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' SURREPLY IN OPPOSITION TO PLAINTIFF'S MOTION FOR A TEMPORARY RESTRAINING ORDER AND A PRELIMINARY INJUNCTION

In its zeal to maintain a monopoly for Lovenox, a life-saving drug, Sanofi challenges FDA's authority to require testing for impurities. But Sanofi misconstrues key statutory provisions that explicitly permit – indeed require – FDA to consider the impurities that a generic product may contain. In short, Sanofi's legal challenge is meritless. Sanofi raises no serious challenge to FDA's scientific conclusions and its effort to identify inconsistent agency practice overlooks the most significant and relevant precedents. Nor can Sanofi show that it will suffer irreparable harm in the absence of preliminary injunctive relief or that the balance of equities weighs in its favor. For all of these reasons and those stated in the federal defendants' opposition brief, Sanofi has not satisfied the stringent standards for extraordinary relief and its motion for a preliminary injunction should be denied.

I. Sanofi Has No Likelihood of Success on the Merits

A. FDA Has Statutory Authority To Require Comparative Impurity Testing

As explained in the government's opening brief, a sponsor of an abbreviated new drug application ("ANDA") need not demonstrate that its product is safe and effective in order to gain approval to market a generic copy of a previously approved innovator drug. Instead, the generic applicant simply needs to establish that its product is the same as the innovator in various ways (*e.g.*, active ingredient, route of administration, dosage form, strength, etc.) because the innovator drug has already been shown to be safe and effective through clinical evidence typically consisting of large-scale trials testing the safety and efficacy of the drug in human volunteers. The generic applicant need not duplicate these expensive and time-consuming trials (nor can FDA require such evidence), because, under the statute, the generic applicant is entitled to rely upon FDA's finding that the innovator company has already shown the brand name drug to be safe and effective and all the generic applicant is required to do is show that its version of the drug is the same as the innovator.

But even after demonstrating that its generic product is a copy of the innovator drug, a generic applicant still must demonstrate, among other things, that it can consistently and reliably produce the drug – *i.e.* that its manufacturing methods, controls, and specifications are such that it can consistently produce batches of drug product with the identity, strength, quality, and purity it is expected to have. Information documenting this ability is submitted as part of the so-called "CMC" section of the ANDA relating to "chemistry, manufacturing, and controls." 21 C.F.R. § 314.94(a)(9). Every ANDA applicant must submit this type of information, and FDA clearly has – and must have – broad discretion to determine the precise nature and quantity of

information necessary to adequately evaluate the manufacturing methods and controls for a given drug.

In the case of enoxaparin, the issue of purity is of particular concern due to a well-known immunogenic effect that can result from impurities in the product, leading to an adverse reaction in patients. *See* AR 3848. Accordingly, even after FDA determined that Sandoz's generic enoxaparin contained the "same" active ingredient as Lovenox, FDA requested that Sandoz (and all enoxaparin ANDA sponsors) perform tests sufficient to assure that any impurities resulting from its manufacturing processes and controls would not generate a greater immune response compared to Lovenox. *See* AR 4167-71. As demonstrated below, and in the government's opening brief, ANDA sponsors are required by statute to provide this type of information to FDA and FDA is fully authorized – indeed obligated – to consider such evidence to the extent necessary to assure itself that an applicant's manufacturing methods and controls are adequate to assure the purity of the drug product.

In these circumstances, Sanofi's claim that FDA could not require the type of impurity data it requested from Sandoz in this case is utterly meritless.[1] Although 21 U.S.C.

[1] Sanofi insists on mischaracterizing the comparative impurity testing Sandoz performed in this case as "safety" testing such as would be required for a full NDA approval. 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. This limited, comparative data is a far cry from the "full reports of investigations" to show safety and efficacy that are required for new drug approvals under 21 U.S.C. § 355(b)(1)(A) – a category of information that Congress specifically excluded from information that FDA can require for ANDAs. *See* 21 U.S.C. § 355(j)(2)(A)(vi) (requiring ANDAs to contain the information specified in 21 U.S.C. § 355(b)(1)(B)-(F), but not (A)). 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' enoxaparin, like any generic drug, was based upon the agency's prior finding that the innovator drug (in this case

§ 355(j)(2)(A) prohibits FDA from requiring information other than what is enumerated in eight subsections, those subsections broadly provide FDA with authority to consider information appropriate to approve an ANDA – including the subsection at issue, 21 U.S.C. § 355(j)(2)(A)(vi), which, together with 21 U.S.C. § 355(b)(1)(D),[2] requires applicants to provide a "full description" of their manufacturing process. Sanofi argues that, because the proscription on additional information in 21 U.S.C. § 355(j)(2)(A) is unambiguous, this case can be resolved under *Chevron* step one. Reply at 5.

