IN THE 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)

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

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INTRODUCTION

In opposing the sanofi-aventis U.S. LLC ("sanofi") motion for a preliminary injunction, the Food and Drug Administration ("FDA") and intervenor Sandoz Inc. ("Sandoz") seek to justify FDA's decision through a series of broad pronouncements regarding the deference owed to FDA scientific decisions, while failing to address the basic statutory and regulatory infirmities of the Agency's approval. FDA's defense of its decision fails for several reasons.

First and foremost, the deference owed to FDA interpretations of the FDCA does not entitle the Agency to ignore the clear statutory mandate governing the ANDA approval process. Section 505(j)(2)(A) of the FDCA bars FDA from requiring an ANDA applicant to submit any information beyond that which is specified by sections 505(j)(2)(A)(i)-(viii) of the Act. FDA's requirement that Sandoz submit additional studies to address the Agency's immunogenicity concerns violated this clear prohibition.

In an attempt to avoid this conclusion, FDA makes two arguments, neither of which excuses its unlawful approval of Sandoz's ANDA. FDA initially argues that it was entitled to demand the basic safety testing it required of Sandoz under section 505(j)(2)(A)(vi), as "information pertaining to manufacturing." FDA Br. at 22. Section 505(j)(2)(A)(vi) will not bear such an interpretation. That section requires an ANDA applicant to tell FDA how it makes a generic drug but does not speak to subsequent testing of whether a drug product is safe. FDA's interpretation is patently unreasonable and would eviscerate the clear prohibition of section 505(j)(2)(A). FDA next argues that section 505(j)(4), which provides standards for approval decisions, somehow adds to the information that FDA may require an ANDA applicant to submit under section 505(j)(2)(A). This argument is similarly foreclosed by the text of the statute.

Second, FDA has failed to provide a reasoned explanation for departing from clear agency precedent rejecting approval of a generic version of a drug that is not fully

characterized and has failed to set forth a reasonable justification for disregarding the scientific evidence that directly contradicts its determination of sameness.

Finally, FDA and Sandoz mischaracterize both the underlying facts of this case and the applicable legal standards in addressing the remaining three factors pertaining to preliminary relief. Sanofi is not required to demonstrate that any unrecoverable economic harms it would suffer pending a decision on the merits would endanger its continuing existence, as FDA and Sandoz contend. Rather, this court has recognized that such a requirement does not apply where, as here, the defendant would be shielded by sovereign immunity in a later lawsuit. Moreover, because sanofi is not seeking recall of product already shipped, a grant of preliminary relief pending a ruling on the merits would have a comparatively minor effect on Sandoz, tipping the balance of equities strongly in favor of injunctive relief. Similarly, because FDA acted contrary to law, the public interest would also be vindicated by a grant of injunctive relief.

Thus, sanofi has satisfied all four criteria necessary for a preliminary injunction.

NEW FACTS FROM THE ADMINISTRATIVE RECORD

Before addressing FDA's response, we briefly summarize facts reflected in the Administrative Record, produced pursuant to the Court's Order on August 4, 2010.

Sandoz submitted an ANDA for generic enoxaparin on August 26, 2005. More than two years later, after Sandoz amended its application seven times, FDA determined that the ANDA was "not approvable." AR 4167. In refusing to approve Sandoz's ANDA, The Agency's "not approvable" letter did not cite section 505(j)(2)(A)(vi) or claim that Sandoz's ANDA failed to fully describe the methods used in, and/or the facilities and controls used for, the manufacture of its product. Nor did the Agency invoke section 505(j)(4)(A) and conclude that Sandoz's ANDA was inadequate because it failed to fully identify or quantify the product's impurities. Rather, FDA determined the ANDA was not approvable because Sandoz failed to "adequately

address the potential for immunogenicity of the drug product." AR 4167. In other words, FDA was not sure that Sandoz's drug was safe. FDA therefore pronounced "[t]he file on this ANDA is now closed," and Sandoz was "required to . . . either amend or withdraw" its ANDA." *Id*.

In a follow-up letter on December 4, 2007, FDA reiterated to Sandoz that "[u]nderstanding the potential for your product to elicit an immune response is critical," and listed several immunogenicity-related "items that you need to address as part of your ANDA." AR 4170-71. FDA then described two sets of studies intended to "assess differences in impurities [between generic enoxaparin and Lovenox] and their potential [e]ffect on immunogenicity." *Id*. at 4172. As to the first set of studies, FDA explained that its objective was to "understand the amount and nature of potential product contaminants [in generic enoxaparin] relative to those in [Lovenox.]" *Id*. at 4171. By contrast, FDA stated that the second set of studies were "functional" in character and intended to evaluate "any potential immunogenic properties of [generic enoxaparin] as compared to [Lovenox]." *Id.* at 4172.

