UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

SANOFI-AVENTIS US LLC, Plaintiff, v. FOOD AND DRUG ADMINISTRATION, *et al.*, Defendants, and SANDOZ INC., Intervenor-Defendant.	Civil Action No. 10-1255 (EGS)

FEDERAL DEFENDANTS' MEMORANDUM IN OPPOSITION TO PLAINTIFF'S MOTION FOR A TEMPORARY RESTRAINING ORDER AND A PRELIMINARY INJUNCTION

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INTRODUCTION

This case concerns the Food and Drug Administration's ("FDA's" or "agency's") approval of the first generic version of enoxaparin sodium injection ("enoxaparin"), an anti-clotting drug that plaintiff Sanofi-aventis U.S. LLC ("Sanofi") manufactures under the brand name Lovenox®. For 17 years, Sanofi has enjoyed a monopoly for this product, which it seeks to perpetuate with this lawsuit. On July 23, 2010, FDA approved a generic version of enoxaparin manufactured by intervenor-defendant Sandoz-Momenta ("Sandoz"). Sanofi's bid to overturn FDA's approval of a competing generic product, which will preserve its own profits, while decreasing the availability of lower cost, reliable, and safe pharmaceuticals, should be rejected.

This case represents the latest in a long line of cases in which a manufacturer of a pioneer drug product has attempted to block generic competition by challenging the regulatory and scientific bases for FDA's approval.[1] Each of these challenges failed, as should this one. These courts have unequivocally held that FDA's scientific determinations concerning the appropriate information required for approval of a generic drug product fall squarely within the broad discretion of the agency, which Congress has determined is in the best position to make such highly technical scientific decisions.

Sanofi offers no plausible basis to overturn FDA's reasoned scientific and technical conclusion that Sandoz's application for generic enoxaparin meets the statutory requirements for

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[1] *See, e.g., Serono Labs., Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998*)*; *Schering Corp. v. FDA*, 51 F.3d 390 (3d Cir. 1995); *Valeant Pharms. Int'l v. Sebelius*, No. 08-0449 (C.D. Cal. Sept. 14, 2009); *Astellas Pharma U.S., Inc. v. FDA*, 642 F. Supp. 2d 10 (D.D.C. 2009); *Biovail Corp. v. FDA*, 519 F. Supp. 2d 39 (D.D.C. 2007); *Glaxo Group, Ltd. v. Leavitt*, No. 06-469, 2006 U.S. Dist. LEXIS 10938 (D. Md. Mar. 7, 2006); *Somerset Pharms., Inc. v. Shalala*, 973 F. Supp. 443 (D. Del. 1997); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212 (D.D.C. 1996); *Fisons Corp. v. Shalala*, 860 F. Supp. 859 (D.D.C. 1994); *Schering Corp. v. Sullivan*, 782 F. Supp. 645 (D.D.C. 1992), *vacated as moot sub nom*. *Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993).

approval. Sanofi alleges that FDA (1) exceeded its authority by requiring additional studies to demonstrate safety beyond what is permitted for generic drug applications; (2) departed from previous agency precedent by approving a generic version of a drug that has not been fully characterized; and (3) approved generic enoxaparin without sufficient evidence that it has the "same" active ingredient as Lovenox.

None of these claims has merit. First, FDA considered additional studies related to the product's purity, which FDA has ample authority to consider – and is required to consider by statute. Thus, FDA did not evaluate impermissible "safety" information. Second, FDA's decision to approve generic enoxaparin is fully consistent with agency precedent. Finally, FDA's determination that Sandoz's generic product has the same active ingredient as Lovenox was based on rigorous criteria and an exhaustive review of the scientific evidence, and took into account Sanofi's views as well as those of FDA scientists. The agency determined that generic applicants can demonstrate enoxaparin sameness by making certain showings embodied by five criteria, and do not need to characterize enoxaparin by isolating each chain, sequencing it, and undertaking a molecule-to-molecule comparison – a task that is not even feasible with available technology. Given the high level of deference that is owed to FDA's exercise of its scientific judgment and expertise, Sanofi's claims are ill-founded and it has no likelihood of success on the merits.

Nor can Sanofi establish that it will suffer irreparable harm in the absence of preliminary injunctive relief or that the balance of equities weighs in its favor. As discussed more fully below, only a small percentage of Sanofi's total world-wide sales are currently derived from sales of Lovenox in the United States, and Sanofi has admitted that sales of a generic version will have no long-term impact on the company. By contrast, every day that the marketing of generic

enoxaparin – which FDA has found to be therapeutically equivalent to Lovenox – is delayed, American consumers remain deprived of a less expensive alternative to a costly drug, and FDA's mandate to approve generic products that meet statutory requirements is hampered. Moreover, any financial harm that Sanofi might suffer in the absence of preliminary injunctive relief is equaled, if not exceeded, by the harm that an injunction would cause Sandoz – whose product has been approved after meeting all statutory requirements and is currently on the market.

For all of these reasons, Sanofi has not satisfied the stringent standards for extraordinary relief and its motion for a preliminary injunction should be denied.

I. Statutory and Regulatory Background

A. New Drug Applications and Abbreviated New Drug Applications

Under the FDCA, pharmaceutical companies seeking to market "pioneer" or "innovator" drugs must first obtain FDA approval by filing a new drug application ("NDA") containing extensive scientific data demonstrating the safety and effectiveness of the drug, including clinical investigations showing the drug product to be safe and effective. 21 U.S.C. § 355(a), (b). After a drug is approved, it is referred to as a "listed" drug. 21 C.F.R § 314.3(b). The 1984 Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman Amendments") provided an alternate pathway for submission of abbreviated new drug applications ("ANDAs") for generic versions of listed drugs. 21 U.S.C. § 355(j). The ANDA process shortens the time and effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to repeat the clinical studies conducted to support approval of the listed drug.[2]

[2] A reference listed drug or "RLD" refers to the listed drug identified by FDA as the drug that an ANDA applicant relies on for approval of its ANDA. *See* 21 C.F.R. § 314.3(b). This

To rely on such a finding, the ANDA applicant must show, among other things, that its proposed drug product is the same as the listed drug with respect to active ingredient, dosage form, strength, route of administration, and, with certain narrow exceptions, labeling, and that its product is bioequivalent to the listed drug. 21 U.S.C. § 355(j)(2). FDA must approve the ANDA unless, among other things, the ANDA applicant provides insufficient evidence of the foregoing. 21 U.S.C. § 355(j)(4).

B. Same Active Ingredient Requirement

For drugs with only one active ingredient, the ANDA must contain "information to show that the active ingredient of the new drug is the same as that of the listed drug." 21 U.S.C. § 355(j)(2)(A)(ii)(I). If an ANDA applicant demonstrates that it has the same active ingredient as the listed drug (and all other approval requirements are met), FDA must approve that ANDA. 21 U.S.C. § 355(j)(4)(C)(i).

FDA regulations define "same as" as "identical in active ingredient(s)." 21 C.F.R. § 314.92(a)(1). In the preamble to this final rule, FDA rejected the suggestion that, to be the same as the listed drug, the ANDA product must "exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process; and that the stereochemistry characteristics and solid state forms of the drug have not been altered." 57 Fed. Reg. 17,950 at 17958-59 (Apr. 28, 1992). Instead, to determine whether two active ingredients are the "same," FDA concluded that it "will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity." *Id.* at 17,959. FDA explained that "[i]n most cases, these standards are described in

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may also be called the "innovator" or "pioneer" drug.

the U.S. Pharmacopeia (U.S.P.). However, in some cases, FDA may prescribe additional standards that are material to the ingredient's sameness." *Id.* Courts accord "a high level of deference" to FDA's determinations of active ingredient sameness. *Serono*, 158 F.3d at 1320 (upholding FDA's decision that an ANDA product had the "same" active ingredient as the listed drug, although neither had been fully characterized).

C. Purity Requirement for Approval of an ANDA

The FDCA enumerates eight categories of information that must be contained in an ANDA, including information showing that the active ingredients are the "same" as described above. *See* 21 U.S.C. § 355(j)(2)(A). The statute further provides that FDA "may not require that an [ANDA] contain information in addition to that required by clauses (i) through (viii) [of 21 U.S.C. § 355(j)(2)(A)]." *Id.* Thus, for example, FDA cannot require an ANDA applicant to conduct full clinical studies to demonstrate safety and efficacy because such studies are not within the scope of clauses (i) through (viii).

Despite this limitation, clauses (i) through (viii) provide FDA with authority to consider a wide range of information appropriate for approval of ANDAs. Of relevance to this case, 21 U.S.C. § 355(j)(2)(A)(vi) requires the submission of information specified in clauses (B) through (F) of 21 U.S.C. § 355(b)(1), which includes "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug." 21 U.S.C. § 355(b)(1)(D). Paralleling the requirement that ANDA applicants provide manufacturing information, 21 U.S.C. § 355(j)(4) requires FDA to approve an ANDA product unless, among other things, FDA finds that the manufacturing methods "are inadequate to assure and preserve its identity, strength, quality, and *purity*." 21 U.S.C. § 355(j)(4)(A) (emphasis added); *see also* 21 C.F.R. § 314.127(a)(1). Thus, by statute, FDA must evaluate the purity of an

ANDA product. If the ANDA applicant has adequately addressed the impurity profile of the ANDA product (and all other approval requirements are met), FDA must approve the ANDA and the ANDA applicant can rely on FDA's previous findings of safety and efficacy of the innovator drug to support the approval of the ANDA product.

FDA has promulgated regulations that further specify the information required for approval under this statute. *See* 21 C.F.R. § 314.94(a). Pursuant to 21 C.F.R. § 314.94(a)(9), FDA requires ANDA sponsors to provide information on chemistry, manufacturing, and controls, as required for NDA sponsors under 21 C.F.R. § 314.50(d)(1). For example, an ANDA applicant must provide such information as:

> a description of the manufacturing and packaging procedures and in-process controls for the drug product; the specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product, including, for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, container closure systems; and stability data with proposed expiration dating. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, and analytical procedures.

21 C.F.R. § 314.50(d)(1)(ii)(a); *see also* 57 Fed. Reg. at 17,959 (Apr. 28, 1992) ("As for possible impurities or residues in the ANDA product, ANDA applicants would be required to provide information on the drug substance and the drug product as part of the chemistry, manufacturing, and controls section of the application.").