But however plain the wording limiting *additional* information may be, the categories of required information are set forth in broad, general terms that provide FDA with ample discretion to determine what specific information it may assess to evaluate an ANDA. *See* 21 U.S.C. § 355(j)(2)(A)(i) - (viii). As the D.C. Circuit has pointed out: "The clauses [21 U.S.C. § 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." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1324 (D.C. Cir. 1998*)*. Thus, FDA has wide latitude under *Chevron* step two to flesh out the statutory requirements by specifying in greater detail the nature and quantity of information that an ANDA must contain. *See Chevron U.S.A.*

Lovenox) was itself safe and effective. The 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. This comparative testing is fully within the bounds of appropriate information for ANDA approvals. *See, e.g.*, FDA Citizen Petition Response for Salmon Calcitonin at 18 (Nov. 17, 2008) (attached as Exhibit P to Cunningham Decl. in support of Mem.).

[2] 21 U.S.C. § 355(b)(1)(D)) requires applicants to provide a "full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of [the] drug."

Inc. v. Natural Res. Def. Council, Inc., 467 U.S. 837 (1984); *Long Island Care at Home, Ltd. v. Coke*, 551 U.S. 158, 165 (2007) ("We have previously pointed out that the "'power of an administrative agency to administer a congressionally created ... program necessarily requires the formulation of policy and the making of rules to fill any gap left, implicitly or explicitly, by Congress.'").

Indeed, FDA's 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. *See* 21 C.F.R. § 314.94(a)(9); *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."). Even for drugs with active ingredients that are far less complex than enoxaparin, FDA may and does ask ANDA applicants to identify and even "qualify" the impurities in their products by conducting tests on those impurities to assess their safety.[3] Such tests may include animal tests to assess any potential toxic effects of the impurity.[4] FDA's construction of the statute, as reflected in its

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[3] "Qualification 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." Guidance for Industry, ANDAs: Impurities in Drug Substances, at 4 (June 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172002.pdf (emphasis added) (attached hereto as Addendum A).

[4] FDA's Guidance document provides that ANDA applicants may conduct analytical studies to compare the impurities in the proposed drug to those of the reference drug and may also conduct toxicity tests (typically in animals) to qualify impurities. *See id.* at 5-6; *see also* Draft Guidance for Industry, ANDAs: Impurities in Drug Products (Aug. 2005), *available at*

regulations and guidances, is entitled to substantial deference under *Chevron* step two and must be upheld unless the statute unambiguously forbids the agency's interpretation or the agency's interpretation exceeds permissible bounds, neither of which is the case here. *See Barnhart v. Walton*, 535 U.S. 212, 218 (2002). Because the statutory language is undoubtedly broad enough to permit FDA to consider drug-specific, relevant impurities information as part of the description of the manufacturing process and controls – which may contribute to such impurities – FDA's interpretation is reasonable and entitled to deference.

Section 355(j)(2)(A)(vi) and 355(b)(1)(D)'s requirement that applicants fully describe their manufacturing process must also be viewed together with a parallel provision that sets forth the importance and purpose of describing the manufacturing process – namely 21 U.S.C. § 355(j)(4), which 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 U.S.C. § 351(a)(2)(B) (providing that drug shall be deemed adulterated if not produced in conformity with current good manufacturing practice to assure drug meets quality and purity characteristics it is represented to possess); 21 C.F.R. § 314.127(a)(1). Thus, while 21 U.S.C.§ 355(b)(1)(D) (as incorporated by 21 U.S.C. 355(j)(2)(A)(vi)) requires ANDA applicants to describe their manufacturing processes and controls, 21 U.S.C. § 355(j)(4)(A) requires FDA to consider that information in order to assess certain properties of the drug itself, including the product's "purity." Sanofi's argument that FDA lacks authority to require information about product purity

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http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072861.pdf.

– which the statute itself says that FDA must consider when approving a drug – does not survive its own articulation.

