IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

SANOFI-AVENTIS U.S. LLC
55 Corporate Drive
Bridgewater, NJ 08807-2854

Plaintiff,

v.

FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

MARGARET A. HAMBURG, M.D.,
Commissioner of Food and Drugs,
Food and Drug Administration,
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

and

KATHLEEN SEBELIUS
Secretary of Health and Human Services,
200 Independence Avenue, S.W.
Washington, D.C. 20201

Defendants.

Civ. No. _____

Case. 1:10-cv-01255
Assigned To : Sullivan, Emmet G
Assign. Date : 7/26/2010
Description: TRO/PI

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff sanofi-aventis U.S. LLC ("sanofi-aventis") brings this Complaint against the Food and Drug Administration ("FDA"); the Commissioner of Food and Drugs, Margaret A. Hamburg, M.D.; and the Secretary of Health and Human Services, Kathleen Sebelius; and avers and alleges as follows:

1

Nature of Action

1. This action seeks a temporary restraining order and a preliminary injunction requiring FDA to withdraw its approval of an abbreviated new drug application ("ANDA") submitted by Sandoz Pharmaceuticals, Inc. ("Sandoz") for a generic version of Lovenox® (enoxaparin sodium injection) ("Lovenox"). Manufactured by the sanofi-aventis group, Lovenox is a leading and widely prescribed anticoagulant that is used to treat and prevent the formation of blood clots. By approving Sandoz's ANDA, FDA has exceeded its authority under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355, ignored its own precedent regarding approval of generic versions of drugs that have not been fully characterized, and has failed to ensure that Sandoz's drug has the same active ingredient as Lovenox, as required by the ANDA provisions of the FDCA. If not remedied, FDA's decision will cause sanofi-aventis irreparable harm and may result in entry into the market of a generic product that is not clinically equivalent to Lovenox with respect to safety or efficacy.

2. FDA's approval of Sandoz's ANDA for generic enoxaparin was arbitrary and capricious and otherwise unlawful under the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2), and improper under section 505(j) of the FDCA, 21 U.S.C. § 355(j). Disregarding the plain language of Section 505(j)(2)(A), FDA approved Sandoz's ANDA for a fully substitutable generic version of Lovenox notwithstanding the fact that the Agency required Sandoz to submit additional data and information demonstrating the safety and effectiveness of its product. Section 505(j)(2)(A) specifically precludes FDA from requiring the submission of such information. There is no basis for requiring or considering such information as part of an ANDA, and doing so effectively allows the generic applicant to rely upon the pioneer's confidential commercial information in a manner not contemplated by the statute.

3. In addition, FDA has ignored Agency precedent relating to generic versions of drugs that have not been fully characterized. Sanofi-aventis emphasized this body of precedent in a Citizen Petition filed with FDA in November 2003 and supplemented on multiple occasions thereafter. FDA has failed to provide a substantive reason why generic enoxaparin should be treated differently from other drugs that cannot be fully characterized. Thus, FDA has acted arbitrarily and capriciously by effectively according different treatment to similarly situated products.

4. FDA has similarly dismissed, without any rational justification or analysis, a wealth of scientific evidence establishing that small variations in the manufacturing process used to create low molecular weight heparins (LMWHs) such as Lovenox can result in significant changes to the structure and pharmacological properties of generic versions of the drug. By allowing generic applicants to deviate from the manufacturing process used by sanofi-aventis to produce Lovenox, FDA has failed to ensure that generic versions of enoxaparin have the same active ingredient and the same safety and effectiveness profile as Lovenox, as required by the ANDA provisions of the FDCA.

5. Sanofi-aventis seeks a declaration that FDA's approval of Sandoz's ANDA for generic enoxaparin is unlawful under the APA and violates the FDCA. In addition, sanofi-aventis seeks an injunction directing FDA to withdraw approval of Sandoz's ANDA, on the ground that sanofi-aventis will suffer irreparable injury if an injunction does not issue.

Parties

6. Plaintiff sanofi-aventis, a member of the sanofi-aventis Group, is a Delaware corporation with its principal place of business at 55 Corporate Drive, Bridgewater, NJ 08807.

