IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

SANOFI-AVENTIS US 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. 10 1255

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF APPLICATION OF PLAINTIFF SANOFI-AVENTIS FOR A TEMPORARY RESTRAINING ORDER AND A PRELIMINARY INJUNCTION

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INTRODUCTION

Plaintiff sanofi-aventis US LLC ("sanofi-aventis") seeks a temporary restraining order ("TRO") and preliminary injunction requiring the Food and Drug Administration ("FDA") to withdraw approval of an abbreviated new drug application ("ANDA") submitted by Sandoz Pharmaceuticals, Inc. ("Sandoz") for a generic version of enoxaparin sodium ("enoxaparin").

Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j), allows FDA to approve generic versions of pioneer drugs (i.e., innovator drugs) if the generic applicant can demonstrate that its product is "the same as" and "bioequivalent" to the pioneer drug on which it is based. In such a case, FDA must rely on its previous findings of safety and effectiveness for the pioneer drug to approve the generic. It also may deem the resulting generic drug to be fully substitutable with the pioneer drug. This means that when a pharmacist is presented with a prescription for the pioneer drug, he may (and in some states must) substitute the new generic version.

The FDCA precludes FDA, however, from approving an ANDA if it has required the generic applicant to submit additional data to demonstrate safety or effectiveness. 21 U.S.C. § 355(j)(2)(A). Where, as here, additional data regarding safety and/or effectiveness is required, a full new drug application under section 505(b) of the FDCA, 21 U.S.C. § 355(b), rather than an ANDA, is the appropriate application for marketing authorization. Furthermore, the resulting generic product generally is not fully substitutable with the pioneer drug. FDA required Sandoz to submit substantial additional safety data in support of its ANDA for a generic version of enoxaparin, yet still approved

Sandoz's ANDA under section 505(j) for a fully substitutable generic enoxaparin product. In doing so, FDA acted contrary to the plain language of the FDCA.

In addition, FDA departed from its own precedent without justification by approving Sandoz's ANDA even though Sandoz's application referenced a drug (enoxaparin) that is not fully characterized. Finally, FDA approved this ANDA without ensuring that Sandoz's generic drug contains the same active ingredient as sanofi-aventis' innovator product, as required by section 505(j). Thus, FDA's approval is arbitrary, capricious, an abuse of discretion, and not in accordance with law, and is therefore unlawful under the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2).

Unless this Court orders FDA to withdraw its approval of Sandoz's ANDA immediately, sanofi-aventis will suffer irreparable harm. Absent injunctive relief, sanofi-aventis will suffer substantial loss of sales of its pioneer drug Lovenox® and resulting financial losses. Because the FDA would be shielded by sovereign immunity in any future suit based on its unlawful approval, sanofi-aventis will be unable to recover these losses even if FDA's decision is reversed at a later time. In addition to these immediate economic harms, sanofi-aventis will also suffer from a permanent drop in price for its pioneer product, loss of preferred formulary status, erosion of goodwill, and cut-backs of employees. A TRO and preliminary injunction should be granted to prevent such irreparable harm.

BACKGROUND

A. Statutory And Regulatory Background: The New Drug Approval Process.

A "new drug" must receive approval from FDA before it may be marketed. 21 U.S.C. § 355(a). Under the FDCA, there are two separate and distinct pathways for FDA

to approve "new drugs." A drug must be the subject of either a New Drug Application ("NDA") under section 505(b) of the FDCA, or an ANDA under section 505(j).

1. The NDA Approval Process for New Pioneer Drugs

The procedure for filing and approval of an NDA is set out in section 505(b). An NDA applicant must submit "full reports of investigations" demonstrating that the proposed new drug is both safe and effective. 21 U.S.C. § 355(b)(1). To satisfy this requirement, developers of new drugs must conduct research, including in most cases at least two clinical studies (*i.e.*, studies on human subjects), and submit to FDA the data needed to establish the drug's safety and effectiveness.

2. The Generic Drug Approval Process

Section 505(j) provides a specific approval mechanism for approving generic drugs — drugs that are demonstrated to be sufficiently similar to the pioneer drugs to which they putatively correspond that the FDA may rely on its prior approval of the pioneer drug in approving the generic. 21 U.S.C. § 355(j). Generic applicants under section 505(j) submit ANDAs, which must reference a previously approved pioneer drug, commonly referred to as the "reference listed drug" ("RLD").

Unlike an NDA applicant, an ANDA applicant under section 505(j) need not establish the safety and effectiveness of its proposed generic drug product. This is because ANDA drugs are required to be copies of a pioneer drug already approved by FDA. As a result, an ANDA applicant is not required to conduct or submit clinical studies. Instead, an ANDA applicant must establish only that the proposed product is "the same as" the RLD in terms of active ingredient(s), route of administration, dosage form, and strength. 21 U.S.C.

§ 355(j)(2)(A). The ANDA applicant must also demonstrate that its proposed generic drug is "bioequivalent" to the pioneer drug. 21 U.S.C. § 355(j)(2)(A)(iv).[1]

If the ANDA applicant makes the statutorily-required showings of sameness and bioequivalence, FDA may rely on its previous findings of safety and effectiveness for the pioneer drug, *i.e.*, on its findings from the clinical studies originally submitted by the pioneer, to approve the proposed generic. *See id.* §§ 355(j)(2)(A), (4).[2]

Importantly, FDA may not require additional information from an ANDA applicant, *id.* § 355(j)(2)(A), and must approve an ANDA meeting the statutory requirements for approval. *Id.* § 355(j)(4). The statute is quite clear, and states as follows:

> The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

21 U.S.C. § 355(j)(2)(A).

The statute forbids FDA from requiring additional information because the ANDA pathway exists to provide an approval mechanism only for those drugs that are essentially duplicates of the RLD and thus need no further testing. Where FDA determines that further testing is required to demonstrate that a generic drug is safe and effective, it implicitly determines that the drug is not actually "the same as" the RLD which has already

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[1] The FDCA defines bioequivalence to mean that the "the rate and extent of absorption of the [proposed generic] drug do not show a significant difference from the rate and extent of absorption of the approved listed drug when administered . . . under similar experimental conditions . . . ." 21 U.S.C. § 355(j)(8)(B)(i); *see also* 21 C.F.R. § 320.1(e).

[2] Section 505(j)(2)(C) permits applicants to submit a "suitability petition" to request FDA's advance permission to file an ANDA with minor changes to the strength, dosage form, route of administration or, for combination drugs, one of the active ingredients. *See* 21 U.S.C. § 355(j)(2)(C). That provision is not applicable here.

been demonstrated to be safe and effective. As a result, these types of generic drugs require full new drug applications under section 505(b). These drugs may not be approved under section 505(j) as fully substitutable drugs.

This is not to say that such drugs cannot be approved or may not rely on data from the RLD. Rather, generic applicants that are required to produce additional safety data beyond that contained in the file of the RLD must use the section 505(b)(2) pathway.[3] FDA has made this pathway available where the RLD and the proposed generic product are substantially similar, but not "the same." In such cases, FDA cannot rely entirely on its previous findings of safety and effectiveness for the pioneer to approve the generic drug. Instead, FDA relies in part on its previous findings of safety and effectiveness, but also on additional data submitted by the 505(b)(2) applicant to demonstrate that the generic drug is still safe and effective despite the differences with the RLD.[4] In such cases, however, because the 505(b)(2) generic and the RLD are not "the same", they are generally not deemed fully substitutable.

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[3] *See* FDA 1999 Draft Guidance: Applications Covered by Section 505(b)(2), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf (the "Draft Guidance").

[4] *See* Letter from FDA to Kathleen M. Sanzo, Esq., Stephan E. Lawton, Esq., and Stephen G. Juelsgaard, Esq. (May 30, 2006) ("Omnitrope Letter"), *available at* http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf. (citing the Draft Guidance). Innovator companies have argued that all applications filed under section 505(b) must be full NDAs and that section 505(b)(2) simply codifies FDA's previous "paper NDA" policy, which permits generic applicants to rely on published studies and can be approved without any reference to safety and effectiveness data submitted by innovators. This issue has not, to date, been resolved by the courts.