Indeed, it is well established that statutes must be read as a whole, giving effect to each provision. Reasoned analysis requires that the words of the statute "'be read in their context and with a view to their place in the overall statutory scheme.'" *Ne. Md. Waste Disposal Auth. v. EPA*, 358 F.3d 936, 944-45 (D.C. Cir. 2004); *see also United Savings Ass'n v. Timbers of Inwood Forest Associates*, 484 U.S. 365, 371 (1988) ("A provision that may seem ambiguous in isolation is often clarified by the remainder of the statutory scheme – because the same terminology is used elsewhere in a context that makes its meaning clear . . . or because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law.") (internal citations omitted). Sanofi's proffered construction, however, would effectively read section (j)(4)(A) out of the statute. Indeed, it would be utterly nonsensical if information FDA needs to make an approval decision under section 355(j)(4) – and that it is required to consider by statute – could not be requested under section 355(j)(2).

Sanofi's contention that section 355(b)(1)(D) limits FDA to requiring a simple "description" of an ANDA sponsor's manufacturing methods and controls is equally unavailing. Reply at 9. Sanofi attempts to draw a distinction between "describing" manufacturing methods and controls (which Sanofi says the statute permits) versus "analyzing the effects" of such methods or controls (which Sanofi says the statute does not permit). However, Sanofi itself admits that, to fully describe its manufacturing process as required by section (b)(1)(D), an applicant must "identify the product (including impurities) this process produces." Reply at 9; *see also id.* at 14 n.7 ("Indeed, information regarding the identity and quantity of impurities in a

generic drug product is exactly the kind of information that section 505(j)(2)(A)(vi) requires an ANDA applicant to submit.").[5] Sanofi provides no principled basis for interpreting the statute's requirement of a "full description" to encompass information about an impurity's identity and quantity (but nothing more), particularly when, as here, other types of information about the impurity may also be important. Indeed, Sanofi appears to concede that FDA may require any type of "standard characterization" of impurities (but nothing more), Reply at 13 – a distinction that Congress certainly did not draw and that FDA would be in the best position to decide in any event.

Thus, the artificial distinction Sanofi attempts to draw cannot bear its own weight. The unduly narrow construction Sanofi proffers is not supported by the statute, caselaw, or common sense. By contrast, FDA has reasonably interpreted 21 U.S.C. §§ 355(j)(2)(A)(vi), (b)(1)(D), and (j)(4)(A) to consider appropriate information relating to impurities – information that is tailored to the drug at issue based on FDA's best scientific judgment.[6] That construction is entitled to

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[5] Sanofi further admits that FDA has "authority under [21 U.S.C. § 355](b)(1)(B)-(F) to establish the identity, strength, quality, *purity*, potency, and bioavailability of the drug product." *Id.* at 10 n. 4 (emphasis added). Sanofi does not explain how identifying and quantifying impurities can be squared with its ostensible view that the statute only permits a basic description of the manufacturing process itself and not an analysis of its effects – thus suggesting that Sanofi's proffered construction of the statute is not only unduly narrow, but also internally inconsistent.

[6] Nor is it relevant that the data Sandoz submitted included animal studies. Although FDA required Sandoz to submit data generally to address impurities, it did not specifically require preclinical animal data. *See* FDA. Br. at 23 n. 10 (citing AR 4171). Sandoz could have addressed immunogenicity in ways different than those suggested by FDA to attempt to meet the statutory requirements for approval. AR 4171. In that sense, contrary to Sanofi's claim, the submission of animal data was in fact "voluntary." *See* Reply at 6-8. More importantly, as *Serono* makes clear, animal data is fully within the bounds of information that FDA may assess when approving an ANDA. *See Serono*, 158 F.3d at 1324 ("the most the provision cited by Serono does is bar the FDA from *requiring* an applicant to submit more information than

Chevron deference and should be sustained. Indeed, to hold otherwise would severely restrict FDA's discretion and prevent it from exercising its best scientific judgment as to the information necessary to properly evaluate generic drugs, a result that would be at odds both with the statutory purpose and the public interest.

B. FDA's Decision is Consistent with Agency Precedent

1. Heparin and Hetastarch

In its opening brief, Sanofi accused FDA of distinguishing precedents for Premarin and hyaluronidase on the sole ground that those drugs were different than enoxaparin. Mem. at 24. Without any awareness of irony, Sanofi now asserts that because heparin undergoes a depolymerization process and is thus different from enoxaparin, "FDA's past practice with heparin therefore is not germane to a discussion of LMWH." Reply at 14. Heparin is in fact the parent of enoxaparin, is also a polysaccharide, and is the most similar molecule to enoxaparin of any of the cited precedents. Certainly, FDA's past approval of several ANDAs for heparin is "germane" to a discussion of whether FDA can approve ANDAs for enoxaparin, notwithstanding the greater complexity of enoxaparin, which FDA has fully accounted for with the five criteria.