FDA also deliberated on a separate aspect of Sandoz's ANDA: what information Sandoz would have to provide in order to establish that its generic enoxaparin product contained the "same active ingredient" as Lovenox. Beginning in 2004, FDA scientists disagreed regarding how a generic applicant could make this showing. The disagreement centered on whether five new criteria established by the Office of Generic Drugs (OGD) were "sufficient to determine active ingredient sameness for enoxaparin." *Id*. at 3836. Scientists in FDA's Office of New Drug Quality Assessment (ONDQA) maintained that the only way to demonstrate active ingredient sameness for enoxaparin was "complete characterization, including sequence elucidation and a molecule-to-molecule comparison" of the purported generic product and

Lovenox. *Id*. at 3842. The scientists therefore insisted that "none of [OGD's] criteria, either individually or combined, are adequate to ensure enoxaparin sameness." *Id.* at 3842.

The dispute regarding active ingredient sameness remained unresolved until July 20, 2010, when Dr. Keith O. Webber, Deputy Director of the Office of Pharmaceutical Science within FDA's Center for Drug Evaluation and Research (CDER), Office of Pharmaceutical Science (OPS), declared in an intra-agency memorandum that OGD's test was a "valid approach for determining enoxaparin sameness for purposes of ANDA approval." *Id*. at 3836. FDA approved Sandoz's ANDA three days later. AR 4441.[1]

I. SANOFI IS LIKELY TO SUCCEED ON THE MERITS

A. FDA Violated Section 505(j) When It Approved Sandoz's ANDA After Requiring Sandoz to Provide Additional Immunogenicity Data

1. The Plain Language of the Statute Clearly Prohibits FDA From Requiring an ANDA Applicant to Submit Information or Data Beyond That Required by FDCA Section 505(j)(2)(A)

Under *Chevron U.S.A. Inc. v. Natural Resources Defense Counsel*, courts must "give effect to the unambiguously expressed intent of Congress." 467 U.S. 837, 843 (1984). Thus, under step one of the familiar *Chevron* standard, a reviewing court asks "whether the

[1] Sandoz devotes multiple pages of its brief to arguments that attempt to impugn sanofi's good faith in bringing this lawsuit and in its prior submissions to FDA. *See*, *e.g.*, Sandoz Br. at 4-5. As the Administrative Record makes clear, however, sanofi's Citizen Petition raised important and complex issues regarding whether and how a proposed generic enoxaparin product may be determined to be equivalent to, and fully substitutable for, Lovenox. FDA seriously considered these questions, as evidenced by both the length of its deliberations—more than seven years—and the difference of opinion within the Agency regarding how a manufacturer of generic enoxaparin may satisfy the statutory requirement of "active ingredient sameness." *See*, *e.g.*, AR 3840; FDA Br. at 10. Ultimately, FDA issued a 45-page, single-spaced memorandum responding to sanofi's arguments and granting its request that any generic version of enoxaparin contain the 1-6 anhydro ring structure at concentrations equivalent to that of Lovenox. AR 2879. Although FDA denied the Citizen Petition in all other respects—a conclusion that sanofi maintains was arbitrary, capricious, and not in accordance with law—the record categorically refutes Sandoz's attack on sanofi's good-faith efforts to ensure that the Agency follow the dictates of the FDCA and its own precedent and minimize risks to consumers.

statutory language is ambiguous." *Am. Forest and Paper Ass'n v. F.E.R.C.*, 550 F.3d 1179, 1180 (D.C. Cir. 2008). Only if the statutory language does not unambiguously speak to the issue in dispute does the court turn to step two of the *Chevron* inquiry, which requires it to determine whether the agency's chosen interpretation is reasonable. *Id.*

Section 505(j)(2)(A) of the FDCA unambiguously prohibits FDA from requiring an ANDA applicant to conduct basic safety testing such as immunogenicity testing. This case can thus be resolved under *Chevron* step one. The section begins by stating that "(A) An abbreviated application for a new drug shall contain," 21 U.S.C. § 355(j)(2)(A), and then lists, in subparagraphs (i) through (viii), eight specific categories of information. The section concludes with a clear and simple prohibition:

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

Id. Thus the FDCA unambiguously provides that FDA may not require an ANDA applicant to submit any information beyond that which is specified by sections 505(j)(2)(A)(i)-(viii).

The D.C. Circuit's decision in *Serono v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998), is not to the contrary; indeed, that decision is perfectly consistent with sanofi's argument and with the unambiguous prohibition of Section 505(j)(2)(A). FDA claims that "[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*." FDA Br. at 24. Sanofi's argument, however, has nothing to do with what kinds of information or data FDA can *consider*. Rather, under the clear statutory mandate, FDA may not *require* an ANDA applicant to submit more information (animal or otherwise) than what is required by section 505(j)(2)(A).

Far from rejecting this argument, *Serono*, in *dicta*, strongly suggested that it is correct. The court stated that "the most [section 505(j)(2)(A)] does is bar the FDA from

requiring an applicant to submit more information than required by the statute." *Serono*, 158 F.3d at 1324 (emphasis in original). FDA's approval decision was plainly unlawful unless the testing it required was authorized by one of the subclauses of section 505(j)(2)(A). As set forth in sanofi's initial memorandum and explained further below, it plainly was not.