Under its regulations, FDA has broad discretion to consider different types of information to demonstrate the purity of the ANDA product, including "alternatives" to the listed methods (tests, analytical procedures, and acceptance criteria) to show that the ANDA sponsor has adequate specifications to ensure the purity of its product.

II. Factual Background

A. Sanofi's NDA

Lovenox is an injectable product used as an anticoagulant. FDA approved the NDA for Lovenox (NDA 20-164, which is now owned by Sanofi) in 1993. Lovenox is currently approved for five separate indications relating to thrombosis. AR 2881.

The active ingredient in Lovenox is enoxaparin sodium, AR 2882, which belongs to a relatively new class of anticoagulants called low molecular weight heparins ("LMWH"). *Id.* Heparin itself has been used as an anticoagulant since 1939. *Id.* Heparin is a natural product extracted from porcine (pig) intestines. Although heparin is still widely used in hospitals and other controlled settings, patients vary widely in their response and its use must be closely monitored. *Id.* Heparin is known to be associated with an adverse event known as heparin-induced thrombocytopenia (an immunologically-based adverse event). AR 3848.

Heparin is a mixture of "polysaccharides"(long chains of sugars) made up of repeating "disaccharide" units.[3] AR 2884. These polysaccharides (and the sequence of disaccharides in them) vary from batch to batch, as is typical for naturally derived products.

LMWHs are manufactured by "depolymerizing" (or breaking up) long heparin polysaccharide chains into smaller chains. These smaller chains are typically called oligosaccharides. *Id.* LMWHs have a more predictable anticoagulant response than heparin, among other advantages, and may be used outside of a hospital. AR 2883. Lovenox, which is made from heparin, is also known to be associated with heparin-induced thrombocytopenia, the immunological adverse event for heparin. AR 3848.

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[3] A disaccharide is a carbohydrate composed of two monosaccharides (which are simple sugar molecules). AR 2878, 2884 n.26.

As with the polysaccharides in the parent heparin, the oligosaccharide chains in Lovenox vary from batch to batch. The "molecular diversity" in Lovenox arises from: (1) different lengths of oligosaccharide chains; (2) different disaccharide units and the sequence of the units within those chains; and (3) different modifications of the end disaccharide units in the chains. AR 2886, 2888. Sanofi has not fully characterized the chemical structure of Lovenox by identifying all of the disaccharide units and their sequence within the oligosaccharide chains. AR 2904 (noting that Sanofi acknowledges that approximately 30% of the polysaccharide chains comprising enoxaparin have yet to be directly analyzed because of limitations of current technology).

B. Sandoz's ANDA

Sandoz submitted an ANDA for generic enoxaparin on August 26, 2005. FDA approved the ANDA on July 23, 2010. Sandoz's product is therapeutically equivalent to (and thus may be substituted for) Lovenox. AR 4441 (July 23, 2010 Approval Letter at 2). As such, Sandoz's product is the first direct competitor of Sanofi's product.

In order to be approved, Sandoz's product had to meet all requirements under 21 U.S.C. § 355(j), including those for active ingredient sameness and those related to impurities. To meet the sameness requirement, Sandoz submitted extensive data to characterize its enoxaparin product, including data to show it has the same physical and chemical characteristics as Lovenox, as well as the same anticoagulant activity. Over a period of nearly five years, FDA reviewed all of the ANDA data and analyses submitted by Sandoz in its voluminous ANDA. Based on this comprehensive review and evaluation, FDA determined that Sandoz's enoxaparin active ingredient is the same as the active ingredient in Lovenox. *See, e.g.,* Sandoz Chemistry Review (Executive Summary) at AR 4326-30.

In addition, Sandoz addressed impurities in its product to assess their potential to generate

a greater immune response (known as an immunogenic response) as compared to Lovenox. Sandoz conducted in vitro and animal assays to address impurities that could cause such a response, thereby demonstrating that its product was not any more immunogenic than Lovenox. *See* AR 2919.

C. Sanofi's Citizen Petition

Aventis Pharmaceuticals, Inc. (hereinafter "Sanofi")[4] submitted a citizen petition on February 19, 2003 (Docket No. 2003P-0064) ("Petition"), requesting that FDA withhold approval of any ANDA for enoxaparin "[u]ntil such time as enoxaparin has been fully characterized . . . unless the manufacturing process used to create the generic product is determined to be equivalent to [Sanofi's] manufacturing process for enoxaparin, or the application is supported by proof of equivalent safety and effectiveness demonstrated through clinical trials." AR 1. Sanofi also requested that FDA withhold approval unless the generic product contained a particular chemical structure at certain terminal ends of the oligosaccharide chains, which Sanofi claimed contributed to enoxaparin's overall pharmacological effect.[5] AR 1, 3. Sanofi filed four supplements to its petition, as well as several comments. Other manufacturers, interested groups, and individuals also submitted comments.

D. FDA's Resolution of Scientific Disagreement Regarding the "Same" Active Ingredient

FDA's Office of Generic Drugs ("OGD") thoroughly considered all of Sanofi's arguments

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[4] Aventis merged with Sanofi to become Sanofi-aventis in 2004. *See* http://en.sanofi-aventis.com/investors/us_investors/faq/sanofi-aventis_merger/sanofi-aventis_merger.asp.

[5] Specifically, Sanofi believed that it was necessary that any generic product contain a 1,6 anhydro ring structure at the "reducing" ends of between 15 and 25 percent of the oligosaccharide chains.

and, after extensive deliberation, ultimately concluded that a generic applicant could satisfy the statutory requirement for active ingredient sameness if it met five specific criteria designed to ensure that the product would have the same active ingredient components as Lovenox's enoxaparin within the context of its variability. *See* Memorandum from Keith Webber to Helen Winkle (July 20, 2010), AR 3841-42. OGD also consulted with (among other components) CDER's Office of New Drug Quality Assessment ("ONDQA"). AR 3840. Some scientists in ONDQA expressed a different view, and believed that a showing of sameness for enoxaparin could only be assessed by isolating each individual disaccharide, identifying their sequences, and comparing them at a molecule-to-molecule level. *Id.*

Such scientific disagreement is common, and FDA resolves such disagreement by seeking diverse views and asking higher level agency officials to resolve the issue. *See id.* ("As with many complicated scientific issues, differences in scientific opinion arose concerning the appropriate approach for assessing enoxaparin sameness."). The scientific disagreement for enoxaparin was ultimately resolved by Dr. Keith Webber, the Deputy Director of the Office of Pharmaceutical Science, which oversees both OGD and ONDQA. AR 3836, 3841. After evaluating (among other things) OGD's criteria and considering ONDQA's views, Dr. Webber concluded that satisfaction of OGD's five criteria "results in a robust and rigorous demonstration of enoxaparin sameness." AR 3842. The agency reached this decision after exhaustive consideration of scientific views over a period of several years.

E. FDA's Response to Sanofi's Petition

In a comprehensive 45-page, single-spaced response, FDA addressed Sanofi's numerous arguments and granted its request that any generic enoxaparin must contain a particular chemical structure at the ends of the oligosaccharide chains, but denied the petition in all other respects.

1. Same Active Ingredient Requirement

With respect to the "same" active ingredient requirement in 21 U.S.C. § 355(j)(2)(A)(ii)(I), FDA explained that it has considerable discretion to determine what constitutes active ingredient "sameness." Lovenox is a natural product and has some degree of batch-to-batch variability. AR 2888. To address the inherent molecular diversity associated with Lovenox's enoxaparin (described in Section II.A., *supra*), FDA developed five criteria as follows:

1. Equivalence of physicochemical properties
2. Equivalence of heparin source material and mode of depolymerization
3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
4. Equivalence in biological and biochemical assays
5. Equivalence of in vivo pharmacodynamic profile

AR 2888.

Satisfaction of the first criterion shows that the generic product's overall physical and chemical properties are equivalent to Lovenox's enoxaparin. AR 2888-89. To satisfy this criterion, the generic applicant compares the molecular weight distribution and overall chemical composition of its product to that of Lovenox. using a variety of analytical methods. *Id.*

Satisfaction of the second criterion shows that the generic product has equivalent heparin source material and uses an equivalent type of chemical reaction to break heparin chains into smaller pieces (depolymerization) as that for Lovenox. AR 2890. Because the parent heparin does not rearrange during the depolymerization reaction, if the heparin source and mode of depolymerization are equivalent, FDA can conclude that the resulting distribution of sequences of disaccharides between the two enoxaparin active ingredients will at least be similar. AR 2891. Satisfying this criterion would likewise allow FDA to conclude that any modified groups at the ends of the oligosaccharide chains would be at least similar. AR 2891-92.

Satisfaction of the third criterion shows that the nature and arrangement of the disaccharide components are equivalent to that of Lovenox's enoxaparin. First, the generic applicant shows that its product and Lovenox have equivalent disaccharide units. This can be done by breaking up (digesting) the oligosaccharides into individual disaccharide units, and then separating and identifying these through various analytical techniques. AR 2893-94. This analysis can show what disaccharide units are in the chain, as well as the modified disaccharide units at the chain ends. AR 2894. Second, the generic applicant shows that the generic product and Lovenox have recurring oligosaccharide sequences unique to enoxaparin, which may be analyzed by a procedure called "fragment mapping." AR 2895-96. Third, the generic applicant shows that the generic product and Lovenox have a subset of critical oligosaccharide chains with the same disaccharide sequences, which may be demonstrated by recent advances in sequencing technology for oligosaccharides. AR 2896-97.

The last two criteria, unlike the first three structure-based criteria, ensure that the generic enoxaparin product has the same degree of anticoagulant activity as Lovenox. AR 2898-900. Satisfaction of the fourth criterion shows that the generic product has equivalent laboratory test results demonstrating anticoagulant activity.[6] AR 2898.

Fifth, the generic applicant shows that its product has an equivalent in vivo pharmacodynamic profile (*i.e.*, equivalent action or effect in the body), based on measuring two anticoagulant markers in humans. AR 2899-900. This final criterion provides important evidence that the generic enoxaparin will have the same anticoagulant activity as Lovenox. AR 2900.