Sanofi fares no better trying to distinguish FDA's approval of ANDAs for hetastarch, which is a mixture of polysaccharides unlike any of the other cited precedents for salmon

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required by the statute. It does not bar an applicant from voluntarily submitting additional information – including animal studies – as part of its ANDA.") (emphasis in original); *see also* Guidance for Industry, ANDAs: Impurities in Drug Substances, at 6 (June 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172002.pdf (discussing toxicity studies, which are typically performed in animals).

calcitonin, hyaluronidase, Omnitrope, or Premarin.[7] Sanofi notes that some of FDA's own experts opined that hetastarch was inapposite to approving enoxaparin (Reply at 15), but the non-final views of individual scientists within the agency are not the final views of the agency. *See Serono*, 158 F.3d at 1320-21 (holding that deference is owed to the "authorized decisionmaker" rather than to the divergent views expressed in non-final, internal agency memoranda). The agency ultimately concluded that both "[h]etastarch and heparin can be cited . . . for the proposition that the Agency has not required complete characterization, including sequence elucidation in a molecule-to-molecule comparison, to assess active ingredient sameness for those ANDA approvals." AR 3847; *see also* AR 2902.

2. FDA's Salmon Calcitonin Decision Supports its Enoxaparin Decision

For salmon calcitonin (synthetic), FDA allowed ANDA sponsors to address FDA's impurity-related immunogenicity concerns by providing information to show that the generic product had a particular immunogenicity-related amino acid sequence; comparable impurity, peptide aggregation, and leachate profiles; and was "free of excipient-peptide interactions that might increase the immunogenic response to salmon calcitonin." *See* FDA Citizen Petition Response for Salmon Calcitonin at 18 (Nov. 17, 2008) (attached as Exhibit P to Cunningham Decl. in support of Mem.). As in this case, FDA required extensive information about impurities – including testing to demonstrate that the interactions between the active ingredient and the excipient (or carrier) did not lead to any significant excipient-peptide bonding that could affect immunogenicity – thus belying Sanofi's implication that FDA's request for impurity studies in

[7] Sanofi did not even attempt to rebut FDA's arguments about Premarin, Omnitrope, or hyaluronidase in its reply brief, and FDA will not further address them here.

this case went beyond the bounds of FDA's past precedent and legal authority.[8]

Sanofi concedes that the impurities information FDA relied on for synthetic calcitonin was appropriate, Reply at 13-14, and relies instead on FDA's decision for a recombinant form of salmon calcitonin. FDA declined to accept ANDAs for that product because FDA determined that it was not feasible at that time to compare the impurity profiles. On that basis, Sanofi asserts that FDA may not approve an ANDA for enoxaparin because Sanofi asserts that "it is not possible to identify and quantify the impurities in Sandoz's product and compare them to those in Lovenox." Reply at 14. But while there may be minute quantities of impurities in enoxaparin that cannot be detected by any available method (which would be true for any drug product, including Lovenox), FDA has nevertheless determined that it has sufficient evidence about its impurity profile to approve an ANDA for enoxaparin, just as it did for the synthetic of salmon calcitonin. Sandoz adequately identified impurities that could directly stimulate the immune system (such as proteins, nucleic acids, lipids, and leachates) and provided sufficient evidence that there were no significant differences in these impurities between its product and Lovenox. *See* AR at 4433 and 4193-94. The statute does not require ANDA sponsors to identify and quantify every impurity down to levels that cannot even be detected, but it does require FDA to consider the purity of the product for ANDA approval, as FDA has done in the most relevant and appropriate manner for enoxaparin**.**

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[8] For example, as one of four general categories of immunogenicity information, Sandoz performed studies to compare the ability of its product and Lovenox to bind with platelet factor four ("PF4"), and further characterized the size and charges of those complexes. *See* AR 4433; AR 4193. Due to inadvertent error, counsel for FDA inaccurately described that first category of information in its opposition brief as an animal study in mice. *See* FDA Br. at 20. The record correctly describes that Sandoz performed a mouse study for the fourth category of information, not the first. *See* AR 4433; 4193-94.