7. Defendant FDA is an agency of the United States Government within the Department of Health and Human Services, with offices at 200 C Street, S.W., Washington, D.C. 20201, and 10903 New Hampshire Avenue, Silver Spring, Maryland 20993. The Secretary of Health and Human Services has delegated to FDA the authority to administer the relevant provisions of the FDCA.

8. Defendant Margaret A. Hamburg, M.D., is Commissioner of Food and Drugs and is the senior official of the FDA. She is sued in her official capacity. Dr. Hamburg maintains offices at 200 C Street, S.W., Washington, D.C. 20201, and 10903 New Hampshire Avenue, Silver Spring, Maryland 200993.

9. Defendant Kathleen Sebelius is Secretary of Health and Human Services and the official charged by law with administering the FDCA. She is sued in her official capacity. Secretary Sebelius maintains an office at 200 Independence Avenue, S.W., Washington, D.C. 20201.

Jurisdiction and Venue

10. This action arises under the APA, 5 U.S.C. § 551 *et seq.*, and the FDCA, 21 U.S.C. § 321 *et seq.* This Court has jurisdiction pursuant to 28 U.S.C. §§ 1331, 1361, and 2201–2202.

11. There exists an actual and justiciable controversy between sanofi-aventis and defendants requiring resolution by this Court. Sanofi-aventis has no adequate remedy at law.

12. Venue is proper in this district pursuant to 28 U.S.C. § 1391(e).

Factual and Legal Background

The Statutory and Regulatory Scheme

13. The FDCA provides that any "new drug" must be approved by FDA before it can be introduced into interstate commerce. 21 U.S.C. § 355(a).

14. Section 505 of the FDCA, 21 U.S.C. § 355, provides for the submission of new drug applications ("NDAs").

15. The basic requirements for an NDA are set out in Section 505(b)(1) of the FDCA. To obtain approval of such an application, an applicant must "submit . . . full reports" of clinical investigations of safety and effectiveness. 21 U.S.C. § 355(b)(1).

16. Section 505(j) of the FDCA sets forth a specific mechanism for the approval of generic drugs. Under the statute, generic applicants submit an abbreviated new drug application ("ANDA"), which must reference a previously approved drug, referred to as the "reference listed drug" ("RLD"). *See* 21 U.S.C. § 355(j). An ANDA does not include full reports of safety and effectiveness. Instead, in approving an ANDA, FDA relies on its previous findings of safety and effectiveness for the RLD, provided that the ANDA applicant submits data establishing that its proposed generic drug is the "same" as, and is "bioequivalent" to, the pioneer drug. *See id.* § 355(j)(2).

17. Section 505(j)(2)(A) specifically prohibits FDA from requiring an ANDA applicant to submit data or information to establish safety or effectiveness. The plain language of the statute, as well as FDA's own statements, make clear that FDA may not require ANDA applicants to submit additional studies (other than bioequivalence studies) as part of an ANDA.

Sanofi-aventis' NDA for Lovenox

18. The sanofi-aventis Group is a leading research-based pharmaceutical company. A sanofi-aventis Group predecessor company developed Lovenox (enoxaparin sodium injection), a widely prescribed anticoagulant that is used for, among other purposes, reducing the risk of the formation of blood clots in patients at risk and treating patients who already have blood clots.

19. Lovenox is indicated for the prevention of deep vein thrombosis ("DVT"), a condition in which a blood clot (thrombus) develops in deep veins of the body. Lovenox is also indicated for prevention of complications associated with unstable angina and certain forms of heart attack, when administered along with aspirin. Lovenox is the first drug in its class indicated for inpatient treatment of acute DVT (with or without pulmonary embolism), and outpatient treatment of acute DVT (without pulmonary embolism). Most recently, FDA approved Lovenox for treatment of acute ST-segment elevation heart attacks.

20. In most cases, these are life-threatening conditions. DVT and pulmonary embolism (collectively known as venous thrombo-embolism or "VTE"), in particular, are significant causes of morbidity and mortality. Approximately 600,000 patients per year are hospitalized for DVT in North America. Symptomatic pulmonary embolism is directly or indirectly responsible for up to 200,000 annual patient fatalities in the United States, with a mortality rate reported as high as 17.5%.