[6] Specifically, the generic applicant demonstrates equivalence in certain biological and chemical assays for three different relevant markers for anticoagulant activity: anti-Xa activity, anti-IIa activity, and anti-Xa/anti-IIa ratio. AR 2899.

FDA explained how all of these criteria are evaluated together to support a conclusion that a generic product's active ingredient is the same as Lovenox:

> These five criteria take into account the inherent molecular diversity associated with Lovenox's enoxaparin and address (1) the polydispersity of chain length, (2) the diversity of the disaccharide units and corresponding distribution of disaccharide unit sequences in the oligosaccharide chains, and (3) the diversity of modified terminal end disaccharide units in the oligosaccharide chains. Lovenox has some degree of batch-to-batch variability, which you acknowledge is expected in any product derived from living organisms. The equivalence evaluation for these criteria generally is based upon qualitative and/or quantitative comparisons of the generic drug product's enoxaparin to multiple batches of Lovenox's enoxaparin and takes into consideration the batch-to-batch variability and sampling of Lovenox, and analytical test variability. The equivalence evaluation for the above five criteria demonstrates that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent. Equivalent molecular diversity demonstrates sameness for enoxaparin. Collectively, the five criteria are designed to provide overlapping evidence upon which we can conclude that the generic drug product's enoxaparin is the same as Lovenox's enoxaparin.

AR 2888-89.[7]

2. Impurities and Immunogenicity

FDA's response also addressed comments regarding the potential for enoxaparin to generate an immune response that could lead to a known adverse event, thrombocytopenia. AR 2918-29. Although FDA believed that a demonstration of active ingredient sameness from the five criteria was a "strong indication that the generic enoxaparin would not differ from Lovenox with respect to its immunogenicity," FDA further concluded that generic applicants should compare their generic enoxaparin and Lovenox for "potential impurities that may have an adverse impact with respect to immunogenicity." *Id.* FDA "determined that it is possible, by satisfying

[7] FDA further noted that, "[a]s with all complex scientific issues, it is possible that with improvement in the understanding of the biological and clinical properties of enoxaparin and/or advances in the analytical technologies that might be used to characterize enoxaparin, other approaches might emerge to establish the sameness of enoxaparin." AR 2880.

the five criteria and (as a conservative measure) by conducting in vitro and in vivo assays to address impurities, to provide scientifically sound assurance that the risk of immunogenicity due to potential impurities in the generic enoxaparin will not be greater than that of Lovenox." *Id.* FDA identified its authority to consider this additional testing as 21 U.S.C. § 355(j)(4)(A), which requires the ANDA applicant to demonstrate that its manufacturing methods "are adequate to assure and preserve the identity, strength, quality and purity of the drug." AR 2918 n.126 (referring to statutory discussion at AR 2886). If an ANDA product could satisfy (among other things) the requirement for active ingredient sameness and address the potential of impurities to cause an immunogenic reaction, FDA expected that such a product would "be therapeutically equivalent to and can be substituted for Lovenox with the expectation that it will produce the same clinical effect and safety profile as Lovenox." *Id.*

F. Sanofi's Application For Emergency Relief

Three days after FDA approved Sandoz's ANDA, Sanofi filed this suit, seeking a temporary restraining order and preliminary injunction to suspend FDA's approval. Sanofi alleges that FDA (1) exceeded its authority by considering data about impurities for approval; (2) departed from previous agency precedent by approving a generic version of a drug that has not been fully characterized; and (3) approved generic enoxaparin without sufficient evidence that it has the "same" active ingredient as Lovenox. Sanofi's motion should be denied.

ARGUMENT

Preliminary injunctive relief is an "extraordinary and drastic" remedy that "may only be awarded upon a clear showing that the plaintiff is entitled to such relief." *Winter v. NRDC, Inc.*, __ U.S. __, 129 S. Ct. 365, 375-76 (2008); *Munaf v. Geren*, 553 U.S. 674, 128 S. Ct. 2207, 2219 (2008). *See also Mpoy v. Fenty*, 674 F. Supp. 2d 163, 165 (D.D.C. 2009) ("Injunctive relief is an

extraordinary remedy, and plaintiff bears a substantial burden to obtain it."). To obtain a preliminary injunction, a party must establish that: (1) it is likely to succeed on the merits; (2) it is likely to suffer irreparable harm in the absence of preliminary relief; (3) the balance of equities tips in its favor; and (4) an injunction would serve the public interest. *Winter*, 129 S. Ct. at 375.

It is "particularly important" for a movant to demonstrate likely success on the merits. *Astellas*, 642 F. Supp. 2d at 16 (absent "substantial indication" of likely success, there would be no justification for court's intrusion into ordinary processes of administration and judicial review). Moreover, a party seeking preliminary injunctive relief must demonstrate an actual "likelihood" of success on the merits, not merely the existence of "questions 'so serious, substantial, difficult and doubtful, as to make them fair ground for litigation . . . ." *Munaf*, 128 S. Ct. at 2219 (citations omitted). Nor is a mere "possibility" of irreparable harm sufficient to justify such relief:

> Our frequently reiterated standard requires plaintiffs seeking preliminary relief to demonstrate that irreparable injury is *likely* in the absence of an injunction. . . . Issuing a preliminary injunction based only on a possibility of irreparable harm is inconsistent with our characterization of injunctive relief as an extraordinary remedy that may only be awarded upon a clear showing that the plaintiff is entitled to such relief.

Winter, 129 S. Ct. at 375-76 (citations omitted, emphasis in original).

In this case, Sanofi's burden is even higher, because it seeks not to preserve the *status quo*, but to overturn FDA's approval of a generic enoxaparin product that is currently being distributed around the country. A court's power to issue such a mandatory injunction "should be sparingly exercised." *Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 36 (D.D.C. 2000).

I. SANOFI HAS NO LIKELIHOOD OF SUCCESS ON THE MERITS

A. Standard of Review

1. FDA's Scientific Decisions Are Entitled to Substantial Deference

FDA's administrative decisions are subject to review under the Administrative Procedure Act ("APA"), and may be disturbed only if "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). This standard is highly deferential to the agency. *Citizens to Preserve Overton Park, Inc. v. Volpe*, 401 U.S. 402, 416 (1971). The agency's administrative decision is entitled to a presumption of validity. *Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 743 (1985); *Camp v. Pitts*, 411 U.S. 138, 142 (1973). The reviewing court must consider whether the agency's decision was based upon consideration of the relevant factors and whether there has been a clear error of judgment. *Overton Park*, 401 U.S. at 416. However, a reviewing court is "not empowered to substitute its judgment for that of the agency," *id.,* and must uphold the agency's action so long as it is "rational, based upon relevant factors, and within the agency's authority." *Motor Vehicle Mfrs. Ass'n of the United States, Inc., v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 42-42 (1983). In applying the arbitrary and capricious standard, the court reviews the administrative record assembled by the agency and does not undertake its own fact finding. *See, e.g., Camp,* 411 U.S. at 142.

When, as here, an agency's decision is based on evaluation of scientific information within the agency's area of technical expertise, its decisions are traditionally accorded great deference. *See Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 653-54 (1973) (The FDA is "peculiarly suited" to evaluate conflicting scientific reports, a matter "not . . . well left to a court without chemical or medical background," because it "necessarily implicates complex chemical and pharmacological considerations."). Courts "review scientific judgments of the agency 'not as the

chemist, biologist, or statistician that [they] are qualified neither by training nor experience to be, but as a reviewing court exercising [its] narrowly defined duty of holding agencies to certain minimal standards of rationality.'" *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (*quoting Ethyl Corp. v. EPA*, 541 F.2d 1, 36 (D.C. Cir. 1976)); *see also Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389 (D.C. Cir. 1992) ("The rationale for deference is particularly strong when [the agency] is evaluating scientific data within its technical expertise."); *Sw. Pa. Growth Alliance v. Browner*, 121 F.3d 106, 117 (3d Cir. 1997); *Bristol-Myers,* 923 F. Supp. at 216 (*citing Federal Power Comm'n v. Fla. Power & Light Co.*, 404 U.S. 453, 463 (1972)).

Such deference has repeatedly been applied in cases under the FDCA. *See, e.g.*, *Serono*, 158 F.3d at 1320 (FDA's determination of "sameness" rests on agency's evaluation of scientific data within its area of expertise and is entitled to high level of deference from court); *Henley v. FDA*, 77 F.3d 616, 621 (2d Cir. 1996) ("FDA possesses the requisite know-how to conduct such [scientific] analyses, by sifting through the scientific evidence to determine the most accurate and up-to-date information regarding a particular drug . . . . We therefore defer to its reasonable findings."); *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (FDA's "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us."); *Tri-Bio Laboratories, Inc. v. United States*, 836 F.2d 135, 142 (3d Cir. 1987) ("in evaluating scientific evidence in the drug field, the FDA possesses an expertise entitled to respectful consideration by this court"); *Astellas*, 642 F. Supp. 2d at 19-20 ("high level of deference" must be afforded to FDA in choosing methodologies to test bioequivalence of given drug).

2. FDA's Statutory and Regulatory Interpretations Receive Deference

In reviewing the FDA's construction of the FDCA, the Court is governed by the two-step analysis of *Chevron, U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984). *See, e.g., Novartis Pharms. Corp. v. Leavitt*, 435 F.3d 344, 349 (D.C. Cir. 2006) ("We have held on a number of occasions that FDA interpretations of the FDCA receive deference . . ."); *Mylan Laboratories, Inc. v. Thompson*, 389 F.3d 1272, 1280 (D.C. Cir. 2004). The first question under *Chevron* is "whether Congress has directly spoken to the precise question at issue." *Id.* at 842. If, after this Court "exhaust[s] the 'traditional tools of statutory construction,'" *Natural Res. Def. Council, Inc. v. Browner*, 57 F.3d 1122, 1125 (D.C. Cir. 1995) (quoting *Chevron*, 467 U.S. 837, 843 n. 9), the intent of Congress is clear, "that is the end of the matter." *Chevron*, 467 U.S. 837, 842. Put another way, the Court must initially decide "whether the statute unambiguously forbids the Agency's interpretation." *Barnhart v. Walton*, 535 U.S. 212, 218 (2002).