B. The Lovenox® NDA

1. Nature and Uses of Lovenox

Lovenox, with its active ingredient enoxaparin sodium ("enoxaparin"), is a unique biological compound[5] in a class of compounds known as low molecular weight heparin ("LMWH"). Sanofi-aventis (then Rhône-Poulenc Rorer) submitted an NDA for Lovenox on December 30, 1991. *See* Declaration of Scott Cunningham ("Cunningham Decl."), Ex. A ("Viskov Decl."), ¶ 16.[6] The application, submitted under section 505(b) of the FDCA, included full reports of preclinical and clinical studies conducted to demonstrate the drug's safety and effectiveness. *Id.* FDA approved the Lovenox NDA in 1993. *Id.*

Lovenox is a widely prescribed anticoagulant used to prevent or treat thromboembolic disease and deep vein thrombosis, a condition in which a blood clot (thrombus) develops in deep veins of the body. Lovenox is indicated for prevention of complications associated with angina and certain forms of heart attack, when administered along with aspirin. *See* Cunningham Decl., Ex. B ("Cohen Decl."), ¶ 14.[7] It is also indicated for inpatient treatment of acute deep vein thrombosis (with or without pulmonary embolism), and outpatient treatment of acute deep vein thrombosis (without pulmonary embolism) when administered in conjunction with warfarin sodium. *Id.* In many cases, these are life

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[5] Enoxaparin is a biological compound in that it is derived from biological starting materials (*i.e.*, pig intestine), as opposed to a traditional synthetic compound.

[6] Dr. Christian Viskov is a Research Investigator employed by Sanofi-Aventis Recherche et Développement, an affiliate of sanofi-aventis. He has extensive expertise on enoxaparin, its chemical structure, and the process used to manufacture it. Viskov Decl. ¶ 1.

[7] Dr. Marc Cohen is Professor of Medicine at Mt. Sinai School of Medicine in New York. He is also Chief of the Division of Cardiology at Newark Beth Israel Medical Center in New Jersey. Cohen Decl., ¶ 2.

threatening conditions.[8] With U.S. revenues of $2.517 billion in 2009, Lovenox represented 26 percent of sanofi-aventis' total 2009 reported U.S. domestic sales, not including developed/co-promotion sales. *See* Cunningham Decl., Ex. C ("Durso Decl."), ¶¶ 9, 13.[9]

2. Production of Low Molecular Weight Heparin

Like all LMWHs, Lovenox is derived from heparin, a biological substance found in mammals. Viskov Decl., ¶ 7. This heparin source material is customarily referred to as "unfractionated heparin" to distinguish it from LMWH. *Id.* Unfractionated heparin consists of a highly intricate collection of linear chains of complex sugar molecules known as "polysaccharide chains." *Id.* ¶ 8. However, LMWH's shorter polysaccharide chains are thought preferable to unfractionated heparin in anticlotting effect. *Id.* ¶ 10.

To manufacture LMWH, the larger unfractionated heparin polysaccharide chains are broken down into smaller polysaccharide chains through chemical or enzymatic processes. *Id.* ¶ 9. The precise parameters of the process used to manufacture LMWHs have important effects on the structure of the active ingredient and, thus, its safety and effectiveness. *Id.* ¶ 11. In other words, the process makes the product. There are three pioneer LMWHs, including Lovenox, available in the United States today. The producers of these LMWHs use different manufacturing processes, and each process varies in certain

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[8] Approximately 600,000 patients per year are hospitalized for deep vein thrombosis in North America. *See* Turpie AGG, Management of Venous Thromboembolism: Optimization by Clinical Trials. *Haemostasis* 1996; 26(4 Suppl):220 at 221. 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 percent. *See* Goldhaber SZ, Pulmonary Embolism. *N. Eng. J. Med.* 1998, 339(2):93.

[9] Mr. Jerome Durso is Senior Vice President and Chief Commercial Officer of U.S. Pharmaceuticals, at sanofi-aventis. Durso Decl., ¶ 1.

specific parameters, including in the type and concentration of reagents used, temperature, and time of reaction. *Id.* ¶ 9. These and other differences in manufacturing process result in LMWHs with distinct chemical structures and different pharmacological activity. *Id.* Hence, the different LMWHs available on the market today have different indications for use and are not prescribed or used interchangeably. *Id.*

Indeed, FDA itself has recognized that the different manufacturing processes used to create LMWHs create chemically distinct drug products. In 1993, FDA issued an alert to physicians stressing that the various branded LMWHs may not be used interchangeably because they are made with different manufacturing processes.[10] This warning also appears in the approved prescribing information for all currently available LMWHs.[11] Thus, the balance of scientific opinion suggests that a generic LMWH not manufactured with an equivalent manufacturing process would *not* be clinically identical to the pioneer LMWH, just as FDA has recognized that pioneer LMWH's with different manufacturing processes are not equivalent to each other.[12]

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[10] *See* Nightingale SL, Appropriate use of low-molecular-weight heparins (LMWHs), *JAMA* 1993; 270(14):1672 (publishing physician alert from then FDA Associate Commissioner for Health Affairs, Stuart L. Nightingale, MD).

[11] *See, e.g.*, Package Insert Information for Enoxaparin, *available at* http://products.sanofi-aventis.us/Lovenox/Lovenox.html.

[12] *See, e.g.,* Jawad Fareed, et al., Heterogeneity in low molecular weight heparins. Impact on the therapeutic profile. *Current Pharm. Design* 2004; 10:983-999; Linhardt RJ, et al., Oligosaccharide mapping of low molecular weight heparins: Structure and activity differences. *J. Med. Chem.* 1990; 33:1639-45; Green, D. Hirsh, J. Heit, J. et al. (1991). "Low molecular weight heparin: A critical analysis of clinical trials." *Pharmacol. Rev.* 2: 45–50; Barrowcliffe, T. W. (1995). "Low molecular weight heparin(s)." *Br. J. Haematol.* 90: 1–7. doi:10.1111/j.1365-2141.1995.tb03373.x.Donayre C. E. (1996). "Current use of low molecular weight heparins." *Semin. Vascul. Surg.* 9: 362–371; Hunt, D. (1998). "Low molecular weight heparins in clinical practice." *S. Med. J.* 91: 2–10; Fareed, J. Jeske, W. Hoppensteadt, D. Clarizio, R. Walenga, J. M. (1998). "Low molecular weight heparins: (continued...)

3. Manufacture of Lovenox

To manufacture Lovenox, sanofi-aventis employs a specific, tightly controlled, validated chemical process to break down the unfractionated heparin polysaccharide chains. Viskov Decl., ¶ 18. The precise details of the manufacturing process are proprietary and confidential trade secrets. *Id.* This manufacturing process creates a highly complex collection of macromolecules with a chemical structure unique among branded LMWHs currently on the market. *Id.*

Like other LMWHs, the pharmacological effects of enoxaparin (the active ingredient in Lovenox) are critically dependent upon the manufacturing process used to create the drug. *Id.* ¶ 19. The structure of Lovenox is marked by distinct structural modifications (or "fingerprints") that are highly sensitive to sanofi-aventis' process. At least two of these "fingerprints"—process-dependent ATIII binding sites and the 1,6 anhydro ring structure—have been shown to make important contributions to the drug's overall pharmacological effect. *Id.* ¶ 21-26. Slight modifications of the process, such as changes in concentration of reagents used, temperature, or time of reaction, have been shown to result in significant changes to these fingerprints and, thus, the pharmacological properties of the drug. *Id.* ¶ 20.

It is almost certain that sanofi-aventis has not yet discovered all of the structural fingerprints that make meaningful contributions to enoxaparin's pharmacological effect. There are two reasons for this. First, current analytical technology does not enable

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Pharmacologic profile and product differentiation." *Am. J. Cardiol.* 82: 3L–10L. doi:10.1016/S0002-9149(98)00105-2. *Cf.* Prandoni P & Nenci GG, Low molecular weight heparins: are they interchangeable? Yes/No, *J. Thromb. Haemost.* 2003; 1:10–13 (citing debate on interchangeability of LMWHs).

scientists to identify all of the structures within enoxaparin. *Id.* ¶ 32. In scientific terms, this means that enoxaparin has not yet been fully "characterized" by direct analysis. As much as 30 percent of enoxaparin cannot be characterized by direct analysis with current technology. *Id.* Second, only a very small fraction of the 70% of enoxaparin that can be characterized has been analyzed for structural fingerprints. *Id.* It is logical to assume that many additional structural fingerprints remain to be discovered in both the 30% of enoxaparin that currently cannot be characterized as well as through continued analysis of the 70% of enoxaparin currently available for analysis. *Id.* Many of these yet-to-be-discovered fingerprints likely affect enoxaparin's overall safety and effectiveness parameters significantly. *Id.*

C. The Lovenox Citizen Petition

On February 19, 2003, sanofi-aventis submitted to FDA a Citizen Petition under sections 505(b) and 505(j) of the FDCA. *See* Cunningham Decl., Ex. D ("Citizen Petition"). Citing patient safety concerns, the Citizen Petition requested that, until such time as enoxaparin has been fully characterized, FDA withhold approval of any application for a purported generic enoxaparin product unless (i) the generic manufacturer uses the same manufacturing process as sanofi-aventis' manufacturing process for enoxaparin; or (ii) the application is supported by proof of equivalent safety and effectiveness demonstrated through clinical trials, *i.e.*, through submission of "full reports of investigations" under section 505(b)(1) of the FDCA. Citizen Petition, at 1-2. Sanofi-aventis also requested that the FDA refrain from approving any ANDA for generic enoxaparin unless the generic

product contains the 1,6-anhydro ring structure at concentrations equivalent to that found in Lovenox.[13] *Id.* at 1.

