

ENDO

PHARMACEUTICALS

September 28, 2007

VIA HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Comments of Endo Pharmaceuticals Inc

RE: Docket No. 2007D-0168 – Draft Guidances for Industry Describing Product-Specific Bioequivalence Recommendations; Availability.

Endo Pharmaceuticals Inc. ("Endo") supports the efforts of FDA's Office of Generic Drugs ("OGD") to create a uniform, streamlined, and public process for the promulgation of bioequivalence ("BE") recommendations.¹ However, Endo believes that FDA erred in including its product, Lidoderm® (lidocaine topical patch, 5%), on FDA's website containing BE recommendations for specific products, which were made available on May 31, 2007.² Accordingly, Endo respectfully requests that the "Draft Guidance on Lidocaine" (the "lidocaine topical patch, 5% guidance") be rescinded and removed from FDA's website.

The draft guidance is premature because FDA and OGD have yet to resolve open issues regarding the BE methodology it contains. Endo raised these challenging issues in a petition filed in December 2006.³ On June 13, 2007, FDA acknowledged that these issues are "complex" and require further "extensive review and analysis by Agency officials" before a decision can be reached regarding the appropriate BE methods for lidocaine topical patch, 5%.⁴ FDA's decision to issue a draft guidance on May 31, 2007, which purports to resolve all outstanding issues, is therefore inconsistent with OGD's June correspondence as well as OGD's standard for developing BE recommendations.⁵

¹ FDA, *Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products*, 72 Fed. Reg. 30388 (May 31, 2007); CENTER FOR DRUG EVALUATION AND RESEARCH, FDA, GUIDANCE FOR INDUSTRY (DRAFT): BIOEQUIVALENCE RECOMMENDATIONS FOR SPECIFIC PRODUCTS (2007) [hereinafter DRAFT GUIDANCE: BE RECOMMENDATIONS FOR SPECIFIC PRODUCTS].

² FDA, DRAFT GUIDANCE ON LIDOCAINE (2007), available at http://www.fda.gov/cder/guidance/bioequivalence/recommendations/Lidocaine_toppatch_20612_%20RC12-06.pdf.

³ See FDA Docket No. 2006P-0522.

⁴ Letter from Jane A. Axelrad, Associate Director for Policy, CDER, FDA, to Endo Pharmaceuticals (June 13, 2007).

⁵ See FDA, DRAFT GUIDANCE: BE RECOMMENDATIONS FOR SPECIFIC PRODUCTS 2 ("As before, BE recommendations will be developed by the agency based on its understanding of the characteristics of the listed

FDA's decision is also inconsistent with OGD's public statements regarding one of the key issues raised in Endo's petition—that pharmacokinetics are not suitable for demonstrating BE to topical products such as the lidocaine topical patch, 5%. In 2003, OGD's Director of Bioequivalence publicly stated that OGD did not have data to support correlating detectable plasma concentrations with local delivery of drug product to the skin.⁶ Moreover, in May 2007, just weeks before OGD published its lidocaine topical patch, 5% guidance, OGD stated that the relationship between detectable blood levels of topically-administered drug products and local delivery of those products "is still unknown."⁷

It appears likely that OGD mistakenly included the lidocaine topical patch, 5% guidance on FDA's website. The guidance is similar to the recommendations OGD offered in controlled correspondence in October 2006 and that were the subject of Endo's December 2006 Citizen Petition. Consequently, the decision to re-publish these recommendations as draft guidance was likely made without consulting the Agency officials who determined that "extensive review and analysis" of complex lidocaine topical patch, 5% BE issues was necessary. By contrast, the fact that notice of this guidance was not published in the Federal Register⁸ is consistent with a decision not to publish the lidocaine topical patch, 5% guidance due to complex outstanding issues. The draft guidance should be removed from FDA's website until the Agency resolves the issues it identified in its June 13, 2007 correspondence.

The lidocaine topical patch, 5% guidance should also be rescinded due to practical considerations. Maintaining two parallel proceedings regarding the same subject matter – one on the lidocaine topical patch, 5% petition, one on the lidocaine topical patch, 5% guidance – is an unnecessary duplication of effort. By contrast, a single docket is consistent with the Agency's policy that once a petition is filed, communications related to the issues raised in the petition should be filed to the petition's docket.

drug, information derived from published literature, agency research, and consultations within different offices in CDER as needed based upon the novelty or complexity of the BE considerations.).

⁶ Dale Conner, Pharm.D., Remarks at the Meeting of the Advisory Committee for Pharmaceutical Science 183 (Mar. 12, 2003) (transcript available at <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3926T1.pdf>).

⁷ OGD, FDA, CRITICAL PATH OPPORTUNITIES FOR GENERIC DRUGS 4.3.3 (2007).

⁸ Of course, this failure to give notice in the Federal Register makes the draft guidance procedurally flawed under OGD's new Guidance and FDA's Good Guidance Practices. See FDA, *Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products*, 72 Fed. Reg. 30388, 30389 (May 31, 2007); CENTER FOR DRUG EVALUATION AND RESEARCH, FDA, GUIDANCE FOR INDUSTRY (DRAFT): BIOEQUIVALENCE RECOMMENDATIONS FOR SPECIFIC PRODUCTS 3 (2007); 21 C.F.R. § 10.115(g)(1)(ii)(A).

Finally, to the extent the Agency declines to remove the lidocaine topical patch, 5% guidance from its website, Endo hereby requests that all filings (including future submissions) to Docket No. 2006P-0522 be cross-filed to—and fully considered as part of—the draft lidocaine topical patch, 5% guidance docket.

We thank you for your consideration.

Sincerely,

A handwritten signature in black ink, reading "Mary Alice Raudenbush". The signature is written in a cursive style with a long, sweeping horizontal line at the end.

Mary Alice Raudenbush
Vice President, Regulatory Affairs
Endo Pharmaceuticals Inc