If, however, the statute "is silent or ambiguous with respect to the specific issue," the Court proceeds to the second prong of *Chevron*, under which "the question for the court is whether the agency's answer is based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843. *See generally County of Los Angeles v. Shalala*, 192 F.3d 1005, 1012-13 (D.C. Cir. 1999). The D.C. Circuit has held that deference to FDA's application of the FDCA is particularly appropriate because of "the complexity of the statutory regime" and "FDA's expertise." *Mylan v. Thompson*, 389 F.3d at 1280.

Furthermore, when, as here, a court is evaluating an agency's interpretation of its own regulations, the agency is entitled to "substantial deference." *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *see Fed. Express Corp. v. Holowecki*, 552 U.S. 389, 397 (2008) (courts accept agency's interpretation of its regulations unless agency's position is plainly erroneous or

inconsistent with regulation); *Novartis*, 435 F.3d at 349 (FDA interpretations of regulations receive deference unless plainly erroneous or inconsistent with regulations).

B. FDA Properly Exercised Its Authority to Assure the Purity of Generic Enoxaparin

1. FDA Reasonably Considered Whether Any Impurities Could Elicit an Immunogenic Reaction

Impurities in enoxaparin may have an immunogenic effect and result in an adverse reaction in a patient, which was known to occur with Lovenox. AR 3848. When FDA first considered the potential for an adverse immunogenic reaction for generic enoxaparin, scientists in the Office of Generic Drugs determined that a conclusion of "same" active ingredient would be sufficient to also conclude that there would be no differences in immunogenicity between the generic product and Lovenox. AR 3849. The Director of the Center for Drug Evaluation and Research ("CDER"), however, stated that generic applicants should be "requested to supply more extensive data on the *impurity* profile of the final product . . . ." AR 3854 (emphasis added). As a result, immunologists in the Office of Biotechnology Products ("OBP") were consulted about the potential for residual impurities to affect the immunogenicity of enoxaparin. AR 3849. Shortly thereafter, FDA sent letters to Sandoz and other ANDA sponsors requesting that they provide information to address immunogenicity. *See* AR 4167-69. In a follow-up letter, FDA provided some "suggested approaches" to address the issues, *i.e.*, whether "product and process derived impurities . . . may modify the biological activity or enhance the immunogenicity of your product." AR 4170-71.

In response, Sandoz provided data to satisfy CDER's concerns about the potential for impurities to affect immunogenicity. The type of immunogenicity information that FDA considered when it approved Sandoz's ANDA falls well within FDA's authority to consider an

ANDA product's purity under 21 U.S.C. § 355(j)(4)(A) and 21 C.F.R. § 314.94(a)(9). That information consisted of the following:

(1) Sandoz provided data derived from various analytical, laboratory techniques to compare the ability of its product and Lovenox to form complexes with platelet factor 4 ("PF4") in mice and generate antibody. This demonstrated that impurities that may impact PF4 binding or impurities that may impact the immune response did not differ between the products. *See* Memo from Keith O. Webber re: OBP Review (July 20, 2010) ("Webber OBP Memo"), at 1 (AR 4433); OBP Review at 3 (AR 4193).

(2) Sandoz provided data to assess the presence of impurities that could directly stimulate the immune system, such as proteins, nucleic acids, lipids, and impurities that could leach from the container. *See* Webber OBP Memo at 1 (AR 4433), OBP Review at 3-4 (AR 4193-4). Sandoz provided sufficient evidence that there were no significant differences in these impurities. *Id.*

(3) Sandoz provided results from an in vitro assay to compare the ability of its product and Lovenox to induce an inflammatory (immune) response using specialized human cells. Webber OBP Memo at 1 (AR 4433), OBP Review at 4 (AR 4194). The results showed that there were no significant differences between Sandoz's product and Lovenox.

(4) Sandoz provided results from an animal assay that compared the ability of its product and Lovenox to complex with (*i.e.*, bind to) PF4 and induce antibodies in mice. Webber OBP Memo at 1 (AR 4433), OBP Review at 4 (AR 4194). No significant differences were detected. OBP Review at 4 (AR 4194).

After reviewing this data, FDA determined that "[i]t is scientifically reasonable, based on the comprehensive data submitted, to conclude that Sandoz' generic enoxaparin would be no

more immunogenic than Lovenox." *See* Webber OBP Memo at 3 (AR 4435). FDA did not require clinical testing, and found that "a comparative clinical study would not necessarily be expected to be more sensitive to meaningful differences between the generic enoxaparin product and Lovenox." *Id.*

2. FDA Has Clear Statutory Authority to Consider Impurities When It Approves An ANDA

a. FDA Must Consider Impurities Under 21 U.S.C. § 355(j)(4)(A)

FDA considered the purity of Sandoz's product pursuant to its authority under 21 U.S.C. § 355(j)(4)(A). *See* AR 2918 n.126 (referring to statutory discussion at AR 2886). As noted in Section I.C. above, FDA has discretion to consider a wide range of information to establish whether the ANDA product is as pure as the listed drug. *See* 21 C.F.R. § 314.94(a)(9) (requiring ANDA applicants to provide the same type of manufacturing information to establish purity that NDA sponsors must provide in 21 C.F.R. § 314.50(d)(1), which may involve "alternatives" to traditional methods).

In *Serono*, *supra*, the D.C. Circuit noted that the statute did not specify either the type of information an applicant must submit to demonstrate "sameness" or the type of information upon which the FDA may rely. *Serono*, 158 F.3d at 1319. Similarly, nothing in the statutory language in 21 U.S.C. § 355(j)(4)(A) restricts FDA from considering any type of information about the ANDA product to ensure its purity. Nor is there any credible public health reason to restrict FDA's ability to consider appropriate information about the purity of ANDA products, which may differ depending on the type of product at issue.

Sanofi argues that the "plain language" of 21 U.S.C. § 355(j) prohibits FDA from requiring safety data from clinical or preclinical (typically animal) studies, citing the limitation on

additional information that FDA can require in 21 U.S.C. § 355(j)(2)(A). Mem. at 17. But that provision clearly allows FDA to require information pertaining to manufacturing (21 U.S.C. § 355(j)(2)(A)(vi)), which parallels the requirement in 21 U.S.C. § 355(j)(4)(A) that FDA must assess certain properties of an ANDA product relating to its manufacturing process, such as purity. *See also* 21 C.F.R. § 314.94(a)(9).

In *Serono*, the court of appeals expressly rejected the plaintiff's argument that 21 U.S.C. § 355(j)(2)(A) precluded FDA from considering animal studies to evaluate an inactive ingredient in an ANDA. *Serono*, 158 F.3d at 1324 ("First, the indicated clauses [21 U.S.C. § 355(j)(2)(A)] do not suggest that animal studies are in any way disfavored."). Similarly, Sandoz has provided information from animal studies in mice to assess one aspect of impurities as they relate to immunogenicity.[8] Webber OBP Memo at 1 (AR 4433), OBP Review at 4 (AR 4194). FDA properly considered animal studies as one of several types of information relevant to that question for enoxaparin, although FDA did not specifically require such a study. *See* AR 4170-74 (noting that other approaches may be acceptable). Contrary to Sanofi's suggestion, such animal studies are appropriate for assessing impurities in ANDAs. *See, e.g.,*Guidance for Industry, ANDAs: Impurities in Drug Substances (June 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172002.pdf (discussing studies done to assess toxicity, which typically involve animals (*see, e.g.*, 21 C.F.R. § 314.50(d)(2)).

[8] FDA did not require a study in humans to evaluate impurities or immunogenicity, as Sanofi implies. *See* Mem. at 12-13 & n.17 (referring to FDA press release discussing studies done on "healthy human volunteers"). These studies were done to satisfy the fifth criterion for *sameness*, discussed *supra* at Section I.E.1 – not to assess immunogenicity. *See, e.g.,* Bioequivalence Review (Oct. 26, 2006), AR 4089; *see also* Chemistry Review at 72 (AR 4391).

b. Sandoz's Product Was Approved Based on Studies Appropriate for ANDAs

Sanofi argues that "whether Sandoz's generic enoxaparin product will induce a more significant immunologic response than does Lovenox is clearly a basic safety question." Mem. at 19. While information concerning immunogenicity certainly relates to a drug's "safety," it is derived from assessing impurities, and falls well within FDA's authority for reviewing ANDAs for manufacturing and process controls, which may influence impurities.

FDA expected Sandoz to assess its product for impurities in comparison to Lovenox in order to ensure that its product would not be any more immunogenic than Lovenox. *See* AR 2919 ("we have determined that it is possible . . . to provide scientifically appropriate assurance that the risk of immunogenicity due to potential impurities in the generic enoxaparin will not be greater than that of Lovenox."). Once Sandoz made that showing and all others required for approval, FDA approved Sandoz's product relying on FDA's previous findings as to the safety and efficacy of Lovenox, the innovator product – not based on a "safety" study independently evaluating the safety of Sandoz's product, as is required for NDAs.[9]

Sanofi acknowledges that FDA permits ANDA applicants to submit limited preclinical data for certain confirmatory purposes, but argues that the "safety" testing required to address immunogenicity exceeded that limited purpose.[10] Mem. at 19-20 (citing FDA press release that

[9] Thus, Sandoz was not required to submit "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use" as required for stand-alone NDAs by 21 U.S.C. § 355(b)(1). *See also* 21 C.F.R. § 314.50(d)(5) (setting forth the requirements for describing clinical (human) data for an NDA).