Between February 2003 and June 29, 2007, sanofi-aventis submitted several supplements and comments to FDA providing additional information and scientific data. Cunningham Decl., Exs. E-K. The supplements, like the petition itself, were supported by affidavits from several highly-regarded scientific experts in the field of LMWH. *See, e.g.*, Cunningham Decl., Ex. H, at 1. Several of these additional filings highlighted FDA precedents involving the agency's treatment of pharmaceutical products where the active ingredient is not fully-characterized. *See, e.g.*, Cunningham Decl., Ex. K. In each case, FDA concluded that because the active ingredient in the drug in question was not fully characterized, the Agency was unable to conclude with certainty that the active ingredient was (or was not) the same as a previously approved active ingredient. *See, e.g., id.*

In support of the Citizen Petition and its Supplements, sanofi-aventis submitted affidavits from highly-regarded scientists and experts in the field of LMWH. Taken together, these declarations explained that use of different manufacturing processes results in different chemical structures for each LMWH and, thus, different safety and effectiveness profiles. Further, because enoxaparin is not fully characterized, it would not be possible to confirm that all of the pharmacologically active structures of enoxaparin are present in a generic enoxaparin product that used a different process. Citizen's Petition, at

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[13] Because sanofi-aventis had not yet discovered the presence of process-dependent ATIII binding sites within Lovenox, the original Citizen Petition did not include a request that FDA withhold approval of any generic product that lacked this additional structural fingerprint. Sanofi-aventis brought this additional fingerprint to FDA's attention in Citizen Petition Supplements dated February 13, 2004, and September 26, 2005. Cunningham Decl., Exs. F-G.

19. Thus, a product that purports to be a generic form of enoxaparin but is manufactured with a different manufacturing process likely differs from Lovenox in its clinical effects, much as the currently marketed LMWHs differ from one another in their safety and effectiveness. *Id.* at 19-21.

D. Sandoz's ANDA

Sandoz's ANDA No. 87-660, filed with FDA on August 26, 2005, sought approval to market generic enoxaparin in doses of 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg, and 150 mg, the same dosages that FDA has approved for Lovenox.[14]

In November 2007, FDA sent Sandoz a "Not Approvable Letter," explaining that Sandoz's ANDA was not approvable because it did not adequately address the potential for immunogenicity.[15] FDA required that Sandoz provide results of additional testing intended to ensure that Sandoz's generic product will not generate a more significant immune response than that seen in Lovenox. The potential to create an immune response (i.e., "immunogenicity") is a significant safety concern with all LMWHs because an immune response can lead to serious adverse events.[16] According to an FDA press release issued on the day of the Sandoz approval, the studies FDA required Sandoz to submit with its ANDA included "a series of sophisticated analytical tests and a study in healthy volunteers to assure

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[14] *See* Letter From Keith Webber, Deputy Director, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, to Sandoz, Inc., July 23, 2010, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/077857s000ltr.pdf ("Approval Letter").

[15] *See* Form 10-K for Momenta Pharm., Inc., Commission File Number 000-50797, *available at* http://www.sec.gov/Archives/edgar/data/1235010/000104746908002434/a2183301z10-k.htm.

[16] *See, e.g.*, Massimo Franchini, *Heparin-induced thrombocytopenia: an update*, THROMBOSIS JOURNAL, October 4, 2005.

that the drug would be as safe and effective as the brand name product."[17] Sandoz conducted the required tests and provided the results to FDA to support its ANDA. FDA relied on this additional data in approving the ANDA.[18] On July 23, 2010, FDA approved Sandoz's ANDA. *See* Approval Letter.

Concurrent with its approval of Sandoz's ANDA, FDA denied sanofi-aventis' Citizen Petition. Cunningham Decl., Ex. E. ("CP Response").[19] In explaining this decision, FDA stated that ANDAs for enoxaparin raise complicated scientific and regulatory issues. CP Response, at 2. Nonetheless, FDA concluded that if an ANDA applicant can meet each of five criteria, it can make the required showing of "sameness." These five criteria include:

1. the physical and chemical characteristics of enoxaparin;
2. the nature of the source material and the method used to break up the polysaccharide chains into smaller fragments;
3. the nature and arrangement of components that constitute enoxaparin;
4. certain laboratory measurements of anticoagulant activity; and
5. certain aspects of the drug's effect in humans

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[17] News Release, Food and Drug Administration, FDA Approves First Generic Enoxaparin Sodium Injection, July 23, 2010 (quotation omitted), *available at* http://www.fda.gov/NewsEvents/ Newsroom/PressAnnouncements/ucm220092.htm.

[18] Food and Drug Administration, Generic Enoxaparin Questions and Answers, July 23, 2010, *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformation forPatientsandProviders/ucm220037.htm.

[19] Technically, the Agency approved the Citizen Petition to the extent that it asked FDA to require the presence of the 1,6 anhydro ring in any generic product. In all other respects, however, the Agency denied the Citizen Petition.

Id. at 11. In addition, FDA's response concluded, contrary to arguments raised by sanofi-aventis, that its approach to approving ANDAs for enoxaparin is consistent with Agency precedent concerning other drugs that are not fully characterized. *Id.* at 23.

Based on this reasoning, and on the additional studies submitted by Sandoz, FDA approved Sandoz's ANDA.

ARGUMENT

Sanofi-aventis seeks a TRO "for a limited period of time until the Court has the opportunity to pass on the merits of the demand for a preliminary injunction." *Barrow v. Graham*, 124 F. Supp. 2d 714, 715-16 (D.D.C. 2000). The Court should grant a TRO, followed by a preliminary injunction, in order to prevent the substantial and irreparable harm that will flow from FDA's wrongful approval of Sandoz's ANDA No. 87-660 in excess of its authority under the FDCA. Sanofi-aventis satisfies the traditional four-part test for interim injunctive relief, which weighs four factors:

> (1) whether there is a substantial likelihood that the plaintiff will prevail on the merits; (2) whether the plaintiff will suffer irreparable injury if the temporary restraining order does not issue; (3) the hardship to the defendants if the temporary restraining order is granted is balanced against the hardship to the plaintiff if the temporary restraining order is not granted; and (4) whether the public interest favors granting the preliminary relief requested.

Boehringer Ingelheim Corp. v. Shalala, 993 F. Supp. 1, 1 (D.D.C. 1997); *see also Virginia Petroleum Jobbers Ass'n v. Federal Power Comm'n*, 259 F.2d 921, 925 (D.C. Cir. 1958). A parallel four-pronged test governs the grant of a preliminary injunction. *See, e.g., Winter v. Natural Res. Def. Council*, 129 S. Ct. 365, 374 (2008) ("A plaintiff seeking a preliminary injunction must establish that he is likely to succeed on the merits, that he is likely to suffer

irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest.").

Traditionally, these four factors have been evaluated on a sliding scale and balanced against each other. *See Serono Labs, Inc. v. Shalala*, 158 F.3d 1313, 1318 (D.C. Cir. 1998).[20] The D.C. Circuit has "recognized that injunctive relief may be justified, for example, 'where there is a particularly strong likelihood of success on the merits even if there is a relatively slight showing of irreparable injury.'" *CSX Transp., Inc. v. Williams*, 406 F.3d 667, 670 (D.C. Cir. 2005) (quoting *CityFed Fin. Corp. v. Office of Thrift Supervision*, 58 F.3d 738, 747 (D.C. Cir. 1995)); *see also Cuomo v. U.S. Nuclear Regulatory Comm'n*, 772 F.2d 972, 974 (D.C. Cir. 1985); *Merriweather v. Lappin*, 680 F. Supp. 2d 142, 143 (D.D.C. 2010).

Each of the four factors weighs in favor of the grant of preliminary relief for sanofi-aventis.

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[20] In *Winter v. Natural Resources Defense Council, Inc.*, 129 S. Ct. 365, 374 (2008), the Supreme Court declared that "[a] plaintiff seeking a preliminary injunction must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest." The D.C. Circuit has stated that "the analysis in *Winter* could be read to create a more demanding burden, although the decision does not squarely discuss whether the four factors are to be balanced on a sliding scale." *Pension Ben. Guar. Corp.*, 571 F.3d 1288, 1292 (D.C. Cir. 2009); *see also id.* at 1295 (Kavanaugh, J., joined by Henderson, J., concurring) ("[T]his Circuit's traditional sliding-scale approach to preliminary injunctions may be difficult to square with the Supreme Court's recent decisions . . ."); *but see, e.g., Brodie v. U.S. Dept. of Health and Human Services*, --- F.Supp.2d ----, 2010 WL 2222431, at *4 (D.D.C. Jun. 04, 2010) ("The plaintiff is not required to prevail on each of these factors. Rather, these factors must be viewed as a continuum, with more of one factor compensating for less of another."). Because all four factors weigh strongly in favor of sanofi-aventis, preliminary relief is warranted under either standard.

