UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

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

MEMORANDUM OPINION

Pending before the Court is the motion for preliminary injunction of Plaintiff Sanofi-Aventis U.S. LLC ("Sanofi"). Plaintiff, manufacturer of the leading and widely prescribed anticoagulant Lovenox, seeks an Order directing the Food and Drug Administration ("FDA") to withdraw its approval of an abbreviated new drug application ("ANDA") submitted by Sandoz Inc. ("Sandoz") for a generic version of Lovenox - enoxaparin sodium injection. Upon consideration of the motion, the response, the reply and surreply thereto, the amicus brief of AARP, the arguments made during the hearing on August 17, 2010, the applicable law, the administrative record, and for the following reasons, the Court hereby **DENIES** plaintiff's motion for a preliminary injunction.

I. BACKGROUND

A. Statutory Background

The Food, Drug, and Cosmetic Act (the "FDCA" or the "Act") provides that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug" without first obtaining FDA approval. 21 U.S.C. § 355(a). To obtain approval of a "new drug" a pharmaceutical company must file either a new drug application ("NDA") or an abbreviated new drug application ("ANDA"). *See id.*

Under the FDCA, a company seeking to market a "pioneer" or "innovator" drug must obtain FDA approval by filing an NDA containing, among other things, "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 . . . a full list of the articles used as components of such drug . . . [and] a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug . . . ." *Id.* § 355(b)(1). After an NDA is approved, this pioneer drug is referred to as the listed drug. 21 C.F.R. § 314.3(b).

Recognizing that the NDA process is costly and time-consuming, and seeking "to make available more low cost generic drugs," Congress amended the FDCA in 1984 to permit a manufacturer of a generic alternative to an RLD to seek FDA

approval by submitting an ANDA. *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1316 (D.C. Cir. 1998) (citing H.R. Rep. No. 98-857, pt. 1 at 14 (1984)). The ANDA process shortens the time and effort needed for new drug approval by, among other things, allowing an ANDA applicant to rely on the FDA's previous findings of safety and effectiveness for the reference listed drug ("RLD").[1] *See generally* 21 U.S.C. § 355(j). Therefore, instead of submitting independent clinical studies in support of the safety and effectiveness of its proposed generic drug, an ANDA applicant must submit sufficient information to establish that its proposed drug is "the same as" the RLD with respect to active ingredient, dosage form, strength, route of administration, and labeling, and that its product is bioequivalent to the listed drug. *See id.* § 355(j)(2)(A); *see also Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 13-14 (D.D.C. 2009) ("Rather than requiring the applicant to make an independent showing that the proposed generic is itself safe and effective, the amended statute requires a showing that the proposed generic operates in the same manner as the pioneer drug on which it is based – its reference listed drug. Thus, the FDA's approval of a new generic drug relies on its prior determination that the RLD is safe and effective."). "The underlying premise of the ANDA approval

[1] An RLD is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." 21 C.F.R. § 314.3(b).

requirements is that the generic drug product and the RLD can be substituted for each other with the full expectation that they will have the same clinical effect and safety profile." AR 2879.

The FDA must approve an ANDA unless, among other things, the ANDA sponsor has failed to make the statutorily-required showings of sameness and bioequivalence, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity. *See* 21 U.S.C. § 355(j)(4).

B. Factual & Procedural Background

On March 29, 1993, the FDA approved plaintiff's NDA for Lovenox. AR 2881. Lovenox is a widely prescribed anticoagulant used to prevent or treat thromboembolic disease and deep vein thrombosis, as well as to prevent complications associated with angina and certain forms of heart attack. Pl.'s Mem. at 4; AR 2881-82. With its active ingredient enoxaparin sodium ("enoxaparin"), Lovenox is part of a relatively new class of anticoagulants known as low molecular weight heparins ("LMWHs"). AR 2882. LMWHs such as enoxaparin are manufactured by depolymerizing heparin sodium polysaccharide chains into correspondingly shorter oligosaccharide chains. AR 2882.

On February 19, 2003, plaintiff submitted a citizen petition to the FDA requesting that the FDA withhold approval of

any ANDA for a generic version of Lovenox "[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.[2] Plaintiff also requested that the FDA refrain from approving any ANDA citing Lovenox as the RLD unless the generic product contained a "1,6 anhydro ring structure" at certain terminal ends of the oligosaccharide chains. AR 1. In its petition, plaintiff argued that "[b]ecause enoxaparin is not fully characterized, utilizing [Sanofi's] process (or an acceptable equivalent) is the only way to ensure that the generic product will contain all of the pharmacologically active components (both known and yet to be discovered) for enoxaparin. Absent that, FDA cannot consider the generic to have the 'same' active ingredient as enoxaparin and must therefore require a demonstration of equivalent safety and effectiveness through clinical testing." AR 4.

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[2] A drug is "characterized" by scientific analysis (or a variety of analyses) to determine the physical and chemical characteristics of the compound. Enoxaparin has not yet been "fully characterized" because scientists have not been able to identify all of the structures within the drug. *See* Pl.'s Mem. at 9-10 (explaining that as much as 30% of enoxaparin cannot be fully characterized by direct analysis given the limitations of current analytical technology).

