



August 18, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1601
Rockville, MD 20852

Re: Comments on Proposed Rule: Definition of Primary Mode of Action of a
Combination Product, Docket No. 2004N-0194

Dear Sir/Madam:

Smith & Nephew Wound Management, a market leader in advanced wound care, appreciates the FDA's efforts through the Office of Combination Products to clarify jurisdiction issues for combination products. We have reviewed the Federal Register notice and offer the following comments on the proposed rule regarding the "Definition of Primary Mode of Action of a Combination Product."

In the proposed rule, several examples are given that would typically fit the definition of combination product. It would be helpful for FDA to clarify if tissue-engineered products would be considered combination products. For example, would a product consisting of human-derived fibroblasts cultured *in vitro* upon a synthetic scaffold material be considered a combination product?

It would be helpful if the agency would clarify what impact, if any, the proposed definition would have on existing products (i.e. those already under review or approved by an agency component). The company is concerned that products currently under the jurisdiction of one particular Center may be subject to reassignment to another agency component through the criteria set forth in this proposed rule. Thus, we are seeking some assurance from the agency that existing products under jurisdiction by a particular agency Center will not be changed due to the publication of this final rule.

Furthermore, the company would like the agency's view, under this proposed rule, how new indications for the same product would be evaluated. As more is learned about mechanisms of action for emerging technologies, it is conceivable that a single product entity is found to have a multiplicity of uses. In our experience, we have engaged the agency in discussions concerning a product that has been approved for use as an interactive wound dressing (a device under CDRH), and as a product to aid in the repair of diseased cardiac tissue due to ischemia. In this latter case, it is possible that FDA, under the proposed rule, would determine the new indication should be reviewed by CBER (under a BLA).

This situation would raise significant issues for the sponsoring company that has developed a business model around a device framework with respect to product release tests, GMP compliance, and post-approval change and safety reporting requirements. Attempting to comply with two sets of regulations would create confusion, undue expense, and operational difficulties.

Because of the significant impact that dual jurisdiction would have on a company, we request that within this proposed rule the agency address how new product indications will be reviewed to prevent more than one set of premarket and postmarket approval requirements to be applied to a single product.

We are pleased that this proposed rule sets forth possible criteria the FDA would use to assign agency component. Beyond this, the company would like to the agency to clarify what criteria would be used to determine the type of premarket approval mechanism that would be employed (i.e. PMA, BLA, or NDA) for a given jurisdiction decision. For example, would products assigned to CDRH always be reviewed and approved through the IDE/PMA pathway and products under CBER through the IND/BLA route? To aid in transparency of the jurisdiction decision it would be important for FDA to establish criteria for designating the approval pathway (PMA, NDA, BLA) used by the agency component assigned jurisdiction.

Finally, the company is concerned that proposed rule would allow the agency to assign an agency component even though definitions in the FD&C Act or PHS Act may not include such products. The obvious case is in the area of Biologics where the definition of a biologic product (and requirements set forth in 21CFR Part 600) do not specifically call out human tissue-derived products. While the proposed rule on definition of primary mode of action may help clarify jurisdictional decisions, we believe FDA is obliged to make changes to statutory definitions of product classifications (i.e. drug, device, biologic) that take into account emerging product technologies developed long after these definitions were first established. Further, we believe it important that new definitions be subject to notice and comment rulemaking considerations. We believe that new statutory definitions of product categories are warranted given the advancement of technologies and treatments being developed.

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Without appropriate statutory redefinitions, we believe the proposed rule could allow assignment of jurisdiction of new technologies based solely on FDA preference particularly where it determines the product raises new questions of safety and effectiveness. With specific reference to tissue engineered products, we believe these technologies will continue to advance. While current therapies are limited to relatively simple constructs, future products will be more analogous to the host tissue they are designed to replace. Moreover, because of their complexity, it is likely the products will prove effective through multiple mechanisms and that new test methods would be required to characterize mode of action and evaluate clinical safety and effectiveness. Therefore, we strongly encourage FDA to establish new statutory definitions that take into account emerging product types, and establish a review framework that will allow more flexibility in the product development approach and testing regime utilized to establish safety and effectiveness.

Thank you for the opportunity to comment on this proposed rule. Please contact me if you have any questions.

Sincerely,

A handwritten signature in blue ink that reads "Ronald S. Warren". The signature is written in a cursive style with a large initial 'R'.

Ronald S. Warren
Executive Director, RA/QA
Smith & Nephew Wound Management (La Jolla)