C. FDA Correctly Decided that Sandoz's Enoxaparin Has the Same Active Ingredient as Lovenox

After extensive consideration within the agency, FDA ultimately concluded that an ANDA applicant could show that it had the same active ingredient as Lovenox by satisfying five separate criteria, and that Sandoz had in fact satisfied those criteria. AR 3845 ("The five criteria ensure that the generic drug product's enoxaparin will have the same active ingredient components as those of Lovenox's enoxaparin (within the context of its variability) even though the contribution of each component has not been fully elucidated."); *see also* AR 4440-4444. Rather than challenge FDA's conclusion head-on, Sanofi argues that *Serono* set forth a standard for approval that is cast in stone for all drugs, and that FDA's approval of enoxaparin fails to meet that standard. Neither contention is correct.

In *Serono*, the D.C. Circuit upheld FDA's approval of a drug for which "complete chemical identification" at a molecule-to-molecule level was impossible, as here. 158 F.3d at 1318. In that case, "FDA interpreted 'same as,' *in the context of menotropins products*, to require: clinical equivalence to the pioneer, chemical identity to the extent possible, and limitations on inherent isoform variation to the same extent as in the pioneer." 158 F.3d at 1321 (emphasis added). FDA's specific conclusion about sameness was inextricably tied to "the kind of drug at issue." *Id* at 1319.

Sanofi argues that FDA's menotropins-specific approval standard should apply to enoxaparin approvals, which entirely misreads the court's decision and fails to advance Sanofi's claims. Reply at 16. Even if the menotropins standard applied to enoxaparin, Sandoz's showing of sameness would far exceed it. Satisfying the five criteria allows FDA to conclude that the

active ingredients in the generic product and Lovenox have all the same constituent components within the variability present in Lovenox's enoxaparin – not just that they share the same basic structure and that any differences between them have no clinical significance. *See, e.g.*, AR 2880.

Sanofi also tries to pick at the edges of the five criteria but makes no real attempt to challenge FDA's conclusion that the five criteria *together* establish sameness, or any of the scientific assumptions underlying those criteria. FDA readily acknowledged that satisfying individual criteria would be insufficient to establish sameness. *See, e.g.*, AR 2890. Thus, FDA expected Sandoz to satisfy all five criteria: "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.

Sanofi points out, for instance, that the third criterion's focus on a subset of shorter oligosaccharide chains for sequencing relies on a scientific assumption that such chains are more chemically sensitive to any differences in manufacturing. Reply at 16-17. FDA concluded that, if there were no differences in the identity of the shorter chains, there would similarly be no differences for the longer chains. Sanofi does not challenge that assumption other than to say that these longer chains "are the most biologically active" (Reply at 17 n. 9) – but, regardless of their activity, Sanofi does not offer any evidence or argument that the longer chains for Sandoz's product do not share the same sequence of disaccharides as those in Lovenox.

FDA derived other information about the sequences in all of the oligosaccharide chains in Sandoz's product, including the longer chains, from the other criteria – particularly the criterion that the generic product use the same heparin source material, and that the sequences in the

chains are not rearranged during the depolymerization process. AR 2890-92 (discussing second criterion); *see also* AR 2895-96 (discussing fragment mapping in third criterion, which examines the sequence of a comparative subsets of oligosaccharide chains, including longer chains). Sandoz's testing to meet all of the five criteria provide overlapping and comprehensive information on the composition, chain length, sequence, and activity of oligosaccharides in enoxaparin. *See* AR 2880.

Sanofi also asserts that criteria four and five fall short of establishing that the generic product has the same degree of anticoagulant activity as Lovenox because other factors, "such as enoxaparin's effect on tissue factor plasma inhibitor (TFPI) may contribute to enoxaparin's overall anticoagulant activity." Reply at 17. FDA addressed Sanofi's speculation that TFPI inhibition may have clinical significance, and rejected it. AR 2909. Regardless, FDA concluded Sandoz has established sameness by satisfying all of the five criteria, and thus any clinically significant portions in Lovenox's enoxaparin related to TFPI would also be present in Sandoz's product. AR 2906.