On August 26, 2005, while Sanofi's citizen petition was pending, Sandoz filed an ANDA with the FDA seeking approval for a generic version of Lovenox. AR 4167. On November 5, 2007, the FDA sent a letter to Sandoz informing the company that the agency had determined that "the ANDA is not approvable because the application does not adequately address the potential for immunogenicity of the drug product." AR 4167.[3] The agency offered, however, to meet with Sandoz "to address what additional information should be provided to adequately address this concern." AR 4167.

In a follow-up letter dated December 4, 2007, the FDA informed Sandoz that:

> FDA is particularly concerned with product and process derived impurities that may modify the biological activity or enhance the immunogenicity of your product. Understanding the potential for your product to elicit an immune response is critical, since [LMWHs] are associated with a serious immune-driven adverse event, heparin induced thrombocytopenia ("HIT"). Impurities can interact with either the product or with the host immune system in ways that alter outcome. Thus, for products that have the potential for immunologic adverse events and certainly for products with known immunologic adverse events, the contribution of impurities needs to be carefully considered.

AR 4170. The letter then provided a list of items that Sandoz needed to address as part of its ANDA, as well as a list of

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[3] Immunogenicity is the potential of a drug substance or product to elicit an immune response, such as an allergic reaction, when introduced to the body.

suggested approaches to address the agency's concerns. AR 4171-73. Following Sandoz's submission of this additional information, the FDA approved Sandoz's ANDA for generic enoxaparin on July 23, 2010. *See* AR 4440-41 ("We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved, effective on the date of this letter. The Office of Generic Drugs has determined that your Enoxaparin Sodium Injection . . . meets the standards for approval (including those for active ingredient sameness and bioequivalence) and, therefore, is therapeutically equivalent to the [RLD], Lovenox Injection[.]").

On the same date that the FDA approved Sandoz's ANDA, the agency denied Sanofi's citizen petition with the exception of approving its request regarding the 1,6 anhydro ring structure. *See* AR 2878-922. In its denial, the FDA explained that "[w]e do not find it necessary for an ANDA applicant seeking approval of generic enoxaparin to submit the information you request." AR 2879. While acknowledging that "the approval of ANDAs for enoxaparin raises complicated scientific and regulatory issues," the agency explained that "[b]ased on our evaluation of all the relevant data and other current relevant scientific information, our experience and expertise, Agency precedent, and applicable

law, we find that enoxaparin has been adequately characterized for the purposes of approving naturally sourced generic enoxaparin; and we conclude that an ANDA applicant for enoxaparin can demonstrate active ingredient sameness by meeting five criteria, each of which captures different aspects of the active ingredient's 'sameness.'" AR 2879-80.[4] The agency also noted that "[i]n addition to the issues raised in your petition, we have also considered issues related to immunogenicity," explaining that "[i]t is important that ANDA applicants assess the potential of the generic product to generate a greater immune response as compared to the RLD, Lovenox." AR 2881.

Three days after Sandoz's ANDA was approved and Sanofi's citizen petition was largely denied, Sanofi filed suit in this Court. Although Sanofi initially requested a temporary restraining order ("TRO"), during a telephonic status hearing on July 26, 2010, Sanofi agreed to consolidate its request for a TRO with its request for a preliminary injunction. *See* Minute Order dated July 26, 2010. On July 27, 2010, Sandoz sought leave to intervene in this lawsuit as a defendant, and on July 28, 2010,

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[4] These five criteria address: (1) the physical and chemical characteristics of enoxaparin; (2) the nature of the source material and method used to break up the polysaccharide chains into smaller fragments; (3) the nature and arrangement of components that constitute enoxaparin; (4) certain laboratory measurements of anticoagulant activity; and (5) certain aspects of the drug's effect in humans. AR 2880; *see also infra* Section III.A.3 (providing further discussion of the five-part sameness test).

the Court granted the unopposed request. The Court also granted the unopposed motion of AARP to file an amicus brief in support of defendants. Having received expedited briefing and heard oral argument from each of the parties, Sanofi's motion for a preliminary injunction is now ripe for determination by the Court.

II. LEGAL STANDARD FOR INTERIM INJUNCTIVE RELIEF

Preliminary injunctive relief is an "extraordinary remedy never awarded as of right." *Winter v. NRDC, Inc.*, 129 S. Ct. 365, 376 (2008); *Munaf v. Geren*, 553 U.S. 674, 128 S. Ct. 2207, 2219 (2008) ("A preliminary injunction is an extraordinary and drastic remedy[.]" (internal quotation marks omitted)). "A plaintiff seeking a preliminary injunction must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest." *Winter*, 129 S. Ct. at 374.