I. SANOFI-AVENTIS IS LIKELY TO PREVAIL ON THE MERITS

It is likely that sanofi-aventis will prevail on the merits. FDA has exceeded its authority under section 505(j) by approving an ANDA for a fully substitutable generic product despite having required Sandoz to submit additional studies to demonstrate safety and effectiveness of the generic drug. Because FDA required Sandoz to submit additional studies to demonstrate safety and effectiveness, the proper approval mechanism was a full NDA under section 505(b), and the resulting generic product should not be fully substitutable for Lovenox. In addition, the agency has departed from Agency precedent governing approval of generic versions of drugs derived from complex biological starting material that have not been fully characterized, without adequate justification for this departure.

Furthermore, the five criteria specified in FDA's response to the sanofi-aventis Citizen Petition plus the additional studies submitted by Sandoz are insufficient to establish that the generic product is the "same as" Lovenox, as required by section 505(j) of the FDCA. By approving the application without sufficient evidence that its active ingredient is "the same as" the active ingredient in Lovenox, FDA has exceeded its authority under the Act.

Section 706(2)(A) of the Administrative Procedure Act ("APA"), 5 U.S.C. § 706(2)(A), instructs that a reviewing court must "hold unlawful and set aside agency action" where—as here—it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." Agency action is arbitrary and capricious when "the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a

difference in view or the product of agency expertise."[21] *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Ins. Co.*, 463 U.S. 29, 43 (1983).

A. FDA Exceeded Its Authority Under Section 505(j) by Approving Sandoz's ANDA After Requiring Submission of Additional Safety Data.

FDA's approval of Sandoz's ANDA despite having required submission of additional studies to demonstrate safety violates section 505(j) of the FDCA. The ANDA approval process that Congress created under section 505(j) is available only in those situations where further studies, other than bioequivalence studies, are not required to support the finding of safety and effectiveness necessary for approval. The plain language of the statute as well as FDA's own prior statements make clear that the Agency may not require submission of such studies from an ANDA applicant. Furthermore, FDA's actions are internally inconsistent and violate the intent of the 505(j) pathway.

1. The Plain Language of Section 505(j) Prohibits FDA from Requiring ANDA Applicants to Submit Safety Data (Other Than Bioequivalence Data) From Clinical or Preclinical Studies.

Section 505(j) specifically prohibits the FDA from approving an ANDA application after requiring ANDA applicants to submit the type of additional data that FDA required Sandoz to submit. Clauses (i) through (viii) of section 505(j)(2)(A) set forth the information and data that an ANDA must contain. An ANDA applicant must submit only information necessary to demonstrate that the proposed generic drug is "the same as" and

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[21] The review of agency action requires a "searching and careful" inquiry into the basis for the agency's decision. *Zotos Int'l, Inc. v. Young*, 830 F.2d 350, 352 (D.C. Cir. 1987) (quoting *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971)). A court does "not hear cases merely to rubber stamp agency actions. To play that role would be 'tantamount to abdicating the judiciary's responsibility under the Administrative Procedure Act.'" *Natural Res. Defense Council, Inc. v. Daley*, 209 F.3d 747, 755 (D.C. Cir. 2000) (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1491 (D.C. Cir. 1995)).

"bioequivalent to" the reference listed drug plus certain manufacturing and labeling information. Section 505(j)(2)(A) concludes by stating quite clearly

> The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

21 U.S.C. § 355(j)(2)(A); *see also Serono Labs v. Shalala*, 158 F.3d 1313, 1324 (D.C. Cir. 1998) (noting that although the FDCA does not preclude an ANDA applicant from *voluntarily* submitting additional safety studies with its ANDA, it likely prohibits FDA from *requiring* submission of such data as a condition of approval). Thus, the plain language of the statute makes clear that Congress did not intend to permit FDA to require the submission of clinical or preclinical data in support of safety or effectiveness for an ANDA.

FDA itself has acknowledged, on several occasions, this basic statutory limitation on the use of ANDAs. For example, in the preamble to the final rule implementing the ANDA provisions of the Hatch-Waxman Act, FDA made clear that

> Section 505(j) of the act permits ANDAs only for duplicate and related versions of previously approved drug products. The ANDA applicant relies on a prior agency finding of safety and effectiveness based on the evidence presented in a previously approved new drug application. *If investigations on a drug's safety or effectiveness are necessary for approval, an ANDA is not permitted.*

57 Fed. Reg. 17950, 17953 (April 28, 1992) (emphasis added). *See also* 54 Fed. Reg. 28872, 28879 (1989) ("Such a product would require investigations to show its safety and effectiveness; thus an ANDA would not be appropriate.").

To be sure, FDA has asserted that ANDA applicants may submit limited preclinical data for certain confirmatory purposes. In its preamble to the proposed rules

implementing the ANDA provisions, FDA discussed the kinds of data that could be submitted with an ANDA[22]:

> under certain circumstances, data from limited confirmatory testing to show that the characteristics that make the proposed drug product different from the listed drug do not alter its safety and effectiveness may be accepted in a petition or as additional data to be included in an ANDA resulting from an approved petition.

54 Fed. Reg. 28880. The scope of additional confirmatory testing data that may be provided in an ANDA, however, is limited. In its preamble FDA defined these limitations:

> By limited confirmatory testing, the agency means simple studies intended to rule out unlikely problems. . . . *A study intended to answer basic safety or effectiveness questions or one that would require substantial scientific review would not be considered limited confirmatory testing.*

Id. (emphasis added and internal citation omitted).

The data that FDA required Sandoz to submit clearly fall outside of this confirmatory testing exception. The question whether Sandoz's generic enoxaparin product will induce a more significant immunologic response than does Lovenox is clearly a basic safety question. In November 2007, FDA sent Sandoz a "Not Approvable Letter," explaining that Sandoz's ANDA was not approvable because it did not adequately address the potential for immunogenicity of the drug product. *See* Form 10-K for Momenta Pharm., Inc. This refusal clearly establishes that the information that Sandoz had submitted under section 505(j)(2)(A) was not enough to ensure that the Sandoz product was safe and effective and that the ANDA procedure was not appropriate.

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[22] Specifically, FDA discussed this exception in the context of applicants who have filed "Suitability Petitions." Such petitions are intended to seek FDA's permission to file an ANDA for a drug that makes minor formulation changes as compared to the RLD.

Moreover, FDA's own press release clearly belies any claim that the data was required for "limited confirmatory testing." The July 23, 2010 press release specifically states that FDA required the information "to assure that the drug would be as safe and effective as the brand name product." News Release, Food and Drug Administration, FDA Approves First Generic Enoxaparin Sodium Injection, July 23, 2010, *available at* http://www.fda.gov/NewsEvents/ Newsroom/PressAnnouncements/ucm220092.htm.. In a Q&A document that FDA released on the same day, FDA stated that

> FDA expects sponsors of generic enoxaparin products to demonstrate that their manufactured versions do not have any higher risk of these or other dangerous reactions than Lovenox. Although conducting immunogenicity testing for this product can be an extensive and time-consuming process for a manufacturer, all manufacturers of generic enoxaparin are expected to do this as part of the application process.[23]

The FDA Response attempts to assert that the tests the Agency required Sandoz to submit are limited simply to analyzing "impurities" rather than the actual active ingredient. CP Response, at 41-42. This is both irrelevant and inconsistent with prior Agency precedent. First, section 505(j)(2)(A)'s prohibition against requiring ANDA applicants to submit additional data is absolute. The plain language prohibits requiring any further data from an ANDA applicant, not just data related to the active ingredient. Second, the fact that FDA felt compelled to require additional immunogenicity data clearly demonstrates that the Agency is not completely confident in its determination that Sandoz's generic product has the "same" active ingredient as does Lovenox. All drugs can (and most

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[23] Food and Drug Administration, Generic Enoxaparin Questions and Answers, July 23, 2010, *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220037.htm.

do) contain impurities. Yet FDA does not require this type of immunogenicity testing from generic versions of most classical molecules. This is precisely because where FDA is confident that it knows the structure of the generic's active ingredient (i.e., where the active ingredient is fully characterized) this kind of testing is not necessary.

