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via Hand Delivery

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

Re: Suitability Petition Docket No. 01P-0209/CP1

Dear Sir or Madam:

These comments are submitted on behalf of our client in response to the above-referenced suitability petition filed by Duramed Pharmaceuticals, Inc. ("Duramed"). In the petition, Duramed asks the Commissioner of Food and Drugs to determine that it is suitable to file an abbreviated new drug application ("ANDA") for progesterone *tablets* even though the reference drug product, PROMETRIUM® Capsules, is listed in the Orange Book only in *capsule* form. Unimed Pharmaceuticals Inc. holds the approved new drug application for PROMETRIUM® Capsules.

Under § 505(j)(2)(C)(i) of the Federal Food, Drug, and Cosmetic Act, the Commissioner will deny a petition seeking permission to file an ANDA for a drug with a dosage form different from the listed drug if it is determined that "investigations must be conducted to show the safety and effectiveness of . . . the dosage form . . . which differ from the listed drug." *See also* 21 C.F.R § 314.93(e)(1)(i). The Agency's implementing regulations elaborate on this standard, explaining that "investigations must be conducted" when "information derived from animal or clinical studies is necessary to show that the drug product is safe or effective." 21 C.F.R § 314.93(e)(2). Additionally, FDA will deny such a petition if the proposed change "would jeopardize the safe or effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or effectiveness problem." 21 C.F.R. § 314.93(e)(1)(iv).

As described in detail in Section I. below, Duramed's suitability petition should be denied because it fails to establish an adequate basis for assuring the safety and efficacy of

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its tablet formulation without additional clinical studies and/or significant labeling revisions. Additionally, as established in Section II. below, Duramed's asserted "justifications" for its petition are without merit.

I. The Suitability Petition Fails to Address Key Issues Relating to Product Safety and Effectiveness

A. Food Effect

The NDA approved labeling for PROMETRIUM® Capsules reflects data demonstrating that its pharmacokinetics are effected by food. Specifically, the bioavailability of progesterone from PROMETRIUM® Capsules increases when administered with food. It is well recognized that any observed food effect is compounded in the presence of exogenous fat.[1] Accordingly, removal of the fat from the formulation, *i.e.*, the peanut oil, changes the local environment surrounding the formulation in the gastrointestinal tract in a significant manner, potentially resulting in a different food effect than that observed with PROMETRIUM® Capsules. This change could translate into a difference in safety and/or effectiveness between the approved capsule dosage form and the proposed tablet. Moreover, because bioavailability of progesterone from PROMETRIUM® Capsules is low,[2] there exists a potential for dramatic differences in bioavailability profiles due to a change in the magnitude of the food effect. If the change results in significant increase in progesterone availability, there may be a risk of serious liver toxicity. In light of the known food effect and the nature of Duramed's proposed changes to the formulation, Duramed, at a minimum, should be required to conduct appropriate studies to characterize the food effect associated with its tablet formulation. If those studies reveal a different food effect the suitability petition should be denied because under such circumstances significant labeling changes and/or additional clinical studies would be necessary to assure safe and effective use of the tablets.

B. Crushing Tablets

Duramed's petition asserts that its proposed tablet formulation will afford healthcare providers and patients with "flexibility" in dosing by facilitating the crushing of the tablet

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[1] *See, e.g.,* Guidance for Industry; Food-Effect Bioavailability and Bioequivalence Studies (Draft), p. 5 (Dec. 30, 1997).

[2] *See* Clinical Pharmacology and Biopharmaceutics Review, NDA 19-781, p. 8 (Aug. 1996).

and sprinkling on food. As an initial matter, it is important to note that crushing a tablet would likely significantly increase the variability of the dose due to product loss and inconsistent administration. Such variability could result in compromised efficacy and safety of the product. Furthermore, because data clearly demonstrate that the bioavailability of PROMETRIUM® Capsules is impacted by concomitant ingestion of food (*see* Section I.A. above), it is reasonable to assume that food would have some, currently unknown, effect upon a crushed progesterone tablet. Finally, the efficacy of "splitting" a dosage form, by crushing the tablet or by puncturing the PROMETRIUM® soft gelatin Capsules and placing the contents on food has not been established and is not addressed in the current prescribing information of PROMETRIUM® Capsules. Accordingly, to establish the safety and efficacy of crushed progesterone tablets sprinkled upon food, Duramed must conduct additional studies. The resulting data would likely necessitate significant labeling changes to address safety and efficacy of a crushed tablet. As a result of this need for additional studies and associated labeling changes, the flexibility to crush tablets is a reason to deny, rather than grant, the suitability petition.

