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BY FEDERAL EXPRESS

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

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

Dear Sir or Madam:

These comments on the regulation of combination products by the Food and Drug Administration ("FDA") are submitted on behalf of the Medical Imaging Contrast Agent Association ("MICAA"). MICAA is a trade association of companies involved in the research, development, manufacturing and distribution of medical imaging drug products in the United States. The following comments reflect the substance of an oral presentation made on behalf of MICAA at FDA's November 25, 2002 public hearing on the regulation of combination products.

1. The Status of Concomitant Use Products

The point that MICAA wishes primarily to emphasize to the FDA is that products used concomitantly are not necessarily combination products. As pertinent here, FDA regulations define a "combination product" as

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> [a] drug, device, or biological product packaged separately that according to its . . . proposed labeling is intended for use only with an approved individually specified drug, device or biological product where both are required to achieve the intended use . . . and where upon approval of the proposed product the labeling of the approved product would need to be changed . . .; or . . .
>
> [a]ny investigational drug, device or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device or biological product where both are required to achieve the intended use . . . .[1]

Accordingly, a separately packaged drug that is proposed to be used together with a device – even where both drug and device must be used together to achieve the intended use – is not a combination product unless the device is "individually specified" in the proposed drug labeling. FDA has recognized that the definition of combination product "is intended to exclude most concomitant use of drugs, devices, and biological products."[2]

Contrast agents and other medical imaging drugs are always used together with imaging devices to achieve their intended use. Typically, the drug labeling refers to a type of imaging procedure (e.g., magnetic resonance imaging; ultrasound; angiography) and does not "individually specify" a device. This is why imaging drugs and imaging devices historically have not been treated by FDA as combination products but instead have been regulated independently, with separate premarket submissions, separate review by the centers for drugs and devices, respectively, and separate post-market regulation. To our knowledge, this independent regulatory treatment has not engendered any difficulties or deficiencies in terms of Agency resources, premarket reviews, or the safety or effectiveness of products.

We urge the Agency to adhere to the current regulatory definition when determining which products are to be regulated as combination products. For medical imaging drugs,

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1 21 C.F.R. § 3.2(e)(3). The definition of "combination product" also includes other types of products (e.g., mixed products and products combined in a single package), but these are not relevant here.

2 56 Fed. Reg. 58754, 58755 (Nov. 21, 1991) (preamble to final rule).

status as a combination product should continue to depend on the proposed labeling, as required under the regulations. If the proposed drug labeling refers to an "individually specified" device (e.g., an ultrasound device of a specific model and manufacturer), the drug and device may be treated as a combination product subject to the designation of a lead center, inter-center coordination of review, and the possibility of a combined application. However, in the typical case where a device is not individually identified in the drug labeling, the medical imaging drug and device should continue to be regulated as independent products.

2. The Importance of Promptly Finalizing the Medical Imaging Drug Guidance

Although contrast agents have not been regulated as combination products to date, there may be instances in the future where a contrast agent is intended to be used with a specifically identified imaging device and therefore should be treated as a combination product. Section 204 of the Medical Device User Fee and Modernization Act of 2002[3] reflects Congress's clear intent that such combination products be reviewed in a "timely and effective" manner. Indeed, this relatively brief section contains six references to the timeliness of reviews. One measure that FDA can take to improve the timeliness and efficiency of premarket review of combination products involving contrast agents is to finalize the draft guidance on developing medical imaging drugs (the "Guidance").[4] The Guidance will improve the quality of the data submitted in marketing applications by setting forth the Agency's expectations for safety and effectiveness data, and advising manufacturers how best to design their studies and image readings. Improvement in submission quality will, in turn, permit more efficient and timely reviews. In addition, for medical imaging drugs designated as having a relatively low safety risk as described in the draft Guidance (i.e., Group 1 drugs), the quantity of safety data to be reviewed will be reduced, which will also reduce review times. We therefore urge FDA to promptly finalize the draft Guidance in order to enhance the timeliness and efficiency of reviews of medical imaging drugs in general, and of those included in combination products in particular.

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3 Pub. L. No. 107-250, 116 Stat. 1588, 1611 (2002).

4 FDA, Guidance for Industry: Developing Medical Imaging Drugs and Biological Products (draft), June 2000.

MICAA appreciates the opportunity to comment on FDA regulation of combination products.

Sincerely,

Alan Kirschenbaum /VAM

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