21. Lovenox is a unique chemical entity in a class of antithrombotic agents known as low-molecular-weight heparins ("LMWHs").

22. LMWHs are derived from the anticoagulant heparin, which is found in mammals. Both LMWHs and regular heparin (also called "unfractionated heparin") are used to reduce the risk of abnormal clotting. LMWHs are composed of a complex mixture of shorter polysaccharide chains as compared to unfractionated heparin and are generally regarded as less variable (and therefore preferable) in their anticlotting effects.

23. Although unfractionated heparin can be found in virtually all species of mammals, in the United States and Europe it is primarily extracted from the intestinal tissue of pigs. In the manufacture of LMWH, larger unfractionated heparin chains are broken down into

smaller polysaccharide chains through various chemical or enzymatic processes. Each LMWH manufacturer uses a distinct process, resulting in LMWHs with distinct chemical structures, different pharmacological activity, and different approved indications for clinical use.

24. FDA has recognized that different processes used to create LMWHs create chemically distinct drug products. In 1993, FDA issued an alert to physicians stressing that the various approved LMWHs are not interchangeable. This warning is also found in the approved prescribing information for all currently available LMWHs.

25. To produce Lovenox, sanofi-aventis employs a proprietary chemical process to break down the unfractionated heparin chains. The chemical process takes place under specified and tightly controlled parameters including concentration of reagents used, temperature, and duration of reaction. This manufacturing process creates a highly complex collection of large molecules with a chemical structure unique among currently approved LMWHs. The structure of enoxaparin is marked by distinct sequences of polysaccharides and structural modifications (or "fingerprints") that are highly sensitive to sanofi-aventis' manufacturing process. At least two of these "fingerprints"—the 1,6 anhydro ring structure and the process-dependent ATIII binding sites—make important contributions to the overall pharmacological effect of Lovenox.

26. Sanofi-aventis has not yet discovered all of the structural fingerprints in enoxaparin. This is because at this point in time it is impossible to fully characterize enoxaparin by direct analysis. It is highly likely that additional structural fingerprints of enoxaparin will be discovered as more of the drug becomes characterized. Until that happens, however, it is impossible to determine that a generic product contains all the pharmacologically active components contained in Lovenox unless the generic is manufactured by an equivalent process.

27. This could pose significant safety concerns for patients because generic drugs approved through an ANDA are considered to be pharmaceutical equivalents and therefore may be substituted for the pioneer drug at the pharmacy or at the hospital. Differences in pharmacological effect caused by the fact that the generic was not manufactured with an equivalent manufacturing process could reduce the effectiveness of the generic product or even cause additional, possibly severe, side-effects.

28. The NDA for Lovenox that was submitted on December 30, 1991, included confidential reports of the results of preclinical and clinical studies that a sanofi-aventis predecessor had conducted using its uniquely-manufactured enoxaparin product.

29. FDA approved the NDA for Lovenox on March 29, 1993, and marketing of Lovenox began soon thereafter. Lovenox is available in two concentrations: either pre-filled single-dose syringes or multiple-dose vials. Revenues from Lovenox were approximately $2.5 billion in 2009.

Sanofi-aventis' Citizen Petition

30. Until now, there have been no approved generic LMWHs in the United States. On February 19, 2003, sanofi-aventis submitted to FDA a citizen petition under Sections 505(b) and 505(j) of the FDCA (the "Citizen Petition"). The Citizen Petition requested that, until such time as enoxaparin has been fully characterized, FDA withhold approval of any application for approval of generic enoxaparin unless (i) the manufacturing process used to create the generic product is determined to be equivalent to sanofi-aventis' manufacturing process for Lovenox; or (ii) an application for approval is supported by proof of equivalent safety and effectiveness demonstrated through clinical trials. Sanofi-aventis further argued that FDA should refrain from approving any ANDA for generic enoxaparin unless the generic product contains the 1,6 anhydro ring structure at concentrations equivalent to that of Lovenox.