These four factors have typically been evaluated on a "sliding scale," whereby if the movant makes an unusually strong showing on one of the factors, then it does not necessarily have to make as strong a showing on another factor. *Davis v. Pension Benefit Guar. Corp.*, 571 F.3d 1288, 1291-92 (D.C. Cir. 2009) (citing *Davenport v. Int'l Bhd. of Teamsters*, 166 F.3d 356, 361 (D.C. Cir. 1999)). While it is unclear whether the "sliding

scale" is still controlling in light of the Supreme Court's decision in ***Winter***, the Court need not decide this issue because plaintiff's request for a preliminary injunction fails even under the less stringent "sliding scale" analysis of ***Davenport***. ***See id.*** (declining, given the facts of the case, to decide if ***Winter*** created a "stricter standard" to obtain interim injunctive relief).[5]

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[5] At least two judges in this Circuit have announced the position that "[i]n light of the Supreme Court's recent decisions . . . the old sliding-scale approach to preliminary injunctions – under which a very strong likelihood of success could make up for a failure to show a likelihood of irreparable harm, or vice versa – is no longer controlling, or even viable." ***Davis***, 571 F.3d at 1297 (Kavanaugh, J., concurring, joined by Henderson, J., concurring) (internal quotation marks omitted); ***see also id.*** ("It appears that a party moving for a preliminary injunction must meet four independent requirements. To be sure, the third preliminary injunction factor requires a balancing of the equities, but that's an additional requirement, not a substitute for the first two requirements. In other words, under the Supreme Court's precedents, a movant cannot obtain a preliminary injunction without showing ***both*** a likelihood of success ***and*** a likelihood of irreparable harm, among other things.").

Notably, since ***Davis*** was decided, a circuit split has emerged regarding the continued viability of the sliding-scale approach. While the Fourth Circuit has rejected the approach as invalid, ***see Real Truth About Obama, Inc. v. Fed. Election Comm'n***, 575 F.3d 342, 347 (4th Cir. 2009) (holding that the circuit's prior test, which permitted "flexible interplay" among the elements, "may no longer be applied" after ***Winter***), ***vacated on other grounds***, 130 S. Ct. 2371, 176 L. Ed. 2d 764 (2010), the Second, Seventh, and Ninth Circuits have found that a "serious questions" version of the sliding-scale test is permissible. Under this modified sliding-scale approach, "'[a] preliminary injunction is appropriate when a plaintiff demonstrates . . .

III. ANALYSIS

Sanofi argues that it has satisfied all four criteria necessary to obtain a preliminary injunction, while the FDA and Sandoz argue that none of the criteria for provisional injunctive relief have been met. The Court will begin by addressing Sanofi's likelihood of success on the merits.

A. Likelihood of Success on the Merits

Sanofi sets forth three reasons that it is likely to succeed on the merits. Specifically, Sanofi argues that the FDA: (1) exceeded its authority under 21 U.S.C. § 355(j)(2)(A) by requiring Sandoz to submit additional studies "to demonstrate safety and effectiveness" beyond what is permitted for ANDAs; (2) departed from agency precedent by approving a generic version of a drug derived from a complex biological starting material that has not yet been fully characterized; and (3) approved generic enoxaparin without sufficient evidence that it has the "same" active ingredient as Lovenox, as required by § 355(j)(2)(A). Pl.'s Mem. at 16. The Court will explore these arguments in turn.

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that serious questions going to the merits were raised and the balance of hardships tips sharply in the plaintiff's favor.'" *Alliance for the Wild Rockies v. Cottrell*, — F.3d —, No. 09-35756, 2010 U.S. App. LEXIS 15537, at *8-19 (9th Cir. July 28, 2010) (analyzing the circuit split surrounding the sliding-scale approach after *Winter*).

1. FDA's Request for Additional Studies by Sandoz

As discussed above, the FDA initially found that Sandoz's ANDA for generic enoxaparin was "not approvable" because the application did not adequately address the potential for immunogenicity of the drug product. AR 4167; *see also* AR 4170 ("FDA is particularly concerned with product and process derived impurities that may modify the biological activity or enhance the immunogenicity of your product."). The FDA therefore required Sandoz to submit three types of studies comparing the immunogenicity of its product with Lovenox. *See* AR 4171-73 ((i) explaining that "the presence of impurities may affect the interaction of enoxaparin with PF4," and requesting that Sandoz "compare the ability of your product with that of the innovator product to bind to and form complexes with chemokine PF4, and characterize the size and charge of the resulting complexes"; (ii) requesting studies to enable the FDA to "understand the amount and nature of potential product contaminants relative to those in the innovator product"; and (iii) requesting functional studies to assess "any potential immunogenic properties of your product as compared to the innovator product"); *see also* Fed. Defs.' Opp'n Br. at 20 (describing the additional immunogenicity data submitted by Sandoz).

Sanofi argues that by requiring Sandoz to submit these additional immunogenicity studies, the FDA violated

§ 355(j)(2)(A) of the FDCA, which prohibits the FDA from requiring an ANDA applicant to submit information beyond that which is specified in §§ 355(j)(2)(A)(i)-(viii). *See* 21 U.S.C. § 355(j)(2)(A) ("The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)."). The FDA counters that the type of immunogenicity information that it requested falls well within the agency's authority to consider whether the manufacturing methods, controls, and specifications of a potential generic drug manufacturer are comparable to those of the innovator drug. *See, e.g., id.* § 355(j)(2)(A)(vi), § 355(b)(1)(D) (requiring an ANDA applicant to submit "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of [its proposed] drug" (quoting § 355(b)(1)(D))); 21 C.F.R. § 314.94(a)(9), § 314.50(d)(1) (requiring an ANDA applicant to submit information regarding its "[c]hemistry, manufacturing, and controls," including "the specifications necessary to ensure the identity, strength, quality, and purity of the drug substance . . . [and] the drug product" (quoting § 314.50(d)(1))). For the reasons discussed below, the Court finds that plaintiff is not likely to establish that the FDA lacked the authority to request

data comparing the immunogenicity of Sandoz's proposed generic enoxaparin with the RLD, Lovenox, as part of Sandoz's ANDA.[6]