II. Duramed's Asserted "Justifications" for its Petition are Without Merit

A. Peanut Oil Used in PROMETRIUM® Capsules

Citing various statistics on peanut allergies, Duramed claims that approval of its suitability petition is "justified" on the grounds that its tablet will not contain the peanut oil excipient used in PROMETRIUM® Capsules. As explained below, Duramed's petition completely mischaracterizes the likelihood of an allergic reaction to PROMETRIUM® Capsules.

The peanut oil used in PROMETRIUM® Capsules goes through a refining process intended to remove many of the proteins and other components from the crude peanut oil. A copy of the refining procedure is enclosed with this submission at Exhibit 1. Allergic reactions to refined and crude peanut oil were evaluated in a double blind, crossover study conducted by Hourihane, *et al.* involving 60 subjects with known peanut allergies. None of the 60 subjects had an allergic reaction to the refined peanut oil, while 10% had a reaction to the crude oil. The authors' conclude that refined peanut oil, if used properly, appears safe for most people with peanut allergies and therefore a distinction should be made between refined peanut oil and crude peanut oil in product labeling. *See* Hourihane, *et al.*, BMJ; Vol. 314; No. 7087; p.1084; 1997, attached hereto as Exhibit 2.

The refined peanut oil used in PROMETRIUM® is NF grade. According to the manufacturer, Arista, Industries, Inc. this grade of peanut oil contains less than 1 ppm peanut protein. *See* Exhibit 1. According to the study cited above, "The minimum amount of

protein considered necessary to cause a reaction in a double blind, placebo controlled food challenge is between 50mg and 100mg." *See* Exhibit 2.

Duramed ignored these data, which collectively indicate that refinement of the peanut oil used in PROMETRIUM® Capsules reduces the likelihood of an allergic reaction significantly. Moreover, the literature review relied upon by Duramed does not support the conclusions it draws concerning the risk of an allergic reaction to PROMETRIUM® Capsules. Specifically:

1. Citing data collected by the American Academy of Allergy, Asthma, and Immunology, the petition states that 20 fatalities have been attributed to allergic reactions triggered by peanut consumption. Significantly, all of these reactions were caused by the ingestion of peanuts or food containing peanuts and none of the fatalities addressed in the literature search attached to the petition were caused by refined peanut oil, or prescription drugs containing refined peanut oil. *See* Bock, *et al.*, J. Allergy Clin. Immunol.; Vol. 107; No. 1; p. 191; 2001, attached as Exhibit 3.

2. The petition suggests that 1.1% of the U.S. population is allergic to peanuts. However, the journal article cited in support of this assertion indicates that 0.6% of the U.S. population are allergic to peanuts alone and 1.1% of the population is allergic to peanuts *and* tree nuts. *See* Sicherer, *et al.*, J. Allergy Clin. Immunol.; Vol. 103; No. 4; p. 559; 1999, attached hereto as Exhibit 4.

3. The literature review asserts that peanut allergies force affected consumers to exercise dietary vigilance, frequently resulting in disruption of normal family and social life and negatively impacting the quality of life. The journal article cited in support of these statements compares the quality of life and family relations of those with rheumatological diseases and those with peanut allergies. *See* Primeau, *et al.*, Clin. & Exper. Allergy; Vol. 30; p. 1135; 2000, attached hereto as Exhibit 5. The authors conclude that parents of children with peanut allergies are very concerned and experience more disruption than adults who have learned to manage their diet. The article focuses on food and food products and does not address medications containing peanuts or derivations of peanuts.

B. Capsule Size

Duramed also claims that approval of its petition is justified on the grounds that its tablet is smaller, and therefore easier to swallow, than PROMETRIUM® Capsules. PROMETRIUM® 100 mg Capsules are 5 round and the 200 mg Capsules are 8.5 oval. Except in rare and unusual circumstances, these sizes should not, and have not, presented

swallowability problems. Further, there is simply no data to support Duramed's hypothesis that the Duramed tablet formulation would, in fact, be easier to swallow than PROMETRIUM® Capsules.

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For the foregoing reasons, our client requests that the Commissioner deny approval of Duramed's suitability petition.

Sincerely,

Thomas O. Henteleff
Jennifer A. Davidson

TOH:JAD/j

Enclosures