[10] Sanofi argues that FDA *required* Sandoz to conduct this testing, Mem. at 19-20, but the record reflects that FDA merely provided suggested approaches to address its concerns about impurities and immunogenicity. *See* AR 4171.

the testing was "extensive and time-consuming"). A similar argument – that FDA could not evaluate preclinical (animal) studies to assess an inactive ingredient – was rejected by the D.C. Circuit in *Serono*. 158 F.3d at 1324 n.6 ("FDA's determination that the animal studies at issue here fall within that category [of limited confirmatory testing] is supported by the fact that the studies were only one of four grounds upon which the agency relied for its conclusion that the lactose in Repronex is safe."). Similarly, for enoxaparin, FDA considered animal assays in mice as only one of four factors to evaluate impurities as they relate to immunogenicity. *See* Webber OBP Memo at 1 (AR 4433). Such confirmatory evidence related to impurities is fully within the scope of FDA's review of ANDAs.[11]

c. FDA's Decision Is Consistent With Salmon Calcitonin Precedent

Contrary to Sanofi's claim, FDA's requirement of immunogenicity data for generic enoxaparin is fully consistent with the agency's prior decision regarding salmon calcitonin nasal spray. Mem. at 21-22. As in this case, ANDA sponsors of a synthetic version of calcitonin provided information to allow FDA to compare the impurity profiles of the generic and the listed drug, but FDA did not require that they conduct clinical trials. *See* FDA Citizen Petition Response for salmon calcitonin at 14-18 (Nov. 17, 2008) (attached as Exhibit P to Cunningham Decl. in support of Mem.).[12] Here too, FDA considered immunogenicity data in the context of

[11] Indeed, FDA may rely not only on animal studies for ANDA approval, but also on human studies. *See, e.g.,* 21 C.F.R. § 320.24(b)(4) (describing "appropriately designed comparative clinical trials" as acceptable for establishing bioequivalence for certain types of ANDA products). Such studies serve a limited purpose to compare properties of the generic and innovator products, and are *not* clinical studies to demonstrate safety and efficacy that are necessary to support approval of a new innovator drug under 21 U.S.C. § 355(b).

[12] An ANDA sponsor would have been required to satisfy a number of conditions to address immunogenicity, such as same chemical structure, impurity profile, effect of aggregates,

comparing the impurity profiles of Sandoz's product and Lovenox, and likewise determined that no clinical safety testing for immunogenicity was required for approval.

Sanofi points out, however, that FDA refused to accept an ANDA for a different (and potentially more complicated) recombinant version of calcitonin – for which it was not feasible to compare the impurity profiles of the generic and reference products. Mem. at 21. Sanofi argues that enoxaparin is analogous to recombinant calcitonin because enoxaparin is not fully characterized and thus "FDA is unsure of the impurity profile of the two drugs." *Id.* (arguing that "actually having to demonstrate lack of immunogenic effect through data is not acceptable in an ANDA"). But, as noted above, the statute *requires* FDA to consider the purity of an ANDA product, and further requires FDA to approve an ANDA product (assuming all other requirements for approval are met) unless it finds that the ANDA sponsor has not provided adequate evidence concerning the "identity, strength, quality, and purity" of the drug. 21 U.S.C. § 355(j)(4)(A). Contrary to Sanofi's claim, FDA is *not* "unsure of the impurity profile" of Sandoz's product as compared to Lovenox, just as it concluded that it would have adequate information about the comparative impurity profiles of generic and innovator versions of *synthetic* calcitonin if an ANDA sponsor addressed immunogenicity concerns by conducting a battery of testing. FDA properly concluded that Sandoz's product is no more immunogenic than Lovenox after reviewing the results of tests to assess impurities – a conclusion that fully squares with FDA's authority and obligation to assess impurities in ANDAs.

3. FDA Properly Approved Sandoz's Product as an ANDA

The FDCA sets forth two general types of applications for sponsors seeking drug approval: NDAs and ANDAs. The FDCA also provides for two different types of NDAs. A

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excipients, and leachates from the container. *Id.*

"stand-alone NDA" is an application that contains full reports of safety and effectiveness that were conducted by the sponsor. 21 U.S.C. § 355(b)(1). Lovenox was approved as a stand-alone NDA. The FDCA also provides a hybrid approval pathway for applications that contain full reports of investigations of safety and effectiveness, but some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. *See* 21 U.S.C. § 355(b)(2). By contrast, ANDAs are submitted for duplicates of a previously approved drug, and the ANDA sponsor relies on FDA's previous finding of safety and effectiveness for the innovator drug product.

Sanofi argues that FDA should have approved Sandoz's application under 21 U.S.C. § 355(b)(2) because FDA allegedly required Sandoz to provide immunogenicity data to demonstrate safety. Mem. at 23.[13] As explained above, however, FDA properly evaluated the potential for impurities in Sandoz's product to affect immunogenicity, which fits well within FDA's authority (and its responsibility) to consider an ANDA product's purity under 21 U.S.C. § 355(j)(4)(A). FDA's decision to consider this data by no means suggests that FDA had implicitly concluded that Sandoz's product is not "the same" as Lovenox. Mem. at 23. As FDA made clear, CDER was concerned about the potential for impurities to affect immunogenicity – which is a distinct question from whether the active ingredients are the same.

In its response to Sanofi's petition, FDA explained that clinical trials for safety and effectiveness were not necessary for FDA to approve an application for enoxaparin, and that FDA could approve a generic product under the ANDA pathway:

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[13] Sanofi does not hide its self-interest motivating its preference for approval of any competitor by the 21 U.S.C. § 355(b)(2) pathway, which could result in a non-substitutable – and less competitive – generic product. Mem. at 30 (urging "that the resulting products should not be substitutable").

> [O]ne of the principal purposes of the ANDA statutory approval provisions . . . is "to encourage competition by decreasing the time and expense of bringing generic drugs to market, and thereby to provide the public with low cost drugs." (quoting 54 Fed. Reg. 28872 at 28874 (July 10, 1989)). Further, the conduct of duplicative studies raises ethical concerns because it could subject humans and animals to medically or scientifically unjustified testing.

AR 2913-14. FDA's conclusion is fully consistent with one of the main purposes of the Hatch-Waxman Amendments – to eliminate the need for generic applicants to duplicate safety studies performed by the innovator. *See* H.R. Rep. No. 98-857, pt. 1, at 16 (1984) ("FDA considers such retesting to be unnecessary and wasteful because the drug has already been determined to be safe and effective. Moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective."). Nor would clinical trials necessarily have provided better information than the data Sandoz submitted in this case. *See* AR 3850 ("In the case of enoxaparin, a comparative clinical study would not necessarily be expected to be more sensitive to meaningful differences between the generic enoxaparin product and Lovenox.").

FDA thus properly concluded that it could approve Sandoz's ANDA after considering data relating to, *inter alia*, active ingredient sameness and impurities – factors that are expressly and appropriately within the ANDA approval regime. FDA did not require Sandoz to submit its application under 21 U.S.C. § 355(b)(2) and provide data from clinical trials to demonstrate safety and effectiveness that FDA judged to be unnecessary. FDA's regulatory decision as to the appropriate approval pathway for a generic version of enoxaparin reflects its scientific judgment about active ingredient sameness and impurities, and is fully consistent with the FDCA. *See* AR 2913-14.

C. FDA Properly Concluded that the "Same" Active Ingredient Provision Does Not Require Molecule-to-Molecule Characterization of the Active Ingredient

1. Legal and Regulatory Precedent Supports FDA's Interpretation of the Sameness Requirement

Sanofi argues that, by approving a complex product that has not been fully characterized, FDA has ignored past precedent. Mem. at 24. To the contrary, as *Serono* demonstrates, FDA may approve complex, naturally-derived products that are not fully characterized (and has done so in the past) without requiring a showing of "complete chemical identity" to establish the sameness of the active ingredients. 158 F.3d. at 1320. Nothing in either the statute or past agency precedent requires that an innovator drug product be fully characterized, molecule-to-molecule, before FDA can approve a generic competitor. Rather, as *Serono* makes clear, FDA has broad discretion to decide what evidence will be sufficient to establish active ingredient "sameness" on a case-by-case basis in light of the "kind of drug at issue." *Id.* at 1319.

In *Serono*, the D.C. Circuit upheld FDA's construction of the statutory "sameness" provision under *Chevron* step two, and unequivocally held that FDA's determination as to the type and quantum of evidence sufficient to establish that two active ingredients are the "same" is entitled to a "high level of deference." 158 F.3d at 1320-21 ("FDA's determination of what is required to establish 'sameness' for purposes of the Act rests on the 'agency's evaluations of scientific data within its area of expertise,' and hence is entitled to a 'high level of deference' from this court.") (quoting in part *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)).[14] In that case, Serono challenged the approval of a competing generic version of Pergonal,

[14] The district court granted FDA less deference than warranted because there had been some disagreement among FDA employees prior to the time the final approval was granted. 158 F.3d at 1320-21. The court of appeals rejected this approach, holding that "*Chevron* deference is owed to the decisionmaker authorized to speak on behalf of the agency, not to each individual agency employee." *Id.*

a naturally derived product whose active ingredient, FSH, consisted of a protein backbone with carbohydrate side chains that exhibited some degree of natural variation. *Id.* at 1317-18.

Although FDA recognized that the active ingredients were slightly different, it found that their "primary structure" was the same, and that any potential variations in FSH isoforms between the generic and innovator product were not "clinically significant for the product's intended uses." *Id.* at 1318-20. Noting that "complete chemical identification of all the carbohydrate variants in a protein product often is not possible or feasible," *id*. at 1318, FDA concluded that so long as the products were otherwise the same (with respect to protein backbone, amino acid sequence and potency), and the degree of batch-to-batch isoform variation was no different in the generic than in Pergonal itself, such clinical identity rendered the generic and innovator products the same for purposes of the statute. *Id.* at 1319-20. Serono argued (and the district court agreed) that this isoform variation in FSH rendered the generic different from Pergonal, and thus ineligible for ANDA approval, because the lack of absolute chemical identity meant that the active ingredients were not the "same" as required by statute. *Id.* at 1317-19.

In reversing the district court's decision, the court of appeals noted that the statute specified neither the type of information an applicant must submit to demonstrate "sameness" nor the type of information upon which the FDA may rely, describing the provision as a "broad grant of discretion to the agency with respect to the information it may consider in making a finding of 'sameness.'" *Serono*, 148 F.3d at 1319. The court observed that, if "absolute chemical identity" were required, it would not be possible to say any generic was the "same" as Pergonal due to the products' batch-to-batch variability. *Id*. at 1320. Indeed, not only Pergonal, but "other categories of protein products" and "other products derived from natural sources besides proteins," including "oligosaccharides" (such as enoxaparin) "can not be fully characterized chemically" and thus

"would be excluded from the ANDA process as well." *Id*. at 1320. The court could find no evidence, however, that Congress meant to exclude more complicated products that cannot be fully characterized from the scope of the Hatch-Waxman Amendments. The court concluded that, because "the statute does not unambiguously require the term 'same as' to be defined as complete chemical identity," FDA could reasonably interpret the statute to permit the approval of a generic version of Pergonal. *Id.* at 1320-22.[15]

In addition to the generic Pergonal product at issue in *Serono*, FDA has approved other generic products without requiring complete molecule-to-molecule characterization, including several generic versions of heparin (the parent of enoxaparin). *See* AR 2900-01. FDA has also approved ANDAs for hetastarch, a mixture of polysaccharides that is derived through a depolymerization reaction from a natural product. AR 2901. Hetastarch ANDA applicants demonstrated sameness using a similar approach to what FDA expects generic enoxaparin applicants to employ. AR 2902. There, as in this case, FDA did not expect hetastarch ANDA applicants to completely characterize hetastarch, use the "same" manufacturing process as the RLD, or conduct clinical trials to demonstrate safety and effectiveness. *Id.* Thus, FDA's regulatory approach for enoxaparin is fully supported by applicable case law and agency precedent.