As a threshold matter, the Court's analysis of the FDA's interpretation of the FDCA is governed by ***Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.***, 467 U.S. 837 (1984). Under ***Chevron***, the Court must first determine "whether Congress has directly spoken to the precise question at issue." ***Id.*** at 842. Courts "use 'traditional tools of statutory construction' to determine whether Congress has unambiguously expressed its intent," ***Serono***, 158 F.3d at 1320, including an examination of

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[6] While Sanofi repeatedly attempts to characterize the FDA's request for additional data on immunogenicity as impermissible "safety testing," the FDA explains that "[t]he additional data sought from Sandoz in this case was limited solely to assuring that Sandoz's manufacturing process would not produce impurities with potential immunogenic effects to any greater degree than Lovenox itself." Fed. Defs.' Surreply at 3-4 n.1. The agency further explains that: "Although information about a product's purity and its impact on immunogenicity is certainly relevant to its safety, the impurity data that FDA considered was intended to compare the respective impurities and potential immune responses of Sandoz's generic enoxaparin with Sanofi's Lovenox. . . . Contrary to Sanofi's implication, FDA did not request or demand anything approaching the type of large-scale clinical safety and efficacy trials mandated for new drugs. Instead, the safety of Sandoz's enoxaparin, like any generic drug, was based upon the agency's prior finding that the innovator drug (in this case Lovenox) was itself safe and effective." Fed. Defs.' Surreply at 3-4 n.1. Because this explanation appears consistent with the administrative record submitted in this case, ***see, e.g.***, AR 4170-74, the Court finds no reason to doubt the FDA's explanation regarding its request for additional information relating to impurities.

the statute's text, structure, purpose, and legislative history. *See Shays v. FEC*, 414 F.3d 76, 105 (D.C. Cir. 2005). "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron*, 467 U.S. at 842-43. If, however, "the statute is silent or ambiguous with respect to the specific issue, the question for the court is whether the agency's answer is based on a permissible construction of the statute." *Id.* at 843. In making such an assessment, "considerable weight" is generally accorded to "an executive department's construction of a statutory scheme it is entrusted to administer[.]" *Id.* Indeed, "under *Chevron*, courts are bound to uphold an agency interpretation as long as it is reasonable – regardless whether there may be other reasonable, or even more reasonable, views." *Serono,* 158 F.3d at 1321.

Sanofi argues that this case should be resolved under *Chevron* step one because § 355(j)(2)(A) "unambiguously prohibits FDA from requiring an ANDA applicant to conduct basic safety testing such as immunogenicity testing." Pl.'s Reply Br. at 5. While it is undoubtedly true that the FDA may not require an ANDA applicant to submit information beyond what is specified in § 355(j)(2)(A)(i)-(viii), the FDA persuasively counters that "the categories of required information are set forth in broad, general terms that provide FDA with ample discretion to determine

what information it may assess to evaluate an ANDA." Fed. Defs.' Surreply at 4; *see also Serono*, 158 F.3d at 1324 ("[T]he clauses [in § 355(j)(2)(A)(i)-(viii)] simply describe what the 'information' in an application must 'show.' They do not specify the kinds of studies that can or cannot be used to satisfy the requirement[s]."). This Court agrees.

The statute itself says nothing about the type of "full description" an ANDA applicant must submit in order to satisfy the FDA that the chemistry, manufacturing, and controls of the generic drug producer are sufficient to ensure the purity of the proposed drug product. *See* 21 U.S.C. § 355(j)(2)(A)(vi), § 355(b)(1)(D). It says only that the full description must allow the FDA to determine that "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are [not] inadequate to assure and preserve its identity, strength, quality, and purity[.]" 21 U.S.C. § 355(j)(4)(A). Accordingly, when reading §§ 355(j)(2)(A)(vi) and 355(b)(1)(D)'s requirement that applicants fully describe their manufacturing process, in conjunction with § 355(j)(4)(A)'s requirement that the FDA assess a drug's "purity" in determining whether to approve an ANDA, the Court cannot agree with plaintiff's assertion that § 355(j)(2)(A) unambiguously prohibits the FDA from requesting the submission of

data comparing the impurity profile of a proposed generic drug with the RLD.

Turning to the second *Chevron* inquiry, the Court must determine whether the FDA's request for data comparing the impurity profiles of Sandoz's generic enoxaparin with Lovenox is "based on a permissible construction of the statute." *Chevron*, 467 U.S. at 843. As noted above, this Court must defer to the FDA's interpretation of the FDCA as long as it reasonable – "regardless whether there may be other reasonable, or even more reasonable, views." *Serono*, 158 F.3d at 1321. Similarly, the Court must defer to an agency's reading of its own regulations unless it is "plainly erroneous or inconsistent with the regulation." *Id.* at 1320 (internal quotation marks omitted).