In supplemental filings to the Citizen Petition, sanofi-aventis suggested that generic versions of enoxaparin similarly should not be approved unless they contain the process-dependent ATIII binding sites contained in enoxaparin. Sanofi-aventis explained that, in light of the life-threatening conditions for which LMWHs are indicated and prescribed, it is essential that a generic LMWH be rigorously scrutinized for identity.

31. In various comments to its Citizen Petition, sanofi-aventis pointed out to FDA its previous Agency decisions relating to drugs that are not fully characterized. These decisions establish that where a drug is not fully characterized, FDA has concluded that it cannot tell if the drug is the same as another.

32. On July 23, 2010, FDA granted in part sanofi-aventis's Citizen Petition with respect to its request that generic versions of enoxaparin contain the 1,6 anhydro ring structure at concentrations equivalent to that of Lovenox. FDA denied the Citizen Petition, however, in all other respects. FDA determined that if an ANDA applicant seeking approval of generic enoxaparin can meet five criteria, it can make the required showing of "sameness" without having to use a manufacturing process equivalent to the process used by sanofi-aventis to produce Lovenox. FDA contended that, contrary to claims raised by sanofi-aventis, its approach to reviewing and approving ANDA applications for generic enoxaparin is consistent with Agency precedent regarding other drugs that have not been fully characterized.

Sandoz's Application for Approval of Generic Enoxaparin

33. On August 26, 2005, Sandoz filed ANDA No. 87-660, seeking approval to market a generic enoxaparin product.

34. In November 2007, Sandoz received a letter from FDA stating that its ANDA application for a generic version of enoxaparin was "not approvable" because additional data was needed to address the potential for Sandoz's generic product to produce an immune

response (i.e., immunogenicity). *See* Momenta Pharmaceuticals, Inc., Annual Report, (Form 10-K), at 6, (March 12, 2008).

35. To address these concerns, FDA required Sandoz to conduct additional studies to assess the immunogenicity of its product. On information and belief, Sandoz conducted these studies and submitted the data to FDA on or about September 26, 2008. Thus, FDA required the submission of materials above and beyond those required by Section 502(j)(2)(A).

36. On July 23, 2010, FDA approved Sandoz's ANDA. In a contemporaneous press release, FDA explained that before approving Sandoz's ANDA, it required Sandoz to submit "a series of sophisticated analytical tests and a study in healthy volunteers to assure that the drug would be as safe and effective as the brand name product." Press Release, FDA Approves First Generic Enoxaparin Sodium Injection (Jul. 23, 2010), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm. FDA relied on this additional data in approving Sandoz's ANDA.

COUNT I

(Administrative Procedure Act: Violation of FDCA)

37. Paragraphs 1–36 are incorporated herein by reference.

38. Section 505(j)(2)(A) of the FDCA specifically prohibits FDA from requiring additional data for the purpose of demonstrating the safety or effectiveness of a generic drug that is the subject of an ANDA application. If FDA requires information beyond what is enumerated in Section 505(j)(2)(A), the ANDA pathway is inappropriate for approval of a generic drug.

39. By approving Sandoz's ANDA after requiring Sandoz to submit additional safety data, FDA exceeded its authority under Section 505(j) of the FDCA.

40. FDA's approval of Sandoz's ANDA was arbitrary, capricious, an abuse of discretion, and not in accordance with law, and therefore violates 5 U.S.C. § 706(2)(A).

41. FDA's approval of Sandoz's ANDA on the basis of additional safety data constitutes agency action in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, in violation of 5 U.S.C. § 706(2)(C).

42. Sanofi-aventis has no adequate remedy at law and will suffer irreparable injury if defendants are not directed by injunction to immediately suspend and withdraw approval of Sandoz's ANDA for generic enoxaparin. In the absence of injunctive relief, Sandoz's generic enoxaparin will compete with, and, in many cases be automatically substituted for, sanofi-aventis' Lovenox.

COUNT II

(Administrative Procedure Act: Violation of the FDCA)

43. In the alternative, and in addition, FDA has violated the FDCA by failing to provide adequate justification for its departure from Agency precedent governing the approval of generic versions of drugs that have not been fully characterized.