2. FDA's Decision Is Consistent with Precedent Cited By Sanofi

Sanofi points to three previous FDA decisions involving unrelated drugs as evidence of inconsistent agency decisionmaking. Mem. at 25-33. Its reliance on these past precedents,

[15] The court also rejected Serono's argument that FDA had improperly examined the safety of the generic product using animal studies: "FDA's 'judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us.'" *Id.* at 1324 (quoting *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995)).

however, is misplaced. Indeed, Sanofi gives these examples far more weight than they can bear, flaunting fact-specific scientific determinations as if they were binding case law or legal precedent, when, as *Serono* makes clear, FDA may and must approve drugs by considering the individual characteristics of the particular drug at issue. 158 F.3d at 1319 (statutory sameness provision "must be read in the context of the kind of drug at issue"). Regardless, FDA's approval of enoxaparin is not an outlier decision, and is consistent with the general principles underlying past agency decisions, as described below.

a. Hyaluronidase

FDA's decision to grant five years of "new chemical entity" exclusivity to Vitrase (hyaluronidase), involved a different statutory provision (relating to new chemical entities), a different drug (a protein product), and a different approval pathway (21 U.S.C. § 355(b)(2)). Nevertheless, Sanofi seizes upon a single footnote that Sanofi asserts is inconsistent with FDA's decision for enoxaparin. In determining that Vitrase was a new chemical entity, FDA speculated that it "currently would also be unlikely to consider these products to have the same active ingredient for purposes of approving an application under section 505(j) of the Act. . . . In short, the active ingredient in Vitrase has not yet been *sufficiently characterized* to permit the Agency to conclude that another hyaluronidase product has an identical active ingredient." Hyaluronidase Citizen Petition Response at 11 n.20 (AR 3600 n.20) (emphasis added). *See* Mem. at 25-27.

In this case, by contrast, FDA has confidence that the active ingredient in Lovenox and in Sandoz's enoxaparin product has been adequately characterized to permit FDA to conclude that Sandoz's product has the same active ingredient. AR 2918. Unlike its hyaluronidase decision – in which FDA merely guessed whether a future, unknown ANDA product could have the same active ingredient – FDA has in this instance compared two actual enoxaparin products that have

been adequately characterized. Sanofi's claim that FDA's hyaluronidase decision "has effectively ruled out approval of ANDAs for products that are not fully characterized" (Mem. at 27) distorts FDA's observation about the inadequate characterization of Vitrase into a rule that would require full characterization through molecule-to-molecule comparison of all products subject to ANDA approval. That is not the rule applied by the courts, *see Serono*, or by FDA (as its enoxaparin, heparin, and hetastarch approvals illustrate) – nor is it a rule required by the statute. Given its extensive knowledge about Sanofi's and Sandoz's enoxaparin products, FDA's decision in this case is fully consistent not only with its hyaluronidase decision, but also with the FDCA – and Sanofi's claim of "arbitrary and capricious" decisionmaking therefore fails.

b. Omnitrope

Sanofi's claims regarding Omnitrope are equally unavailing. FDA approved Omnitrope under 21 U.S.C. § 355(b)(2) instead of 21 U.S.C. § 355(j). Mem. at 28-32.[16] Sanofi argues that enoxaparin is more complex than Omnitrope, and thus the pathway for approval for Omnitrope "should serve as a floor" for enoxaparin's approval. Mem. at 30. But Omnitrope, unlike enoxaparin, was never determined to have the "same" active ingredient as the innovator reference listed drug ("RLD"), and in fact had acknowledged differences in certain respects.[17] Thus, it was not approvable as an ANDA under 21 U.S.C. § 355(j)(2)(A). By contrast, FDA has determined that Sandoz's enoxaparin has the "same" active ingredient as the listed drug, Lovenox, because it

[16] Sanofi asserts that it brought the Omnitrope approval to FDA's attention in a "Citizen Petition supplement," and complains that "FDA's response to the Citizen Petition does not even mention the drug." Mem. at 29 n. 29. Although Sanofi raised the Omnitrope precedent in a letter dated September 22, 2008 (attached as Ex. L to Sanofi's Cunningham Decl.; *see also* AR 4526-4530), that letter was never submitted to the Citizen Petition docket for reasons that are not clear to FDA. As such, it was not part of the public docket available for comment.

[17] *See* Omnitrope Citizen Petition Response at 14 (May 30, 2006), *available at* http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf.

has been adequately characterized and has met the five criteria.

Sanofi speculates that FDA's five criteria are somehow deficient because the "[t]he secondary and tertiary structure of enoxaparin is not understood and no physicochemical tests exist to determine the secondary or tertiary structure." Mem. at 30.[18] Secondary and tertiary structures are typical of protein molecules such as Omnitrope, and refer to local three-dimensional folding (secondary) and the larger three-dimensional configuration (tertiary) characteristic of those molecules.[19] Sanofi confuses protein molecules with the carbohydrate oligosaccharide chains in enoxaparin, for which "no significant higher order structure [i.e., secondary or tertiary three-dimensional structure] has been found." Webber Memo at 13 (AR 3848) (noting that "[t]he structural characteristics of enoxaparin required for activity are much less complex and more stable than those of most proteins."). FDA has exercised its regulatory and scientific judgment to determine that enoxaparin's characteristics fit within the ANDA approval pathway, a decision that is consistent with its decision for Omnitrope based on the indisputable differences between those products.

c. Premarin

Sanofi fares no better with Premarin, a complex mixture of naturally derived estrogens. In its Premarin decision, FDA determined that it would not accept an ANDA for a *synthetic* (laboratory-synthesized) version of Premarin because the RLD was not adequately characterized.

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[18] In support, Sanofi cites to the Cunningham Decl., Exh. H, at 10-11, but that document (Citizen Petition Supplement No. 3 (Sept. 14, 2006)) does not say anything about secondary or tertiary structures. *See also* AR 1650-51). Sanofi did mention these structures in a September 22, 2008, letter to FDA (AR 4526-30), but that letter was not submitted to the public citizen petition docket.

[19] *See* Omnitrope Citizen Petition Response at 16 (May 30, 2006), *available at* http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf.

AR 3607. FDA stated, however, that it could approve generic copies of Premarin if they originated from the same *natural source material* (pregnant mares' urine) and were subject to similar manufacturing controls. AR 3643.

FDA's enoxaparin decision is consistent with its decision for natural sourced Premarin because generic enoxaparin is derived from the equivalent source material and is manufactured using a well-controlled process. *See* AR 2980-92; *see also* AR 3853. Sanofi argues that the FDA's reasoning for the *synthetic* product (*i.e.*, that it would not accept ANDAs because it was not adequately characterized) should apply to enoxaparin, because neither Lovenox nor the generic version has been subject to full chemical structural characterization. Mem. at 32. But FDA has decided that enoxaparin is adequately characterized for purposes of determining whether a generic version may contain the same active ingredient, in direct contrast to its scientific determination for Premarin. AR 2916. Accordingly, Sanofi's claims of inconsistency with agency precedent are all unfounded.

D. FDA Correctly Determined That Sandoz's Active Ingredient Is the Same as Lovenox

Sanofi fails to challenge the substance of the five criteria FDA employed to establish active ingredient sameness between Lovenox and generic enoxaparin except to assert that FDA's reasoning is "circular" because a conclusion that the molecular diversity of a generic product and Lovenox is "equivalent" allows FDA to conclude that those products are the "same." Mem. at 36. But FDA has decided that "sameness" for enoxaparin ANDAs can be satisfied by showing equivalent molecular diversity because Lovenox itself has batch-to-batch variation, *i.e.*, it cannot even be shown to be the "same" as itself in the manner Sanofi deems necessary. AR 2888. That is not circular reasoning, but an interpretation of the "same" active ingredient requirement in 21

U.S.C. § 355(j)(2)(A)(ii)(II) that is consistent with the interpretation upheld in *Serono*. 158 F.3d at 1319 (upholding FDA's determination that, for glycoprotein products with differences in microheterogeneity, ANDA sponsors need only demonstrate that their products have the same degree of batch-to-batch uniformity as the innovator); *see also* AR 2902 (describing FDA's approval of hetastarch ANDAs, which similarly account for that drug's lot-to-lot variation).

Sanofi asserts that FDA "ignored voluminous scientific evidence" that small changes in the manufacturing process can significantly affect the pharmacological activity of the drug. Mem. at 33-4. To the contrary, FDA's response to Sanofi's petition reflects the agency's clear awareness of the impact of process conditions, which is why FDA expects generic applicants not only to show that they use the same mode of "depolymerization" to break up the parent heparin molecule into smaller chains, but to adjust their manufacturing process conditions to ensure that the chemical selectivity of the depolymerization reaction is equivalent. *See* AR 2891-93 (describing, *e.g.*, second and third criterion for sameness). Moreover, the third criterion for sameness evaluates the sequences of disaccharides in the shorter chain oligosaccharides, which have resulted from the most cleavage reactions and are therefore most dependent on the chemical selectivity of the depolymerization reaction. AR 2897. Sandoz provided information that the sequences in these extremely process-sensitive shorter chains are equivalent to those in Lovenox, which provides further evidence to confirm that any differences in process do not alter the identity of Sandoz's product *vis-a-vis* Lovenox.