Here, the FDA argues that its regulations "have long construed the statutory requirement of a 'full description' of manufacturing methods and controls, 21 U.S.C. § 355(b)(1)(D), and the parallel provision in 21 U.S.C. § 355(j)(4)(A), to include, among other things, detailed information related to the assessment of impurities." Fed. Defs.' Surreply at 5; *see, e.g.*, 21 C.F.R. § 314.94(a)(9) (requiring the specifications necessary to ensure the purity of the drug product, including, for example, tests, analytical procedures, and acceptance criteria); 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. This would include information on impurities and residues. The 'Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances' suggests that impurities 'should not only be detected and quantitated, but should also be identified and characterized when this is possible with reasonable effort.'" (internal citations omitted)).[7] Despite Sanofi's protestations to the contrary, *see* Pl.'s Reply Br. at 8-12, the Court concludes that the FDA's construction of the FDCA as permitting the agency to request information to assess whether impurities resulting from a generic drug producer's manufacturing processes and controls would generate a greater immune response than the RLD is both reasonable and consistent with its regulations. Moreover, because the FDA's determination of what is required to assess the "purity" of a generic drug for purposes of the FDCA "rests on the

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[7] The federal defendants also submitted a guidance document regarding the FDA's evaluation of impurities with its surreply. *See* Docket No. 22-1, Guidance for Industry, ANDAs: Impurities in Drug Substances (June 2009). This guidance document discusses, among other things, the "qualification of impurities," which is "the process of acquiring and evaluating data that establish the biological safety of an individual impurity or a given impurity profile at the level(s) being considered." *Id.* at 4. The guidance document indicates that "[w]hen appropriate, we recommend that [ANDA] applicants provide a rationale for establishing impurity acceptance criteria that includes safety considerations," *id.*, and provides recommendations regarding "methods for qualifying impurities." *Id.* at 5.

'agency's evaluations of scientific data within its area of expertise,'" it is "entitled to a 'high level of deference' from this court." *Serono*, 158 F.3d at 1320 (quoting *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1490 (D.C. Cir. 1995)). Accordingly, the Court concludes that Sanofi is unlikely to demonstrate that the FDA exceeded its authority under the FDCA when it approved Sandoz's ANDA despite having required Sandoz to submit additional information comparing the impurity profiles of its generic enoxaparin with Lovenox.

2. FDA's Approval of a Generic Drug that is Not Fully Characterized

Next, Sanofi argues that the FDA departed from agency precedent by approving a generic version of a drug derived from a complex biological starting material that has not yet been fully characterized. Specifically, Sanofi asserts that the FDA's approval of Sandoz's ANDA "represents a significant departure from well-established agency precedent regarding complex products – like enoxaparin – that are not fully characterized," and must therefore be enjoined as an arbitrary and capricious decision under the Administrative Procedure Act (the "APA"), 5 U.S.C. § 706(2)(A). Pl.'s Mem. at 24-25. In support of its argument, plaintiff asserts that the FDA's approval of generic enoxaparin is inconsistent with its decisions for (i) hyaluronidase, (ii) Omnitrope, and (iii) Premarin. *See* Pl.'s Mem. at 25-33. Sanofi further argues that the FDA "fails to address that enoxaparin is

not fully characterized or to provide a substantive reason for why it should be treated differently than other drugs that are not fully characterized." Pl.'s Mem. at 24.

The FDA responds that Sanofi's reliance on these past decisions is "misplaced," explaining that the FDA "may and must approve drugs by considering the individual characteristics of the particular drug at issue." Fed. Defs.' Opp'n Br. at 31. The FDA further responds that its decision to approve Sandoz's ANDA is "consistent with the general principles underlying past agency decisions[.]" Fed. Defs.' Opp'n Br. at 31; ***see also*** AR 2900-02 (explaining how the agency's approach for determining the "sameness" of enoxaparin is "consistent with [its] previous ANDA approval decisions for other generic drug products containing active ingredients that are heterogeneous polysaccharides," including heparin and hetastarch). For the reasons discussed below, the Court finds the FDA's explanations regarding its past decisions persuasive and concludes that Sanofi is unlikely to succeed on its claim that the FDA's approval of generic enoxaparin was arbitrary and capricious.

In reviewing Sanofi's claims that the FDA violated the APA, it is well established in this Circuit that the Court's review is "highly deferential." ***Bloch v. Powell***, 348 F.3d 1060, 1070 (D.C. Cir. 2003). This is particularly true when, as here, the agency's decision is based on the evaluation of complex

scientific information within the agency's technical expertise. *See Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (emphasizing that "considerable deference" must be shown because courts "review scientific judgments of the agency not as the chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality" (internal quotation marks omitted)). Therefore, when reviewing agency action under the APA, the Court must only assess whether the challenged decision was "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); *see also Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto Ins. Co.*, 463 U.S. 29, 43 (1983) (explaining that courts may only set aside agency action under the APA if the agency "relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise"). As long as the "agency's reasons and policy choices . . . conform to 'certain minimal standards of rationality' . . . the [agency decision] is reasonable and must be upheld." *Small*

Refiner Lead Phase-Down Task Force v. EPA, 705 F.2d 506, 520-21 (D.C. Cir. 1983) (citation omitted).

