

COOK®

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August 28, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD. 20852

Re: Draft Guidance for Industry – Chronic Cutaneous Ulcer and Burn Wounds
Developing Products for Treatment (Docket No. 00D-1318)

Dear Sir or Madam:

We submit the following comment on the above-referenced policy document on behalf of Cook Group Inc. Since 1963, Cook Group companies have participated in the development of numerous health care advances that have improved lives of patients around the world. COOK has been at the forefront of medical research and product development for interventional radiology, interventional cardiology, urology, neuroradiology, vascular medicine, critical care and other evolving diagnostic and therapeutic practices. Led by Cook Incorporated, one of the largest privately held medical device manufacturing companies in the world, the Cook Group consists of numerous companies in North America, Europe, Asia and Australia concentrating on diagnostic and therapeutic product development and manufacturing.

Cook appreciates FDA's solicitation of comments on the draft guidance and submits the following as the company's comments.

Claim Versus Indication for Use

The guidance document confuses the concept of "claim" with the concept of "indications for use" and should be revised to use the term "indication" in place of the word "claim." The document states that "the claim (also referred to as the *indication*) refers not only to the beneficial effects of a product, as determined through clinical investigations, but also to the type of wound for which a product is intended (e.g., venous stasis ulcer, diabetic foot ulcer, burn sites, donor sites)." Page 1. Claims and indications can be synonymous where a claim is descriptive of the use of a product subject to a clearance and serves as the indication statement. However, within an indication for use there can be a host of claims, for example, performance claims like "my product is better for X than a competitor's product"; "my product works 90% of the time"; "physicians prefer the ease of use of Y" and similar statements. These are not indications for use and do not need to be substantiated within the premarket process. The premarket notification process is for determining the substantial equivalence of one product to another. See §§

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510(k), 513(f) & 513(i). It is not a means for FDA to obtain substantiation of every claim a manufacturer wishes to make about its product. Similarly, the premarket approval process is a process in which the safety and effectiveness of a particular product is established for a specified intended use or indication for use. It is not a means by which FDA can require submission of substantiation for every claim a manufacturer wishes to make.

We agree that those who make claims for their products must have substantiation for their claims. Such substantiation should be determined based upon what is reasonably needed to support a particular claim. The fact that some type of substantiation is necessary for a broad array of claims, however, does not necessitate the conclusion that all claims and all substantiation are legally required to be pre-cleared through FDA's premarket process. If the agency believes that a claim made by a manufacturer of a medical device is false or misleading, it has a host of enforcement options it may choose. This, not denial of substantial equivalence, is the lawful route to take to regulate postmarket product representations that are not lawful indications for use.¹

Nor is the agency correct in stating that a claim regarding the benefits of a product is "determined through clinical investigations." Many claims can be substantiated by nonclinical data and information. Indeed, the vast majority of 510(k) devices are classified and cleared for marketing without clinical data.

This is a very significant issue. By making substantiation of claims a premarket issue, FDA is not only changing the fundamental character of premarket clearance and approval, it is in effect altering the burden of proof in litigation. Currently, the agency must adduce a preponderance of the evidence to prevail in an enforcement action against a manufacturer for misbranding or adulteration. In contrast, if FDA were to refuse to clear a claim, a manufacturer would become the plaintiff and be required to show that the agency was arbitrary, capricious or otherwise not in compliance with the law when the agency denied a product clearance. The arbitrary and capricious standard describes a much greater burden than the preponderance of the evidence standard and, of course, it would be borne by the manufacturer not the agency.

Additionally, the agency's approach, if pursued, will lead to results inconsistent with the regulations pertaining to 510(k)s. The FDA's regulations require that a manufacturer of a device submit a new 510(k) when the device is "about to be significantly changed or modified in . . . intended use" and explains that this means a new 510(k) is required when there is a "major change or modification in the intended use of the device". 21 C.F.R. 807.81(a)(3)(ii). In contrast, FDA's ulcer and burn wound guidance document in effect

¹ Of course, where a manufacturer, for example, promotes an uncleared indication which is also false, the agency may pursue enforcement of the Act for failure to file a premarket notification and for making false statements.

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states that a performance claim within a cleared indication for use is a major change in intended use and requires 510(k) clearance. This position is not supported by the law.

FDA's proposed new approach also conflicts with the agency's own guidance document covering when 510(k) submissions are expected.² The 510(k) guidance document traces through a logic scheme that a manufacturer should use when contemplating whether to submit a new 510(k) for a labeling change. The document states nothing about the mere addition of claims to a device's labeling, instead concentrating on changes to indications for use, changes to warnings and precautions, additions and deletions of contraindications, and similar modifications. While all changes other than those specifically listed on the flow chart (and some of those listed as well) are directed to the "new 510(k)" box, it is clear from FDA's text explaining the flow charts that the agency only wanted submissions on changes in labeling that "pose the potential to significantly impact safety and effectiveness." Page 12. In addition, while FDA states that most changes in indications for use would have to be submitted, it explained that expanding a use to "closely related populations" with "similar demographics, diagnosis, prognosis, comorbidity and potential for complications as the original" population would not normally need a new 510(k). By extension, a performance claim within a specific indication for use cannot result in a new 510(k). Thus, not all changes in indications for use would require submission of a 510(k) and clearance by the agency, and certainly no change in an indication for use can require a premarket notification. FDA's well established position on when new 510(k)s are required is drastically at odds with its proposed position that "claims" require 510(k) clearance, even when such claims are within a cleared indication for use.