This is illustrated by FDA's November 17, 2008 response to a Citizen Petition regarding the drug calcitonin nasal spray. Cunningham Decl., Ex. P ("Calcitonin Response"). In that case FDA considered how impurities might affect the immunogenicity in separate synthetic and recombinant versions of salmon calcitonin. To address that issue, FDA stated, "[f]or that reason, to ensure acceptable immunogenicity an ANDA applicant must show that its generic product has an impurity profile that is comparable [to the RLD]." Calcitonin Response, at 11. For synthetic calcitonin, FDA stated that because the impurity profiles of the generic and the RLD could be compared, no immunogenicity testing was required.

By contrast, FDA stated that differences regarding the impurity profiles of recombinant salmon calcitonin and the RLD might be unpredictable, and might exert potent immunogenic effect. Because of the complexity of recombinant calcitonin it was not feasible to compare the impurity profiles of the proposed generic and the RLD. Thus, FDA stated, it "would not at this time accept for review an ANDA" for recombinant salmon calcitonin. Calcitonin Response, at 12. In other words, actually having to demonstrate lack of immunogenic effect through data is not acceptable in an ANDA.

Similarly, were FDA able to identify the impurities in the Sandoz product and conclude that they are the same as those in Lovenox, it would not have need to require Sandoz to conduct additional immunogenicity testing. Because enoxaparin is not fully

characterized, FDA is unsure of the impurity profile of the two drugs so immunogenicity testing was required. Faced with this fact, FDA decided to deviate from its own statements in the Calcitonin Response and require further immunogenicity testing from an ANDA applicant. This is directly contrary to the position taken by FDA in the Calcitonin Response and is barred by the statute.

Thus, FDA exceeded its authority under section 505(j) when it approved Sandoz's ANDA despite having required Sandoz to submit additional data to confirm the drug's safety and effectiveness.[24]

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[24] The FDCA's Suitability Petition provisions further make clear that FDA may not require an ANDA applicant to submit animal or clinical studies. Section 505(j)(2)(C) permits potential ANDA applicants to request FDA permission to file an ANDA for a drug that has a different active ingredient, or whose route of administration, dosage form, or strength differs from that of the listed pioneer drug, by filing a Suitability Petition with FDA. 21 U.S.C. § 355(j)(2)(C). FDA must, however, disapprove a Suitability Petition if the agency finds that "investigations must be conducted to show the safety and effectiveness of the drug or any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug." 21 U.S.C. § 355(j)(2)(C)(i). FDA's regulations, in turn, explain 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).

The Suitability Petition provision reflects Congress's determination that the 505(j) approval mechanism for generic products applies only where the pioneer and generic product are sufficiently identical such that additional preclinical and clinical data (other than bioequivalence data) are not required to approve the application. FDA's approval of Sandoz's ANDA for generic enoxaparin after requiring clinical and pre-clinical studies to support the safety and/or efficacy of the drug rests on an untenable interpretation of the FDCA under which Congress would have precluded submission of such data in the context of an ANDA subject to a suitability petition but permitted it in the context of an ANDA not subject to such a petition. Congress clearly provided that FDA may not require clinical trials in support of ANDA approval, and FDA's determination to the contrary thus conflicts with the plain meaning of the FDCA's provisions governing FDA's approval of generic drugs.

2. FDA's Actions Are Internally Inconsistent And Violate the Intent of the 505(j) Generic Approval Pathway.

As discussed above, the 505(j) ANDA pathway exists to provide an abbreviated approval mechanism for drugs that are "the same" as the RLD. Because ANDA generics submit information to show that their product is the same as the RLD, it is not necessary for the generic applicant to submit additional studies demonstrating that the drug is safe and effective. In addition, because of this finding of sameness, ANDA generics are fully substitutable for the RLD unless they are not also bioequivalent. Congress clearly demonstrated its intent that the ANDA pathway be used only for those generic drugs that need no further study to demonstrate safety or effectiveness by prohibiting FDA from requiring an ANDA applicant to submit any additional data beyond the data listed in 505(j)(2)(A). Sandoz submitted this required information with its original ANDA.

By requiring Sandoz to submit additional data to demonstrate safety and effectiveness, FDA implicitly concluded that Sandoz's generic drug is not "the same" as Lovenox. FDA's conclusion, however, is flatly inconsistent with the Agency's requirement that Sandoz submit additional immunogenicity data to demonstrate that the generic product is safe. By clearly stating that all generic versions of enoxaparin will have to perform additional safety studies, FDA recognized that more safety data is needed and the §505(j) criteria are not sufficient. Its approval of Sandoz's generic enoxaparin under § 505(j) is therefore unlawful.

Once FDA made the determination that additional studies were needed to demonstrate safety and effectiveness, FDA should have required Sandoz to withdraw its

ANDA and resubmit its application as a full application under section 505(b)(2).[25] By circumventing Congress's requirements for different pathways for generic approvals, FDA acted outside its authority under the FDCA and contrary to law under the APA.

B. FDA Failed to Explain Its Departure from Agency Precedent in Approving a Generic Version of a Drug That Is Not Fully Characterized.

FDA's approval of Sandoz's ANDA represents a significant departure from well-established agency precedent regarding complex products—like enoxaparin—that are not fully characterized. FDA, however, has failed to provide a legitimate reason for its departure from that precedent. Instead, the Agency's treatment of these precedents is wholly conclusory, in most cases stating only the obvious fact that the drugs at issue in those cases are different from Lovenox. It fails to address the fact that enoxaparin is not fully characterized or to provide a substantive reason for why it should be treated differently than other drugs that are not fully characterized.

FDA cannot simply gloss over its earlier decisions or choose to ignore their clear import without providing a rational explanation for why it has decided to treat similarly situated products differently. *See, e.g.*, *United States v. Diapulse Corp. of Am.*, 748 F.2d 56 (2d Cir. 1984) (enjoining FDA's disparate treatment of two similar medical devices); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) (holding that federal agencies must have a "rational basis" for treating two similar products distinctly); *U.S. v. Undetermined Quantities of an Article of Drug Labeled as Exachol*, 716 F. Supp. 787

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[25] The shift of an application from 505(j) to 505(b)(2) is not a formality. Among other differences, 21 U.S.C. § 379h(a)(1) requires persons submitting applications under section 505(b)(2), which qualify as "human drug applications" to pay user fees of up to $1,405,500 for applications containing clinical data and $702,750 for applications not requiring clinical data. *See* 74 Fed. Reg. 38451 (August 3, 2009).

(S.D.N.Y. 1989) (denying FDA request for summary judgment because of agency's inconsistent application of regulatory policy with respect to "special dietary foods"). By approving Sandoz' ANDA, and treating Lovenox differently from other products it has considered without any rational explanation for doing so, the agency's decision is arbitrary and capricious under the APA and should be enjoined.

1. Hyaluronidase

FDA's approval of Sandoz's ANDA conflicts with its previous determinations regarding the status of ISTA Pharmaceuticals, Inc.'s ("ISTA") hyaluronidase product, Vitrase, which, like enoxaparin, is not fully characterized. On October 25, 2005, FDA denied a citizen petition filed by ISTA regarding marketing exclusivity for Vitrase. Cunningham Decl., Ex. K, Attachment A ("ISTA Rejection"). ISTA had requested that FDA reverse its decision to grant ISTA 5-year marketing exclusivity for its product (so-called "new chemical entity" exclusivity) rather than a separate 3-year exclusivity.[26] Like enoxaparin, hyaluronidase is derived from biological starting material (in Vitrase's case, mammalian testicles). ISTA Rejection, at 3. Resolving the exclusivity issue for ISTA's product required the agency to determine whether FDA had previously approved a separate product with the same active ingredient. *Id*

In determining that Vitrase should receive 5-year new chemical entity exclusivity rather than 3-year exclusivity, FDA relied heavily on the fact that the chemical structure of hyaluronidase products has never been fully characterized. As FDA pointed out

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[26] In the peculiar circumstances of hyaluronidase, 5-year NCE exclusivity would have resulted in virtually no exclusivity for ISTA's product, whereas receipt of the separate 3-year exclusivity would have given ISTA a measure of market protection.

in its rejection of ISTA's citizen petition, because hyaluronidase is not fully characterized, "the Agency does not know whether these products, in fact, contain any previously approved active moieties." *Id.* at 2.[27] FDA went on to note that "[g]enerally, if the Agency has insufficient information to know whether a product contains a previously approved active moiety, the applicant would be required to submit an NDA containing substantial clinical safety and efficacy data." *Id.* at 9. In short, FDA reasoned that, because hyaluronidase is not fully characterized, the agency could not determine whether ISTA's product contained the same active ingredient as a previously approved product.