As discussed above, Sanofi argues that the FDA's decision to approve Sandoz's ANDA for enoxaparin is inconsistent with its past "precedent" regarding complex drugs that have not yet been fully characterized. Pl.'s Mem. at 24-25. While it is undoubtedly true that "an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so," *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 1997) (quoting *Indep. Petroleum Ass'n of America v. Babbitt*, 92 F.3d 1248, 1258 (D.C. Cir. 1996)), this is not a case in which the FDA treated drugs that were "identical in all material respects" differently. *Id.; see, e.g.*, AR at 2916-17 ("While both enoxaparin and hyaluronidase are heterogeneous mixtures of molecular entities, these two active ingredients are derived from different origins and are composed of entirely different molecular structures."; "Enoxaparin consists of a heterogenous mixture of oligosaccharides produced through alkaline depolymerization of the benzyl ester of heparin derived from porcine intestinal mucosa, whereas hyaluronidase is a mixture of glycosylated protein isoforms (isoenzymes) that is derived from either naturally sourced tissue – ovine tissue (Vitrase) or bovine tissue (Amphadase, Hydase) – or through recombinant means (Hylenex)."); AR at 2915-16 (explaining that

the active ingredients of Premarin and enoxaparin "are derived from different origins and are composed of entirely different molecular structures"; "Enoxaparin is a heterogenous mixture of oligosaccharides produced through alkaline depolymerization of the benzyl ester of heparin derived from porcine intestinal mucosa, whereas Premarin's conjugated estrogens are a mixture of steroids derived from pregnant mare's urine.").[8] Nor is this a case in which the FDA "simply gloss[ed] over its earlier decisions." Pl.'s Mem. at 24. To the contrary, the FDA provided "legitimate reason[s]" for deciding that enoxaparin should be treated differently than the drugs cited by Sanofi. *Bracco*, 963 F. Supp. at 27; *see* AR 2900-02, 2914-18 (explaining why approval of an ANDA for enoxaparin is consistent with FDA precedent).[9]

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[8] *See also* AR at 2914-15 (explaining that the active ingredients of enoxaparin and Pergonal "have different origins and are composed of entirely different molecular structures"; "Enoxaparin is a heterogenous mixture of oligosaccharides produced through alkaline depolymerization of the benzyl ester of heparin derived from porcine intestinal mucosa, whereas Pergonal's menotropins are a mixture of protein isoforms of FSH and LH derived from the urine of post-menopausal women.").

[9] *See also* Fed. Defs.' Opp'n Br. at 31 (explaining that the FDA denied an ANDA to manufacture generic hyaluronidase because the active ingredient in hyaluronidase had "not yet been sufficiently characterized to permit the Agency to conclude that another hyaluronidase product has an identical active ingredient"; "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." (citing AR 2918) (internal quotation marks omitted)); Fed. Defs.'

Having carefully reviewed the FDA's denial of Sanofi's citizen petition and its explanations regarding its past decisions, the Court is unpersuaded that the FDA failed to "conform to 'certain minimal standards of rationality'" in its evaluation of enoxaparin. *Small Refiner Lead Phase-Down Task Force*, 705 F.2d at 521. Therefore, given the deferential standard of review that this Court must accord the FDA's scientific determinations, the Court finds it unlikely that Sanofi will succeed in its argument that the FDA's approval of generic enoxaparin is inconsistent with its past precedent.

3. FDA's Determination that Sandoz's ANDA has the Same Active Ingredient as Lovenox

Finally, Sanofi argues that it is likely to succeed on the merits because the FDA approved generic enoxaparin without

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Opp'n Br. at 32 ("Omnitrope, unlike enoxaparin, was never determined to have the 'same' active ingredient as the innovator [RLD], and in fact had acknowledged differences in certain respects. 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 has been adequately characterized and has met the five criteria."); Fed. Defs.' Opp'n Br. at 33-34 ("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. 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. 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." (internal citations omitted)).

sufficient evidence that Sandoz's ANDA has the "same" active ingredient as Lovenox as required by § 355(j)(2)(A). Sanofi contends that in approving Sandoz's ANDA, the FDA "ignored voluminous scientific evidence demonstrating that until enoxaparin is fully characterized, generic enoxaparin products that do not use a manufacturing process that is equivalent to [Sanofi's] process will not be the same as Lovenox." Pl.'s Mem. at 33. It further asserts that the FDA failed to provide a "rational explanation for its decision to disregard scientific evidence that directly contradicts its administrative findings," and therefore is arbitrary and capricious. Pl.'s Mem. at 33-34. The Court finds these arguments unavailing.