44. In its Citizen Petition, sanofi-aventis emphasized to FDA previous Agency decisions establishing that, where a drug cannot be fully characterized, FDA cannot determine that the drug is the same as another. FDA has failed to provide a legitimate reason for departing from these prior decisions.

45. By effectively according different treatment to similarly situated products, FDA has acted arbitrarily, capriciously, and not in accordance with law and has therefore violated 5 U.S.C. § 706(2)(A).

46. Sanofi-aventis has no adequate remedy at law and will suffer irreparable injury if defendants are not directed by injunction to immediately suspend and withdraw

approval of Sandoz's ANDA for generic enoxaparin. In the absence of injunctive relief, Sandoz's generic enoxaparin will compete with, and in many cases be automatically substituted for, sanofi-aventis' Lovenox.

COUNT III

(Violation of APA; Violation of FDCA)

47. In the alternative, and in addition, FDA has violated the FDCA by approving Sandoz's application without sufficient evidence that the active ingredient in Sandoz's generic enoxaparin product is the "same" as the active ingredient in sanofi-aventis' Lovenox.

48. In support of its Citizen Petition, sanofi-aventis provided hundreds of pages of scientific data establishing that small differences in the manufacturing process for LMWHs such as Lovenox can have significant effects on the resulting pharmacological properties of a drug. FDA has rejected this evidence and has declared that applicants seeking approval for generic enoxaparins can make the required showing of "sameness" by meeting five newly-announced criteria, rather than by using a manufacturing process equivalent to the process used by sanofi-aventis to produce Lovenox. FDA has failed to provide sufficient justification for this approach.

49. The approach to "sameness" that FDA articulated in its response to sanofi-aventis' Citizen Petition, and by which it approved Sandoz's ANDA, is wholly unprecedented, without support in law, contrary to established Agency precedent, and therefore violates 5 U.S.C. § 706(2)(A).

50. FDA's approval of Sandoz's ANDA in the absence of sufficient evidence that Sandoz's generic has the same active ingredient as Lovenox is arbitrary, capricious, and not in accordance with law and therefore violates 5 U.S.C. § 706(2)(A).

51. Sanofi-aventis has no adequate remedy at law and will suffer irreparable injury if defendants are not directed by injunction to immediately suspend and withdraw approval of Sandoz's ANDA for generic enoxaparin. In the absence of injunctive relief, Sandoz's generic enoxaparin will compete with, and in many cases be automatically substituted for, sanofi-aventis's Lovenox.

Relief Requested

WHEREFORE, sanofi-aventis requests that the Court enter judgment in its favor and against defendants and award the following relief:

a. A declaratory judgment that defendants acted unlawfully in approving Sandoz's ANDA;

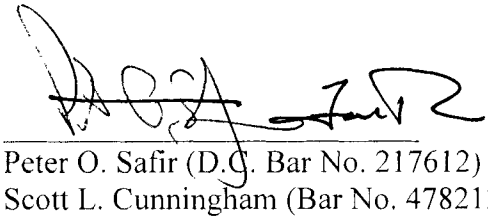
b. A temporary restraining order and a preliminary injunction directing FDA to immediately suspend and withdraw approval of Sandoz's ANDA;

c. A permanent injunction under the terms set forth in subparagraph b above; and

d. Such other and further preliminary and final relief as the Court may deem just and proper.

July 26, 2010

Respectfully submitted,



Peter O. Safir (D.C. Bar No. 217612)
Scott L. Cunningham (Bar No. 478213)
Fuad Rana (D.C. Bar. No. 488153)
COVINGTON & BURLING LLP
1201 Pennsylvania Ave., N.W.
Washington, DC 20004-2401
(202) 662-6000 (Telephone)
(202) 662-6291 (Fax)

Emily Johnson Henn (Bar No. 471077)
COVINGTON & BURLING LLP
333 Twin Dolphin Drive, Suite 700
Redwood Shores, CA 94065-1418
(650) 632-4700 (Telephone)
(202) 632-4800 (Fax)

Attorneys for Plaintiff sanofi-aventis U.S. LLC