FDA went on to note that "[g]enerally, if the Agency has insufficient information to know whether a product contains a previously approved active moiety, the applicant would be required to submit an NDA containing substantial clinical safety and efficacy data." *Id.* at 9. In short, FDA reasoned that because hyaluronidase is not fully characterized, the agency could not determine whether ISTA's product contained the same active ingredient as a previously approved product. Thus, FDA could not be certain that it had previously approved that active ingredient.[28]

FDA's approval of Sandoz's generic product is directly at odds with the agency's treatment of hyaluronidase exclusivity. Like organic hyaluronidase, enoxaparin comes from organic source material and its chemical structure cannot be fully characterized (by direct examination) due to limitations of available analytical technology. FDA's

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[27] FDA interprets the term "active moiety" to mean a drug's active ingredient, including any ester or salt of the active ingredient. *See* ISTA Rejection, at 7.

[28] Sanofi-aventis brought this clear precedent to FDA's attention on March 16, 2006 through a comment to the Citizen Petition. Cunningham Decl., Ex. K.

reasoning with respect to hyaluronidase makes clear that where a biologically-derived product has not been fully characterized, the agency cannot determine whether one version of the product contains the same active ingredient as another. Because the ANDA provisions of section 505(j) require that an ANDA demonstrate that the generic product has "the same" active ingredient as the pioneer drug on which it is based, FDA has effectively ruled out approval of ANDAs for products that are not fully characterized.

FDA's sole justification for its departure from the hyaluronidase precedent is that the drugs are just different: "[hyaluronidase and enoxaparin] are derived from different origins and are composed of entirely different molecular structures." CP Response, at 40. But, this explanation fails to sustain FDA's burden under the APA that an agency "changing its course . . . [by] departing from precedent is obligated to supply a reasoned analysis for the change." *Global Cross Telecom, Inc. v. FCC*, 259 F.3d 740, 746 (D.C. Cir. 2001) (internal citation and quotation omitted); *see also Nebraska, Dept. of Health & Human Servs. v. U.S. Dep't. of Health and Human Servs.*, 340 F. Supp. 2d 1, 16 (D.D.C. 2004) ("If an agency decides to act in a manner inconsistent with the manner in which it previously acted, it must cogently explain why it has exercised its discretion in a given manner and must supply a reasoned analysis when it changes course.") (internal quotation and citation omitted).

In particular, FDA's explanation proves too much, as all drugs are different in one respect or another; indeed, if the only justification FDA needs for a significant departure from Agency precedent is that two drugs are "different," then FDA would have no need to pay heed to its previous decisions. Moreover, nowhere in the ISTA Rejection does FDA state that its decision was based on the particular structure of hyaluronidase in combination with the fact that the drug is not fully characterized. Rather, the sole basis for FDA's

determination that it could not say for sure if Vitrase was "the same" as a previously approved drug was the fact that hyaluronidase is not fully characterized. ISTA Rejection, at 5. Thus, FDA's contention that the two situations can be distinguished on the ground that the drugs are different, is not supported by its own prior decision. Neither drug is fully characterized, and FDA has clearly stated that when a drug is not fully characterized, the Agency cannot tell if it is "the same" as another drug. In short, FDA has failed to offer a reasonable justification for treating two similarly situated drugs differently, and its decision to approve Sandoz's ANDA for generic enoxaparin should be enjoined as arbitrary and capricious.

2. Omnitrope®

FDA's approval of Sandoz's enoxaparin ANDA is also at odds with FDA's 2006 approval of Sandoz's generic recombinant human growth hormone ("rhGH") product, Omnitrope®. There, FDA required that Sandoz file a 505(b)(2) (rather than an ANDA) and declined to make a substitutability determination despite the fact that recombinant human growth hormone is fully characterized and less complex than enoxaparin. Omnitrope Letter, at 12. In addition, FDA required that Sandoz conduct additional immunogenicity studies in support of its approval of Omnitrope, similar to those that Sandoz was required to conduct for enoxaparin. *Id.* at 10-12. FDA has offered no explanation for its departure from its finding that an ANDA was not permissible for Omnitrope but is permissible for generic enoxaparin, when enoxaparin is more complex, is not fully characterized, and where the

Agency required similar immunogenicity testing. *See Global Cross Telecom, Inc.*, 259 F.3d at 746; *Nebraska, Dept. of Health & Human Services*, 340 F. Supp. 2d at 16.[29]

Omnitrope (somatropin [rDNA origin] for injection) is a generic version of Pfizer's pioneer recombinant human growth hormone ("rhGH") product, Genotropin®. Like Lovenox, Omnitrope is a biological product (*i.e.*, derived from biological sources) and is far more complex than the traditional small-molecule synthetic drugs that are typically the subject of ANDAs. Because of this complexity, FDA expressed concerns over the potential immunogenicity of generic rhGH products, and did not permit Sandoz to file for approval via the 505(j) ANDA process. Instead, the agency required Sandoz to submit data from original clinical trials to assess, among other things, immunogenicity, and submit its application under FDCA section 505(b)(2) rather than 505(j). Omnitrope Letter, at 8-12.

In explaining its decision, the FDA specifically noted that approval through the 505(b)(2) pathway was possible in the case of Omnitrope only because Omnitrope is a relatively simple compound (for a biologically-derived product) with "several characteristics that facilitate comparisons between two rhGH products" for purposes of approval under 505(b)(2). *Id.* at 7-8 These characteristics included:

- That hGH is well characterized;
- That hGH is non-glycosylated (*i.e.*, sugar molecules are not added to the protein);
- That the primary structure of hGH is known and physicochemical tests exist for the determination of an hGH product's secondary and tertiary structures;
- Clinically relevant bioassays and qualified biomarkers are available for hGH;
- That hGH has a long and well documented history of clinical use; and

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[29] Despite the fact that sanofi-aventis specifically brought the precedent of the Omnitrope® approval to FDA's attention in a Citizen Petition supplement, FDA's response to the Citizen Petition does not even mention the drug. Cunningham Decl., Ex. L.

- That hGH's mechanism of drug action is known and its human toxicity profile is well understood.

See id. at 7-8.

Enoxaparin, by contrast, bears few, if any, of these qualities. As the Citizen Petition pointed out to FDA in great detail, enoxaparin's structure is significantly more complex than that of hGH products. Enoxaparin has not been fully characterized and, indeed, cannot be directly and completely characterized using current technology. Citizen Petition, at 11, 18-19; Cunningham Decl., Ex. H. The secondary and tertiary structure of enoxaparin is not understood and no physicochemical tests exist to determine the secondary or tertiary structure. Cunningham Decl., Ex. H, at 10-11. Bioassays and biomarkers available for LMWHs like enoxaparin are of limited value, and enoxaparin's mechanism of action is not fully understood. *See* Citizen Petition, at 13-19; *see also* Cunningham Decl., Ex. F.

Because, by FDA's own admission, hGH is a relatively simple compound, the requirements for approval applied to Omnitrope should serve as a floor for approval of generic versions of more complex products such as enoxaparin. This requires, at a minimum, that FDA require any applicants for generic versions of enoxaparin to file their applications as 505(b)(2) applications rather than ANDAs, and that the resulting products should not be substitutable. Thus, FDA has failed to provide any rational justification for applying less rigorous generic approval requirements to the more complex enoxaparin product, and its decision is arbitrary and capricious.

3. Premarin

Finally, FDA previously considered the issue of characterization in a ruling involving Premarin, a conjugated estrogen product used to treat the symptoms of menopause

and to prevent osteoporosis. *See* Food and Drug Administration, FDA Backgrounder on Conjugated Estrogens, last update, July 7, 2005, *available at* http://www.fda.gov/Drugs/DrugSafety/ InformationbyDrugClass/ucm168838.htm. Like Lovenox, Premarin is derived from biological starting materials (in Premarin's case, pregnant mare's urine). *Id.* Originally, although it was well-known that Premarin contained several different estrogenic compounds, it was thought that all estrogens were the same. *Id.* As a result, there was a belief that generic Premarin products could be manufactured simply by duplicating Premarin's total estrogen content, without regard for the specific amounts of its component estrogenic compounds. *Id.*

On November 30, 1994 Wyeth Pharmaceuticals ("Wyeth"), the manufacturer of Premarin, filed a citizen petition with FDA challenging the assertion that all estrogenic compounds are the same. *See* Memorandum, Department of Health and Human Services, Conjugated Estrogens-Letter from Dr. Janet Woodcock, May 5, 1997, *available at* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm168836.htm. It argued that because it was impossible to identify all of the different estrogens in Premarin, the product could not be fully characterized and therefore could not be duplicated by a synthetic generic (*i.e.*, one manufactured by physically combining estrogens, rather than by processing pregnant mare's urine in the manner Wyeth did). *Id.*

FDA eventually agreed with Wyeth, based on new discoveries about the nature of estrogenic compounds. In particular, research revealed that certain estrogenic compounds in Premarin had a significant effect on Premarin's overall therapeutic effect, despite the fact that they were present in only small amounts. For example, research showed that an estrogenic compound known as DHES significantly influenced Premarin's therapeutic

effect, despite the fact that it was present in less than 5% of the mixture. FDA cited this finding as demonstrating the need for further characterization of Premarin. *Id.*

