

Bonnie J. Goldmann, M.D.
Vice President
Regulatory Affairs

Merck & Co., Inc.
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2383
215 652 5000

April 8, 2002

8071 '02 APR -9 A9:28

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



RE: [Docket No. 01D-0582] Draft *Guidance for Industry* on Available Therapy

Merck & Co., Inc, is a leading worldwide, human health product company that has produced many of the important pharmaceutical products on the market, today. Merck's multidisciplinary Research and Development is a highly risk-intensive process that depends upon a predictable regulatory environment. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. It is incumbent upon regulators and industry to see that important therapeutic breakthroughs reach patients without unnecessary or unusual regulatory delays.

Merck's regulatory affairs professionals routinely work with FDA staff to devise strategies for ensuring that FDA's approval to market a product will be secured efficiently. Through this experience, we have gained significant understanding of the laws, regulations and guidances that are used to expedite products to the market. Therefore, Merck is well qualified to respond to this request for input on the definition of "*available therapy*," as discussed in *the Draft Guidance for Industry: Available Therapy* (hereafter referred to as *The Draft Guidance*).

We offer the following comments with rationale for our concerns.

Comment 1: *The Draft Guidance* adds little clarity to the ambiguity of *available therapy* which it attempts to redefine. For each clarification added, another phrase confuses the issue, thereby making the new definition as unreliable as the old for purposes of removing regulatory uncertainty. Some examples are noted below.

Lines 163-166 read: "CDER and CBER have determined that in regulations and policy statements, where the terms are not otherwise defined, *available therapy* (and the terms *existing treatments* and *existing therapy*) should be interpreted in **almost** all cases [**emphasis added**] as therapy that is **reflected** [**emphasis added**] in the approved labeling of regulated products."

The phrases, "*almost all cases*" and "*reflected in the approved labeling*" are imprecise. Does "*reflected*" in the approved labeling mean clearly stated in the Indications section of the FDA approved package insert, noted in the Clinical Studies section of the labeling as a related disease/condition or subpopulation?

Comment 2: Of more significant concern is the *limited exception*¹ for inclusion of *off-label therapies that are well documented*, in the new definition of *available therapy*. Indeed, the singular common purpose

01D-0582

¹ *The Draft Guidance* states that this limited exception will not apply to the pediatric rule.

C 1

of most of the regulations and guidances cited² in *The Draft Guidance*, for which this new definition of available therapy is being provided, is to allow expedited or priority review procedures for products when alternate therapies are not available. By allowing this new definition of *available therapy* to include *off-label* therapies, FDA assumes the discretion to consider *off-label* indications as alternate *available therapy*, for example:

- "in the absence of satisfactory alternative therapy." (21 CFR 312.84-Subpart E Regulations); or
- when "there is no comparable or satisfactory alternative drug or other therapy available..."(21 CFR 312.34-Treatment INDs); or,
- "...over existing treatments..."(21 CFR 314.500 or 601.40-Accelerated Approval Regulations).

FDA thereby provides itself with the opportunity to deny expedited review options to sponsors when *off-label* therapies are considered. Sponsors, patients, providers and public health administrators should be concerned about potential delays of products for patients for whom the expedited approval procedures were explicitly intended. Ordinarily, FDA does not consider *off-label* treatments within its purview, except to exclude them from labeling. With rare exception, e.g., for well-established *off-label* oncologic therapies, FDA should not allow *off-label* therapies to be considered in this definition of *available therapy*. That addition would be counterproductive to the purpose of the rules in which this definition of *available therapy* would apply.

Comment 3: The reference to the 23-page Guidance on substantial evidence of effectiveness (noted in lines 166-170)³ is ambiguous and confounds these definitional issues further.

Conclusions

Merck recommends that FDA adhere to its legislative mandate and limit the definition of *available therapy* to the context of FDA approved labeling, which does not include *off-label* therapies. In addition, confusion would be alleviated by removal or clarification of some phrases, such as "*almost all*," "*reflected in*" and "*unusual therapies*" and addition of specificity in references to important guidances.

We welcome the opportunity to comment on *The Draft Guidance* and, if appropriate, to meet with you to discuss these issues.

Sincerely,



Bonnie J. Goldmann, MD
Senior Vice President
Global Strategic Regulatory Development

² The Draft Guidance notes that these terms are used in the following regulations and policies without definitions: Treatment INDs, Subpart E Regulations, Accelerated Approval Regulations, The Pediatric Rule, Fast Track Development Programs, and Priority Review Policies

³ In lines 166-170, FDA states: "In unusual cases, a treatment that is not FDA-regulated (e.g., surgery) or that is not labeled for use, but is supported by compelling literature evidence (see the FDA Guidance for Industry on Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)) can be considered available therapy."

2002 APR -5 P 2:04
FBI - CONSTITUTIONS