In sum, FDA clearly did not contemplate clearance for mere claims that are within cleared indications for use, or even those which did not constitute a major change in labeling. FDA's past policy, which should be currently followed, clearly indicates that only changes in indications that create new uses or pose legitimate safety and effectiveness concerns that rise to the level of major changes in intended use should be subject to 510(k) review.

Improved incidence of closure and accelerated wound closure.

The guidance document states that:

When an improvement in time to closure results from an improvement in the incidence of closure, a claim of *improved incidence of closure* suffices to explain the

² While guidance documents are not binding, the contradictions between the proposed and the more mature guidance highlight the error of the agency's new thinking.

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clinical benefit and should not be supplemented by an additional claim of *accelerated wound closure*.

Page 3. We firmly disagree with this statement. If the claim of accelerated wound closure is substantiated, a manufacturer should be able to make it. Not all users or potential purchasers of the product may view an "improved incidence of closure" claim as including an "accelerated wound closure" claim. Indeed, a common sense reading of both claims indicates that they mean different things. Moreover, even if every potential reader would read the one claim as meaning both "improved incidence" and "accelerated closure", there is no basis for FDA saying that both claims cannot be made. This limitation is arbitrary and should be deleted.

In addition, we disagree that either claim should be subject to premarket notification clearance. Both are performance claims that are either substantiable or not. These are not indications for use and should not be reviewed premarket by FDA. If the claims are not substantiated and yet the manufacturer makes them, FDA may pursue an enforcement or other action in order to prohibit unlawful representations.

Another claim discussed in the guidance document that should not need premarket clearance is "*improved cosmesis*" on page 4. This is not an indication for use and is not appropriate for premarket review. Again, while any manufacturer making such a claim should have substantiation for it, it is not an appropriate subject for premarket review, unless such a claim implicates a new and different patient population and contemplates a separate indication for use.

Partial Healing

The agency states that it "does not consider partial healing per se to be an appropriate claim for wound healing agents because the clinical benefit of statistically significant decreases in wound size has not been established." Pages 3-4. This is also not an issue for premarket notification. Moreover, postmarket, such a claim should be allowable so long as it is substantiable and no unsubstantiable implications regarding the clinical benefit of such decreases in wound size are made.

Safety Studies

The draft guidance document, at page 2, states that "[s]eparate safety and efficacy data should be submitted for each wound type for which an indication is sought." Although we generally support FDA's position that differing wound types typically require different efficacy studies, we respectfully disagree that separate studies should be required for safety. For example, once a company studies and documents toxicity, sensitization, or any other safety consideration relating to the body's topical or systemic response to a material or compound, differing wound types should not require a repetition of such studies. There is no reasonable basis to argue that a material or compound that is safe in one wound context will be unsafe in another. So, for example, once chronic

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toxicity tests are completed for a material or compound, a company should not have to re-evaluate chronic toxicity again because of an expansion of an indication to a different wound type.

Animal Models

At page 6 of the draft guidance, various animal models are identified as useful for purposes specified in the document. Our only concern is that the usefulness of the animal models as well as their limitations should be discussed in order to ensure common expectations regarding results from animal testing. For example, the draft guidance states that pigs "are often useful models since their cutaneous architecture is most similar to that of human skin," while omitting that pig skin contracts during healing more than human skin. In short, we believe it is important to spell out the pros and cons of each recommended animal model.

Wound Size

At page 9 of the draft guidance, the agency recommends a method of measuring wound size for superficial wounds. We suggest that the guidance specifically describe a method of measuring wound size whereby the act of measurement does not involve contact with a wound. Many physicians prefer not to touch an open wound because of patient discomfort and pain, and therefore, we believe that a description of a non contact means of measurement would be helpful in ensuring correct and acceptable measurements.

Product Effects on Wounds

We agree that all wound treatment studies should include an evaluation of the wound product's effect on a wound. However, we disagree with the breadth of the last two sentences in F.1. on page 15. Specifically, those sentences state, in the context of the guidance's paragraph, that certain types of outcomes should be evaluated, including the microbiology associated with use of the wound product. We recommend that these sentences specifically relate to unhealed deep wounds because, for among other reasons, healed, intact skin is not amenable to the type of follow-up evaluation being suggested.

Statistics

Pages 16 and 17 discuss statistical analyses, yet omit any discussion of when a one tailed or two tailed test would be appropriate. We raise this issue because of the advisory panel's extensive discussion of these statistical tests in the context of the ATS submission. It is important to know when each such test would be appropriate to support a premarket submission.

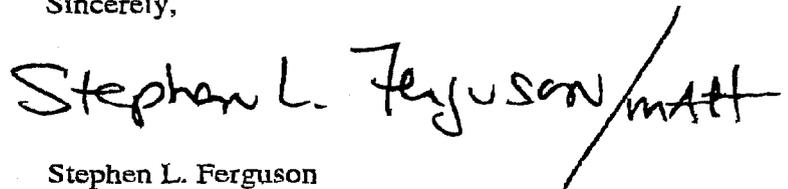
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"Drugs to treat antimicrobials"

It appears that there is a typographical error in footnote 3, which states that the FDA "published a series of draft guidances on developing drugs to treat antimicrobials." We believe that the agency meant to say microbes or microbials.

In closing, in addition to the specific comments made above, we request that FDA consider the draft guidance document in the context of international standards, laws and guidance. It is very important that as much international regulatory consistency as possible is achieved by the United States and other nations that regulate medical devices. We appreciate the opportunity to comment on the proposed guidance.

Sincerely,



Stephen L. Ferguson
Executive Vice President
Cook Group Incorporated