II. Sanofi Has Not Demonstrated Irreparable Injury

Sanofi asserts that it would suffer "substantial and irreparable" losses in the absence of preliminary relief, Reply at 18, but does not even attempt to demonstrate that its financial harm would cause it severe hardship or threaten its existence, as required by *Wisconsin Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985) and *Gulf Oil Corp. v. Dep't of Energy*, 514 F. Supp. 1019, 1026 (D.D.C. 1981) and their progeny. Rather than attempt such a showing – which it

cannot make, given its substantial size and diverse product line[9] – Sanofi argues that *Wisconsin Gas* does not apply because FDA has sovereign immunity that precludes Sanofi from recovering its losses from the government. Reply at 19-20. But, as set forth at length in the government's opening brief, even irrecoverable economic harm will not rise to the level of irreparable harm unless it is so substantial as to cause extreme hardship to the plaintiff's business or threaten its existence.[10]

Sanofi cites cases suggesting that any loss that is irrecoverable due to sovereign immunity is per se irreparable. Reply at 20-21. If that were the standard, however, it would eviscerate any

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[9] As noted in the government's opening brief, Sanofi is a global pharmaceutical giant with annual worldwide revenue of approximately $40 billion. Its domestic sales of Lovenox account for only a small portion of that revenue, and Sanofi has conceded that generic competition in the United States would not have an appreciable long-term impact on the company. *See* Br. at 40-42.

[10] *See, e.g., Gulf Oil Corp. v. Dep't of Energy*, 514 F. Supp. 1019, 1026 (D.D.C. 1981); *Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 32 (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); *Astellas Pharma. US, Inc. v. FDA*, 642 F. Supp. 2d 10, 22 (D.D.C. 2009) ("it is well-settled that economic loss alone will rarely constitute irreparable harm"); *Hi-Tech Pharmacal Co., Inc. v. FDA*, 587 F. Supp. 2d 1, 11 (D.D.C. 2008) ("In this 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").

requirement that the plaintiffs demonstrate anything other than a nominal degree of loss, and would fly in the face of the requirement to demonstrate any meaningful "irreparable" harm. Nor do those cases express the prevailing view in this circuit, as noted above. Indeed, the only significance of sovereign immunity is that it means the plaintiff would not be able to recover its financial losses. But, the weight of authority in this circuit holds that such irrecoverable losses must nevertheless be of sufficient magnitude in comparison to the size of the business to cause a severe impact or even threaten its existence. *See, e.g.*, *supra* n.10. Further, as *Coalition for Common Sense* makes clear, courts in this circuit have not hesitated to deny injunctive relief where plaintiff did not meet the standard of irreparable harm, notwithstanding the court's express recognition that the losses were irrecoverable due to sovereign immunity. 576 F. Supp. 2d at 169 n.3.

In any event, the cases cited by Sanofi do not even purport to follow the "per se" irreparable harm standard that they articulate. In *Feinerman v. Bernardi*, 558 F. Supp. 2d 36, 51 (D.D.C. 2008), the court stated that any loss of income from a loss that is irrecoverable due to sovereign immunity is per se irreparable, citing a Second Circuit decision, *U.S. v. New York*, 708 F.2d 92, 93-94 (2d Cir. 1983). But the court's own decision makes clear that it was not applying a per se standard, but relied on the finding that the plaintiff's claimed losses implicated forty percent of its business. *Feinerman,* 558 F. Supp. 2d at 50-51. In *Smoking Everywhere, Inc. v. FDA*, 680 F. Supp. 2d 62, 77 n. 19 (D.D.C. 2010), appeal pending *sub nom*, *Sottera, Inc., et al. v. FDA, et al*., No. 10-5032 (D.C. Cir.), the court repeated this standard, citing *Feinerman,* and found irreparable harm because plaintiff's entire product line was at stake under FDA's regulatory decision. In *Alf v. Donley*, 666 F. Supp. 2d 60, 70 (D.D.C. 2009), although the court

similarly cited *Feinerman's* "per se" irreparable harm standard, it failed to strictly apply that standard because it evaluated the extent of the harm, the fact that plaintiff lost income (as opposed to lost profits), and also considered other non-monetary factors. Thus, none of the cited cases provide any justification to diverge from the prevailing line of cases requiring irreparable injury to be, in fact, irreparable – a prerequisite that Sanofi wholly fails to meet.

III. The Balance of Harms and the Public Interest Weigh Against Preliminary Injunctive Relief

For all of the reasons stated in FDA's opposition brief, 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. Br. at 44-45.

CONCLUSION

For the foregoing reasons and those stated in FDA's opposition brief, Sanofi's motion for a temporary restraining order and preliminary injunction should be denied.

Respectfully submitted,

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Dated: August 16, 2010

CERTIFICATE OF SERVICE

I hereby certify that I caused a copy of the foregoing Surreply 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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