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From: Dara S. Katcher [DSK@hpm.com]  
Sent: Friday, January 24, 2003 2:21 PM  
To: FDADockets@oc.fda.gov  
Cc: Anne Marie Murphy; Jim Phelps; Roger C. Thies  
Subject: Comments - Docket No. 02N-0445

On behalf of Disetronic Medical Systems AG, Hyman, Phelps & McNamara, P.C., respectfully provides the attached comments on FDA regulation of combination products.

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Dara S. Katcher  
Hyman, Phelps & McNamara, P.C.  
700 Thirteenth Street, N.W.  
Suite 1200  
Washington, D.C. 20005-5929  
(202) 737-5600 (main)  
(202) 737-4290 (direct dial)

LAW OFFICES  
**HYMAN, PHELPS & MCNAMARA, P.C.**

JAMES R PHELPS  
PAUL M HYMAN  
ROBERT A DORMER  
STEPHEN H MCNAMARA  
ROGER C THIES  
THOMAS SCARLETT  
JEFFREY N GIBBS  
BRIAN J DONATO  
FRANK J. SASINOWSKI  
DIANE B McCOLL  
A WES SIEGNER, JR  
ALAN M KIRSCHENBAUM  
DOUGLAS B FARQUHAR  
JOHN A GILBERT, JR  
JOHN R FLEDER  
MARC H SHAPIRO

ROBERT T ANGAROLA  
(1945-1996)

700 THIRTEENTH STREET, N.W  
SUITE 1200  
WASHINGTON, D C 20005-5929  
(202) 737-5600  
FACSIMILE  
(202) 737-9329

www.hpm.com

direct dial  
(202) 737-7557

MARY KATE WHALEN  
OF COUNSEL

JENNIFER B DAVIS  
FRANCES K WU  
DAVID B CLISSOLD  
CASSANDRA A SOLTIS  
JOSEPHINE M TORRENTE  
MICHELLE L BUTLER  
ANNE MARIE MURPHY  
PAUL L FERRARI  
JEFFREY W WASSERSTEIN  
MICHAEL D BERNSTEIN  
LARRY K HOUCK  
DARA S KATCHER \*  
KURT R KARST \*  
MOLLY E CHILDS \*

\*not admitted in dc

January 28, 2003

**BY ELECTRONIC MAIL**

Dockets Management Branch  
HFA-305  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

**Re: Docket No. 02N-0445: FDA Regulation of Combination Products**

Dear Sir or Madam:

On behalf of Disetronic Medical Systems AG, Hyman, Phelps & McNamara, P.C., provides the following comments on FDA regulation of combination products. Specifically, we address questions 1, 2, 3, 4, and 7, which were raised by FDA in the Federal Register notice of public hearing and request for comments on this subject. 67 Fed. Reg. 65801 (Oct. 28, 2002). As requested, our comments below are organized according to the question they address.

**1. Revising FDA's intercenter agreements on allocation of review responsibility.**

The intercenter agreements should be revised to address the sponsor's right to file a request for designation (RFD) for a combination product. Specifically, the following issues should be addressed:

2603 MAIN STREET  
SUITE 760  
IRVINE, CALIFORNIA 92614  
(949) 553-7400  
FAX (949) 553-7433

4819 EMPEROR BOULEVARD  
SUITE 400  
DURHAM, NORTH CAROLINA 27703  
(919) 313-4750  
FAX (919) 313-4751

- The sponsor has the right to file an RFD to determine the Center with primary jurisdiction and to suggest the appropriate Center and provide a rationale;
  - FDA's deadline for responding to the RFD is 60 days; and
  - FDA's decision is binding on the agency and, absent a compelling reason, may not be changed without sponsor's written consent. Any nonconsensual change requires written notice and an opportunity to respond. 21 C.F.R. Part 3.
  - In addition, FDA should state in its letter of designation any particular concerns it has with regard to the combination product (e.g., cross-labeling issues) and propose how the agency and the sponsor may address such concerns. Failure to raise issues such as cross-labeling early in the process can halt development of important new products.
  - The intercenter agreements should also be revised to describe the role of the new Office of Combination Products within the Office of the Commissioner.
2. **Determining the primary mode of action of a combination product.**

In determining the primary mode of action of a combination product, FDA should consider the following factors:

- The intended use of the combination product;
- The role of each component of the combination product;
- The extent to which the use of each component has changed because of the combination product;
- The risk associated with each component and any potential new risks due to the combination of the components;
- The potential clinical benefit of the combination product.

3. Selecting the premarket regulatory authorities to be applied to combination products.

Once FDA has determined the primary mode of action and the primary reviewing Center, in most cases the premarket approval process should be consistent with the process that is typically used by the primary reviewing Center (e.g., NDA (CDER), PMA or 510(k) (CDRH), BLA (CBER)).

Within CDRH, the fact that a product is a combination product should not necessarily mean that premarket approval (PMA) rather than premarket notification (510(k)) is required. That is, although combination products are typically innovative, they do not necessarily pose a higher risk or require a more burdensome regulatory approval process. Provided there is a predicate device with which the applicant can establish substantial equivalence, a 510(k) submission is appropriate. It may be proper, however, for the agency to request that clinical data be included in the 510(k) submission.

4. Determining whether a single application or separate applications for the individual components are required.

Even if particular expertise is found only in one Center, the individual(s) with that expertise may participate and collaborate on the review of a single application. FDA should require a single premarket application for most combination products.

7. Other comments: "Cross-labeling" of products intended to be used together, though manufactured by different companies.

FDA should refine its policy and provide specific guidance on complying with the requirement that labeling for components of combination products be mutually conforming. Failing to do so prevents important innovative medical products from entering the market place.

For example, certain innovative combination products consist of a medical device used in conjunction with an "off-label" use of an approved drug. FDA will not approve a device that employs such an "off-label" use of an approved drug, and the agency has no workable policy to address this issue. This impasse can halt the development of innovative products.

Where a combination product calls for off-label use of an approved drug, FDA has in the past advised device companies to collaborate with drug companies

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to supplement the drug labeling to include the new use. Where such collaboration has not been feasible, FDA has provided no further guidance. This outcome has prevented the development of new products that are important to the public health. FDA should consider this issue and provide appropriate guidance to sponsors and reviewers alike.

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Thank you for the opportunity to submit these comments.

Sincerely,

Anne Marie Murphy

AMM/vam