COVINGTON & BURLING LLP

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662.6291
WWW.COV.COM

WASHINGTON
NEW YORK
SAN FRANCISCO
LONDON
BRUSSELS

March 2, 2007

VIA HAND DELIVERY

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

Re: FDA Docket Number 2003P-0064

Ladies and Gentlemen:

The undersigned submit this letter to you on behalf of sanofi-aventis U.S. LLC, successor-in-interest to Aventis Pharmaceuticals, Inc. ("sanofi-aventis"). Sanofi-aventis is the manufacturer of Lovenox® (enoxaparin sodium injection), a low molecular weight heparin ("LMWH"). On February 19, 2003, sanofi-aventis filed a citizen petition to the above-referenced docket (the "Citizen Petition") requesting that FDA not approve a generic version of enoxaparin until the conditions set forth in the Citizen Petition are satisfied.[1] This letter provides additional information for FDA's consideration in ruling on the Citizen Petition.

As FDA is aware, the European Medicines Agency ("EMEA") has determined that generic versions of LMWHs should be considered biological medicinal products. As a result, applicants for marketing authorization for generic LMWH products in the European Community (EC) may not seek approval of their products as generic medicinal products (the EC's version of the ANDA).[2]

---

[1] FDA Docket Number 2003P-0064(CP1).

[2] *See* Letter from sanofi-aventis to FDA, FDA Docket Number 2003P-0064(C11) (August 25, 2006).

2003P-0064

SUP4

On January 24, 2007, the EMEA's Committee for Medicinal Products for Human Use ("CHMP") published a draft "Concept Paper on Similar Biological Medicinal Products Containing Low Molecular Weight Heparins - (Non) Clinical Issues" (the "Concept Paper").[3] According to the Concept Paper,

> Marketing authorisation applications for LMWH have been submitted in several EU Member States. Assessment of these applications is difficult for several reasons: the physico-chemical characterisation of the LMWHs is limited due to the high complexity of the molecules and the limited knowledge about qualitative and quantitative contribution to safety and efficacy of each fraction.
>
> The kinetics of LMWH is based on pharmacodynamic measurements. However, the quantitative correlation between the pharmacodynamics and clinical efficacy has not been demonstrated. Furthermore, the relative contribution of various interactions with proteins and cells of LMWHs to the efficacy in different therapeutic indications is controversial.
>
> Classical bioequivalence studies are not sufficient to establish therapeutic equivalence between LMWHs. The design of an appropriate comparability program is complicated by the unknown pharmacodynamic and clinical significance of the numerous interactions with plasma components and cells and by the rather complex mixture of the drug substances.[4]

In light of these difficulties, the Concept Paper recommends drafting a guideline on the (non)clinical aspects of the development and assessment of similar biological medicinal products containing LMWHs. The EMEA also has requested public comment on the Concept Paper.[5]

---

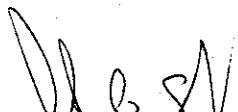
[3] *See* EMEA, Committee for Medicinal Products for Human Use, Concept Paper on Similar Biological Medicinal Products Containing Low Molecular Weight Heparins - (Non) Clinical Issues (January 24, 2007) (attached hereto as Appendix A).

[4] *See id.* at 2.

[5] *See id.*

This recent publication by the CHMP has relevance for FDA's consideration of the above-referenced Citizen Petition. Sanofi-aventis therefore requests that FDA give this important development from FDA's peer European regulatory agency significant consideration in its evaluation of the issues raised by the Citizen Petition.

Respectfully submitted,



Peter O. Safir
Scott L. Cunningham
Attorneys for sanofi-aventis U.S. LLC

Covington & Burling LLP
1201 Pennsylvania, N.W.
Washington, D.C. 20004-2401