Because an ANDA applicant would likely need to adjust its process to ensure that it meets the criteria for active ingredient sameness, FDA explained that "[a]n ANDA applicant would not need to know Sanofi's exact manufacturing process parameters and conditions (*e.g.*, depolymerization time, pH, and temperature) to manufacture the same active ingredient as

Lovenox's enoxaparin." AR 2906. FDA further noted that it was "unclear to what processes" Sanofi was referring in requesting that generic applicants be required to use a manufacturing process equivalent to Sanofi's, because Sanofi had submitted twenty-four chemistry and manufacturing supplements (sixteen of which were drug product related, and eight of which were not solely drug product related) between March 1996 and April 2004. *Id.* at 2906 & n.104. These changes to Sanofi's own manufacturing process undermine its claim that only one process may produce enoxaparin, and that Sandoz must use the same process as Sanofi.

Sanofi also contends that FDA has not provided a "rational explanation" for disregarding evidence that "directly contradicts" its administrative findings, asserting that slight changes in concentrations of reagents used or the temperature or time of reaction can change the structure of enoxaparin and thus its pharmacological properties. Mem. at 33-4. But, in addition to addressing Sanofi's arguments about process conditions as described above, FDA responded to Sanofi's structural arguments at considerable length. *See* AR 2905-2913 (addressing arguments about the 1,6 anhydro ring structure, AT-III binding, and other "structural finger prints"). Although FDA was not convinced that there was evidence that the 1,6 anhydro ring structure was clinically significant, FDA nevertheless granted Sanofi's request that any ANDA applicant show that it appeared at a frequency of 15 to 25% because that would necessarily result if the ANDA applicant met the five criteria. AR 2910. Similarly, FDA determined that the other portions of enoxaparin that Sanofi asserted were clinically significant would also be present in any approved generic ANDA within the variation present in Lovenox. AR 2911-13.

Sanofi argues that "several independent scientific/medical third parties" support its view that the product depends on the manufacturing process, a proposition of dubious accuracy considering that each of the assertedly "independent" parties named in its memorandum appears

to have received funding from Sanofi.[20] Moreover, none of the experts who submitted declarations in support of Sanofi's motion for preliminary relief evaluated the sameness of Sandoz's product in view of the five criteria that Sandoz' product has met. *See* Decl. of Christian Viskov, attached as Ex. A to Cunningham Decl.; Decl. of Marc Cohen, M.D., attached as Ex. B to Cunningham Decl., at ¶ 10.[21]

Sanofi also points to the European Medicines Agency ("EMEA"), which has required generic enoxaparin applicants to conduct clinical trials to show comparative safety and efficacy to the reference product. Mem. at 35. Although FDA considered the EMEA's views, it is not bound by them and had ample reasons for choosing a different path. *See* AR 2920-21. FDA explained, for instance, that the EMEA Guideline did not consider two of FDA's five criteria for enoxaparin (the second and third), and noted that FDA would not conclude that a generic product was the same based only on the other three criteria. AR 2920. FDA also explained that the five criteria it has established "are more sensitive to differences between two enoxaparin products than the clinical studies recommended in the EMEA Guideline" because, although enoxaparin and tinzaparin (a different low molecular weight heparin product) were shown to have equivalent

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[20] Each of the "independent" parties appears to have numerous financial links to Sanofi, including the Society for Hospital Medicine, which has launched a mentorship quality improvement project with funding from Sanofi (*see, e.g.,* Front Line of Change, *available at* http://www.hospitalist.com/assets/001/5098.pdf); the Director of the Pulmonary Vascular Disease Center of Duke University Medical Center, which is a paid consultant and speaker for Sanofi, and receives research support (*see* ClotCAre Online Resource, *available at* http://www.clotcare.com/clotcare/displayeb.aspx?eb=tapson.aspx); and the North American Thrombosis Forum, whose president has served as a consultant for Sanofi and receives research support (*see* Clotcare Online Resource, *available at* http://www.clotcare.com/clotcare/displayeb.aspx?eb=goldhaber.aspx).

[21] Because judicial review of FDA's action must be based on the agency's administrative record, *see Camp v. Pitts*, 411 U.S. 138, 142 (1973), this Court should not consider Sanofi's expert declarations in any event.

clinical activity in one study, the two products clearly do not have the same active ingredient. AR 2920-21.[22] Finally, FDA noted that the EMA Guidelines apply to products that are "similar" – not the "same" – and thus they could exhibit differences relating to safety and effectiveness that would be assessed by clinical studies. AR 2920.

* * *

In sum, FDA has considered all factors relevant to approval of Sandoz's ANDA, including the agency's regulatory authority, its precedent, and the drug at issue. FDA's Citizen Petition Response and the administrative record demonstrate that FDA examined all important aspects of the issues relevant to approval, and explained its decision in a manner consistent with all of the evidence before it. The agency's carefully reasoned decision, grounded in the exercise of its best scientific judgment, is the very antithesis of arbitrary and capricious decisionmaking and easily passes muster under the standards of the Administrative Procedure Act. *See FCC v. Fox Television Stations, Inc.*, 129 S. Ct. 1800, 1810 (2009) (under the narrow standard of APA review, the agency need only "examine the relevant data and articulate a satisfactory explanation for its decision") (citing *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Automobile Ins.*, 463 U.S. 29, 43 (1983)). Thus, Sanofi has not shown that it is likely to succeed on the merits of its claims.

II. SANOFI HAS NOT SHOWN THAT IT WILL SUFFER IRREPARABLE INJURY IN THE ABSENCE OF PRELIMINARY INJUNCTIVE RELIEF

Sanofi has also failed to demonstrate that it will suffer irreparable harm absent injunctive relief or that the balance of hardships tips in its favor. Courts insist that only *irreparable* harm

[22] Although FDA did not specifically address the recommendation of the International Society on Thrombosis and Haemostasis ("ISTH"), Mem. at 36 and 37 n.33, Sanofi acknowledges that ISTH's recommendations are similar to EMEA's. FDA's discussion of the five criteria and its decision to not require clinical trials to demonstrate safety and effectiveness (as proposed by the EMEA) thus similarly applies to the ISTH's recommendations.

that is *likely* justifies the issuance of a preliminary injunction. *Winter*, 129 S. Ct. at 376. Indeed, "if a party fails to make a sufficient showing of irreparable injury, the court may deny the motion for injunctive relief without considering the other factors." *Astellas*, 642 F. Supp. 2d at 16.[23] Irreparable injury is a "very high standard." *Ark. Dairy Coop., Inc. v. USDA*, 576 F. Supp. 2d 147, 160 (D.D.C. 2008); *Bristol*, 923 F. Supp. at 220. The injury alleged must be certain, great, actual, and imminent, *Wis. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985), and it must be "more than simply irretrievable; it must also be serious in terms of its effect on the plaintiff." *Gulf Oil Corp. v. Dep't of Energy*, 514 F. Supp. 1019, 1026 (D.D.C. 1981).

In this circuit, mere economic loss – even irrecoverable economic loss, such as Sanofi alleges here – does not constitute irreparable harm unless the financial injury is so great as to threaten the continued existence of the movant's business:

> To satisfy the standard of irreparable injury to justify a preliminary injunction, the movants' loss must be "more than simply irretrievable." *Mylan Labs., Inc. v. Thompson*, 139 F. Supp. 2d 1, 27 (D.D.C. 2001); *see also Wisc. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985). Instead, the injury must be such that it "cause[s] extreme hardship to the business, or even threaten[s] destruction of the business." *Gulf Oil Corp. v. Dep't of Energy*, 514 F. Supp. 1019, 1025 (D.D.C. 1981); *see also, Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26 (D.D.C. 2006) (noting that "[t]o successfully shoehorn potential economic loss into the irreparable harm requirement, a plaintiff must establish that the economic harm is so severe as to 'cause extreme hardship to the business' or threaten its very existence.").

Mylan Laboratories, Inc. v. Leavitt, 484 F. Supp. 2d 109, 123 (D.D.C. 2007). *See also Astellas*, 642 F. Supp. 2d at 22 ("it is well-settled that economic loss alone will rarely constitute irreparable harm"); *Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 1, 11 (D.D.C. 2008) ("In this

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[23] As Judge Kavanaugh recently pointed out, "the *Winter* Court rejected the idea that a strong likelihood of success could make up for showing only a possibility (rather than a likelihood) of irreparable harm. In other words, the Court ruled that the movant always must show a likelihood of irreparable harm." *Davis v. Pension Benefit Guar. Corp.*, 571 F.3d 1288, 1296 (D.C. Cir. 2009) (Kavanaugh, J., joined by Henderson, J., concurring)

jurisdiction, harm that is 'merely economic' in character is not sufficiently grave under this standard."); *Coal. for Common Sense in Gov't Procurement v. United States*, 576 F. Supp. 2d 162, 168-69 (D.D.C. 2008) (finding that "degree of harm" asserted by coalition of pharmaceutical manufacturers did not approach "the level required in this case (*i.e.* so severe as to cause extreme hardship to the business or threaten the very existence of Coalition members")); *Apotex v. FDA*, No. 06-0627, 2006 WL 1030151 (D.D.C. Apr. 19, 2006) at * 17 (where plaintiff did not establish that lost sales and market share would cause "extreme hardship" to company, claim of harm fell "well short of the serious, irretrievable damage to its business required to warrant a preliminary injunction"); *Sociedad Anonima Vina Santa Rita v. Dep't of Treasury*, 193 F. Supp. 2d 6, 14 (D.D.C. 2001) ("financial harm alone cannot constitute irreparable injury unless it threatens the very existence of the movant's business").

Thus, in order to prevail on its motion for preliminary injunctive relief, Sanofi must make "a strong showing" that any economic loss it would suffer in the absence of preliminary injunctive relief "would significantly damage its business above and beyond a simple diminution in profits." *Mylan v. Shalala*, 81 F. Supp. 2d at 42-43; *see also Wash. Metro. Area Transit Comm'n v. Holiday Tours, Inc.*, 559 F.2d 841, 843 n. 3 (D.C. Cir. 1977) ("The mere existence of competition is not irreparable harm, in the absence of substantiation of severe economic impact."). Sanofi does not come close to satisfying this standard. Although Sanofi claims that Lovenox accounted for 26% of its domestic revenue in 2009 (Mem. at 7, 37), Sanofi is a global company with "a broad portfolio" of prescription medicines, consumer healthcare (OTC) products, generics, and vaccines, and worldwide revenues of some $40 billion annually. *See* http://en.sanofi-aventis.com/at-a-glance/profile/profile.asp (2009 sales of 29.3 billion euros

translates to approximately $38.3 billion dollars at current rate of exchange).[24] The $2.5 billion in U.S. sales generated by Lovenox in 2009 (Mem. at 37) amounted to only 6 percent of the company's overall annual revenue. Even if Sanofi were to lose some portion of those sales as a result of competition from Sandoz, the resulting financial harm would be far too insignificant to cause "extreme hardship" to Sanofi overall, much less threaten its existence. *Cf. Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 29 (D.D.C. 1997) (recognizing injury to one-product line company).