In its response to Sanofi's citizen petition, the FDA provided a detailed explanation regarding its determination that an ANDA applicant for enoxaparin can demonstrate "active ingredient sameness" by meeting five criteria, "each of which captures different aspects of the active ingredient's 'sameness.'" AR 2879-80. In particular, the FDA found that an ANDA applicant seeking approval for generic enoxaparin must demonstrate: (1) equivalence of physicochemical properties, such as molecular weight distribution and overall chemical composition; (2) equivalence of heparin source material (i.e., heparin that is derived from porcine intestinal mucosa and that meets USP monograph standards for Heparin Sodium USP) and mode of

depolymerization (i.e., cleavage by alkaline β-elimination of the benzyl ester derivative of heparin); (3) equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species; (4) equivalence of in vitro biological and biochemical assay results; and (5) equivalence of in vivo pharmacodynamic profile based upon measurements of in vivo anti-Xa and anti-IIa profiles. *See* AR 2888-900. The FDA also provided an exhaustive response to the arguments raised in Sanofi's citizen petition, *see generally* AR 2904-21, including Sanofi's claim that the FDA should refrain from approving any ANDAs citing Lovenox as the RLD unless, among other things, the manufacturing process used to create the generic drug product was deemed to be equivalent to Sanofi's manufacturing process for Lovenox. *See* AR 2905-13 (explaining why ANDA applicants for enoxaparin do not need to demonstrate that they use the same manufacturing process as Sanofi).

While Sanofi may not agree with the FDA's determination that an ANDA applicant for enoxaparin can demonstrate sameness by satisfying the five-part test discussed above, the Court concludes that the FDA's definition of "sameness," as applied to enoxaparin products, is reasonable. AR 2888; *see also Serono*, 158 F.3d at 1320 ("The 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." (internal quotation marks omitted)). It was similarly reasonable for the FDA to conclude that an ANDA applicant need not use the same manufacturing process as Sanofi in light of its determination 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. In sum, just because the FDA – after seven years of careful consideration of Sanofi's citizen petition and five years of examination of Sandoz's ANDA – reached a conclusion at odds with the position advanced by Sanofi, does not mean that the FDA's decision was arbitrary and capricious. To the contrary, a review of the FDA's response to Sanofi's citizen petition demonstrates that the FDA "'examine[d] the relevant data and articulate[d] a satisfactory explanation for its decision.'" *FCC v. Fox Television Stations, Inc.*, 129 S. Ct. 1800, 1810 (2009) (quoting *Motor Vehicle Mfrs. Assn.*, 463 U.S. at 43). The Court, therefore, finds it unlikely that Sanofi will succeed on the merits of its claims.

B. Irreparable Harm

Next, the Court must determine whether Sanofi will suffer irreparable harm in the absence of injunctive relief. Explaining that its annual domestic net sales for Lovenox were approximately

$2.5 billion in 2009, Sanofi argues that it would suffer "very substantial economic loss if generic sales could continue until a merits ruling issued." Pl.'s Mem. at 37-38. Sanofi further argues that because the FDA would be shielded by sovereign immunity in any subsequent lawsuit based on the agency's allegedly unlawful approval of Sandoz's ANDA, its harm would be "'irreparable per se'" as it has no adequate remedy at law to recover its lost sales. Pl.'s Mem. at 38-39 (quoting ***Feinerman v. Bernardi***, 558 F. Supp. 2d 36, 51 (D.D.C. 2008)). Sanofi also asserts that "permitting Sandoz's product to reach the market without sufficient evidence that it is indeed clinically identical to Lovenox could permanently damage [Sanofi's] reputation and the reputation of the Lovenox brand, as well as present significant risks of harm to patients." Pl.'s Mem. at 40.[10]

In response, the federal defendants argue that the Court must reject Sanofi's assertion of irreparable harm, explaining that "[i]n this circuit, mere economic loss – even irrecoverable

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[10] Despite its vague assertions regarding potential risk of harm to patients in its brief, plaintiff's counsel conceded during oral argument that Sanofi was not challenging the safety of Sandoz's generic enoxaparin. ***See*** Hr'g Tr. 32:2-7, Aug. 17, 2010 (Plaintiff's Counsel: ". . . [O]ur argument is not that [the generic] product shouldn't be marketed or sold."; The Court: "Right. And I want to say that again, you're not arguing that it's unsafe at all, right?"; Plaintiff's Counsel: "I'm not arguing that, no, Your Honor, and we have not taken that position.").

economic loss, such as Sanofi alleges here – does not constitute irreperable harm unless the financial injury is so great as to threaten the continued existence of the movant's business." Fed. Defs.' Opp'n Br. at 39 (citing ***Wisc. Gas Co. v. FERC***, 758 F.2d 669 (D.C. Cir. 1985) and its progeny). The federal defendants then explain that even though Lovenox accounted for 26% of Sanofi's domestic revenue in 2009, Sanofi has failed to establish irreparable harm because "Sanofi is a global company with a broad portfolio of prescription medicines, consumer healthcare products, generics, and vaccines, and worldwide revenues of some $40 billion annually." Fed. Defs.' Opp'n Br. at 40-41 (emphasizing that the $2.5 billion in domestic sales generated by Lovenox in 2009 amounted to only 6% of the company's overall annual revenue). The federal defendants also point to several public admissions by Sanofi, belying its claim of irreparable harm. ***See*** Fed. Defs.' Opp'n Br. at 41-42 and n.25.[11]