As a result of these findings, FDA concluded that Premarin must be fully characterized (*i.e.*, all the different estrogenic compounds in Premarin must be identified) before synthetic generic Premarin could be approved. *Id.* FDA reasoned that no synthetic generic Premarin could claim to have the "same" active ingredients as did Premarin until all of the estrogenic compounds in Premarin were identified and their contributions to the drug's effect understood. How, FDA reasoned, could a manufacturer claim to have included all of the relevant estrogenic compounds if it was not known what estrogenic compounds were present and active in Premarin in the first place? FDA declared that it would not approve any ANDA for synthetic generic Premarin until such time as Premarin became adequately characterized. *Id.*

This reasoning is fully applicable to Lovenox. While Sandoz's generic drug is not synthetic, the fact that the structure of enoxaparin is dependent on the manufacturing process is a similarly confounding factor. Because Sandoz was not required to use a process equivalent to sanofi-aventis' process, it is impossible to be sure that all of the clinically relevant components of enoxaparin are present in the generic product. The inability to confirm that all of the clinically relevant components are present in non-synthetic generic versions of enoxaparin is precisely what led FDA to bar synthetic generics until Premarin becomes fully characterized. Sanofi-aventis brought the Premarin precedent to FDA's attention in its original Citizen Petition. Citizen's Petition, at 22.

FDA's justification for ignoring the Premarin precedent is familiar: "[Premarin and enoxaparin] are derived from different origins and composed of entirely

different molecular structures." CP Response, at 39. The only addition rationale that FDA provides is to point out the obvious fact that in the Premarin case, FDA was trying to determine whether to approve synthetic generic products and that its ruling in Premarin would not have precluded approval of a naturally sourced product. This response, however, completely ignores the fact that the process-dependent nature of enoxaparin has the same practical confounding effect of attempting to make a synthetic Premarin generic. In both cases, the lack of full characterization of the product makes it impossible for FDA to determine if the proposed generic product (synthetic for Premarin, naturally sourced for enoxaparin) contains the same active ingredient as the RLD. FDA's decision to approve Sandoz's ANDA for generic enoxaparin is thus arbitrary and capricious, departing markedly from well-established agency precedent without providing a rational explanation for the change.

C. FDA Has Not Provided A Rational Justification for Ignoring the Arguments Set Forth In the Citizen Petition.

In approving Sandoz' ANDA, FDA ignored voluminous scientific evidence demonstrating that until enoxaparin is fully characterized, generic enoxaparin products that do not use a manufacturing process that is equivalent to sanofi-aventis' process will not be the same as Lovenox. Although the courts may show deference to an Agency's determinations of scientific evidence, FDA must at least provide some rational explanation for its decision to disregard scientific evidence that directly contradicts its administrative findings. *Motor Vehicle Mfrs. Ass'n, Inc. v. State Farm Mut. Auto. Ins. Co.,* 463 U.S. 29, 43 (1983) (agency is required to "articulate a satisfactory explanation for its action including a

rational connection between the facts found and the choice made").[30] FDA's failure to do so here in connection with the approval of the Sandoz ANDA is arbitrary and capricious, and the approval should therefore be enjoined.

Sanofi-aventis's Citizen Petition demonstrates that small differences in the manufacturing process used to create a given LMWH can have significant effects on the pharmacological activity of the drug. Specifically, the Citizen Petition provided literally hundreds of pages of scientific data from scientific studies that clearly demonstrate that slight modifications of the process, such as changes in concentration of reagents used, temperature, or time or reaction, result in significant changes to the structure of the LMWH and, thus, the pharmacological properties of the drug. *See* Cunningham Decl., Exs. D, F-L.

In making these arguments to the Agency, sanofi-aventis is not alone. In fact, the balance of worldwide scientific opinion appears to side with sanofi-aventis' basic premise. Several independent scientific/medical third parties, including the Society for Hospital Medicine, the director of the Pulmonary Vascular Disease Center and Duke University Medical Center, and the North American Thrombosis Forum, submitted comments supporting sanofi-aventis' petition. Cunningham Decl., Exs. M-O. Sanofi-aventis is not aware of a single independent third-party that filed a comment in opposition of the Citizen Petition.

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[30] Although courts afford FDA a certain degree of deference on matters of science and interpretation of the FDCA, that deference, however, has its limits. *See, e.g., A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490-91 (D.C. Cir. 1995) (explaining that "courts give a high level of deference to an agency's evaluations of scientific data within its area of expertise" but noting that "[d]eferring to an agency's exercise of its discretion, however, is not tantamount to abdicating the judiciary's responsibility under the Administrative Procedure Act").

FDA's sister regulatory agency in Europe, the European Medicines Agency (EMEA) also appears to agree with sanofi-aventis's position. Due to the complexity and difficulty of characterization of LMWH, applicants seeking approval of generic versions of LMWHs in the European Community (EC) may not seek approval of their products as generic medicinal products (the EC's version of the ANDA). They must instead seek approval of their products as similar biological medicinal products under Article 10(4) of 2001/83/EC, as amended. European Medicines Agency, Committee for Medicinal Products for Human Use, June 2006 Plenary Meeting, Monthly Report (July 12, 2006), at 22, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2009/10/WC500006362.pdf. In addition, applications for approval of a generic LMWH product in the EC must include data from at least one adequately powered, randomized, double-blind, parallel group clinical trial to show comparative safety and efficacy to the reference product. European Medicines Agency, Committee For Medicinal Products For Human Use, March 2009 Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing Low-Molecular-Weight-Heparins, *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003927.pdf.

More recently, in July 2009, the Journal of Thrombosis and Haemostasis published "Recommendations on biosimilar low-molecular-weight-heparins" from the Scientific and Standardization Committee of the International Society on Thrombosis and

Haemostasis (the "ISTH Recommendations").[31] The International Society on Thrombosis and Haemostasis (ISTH) is the world's foremost medical/scientific society focusing on issues relating to thrombosis and abnormalities of hemostasis and vascular biology. Similar to the EMEA Guideline, the ISTH Recommendations suggest a five-part development program for any generic LMWH that purports to be therapeutically equivalent to a reference LMWH. This development program includes comparative clinical safety and effectiveness trials "for every indication for which regulatory approval is sought."[32]

FDA has failed to provide a rational justification for its apparent rejection of the massive amount of scientific data contained in the Citizen Petition. Although the Agency's response to the Citizen Petition is lengthy, it does not refute the results or accuracy of any of the numerous studies that sanofi-aventis provided to the Agency. Nor does FDA dispute the basic proposition that small changes in the manufacturing process used to create an LMWH cause changes in the drug's structure and resulting pharmacological activity. Instead, FDA's response merely sets forth the Agency's newly-created five criteria for showing sameness in a generic enoxaparin product and, with circular reasoning, concludes that meeting the five criteria "demonstrates that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent" and, therefore, "the generic drug product's enoxaparin is the same as Lovenox's enoxaparin." FDA Response at 3, 11, 13, 16, 21, 23, 24, 26, 28, 30, 35, 36, 38, and 44.

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[31] Kakkar HJ, et al. on behalf of the Subcommittee on Control of Anticoagulation of the SSC of the ISTH. Recommendations on biosimilar low-molecular-weight heparins. *J Thromb Haemost* 2009; 7: 1222-5.

[32] *Id.*

FDA's response similarly dismisses the EMEA's decision to consider applications for generic LMWHs under Europe's equivalent to the 505(b)(2) application, rather than their equivalent to the ANDA. FDA's response does not challenge or contradict the findings that have been expressed by the EMEA on the subject. Rather, FDA's response simply states that FDA is not bound by the EMEA's determinations. FDA's only effort to distinguish the EMEA's decision is to state that the EMEA has "set forth guidelines for LMWH products that contain a *similar* (as opposed to the same) active ingredient as that contained in another already marketed LMWH product." CP Response, at 43. This response is, of course, tautological. The only reason why the EMEA's guidelines don't apply to LMWH products that contain the same active ingredient is that the EMEA has concluded that a generic LMWH product cannot be the same as the RLD.[33]

In sum, FDA has offered no explanation for why it disregarded the voluminous scientific evidence demonstrating that generic enoxaparin product is not the same as Lovenox. Its failure to do so is in violation of the APA.