Indeed, Sanofi does not even suggest that the loss of some portion of Lovenox sales to generic competition during the pendency of this litigation would seriously harm its overall business. To the contrary, Sanofi "all but concede[s]" that the advent of generic competition in the United States will have minimal impact on the company as a whole, predicting that a substitutable generic such as Sandoz's "would have some impact on our 2010 numbers," but "doesn't really have an impact longer term." *See* Full Year 2009 SanofiAventis Earnings Conference Call, Full Disclosure Wire, Feb. 10, 2010, at 14, *available at* LEXIS, News Library, 90 Days File; *see also* Q2 Results: Transcript of video interview with Chris Viehbacher, Chief Executive Officer, *available at* http://en.sanofi-aventis.com/binaries/20100729_Q2_2010_Transcript_en_tcm28-29027.pdf ("Most of the volume that we sell is outside of the US. It still remains a blockbuster product, even without the US sales.").[25] *Cf. Mylan v. Shalala*, 81 F. Supp. 2d at 43 ("Mylan has all but

[24] *See also* Sanofi press release at 1, 16 (Feb. 10, 2010), *available at* http://en.sanofi-aventis.com/binaries/20100210_Results2009_en_tcm28-27173.pdf (reporting 29,306 million euros ($38.3 billion) in 2009 total net sales, and 1,822 million euros ($2.4 billion) in 2009 U.S. Lovenox sales).

[25] Indeed, Sanofi has projected that the company's 2010 earnings will be virtually unchanged from 2009, despite the Sandoz approval. *See* Sanofi Press release at 1, 13 (July 29,

conceded that its estimated lost revenues . . . will not cause serious damage to the company.").

Nor does Sanofi make any attempt to quantify the actual loss it may suffer due to generic competition. Relying on unspecified "past examples," Sanofi claims that unit sales of the brand name product fall by up to 90% within the first few months after the introduction of a generic product. Mem. at 38. Sanofi further speculates that, even if it reduces the price of Lovenox to compete with Sandoz's generic, it "could" lose fifty percent of its sales. *Id.* But a fifty percent reduction in Lovenox sales, even at a reduced price, would not "significantly damage" Sanofi's business over the likely 3-4 month duration of this litigation. *Mylan v. Shalala*, 81 F. Supp. 2d at 43. *See Apotex*, 2006 WL 1030151 at *17 ("the actual relevant period for assessing harms is probably only a few months" – from the time of generic launch to the time the case is resolved on the merits); *Bristol-Myers*, 923 F. Supp. at 221 ("If it ultimately prevails on the merits, Bristol's total sales will be insignificantly affected over the duration of the litigation.").

Even if Lovenox's monthly U.S. sales revenue of $210 million were reduced by 60 percent due to competition with Sandoz's generic product, the resultant loss of $378 million over the next three months comprises less than 1% of Sanofi's total annual revenue – a significant figure to be sure, but not of sufficient magnitude to cause irreparable harm to a company the size of Sanofi, as courts in this Circuit have repeatedly held. *See LG Elecs. U.S.A., Inc. v. DOE*, 679 F. Supp. 2d 18, 36 (D.D.C. 2010) (citing cases). "Monetary figures are relative, and depend for their ultimate quantum, on a comparison with the overall financial wherewithal of the corporation involved." *Mylan v. Leavitt*, 484 F. Supp.2d at 123. When, as here, a company seeking preliminary

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2010), *available at* http://en.sanofi-aventis.com/binaries/20100729_Q2_2010_Results2_en_tcm28-29020.pdf ("Sanofi-aventis expects business EPS for the year 2010 to be flat to minus 4% versus 2009 . . . taki[ng] into account the recent approval of a generic of Lovenox in the U.S.").

injunctive relief does not establish that its alleged losses "would threaten the continued existence of [its] business," it "fail[s] to demonstrate irreparable injury." *Id*.[26]

Sanofi's speculative claims of lost goodwill and reputational harm are equally unavailing. Mem. at 40-41. Sanofi contends that its reputation could be damaged, and patients harmed, if Sandoz's generic product is substituted for Lovenox and it fails to perform as expected. But FDA has determined that Sandoz's product has the same active ingredient as Lovenox, and Sanofi has offered no evidence – indeed, cannot – to suggest that Sandoz's product will not be as safe and effective as Lovenox or otherwise fail to provide the expected relief. Nor does Sanofi offer anything beyond speculation to support its claim that patients and physicians would turn away from both generic and branded Lovenox should they have a bad experience with Sandoz's generic product. In these circumstances, courts have consistently rejected claims of anticipated reputational harm stemming from the introduction of a new generic drug. *See, e.g.*, *Astellas*, 642 F. Supp. 2d at 23 ("The plaintiff's concerns about the potential loss of goodwill and reputation are founded entirely on its belief that the approved generic . . . may be more harmful than [the brand-name drug], a belief that . . . lacks evidentiary support and is entirely speculative."); *Somerset Pharms., Inc. v. Shalala*, 973 F. Supp. 443, 454-55 (D. Del. 1997) (rejecting claim of reputational harm and loss of goodwill based on plaintiff's "bare assertion" that patients and physicians would confuse generic with plaintiff's product); *Bristol-Myers*, 923 F. Supp. at 221 (rejecting Bristol's

[26] Sanofi's claim that it has no remedy to recover its lost sales due to FDA's sovereign immunity (Mem. at 38-39) is "inconsequential" given its failure to demonstrate, or even allege, that such losses would cause it serious harm. *Bristol-Myers*, 923 F. Supp. at 221; *see also, e.g., Astellas*, 642 F. Supp. 2d at 22-23 (rejecting similar argument); *American Ass'n for Homecare v. Leavitt*, No. 08-0492, 2008 WL 2580217 at *4 & n.3 (D.D.C. June 30, 2008) (rejecting argument that unrecoverable financial losses of any magnitude constitute irreparable injury). Indeed, the magnitude of harm facing the plaintiffs in the two cases cited by Sanofi is not comparable to the present case, where the overall impact of reduced product sales on a multi-billion dollar company is minimal.).

claim that its reputation would suffer if there were any adverse health effects from use of the generic where there was nothing in the record to support such a claim).[27]

For all of these reasons, Sanofi cannot meet its burden of establishing that it will suffer irreparable injury in the absence of preliminary injunctive relief.

III. THE BALANCE OF HARMS AND THE PUBLIC INTEREST WEIGH AGAINST THE ENTRY OF PRELIMINARY INJUNCTIVE RELIEF

Sanofi has also failed to show that any harm it may suffer in the absence of injunctive relief outweighs the potential harm to FDA and the public. Although FDA has no commercial stake in the outcome of this litigation, FDA's interest and the public's interest in generic drug approvals are the same. *See Serono*, 158 F.3d at 1326 (determining that the public interest is "inextricably linked" to Congress's purpose in passing the Hatch-Waxman Amendments). FDA must implement the statutory scheme governing the approval of generic drugs to make lower cost drugs available to the public when those drugs are found to meet the requirements for approval. *See In re Barr Laboratories, Inc.*, 930 F.2d 72, 76 (D.C. Cir. 1991) ("Congress sought to get generic drugs into the hands of patients at reasonable prices – fast.").

In this case, after careful consideration of both Sandoz's ANDA and Sanofi's citizen petition, FDA determined that Sandoz's generic enoxaparin had met all requirements for approval and that none of Sanofi's arguments were meritorious or otherwise justified any further delay in approval of Sandoz's application. The preliminary injunction Sanofi seeks would thwart Congress's generic drug approval scheme and FDA's lawful implementation of that scheme by

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[27] Sanofi's claim that it will suffer a loss of goodwill if Sandoz's generic product is withdrawn from the market after a trial on the merits is non-sensical considering that Sandoz's product is already on the market. Mem. at 39-40. To the extent purchasers will "inevitably" blame Sanofi for the removal of a lower-priced generic alternative, the preliminary relief Sanofi seeks would result in the exact same harm.

forcing FDA to suspend its approval of a drug that the agency has determined meets the scientific and statutory requirements for approval. A court-ordered delay of approval of a lawfully approved drug application would directly undermine FDA's interest in approval of safe and effective generic drugs and would harm the public which benefits from the increased competition incident to FDA's approval of a generic version of Lovenox.[28] In light of the considerable harm that would befall both FDA and the public from suspension of Sandoz's approval (to say nothing of the harm to Sandoz itself), the balance of harms and the public interest weigh heavily against Sanofi's request for preliminary injunctive relief.

CONCLUSION

For the foregoing reasons, Sanofi's motion for a temporary restraining order and preliminary injunction should be denied.

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[28] In addition, any financial harm that Sanofi would incur in the absence of preliminary injunctive relief will be matched, if not exceeded, by the financial harm that Sandoz will suffer by being wrongfully deprived of its right to market a competing generic product during the period that a preliminary injunction is in effect. Sandoz has invested significant resources into seeking approval of its generic application for enoxaparin, a five-year process that has finally culminated in FDA approval. The D.C. Circuit has found in similar circumstances that the balance of harms "results roughly in a draw." *Serono*, 158 F.3d at 1326; *see also Bristol-Myers*, 923 F. Supp. at 221 (noting that generic company had "endured a seven year process to obtain FDA approval" and that "the effect of an injunction [on the generic company] . . . would be dramatically greater" than the harm to plaintiff); *cf. Ark. Dairy Cooperative,* 576 F. Supp. 2d at 161 (noting that any harm plaintiffs would suffer absent preliminary injunctive relief would be offset by substantial harm to defendant-intervenors if injunction were granted).

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CERTIFICATE OF SERVICE

I hereby certify that I caused a copy of the foregoing Memorandum in Opposition to Plaintiff's Motion for a Temporary Restraining Order and a Preliminary Injunction to be served via the District Court's electronic filing (ECF) system upon:

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