[11] The federal defendants cite, among other things: Full Year 2009 SanofiAventis Earnings Conference Call, Full Disclosure Wire, Feb. 10, 2010, at 14 (explaining that a substitutable generic such as Sandoz's ANDA "would have some impact on our 2010 numbers," but "doesn't really have an impact longer term"); Interview with Chris Viehbacher, SanofiAventis Chief Executive Officer, Q2 Results, ***available at*** http://en.sanofi-aventis.com/events/2010_2ndQR/docs/20100729_Q2_2010_Transcript_en.pdf ("Most of the volume that we sell is outside of the US. [Lovenox] still remains a blockbuster product, even without the US sales."); Sanofi-aventis Press Release, EPS Growth in Q2 2010, July 29, 2010, ***available at*** http://en.sanofi-aventis.com/binaries/20100729_Q2_2010_Results2_en_tcm28-29020.pdf ("Sanofi-aventis expects business [earnings per share] for the year 2010 to be

While the Court finds it unlikely that Sanofi has met this Circuit's stringent standard for irreparable harm, the Court will nevertheless assume that Sanofi's unrecoverable loss of sales to Sandoz constitutes irreparable harm. *See Serono*, 158 F.3d at 1326 (assuming that the plaintiff would be irreparably injured if the FDA was not enjoined from approving an ANDA where the plaintiff would suffer an unrecoverable loss of sales to the generic manufacturer). As discussed below, however, the Court finds that this factor does not weigh in favor of Sanofi because when weighed against the harm that an injunction would inflict on Sandoz, "that balance of harm results roughly in a draw." *Serono*, 158 F.3d at 1326; *see infra* Section III.C.

C. Balance of Equities

Because Sandoz has been selling and distributing its generic enoxaparin for the last month, Sandoz would undoubtedly face significant harm if the Court entered an interim injunction. *See* Sandoz Opp'n Br. at 26-27 (explaining that "millions of doses are already in the hands of customers and being used by patients" and arguing that an interim injunction would cause it significant financial harm as well as an "incalculable impact to its goodwill and reputation with customers if [the customers] were asked to

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flat to minus 4% versus 2009, at constant exchange rates, barring major unforeseen adverse events. This guidance takes into account the recent approval of a generic of Lovenox in the U.S. It also incorporates the financial impact of U.S. healthcare reform and recent EU price cuts.").

stop their use of the Sandoz generic mid-stream"; noting that Sandoz is expecting sales in the range of over $40 million in the next six weeks alone for its generic enoxaparin). Therefore, because whatever sales Sanofi will lose to Sandoz in the absence of an injunction, Sandoz will lose to Sanofi in the presence of one, the Court concludes that the harm alleged by Sanofi and the harm faced by Sandoz are essentially "a wash." *Serono*, 158 F.3d at 1326; *see also id.* (quoting *Delaware & Hudson Ry. Co. v. United Transp. Union*, 450 F.2d 603, 620 (D.C. Cir. 1971) for the proposition that: "It often happens that . . . one party or the other will be injured whichever course is taken. A sound disposition . . . must [then] depend on a reflective and attentive appraisal as to the outcome on the merits." (alterations in original)).

D. Public Interest

The last factor the Court must consider is whether the public interest favors entry of a preliminary injunction. Sanofi argues that an injunction should be granted because "the public interest would be served by requiring the FDA to comply with the law." Pl.'s Mem. at 42. While it is undoubtedly true that the public has an interest in governmental agencies following the

law, given the facts of this case, an injunction would serve the public interest only if Sanofi is likely to succeed on the merits. Because, however, the Court has found that Sanofi is unlikely to establish that the FDA exceeded its authority in granting Sandoz's ANDA, the Court concludes that the public would be harmed by a court-ordered delay in the distribution of a generic drug that is approximately 30-35% cheaper than Lovenox. Hr'g Tr. 74:9-10, Aug. 17, 2010;[12] ***see generally*** AARP Amicus Br. (arguing that interim injunctive relief would harm the public). Accordingly, in light of the Court's determination that Sanofi is unlikely to succeed on the merits, and given that no parties are challenging the safety of Sandoz's generic enoxaparin, the Court concludes that Sanofi has failed to establish that the public interest favors interim injunctive relief.

IV. CONCLUSION

For the foregoing reasons, the Court **DENIES** Sanofi's motion for a preliminary injunction. This opinion does not foreclose the possibility that upon a more developed record, Sanofi may be able to establish that there are grounds for overturning the grant of Sandoz's ANDA. The Court holds only that upon the

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[12] Although the parties were unable to apprise the Court of the cost of Lovenox or Sandoz's generic enoxaparin, the Court was informed that the cost was substantial. ***See*** Hr'g Tr. at 74:5 – 75:13. Indeed, Lovenox represents the single largest pharmacy expenditure for most hospitals in the United States. ***See*** Sandoz Opp'n Br. at 28.

current record, Sanofi has failed to establish that it meets the criteria for the grant of a preliminary injunction. An appropriate Order accompanies this Memorandum Opinion.

SIGNED: Emmet G. Sullivan
United States District Court Judge
August 25, 2010