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August 5, 1998

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BY HAND

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 10-61
Rockville, MD 20857

Re: No. 98P-0311

Dear Sir or Madam:

Please substitute the enclosed revised version of the comment we submitted yesterday to this docket. In the last line of the first paragraph, the parenthetical reference to "an NDA submitted by Barr Laboratories, Inc." should have read "any NDA submitted by Barr Laboratories, Inc." The revised version simply corrects this error.

Sincerely,



Michael W. Kirk

98P-0311

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August 5, 1998

BY HAND

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 10-61
Rockville, MD 20857

Re: No. 98P-0311

Dear Sir or Madam:

The undersigned, on behalf of Duramed Pharmaceuticals, Inc. ("Duramed"), submits this comment on the Citizen Petition filed by Wyeth-Ayerst Laboratories ("Wyeth-Ayerst") requesting that the Food and Drug Administration ("FDA") take certain actions in connection with its review of New Drug Application ("NDA") submitted by Duramed (as well as any NDA submitted by Barr Laboratories, Inc.).

To the extent Wyeth-Ayerst is asking that FDA apply the standards set forth in Section 505 of the Federal Food, Drug, and Cosmetic Act (the "Act"), 21 U.S.C. § 355, and its implementing regulations, its request is not objectionable, though hardly necessary. To the extent that Wyeth-Ayerst seeks to create and engraft additional requirements for the approval beyond those established in the Act and by FDA's regulations, its request must be denied. We address each of the actions sought by Wyeth-Ayerst in turn.

1. Wyeth-Ayerst first requests that FDA, in reviewing Duramed's NDA, "make its determination as to whether the products meet the requirements of Section 505 of the Act relating to safety and effectiveness by applying the same strict standards it applies to all other new chemical entities." Citizen Petition at 3. Of course, we have no objection to this request; indeed, we take it as a matter of course that FDA will apply the statutory standards to Duramed's NDA in the same manner that it applies them to other applicants in like circumstances.

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However, Wyeth-Ayerst goes on to suggest that Duramed may not support its NDA with particular studies – “animal and human clinical studies of other estrogens such as estrone, equilin, or conjugated estrogens,” *id.* – because evidence concerning the safety of the particular estrogens contained in Duramed’s product “does not show the five-estrogen mixture to be safe.” *Id.* at 4. Wyeth-Ayerst goes on to speculate that Duramed may have failed to submit studies that would satisfy Wyeth-Ayerst’s standards for approval of an NDA. It would be inappropriate here to address the content or the adequacy of Duramed’s showing with respect to the safety of its NDA product; that issue is being comprehensively addressed and resolved by FDA in the context of its review of the NDA. It suffices for present purposes to note that FDA commonly considers information available to it with respect to other drugs containing the same ingredients as the subject of an NDA in evaluating safety.

2. Wyeth-Ayerst requests that FDA seek revocation of the current United States Pharmacopeia (“USP”) monograph for conjugated estrogens on the basis of the May 5, 1997, memorandum issued by the Center for Drug Evaluation and Research (“CDER”) in connection with Duramed’s Abbreviated New Drug Application (“ANDA”) seeking approval of a generic version of Premarin®. This request is premature for two reasons. First, the conclusions reached in the CDER memo are subject to review in Duramed’s currently pending appeal of the proposed denial of its ANDA in Docket No. 97N-0325. Because the FDA’s final decision in the matter could very well alter the conclusions set forth in the CDER memo, it is simply too early to request that the USP alter its monograph.

Second, even if the CDER memo is ultimately upheld, it merely concluded that additional ingredients of Premarin® beyond those identified as active by the USP monograph *might* also be active. Even under CDER’s view, it is equally possible that the monograph has accurately identified all of the active ingredients. Indefinite withdrawal of the USP monograph until the uncertainty perceived by CDER is resolved could conceivably be appropriate if the task of determining the active ingredients of Premarin® was unlikely to be completed in the near term. But CDER specifically found that “[i]nvestigations designed to produce scientific data needed to determine the active ingredients are feasible. . . . It is both feasible and desirable for the constituent active ingredients in Premarin to be characterized to this extent.” CDER Memo at 31. As we have urged in the Citizen Petition filed under Docket No. 97P-0327, Wyeth-Ayerst, as the sponsor of Premarin®, has an obligation to identify the active ingredients of its product on its label. Wyeth-Ayerst’s suggestion that the monograph ought to be indefinitely

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withdrawn – thus apparently insinuating that it will not fulfill its responsibility to conclusively identify the active ingredients in its product any time soon – can only be understood as an attempt to lock in indefinitely the effective monopoly granted to it by CDER's decision to refuse to approve generic versions of Premarin®.

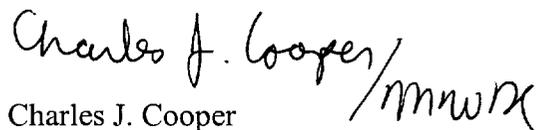
3. Wyeth-Ayerst next argues that the name of Duramed's NDA product should not include "the term 'conjugated' . . . in conjunction with 'estrogens.'" Citizen Petition at 9. Once again, the appropriate forum for determining the name of Duramed's product is FDA's review of the NDA. For present purposes, it suffices to observe that Duramed's product unquestionably includes "estrogens" that are "conjugated," so a blanket prohibition on the use of these terms would plainly be inappropriate. Beyond that, we are confident that FDA will ensure that no confusion arises from the name of Duramed's new product.

4. Finally, without pointing to any supporting provision in the Act or in the regulations, Wyeth-Ayerst asks that approval of Duramed's NDA be conditioned upon a requirement that "any marketing of such a product must, in order not to be misleading, be accompanied by clear statements in all labeling and promotion that this product is not equivalent to and should not be substituted for Premarin." Citizen Petition at 10. Aside from the fact that Wyeth-Ayerst's request lacks statutory and regulatory support, the statement it requests is itself misleading in that Duramed's NDA product will be appropriate for at least some indications for which Premarin® is approved – for example, to treat vasomotor symptoms. Thus, in that context, a physician could very well decide that Duramed's product may be prescribed in lieu of Premarin®.

* * *

In sum, FDA should take no action in response to Wyeth-Ayerst's Citizen Petition beyond reviewing Duramed's NDA in accordance with the standards set forth in the Act and the regulations.

Sincerely,

 Charles J. Cooper / mnrwx

Charles J. Cooper
Counsel to Duramed