II. SANOFI-AVENTIS WILL SUFFER IRREPARABLE INJURY IN THE ABSENCE OF INJUNCTIVE RELIEF.

Unless FDA is required promptly to withdraw its approval of Sandoz's ANDA for generic enoxaparin, sanofi-aventis will suffer irreparable injury. Sanofi-aventis' annual domestic net sales for Lovenox in 2009 were approximately $2.5 billion, which translates to nearly $210 million per month. Durso Decl., ¶ 9. If FDA's unlawful approval of Sandoz's ANDA is permitted to stand, it is likely that the Sandoz generic product will

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[33] FDA's response makes no mention, whatsoever, of the ISTH Recommendations.

enter the market within a short period of time. *Id.* ¶ 12. As a result, sanofi-aventis may immediately begin losing sales as group purchasing organizations ("GPOs") switch to the lower cost generic for institutional (hospital) use and retail pharmacists substitute the generic product when patients present subscriptions for Lovenox.[34]

Sanofi-aventis would suffer very substantial economic loss if generic sales could continue until a merits ruling issued. Past examples in the U.S. show that unit sales of the brand name product fall by up to 90 percent of its sales within the first few months following the introduction of a generic product. Durso Decl. ¶ 14. Even if sanofi-aventis reduced its price to compete with a lower priced generic, sanofi-aventis could lose a minimum of 50 percent of Lovenox sales. *Id.* ¶ 26. Under either scenario, sanofi-aventis would suffer substantial economic loss.

Sanofi-aventis has no adequate remedy at law to recover these lost sales. Such loss of sales resulting from unlawful approval of a generic drug satisfies the irreparable injury component of the standard for injunctive relief. *See Serono Labs., Inc. v. Shalala*, 974 F. Supp. 29, 35-36 (D.D.C. 1997) (granting preliminary injunction in challenge to ANDA approval), *vacated on the merits*, 158 F.3d 1313 (D.C. Cir. 1998). Sanofi-aventis' satisfaction of the irreparable harm requirement is made even more obvious by the fact that the only possible defendant, the FDA, would be shielded by sovereign immunity in any subsequent suit based on its unlawful approval. This court has made clear on multiple occasions that when "the plaintiff in question cannot recover damages from the defendant

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[34] Under state law, pharmacists are permitted (and in some states required) to substitute an available generic when presented with a prescription for a brand-name drug. *See, e.g.*, N.Y. Educ. Law § 6816-a (requiring substitution when certain conditions are met); Fla. Stat. § 465.025 (same).

due to the defendant's sovereign immunity any loss of income suffered by a plaintiff is irreparable per se." *Feinerman v. Bernardi*, 558 F. Supp. 2d 36, 51 (D.D.C. 2008); *see also Smoking Everywhere, Inc. v. U.S. Food and Drug Admin.*, 680 F. Supp. 2d 62, 77 n.19 (D.D.C. 2010) (expressing same point and noting that, because the plaintiffs in that case could not recover money damages from the FDA, irreparable harm would have been shown "even if the claimed economic injury did not threaten plaintiffs' viability"). Although the APA and the Federal Tort Claims Act, 28 U.S.C. § 2680 *et seq.*, provide a limited waiver of sovereign immunity under certain circumstances, neither statute would apply here, for the same reasons this court set forth in *Smoking Everywhere*. *See* 680 F. Supp. 2d at 77 n.19.

The irreparable harm sanofi-aventis would suffer if the FDA's unlawful approval decision were permitted to stand is not limited to immediate, unrecoverable losses in sales revenue. In addition, if sanofi-aventis were to lower the price of Lovenox to compete with a generic product, as it would be forced to do, Sandoz will undoubtedly respond by further lowering its price. This will result in a downward price spiral as both companies attempt to preserve sales. Durso Decl., ¶ 25. Both the loss in sales volume and the price erosion sanofi-aventis will experience as a result of generic entry will be, for the most part, irreversible. Once institutional and retail purchasers become accustomed to a lower price for enoxaparin, they will be reluctant or unwilling to pay a higher price again even if the generic is pulled from the market. Rather than paying the old, higher price for Lovenox, many GPOs will attempt to negotiate contracts to the new, lower price. *Id.* ¶ 31. In addition, generic competition could cause Lovenox to lose its preferred formulary position on some hospital pharmacy formularies and managed care (retail) formularies. *Id.* ¶ 30. If Sandoz's generic product is withdrawn from the market after a trial on the merits, many purchasers will

inevitably blame sanofi-aventis for removal of the lower priced alternative. *Id.* ¶ 29. This will result in a loss of goodwill for sanofi-aventis, which will make it even more difficult for sanofi-aventis to regain sales volume or price levels for Lovenox. *Id.*

As this court recently recognized, "[i]njury to reputation or goodwill is not easily measurable in monetary terms, and so often is viewed as irreparable." *LG Elecs. U.S.A., Inc. v. Dep't of Energy*, 679 F. Supp. 2d 18, 35 (D.D.C. 2010) (quoting 11A Wright & Miller, Federal Practice and Procedure § 2948.1 (2d ed.1995)). Furthermore, a large reduction in revenue from Lovenox would inevitably lead to cut-backs of employees who currently support Lovenox. Sanofi-aventis currently has dozens of employees supporting Lovenox in the areas of R&D, marketing, finance, and other support functions, as well as over 1,000 representatives who sell Lovenox to hospitals and other health care facilities and practitioners. Durso Decl. ¶ 36. Although sanofi-aventis might be able to reassign some of these people, it would most likely have to lay off a significant number. *Id.* It would be difficult to hire back all of these people if sanofi-aventis ultimately prevailed and FDA approval of a generic were later withdrawn. Training of new people would be costly and would take time, and relationships the sales force personnel had developed would be lost. *Id.*

Finally, permitting Sandoz's product to reach the market without sufficient evidence that it is indeed clinically identical to Lovenox could permanently damage sanofi-aventis' reputation and the reputation of the Lovenox brand, as well as present significant risks of harm to patients. As a generic, Sandoz's product will be held out to patients as equivalent to Lovenox in terms of safety and effectiveness. Patients who use Lovenox to prevent or treat life-threatening conditions may suffer harm if generic substitutes are clinically different from Lovenox. As Dr. Cohen explains, if a generic provided less

antithrombotic protection due to the differences described above, patients undergoing major orthopedic procedures would face increased risk of developing a serious or even fatal pulmonary embolism. Cohen Decl., ¶ 16. If inadequate protection should occur in patients with unstable angina, the risk of a heart attack would increase. *Id.* And use of a generic with increased antithrombotic effectiveness after orthopedic surgery could cause patients to bleed more. *Id.* The result could be bleeding into the operated joint, requiring the patient to undergo re-operation with the accompanying risks of an invasive surgical procedure. *Id.*

Patients harmed by use of this product may lose faith in both the generic *and* the branded Lovenox product. Moreover, once a prescribing physician experiences a few instances of "bleeds" or reduced antithrombotic protection, he or she is likely to turn away from enoxaparin and start to use a different anticoagulant (particularly if he or she does not realize a generic is being used and believes the active ingredient is to blame). *Id.* ¶¶ 17-18. Once a physician turns from enoxaparin, it is unlikely that he or she will later return to either Lovenox or the generic product. *Id.* ¶ 19. This could lead to a permanent loss in market share for sanofi-aventis that could not be recovered even if sanofi-aventis were to prevail in a later court proceeding.

III. THE BALANCE OF HARM FAVORS SANOFI-AVENTIS

By contrast, FDA would not be harmed by an injunction barring the agency from unlawfully approving Sandoz's ANDA. Thus, the balance of harm tips strongly in favor of sanofi-aventis. While Sandoz may suffer some harm as a result of delay in bringing its product to market, that harm does not outweigh sanofi-aventis' interest in obtaining the

preliminary relief necessary for meaningful judicial review of FDA's decision.[35] In any event, sanofi-aventis' strong showing on the merits outweighs any harm to FDA or other parties.

IV. THE PUBLIC INTEREST FAVORS GRANT OF INJUNCTIVE RELIEF.

The public interest also favors granting injunctive relief in this case. As a threshold matter, the public interest would be served by requiring the FDA to comply with the law. *See, e.g., Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993) ("[T]here is a strong public interest in meticulous compliance with the law by public officials."); *see also Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1062-63 (D.C. Cir. 1998) (discussing the district court's determination that "the public's interest in the 'faithful application of the laws' outweighed its interest in immediate access to the generic product."). In addition, because FDA approved Sandoz's generic without adequate assurances that it was equivalent to Lovenox, the public interest is served by meaningful judicial review of that decision before patients are subjected to treatment of the generic.

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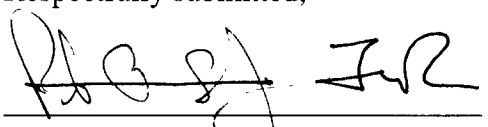
[35] Sanofi does not seek recall of product already shipped by Sandoz pursuant to its approval; only that additional product may not be shipped during the period of any preliminary injunction.

CONCLUSION

For the foregoing reasons, sanofi-aventis' Application for a Temporary Restraining Order and a Preliminary Injunction should be granted.

Respectfully submitted,



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