IOMED invested in the effort to interact with representatives from CDRH and CDER in order to get an understanding regarding the "approvability" of the Iontocaine[®] product which led to an approved NDA. To our knowledge, IOMED is the only company to obtain FDA approval of an iontophoretic drug/drug delivery system combination (ie, Iontocaine[®] for Dermal Iontophoresis with the Phoresor[®] System). IOMED also is presently conducting Phase 3 clinical trials with its active transdermal delivery system and a 0.4% USP formulation of dexamethasone sodium phosphate for acute soft tissue inflammation.

There are those who may purport that an IDDS is an alternative to the hypodermic syringe, that any medication approved for "injection" should be deliverable via any "cleared" IDDS under the supervision and at the discretion of a clinician and that one IDDS is the same as another. This is simply not the case as factors such as the nature of the materials used (drug containment and conductive elements), the efficiency and distribution of current across the drug delivery electrode (patch), the formulation of the medication used, the pH of the system, the total charge delivered across the electrode, the effectiveness and efficiency with which the patch adheres and conforms to the skin as well as other factors can effect the rate and amount of drug delivered. The FDA recognized this during their review of the Iontocaine[®] NDA. The "injectable lidocaine labeling" text was changed to reflect a "topical solution" of Iontocaine[®] to be delivered with the IOMED Phoresor[®] System. Add to this the rigor of the quality systems under which the IDDS is manufactured and extensiveness to which the systems have or have not been tested *in vitro* and in humans for safety and efficacy and the potential for significant differences in quality and performance becomes self-evident.

Iontophoresis is a complex process involving, among other things, an integration of materials science, electrochemistry, transdermal drug delivery and pharmacokinetics. The iontophoresis devices that have been cleared for marketing by CDRH through the 510(k) process are not equivalent. The ability of different IDDS's to perform identically in the delivery of a specific drug to treat a specific indication is not only uncertain but also unlikely. If other IDDS manufacturers are allowed to label their systems for the delivery of our approved drug (ie, Iontocaine[®]), without conducting the necessary human clinical trials, there are two likely outcomes. They are:

- No further human clinical studies would be conducted with IDDS's since there would be no protection or proprietary benefit gained from such trials. This would halt the further development of a unique non-invasive drug delivery technology. This would be unfortunate since iontophoresis can potentially elevate the safety profile of a drug through reduction in side effects and adverse events associated with other drug delivery methods.
- The public interest would not be served since the safety and effectiveness of all future IDDS applications would remain untested.

Iontophoretic drug delivery systems may be used to deliver a wide variety of compounds into humans for systemic or local applications. Some examples include peptides, proteins, antivirals, antimicrobials, anti-inflammatories, analgesics, anti-angiogenics, and other ionic prescription medications. Factors such as molecular weight, ionic strength, pharmacokinetics, drug stability, body site, and skin type all must be considered. Delivery of such compounds via an IDDS can significantly improve the safety, compliance, and efficacy profile of the delivery of such compounds, improving medicine for patients, physicians, and payers. However, because of the many variables and factors that can again effect safety and efficacy, a blanket clearance that allows the marketing of any IDDS without specific testing in humans with the compound to be delivered is not in the best interest of public health and seems inconsistent with the objectives of the FDA.

Three important elements need to be addressed if this rule is to serve a constructive purpose in the interests of the FDA and public health. The elements are:

- No IDDS should be allowed on the market by the FDA without an approved NDA for a drug tested in that specific IDDS.
- No IDDS manufacturer should be allowed to reference any drug or therapeutic indication in their labeling unless they have conducted adequate human safety and efficacy studies and have obtained an approved NDA.
- CDRH should only oversee modifications to an IDDS that is already approved under an NDA.

Today, with minimal testing and certainly no human testing, any company can bring an IDDS to market for the transdermal delivery of drugs without CDER oversight. We feel this creates a potential threat to public safety and the quality of medicine. We believe agency efforts should be focused on the need to have adequate safety and efficacy data supporting the use of any IDDS to deliver drug into the body. These data need to be

Docket No. 00N-1409
December 15, 2000
Page 4

reviewed and approved by the agency before the device labeling bears adequate directions for the device's use with the drug. There is a pressing need to have both CDER and CDRH oversight in getting properly labeled iontophoretic (drug delivery) devices to the market.

Sincerely,



W. Tim Miller
Executive Vice President, Inflammation

cc: Jonca Bull, MD, Acting Director (HFD-550)
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