2. There Can Be No Question That FDA Required Sandoz to Submit Immunogenicity Testing as a Condition of Approval.

Apparently recognizing the distinction between what FDA can *consider* under Section 505(j)(4) and the limitations on what FDA can *require* under Section 505(j)(2)(A), FDA and Sandoz assert that FDA did not require Sandoz to submit immunogenicity testing at all. FDA claims that it "merely provided suggested approaches to address [FDA's] concerns." FDA Br. at 23 n.10. And Sandoz, while acknowledging that FDA required additional immunogenicity data, suggests it is significant that the Agency did not mandate any "specific tests." Sandoz Br. at 13, 14. These arguments are facially implausible.

The Administrative Record, and in particular, FDA's "not-approvable" letter of November 5, 2007, conclusively establish that FDA required Sandoz to submit immunogenicity testing as a condition for approval. On November 5, 2007, more than two years after Sandoz submitted its ANDA, FDA determined that the "ANDA is not approvable because the application does not adequately address the potential for immunogenicity of the drug product." AR 4167. FDA thereby pronounced that the file on Sandoz's ANDA was "closed" and directed that any amendment respond to the deficiency. *Id.* In a subsequent follow-up letter, dated December 4, 2007, FDA reiterated that "[u]nderstanding the potential for your product to elicit an immune response is critical," and listed for Sandoz several immunogenicity-related "items that *you need to address* as part of your ANDA." AR 4170-71 (emphasis added). FDA also

outlined, in detail, its approach for addressing these required items, noting that "[o]ther approaches may also be acceptable." AR 4171.

FDA and Sandoz place heavy reliance on this latter statement, to no avail. Under FDA regulations in force at the time, an ANDA applicant that received a "not approvable" letter had four choices. The applicant could (1) amend its application to address the deficiencies identified by the Agency, (2) withdraw its ANDA, (3) request a formal administrative hearing to dispute FDA's findings, or (4) request additional time. 21 C.F.R. § 314.120 (2007). FDA's November 5, 2007 letter, which specifically referenced this regulation, stated that Sandoz was "required to … either amend or withdraw [its] ANDA." AR 4167. FDA clearly conditioned amendment and any subsequent approval of Sandoz's ANDA on the submission of further immunogenicity testing. It is not unlike courthouse security requiring either a bar card, a driver's license, or another form of picture identification as a condition for entrance to the courthouse. The *requirement* is not transformed into a *suggestion* by virtue of the choice among acceptable forms of identification. FDA's assertion that it did not require Sandoz to submit immunogenicity testing is flatly contradicted by the facts.[2]

This case thus presents an issue entirely different from *Serono*, in which the plaintiff argued that the Agency may not rely on animal studies in reviewing an ANDA. There, FDA never determined that the ANDA for Repronex was "not approvable" absent submission of safety studies. Rather, the Agency relied on studies voluntarily submitted as part of the

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[2] Indeed, as recounted in sanofi's opening memorandum, Mem. at 20, in a Q&A document released on the day it approved Sandoz's ANDA, FDA stated "[a]lthough conducting immunogenicity testing for this product can be an extensive and time-consuming process for a manufacturer, all manufacturers of generic enoxaparin are *expected to do this* as part of the application process." Generic Enoxaparin Questions and Answers, Food and Drug Administration, July 23, 2010, *available at* http://www.fda.gov/Drugs/DrugSafety/PostmarketDrug SafetyInformationforPatientsandProviders/ucm220037.htm (emphasis added).

application. Here, FDA has plainly done what by statute it is prohibited from doing: it required additional safety testing as a condition for approval of an ANDA. Again, the D.C. Circuit in *Serono* recognized the importance of this distinction. *Serono*, 158 F.3d at 1324.

3. Section 505(j)(2)(A) Does Not Permit FDA To Require Submission of Immunogenicity Data To Support an ANDA.

FDA required Sandoz to submit additional preclinical testing to assure "that the risk of immunogenicity due to potential impurities in the generic enoxaparin will not be greater than that of Lovenox." CP Response at 42. According to FDA's own Q&A document, FDA required the immunogenicity testing "to demonstrate that [generic] manufactured versions do not have any higher risk of these or other *dangerous reactions* than Lovenox."[3] There is no question that studies intended to demonstrate the safety of a generic product are not contemplated by section 505(j)(2)(A). As sanofi explained in its initial memorandum, FDA itself has repeatedly recognized this basic limitation on its statutory authority. Mem. at 18-19. Section 505(j)(2)(A) states that "The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)." 21 U.S.C. § 355(j)(2)(A). Nothing in any of subparagraphs (i) through (viii) says anything whatsoever about basic safety testing such as tests to evaluate the risk of an immunogenic response. Regardless of whether FDA could consider such testing if it were properly placed before the Agency, the statute plainly provides that FDA may not *require* it. *Cf. Serono*, 158 F.3d at 1324.

FDA attempts to bootstrap basic safety testing into one of the eight subparagraphs of 505(j)(2)(A) in two related ways, neither of which is plausible.

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

First, FDA argues that it is authorized to require immunogenicity testing under section 505(j)(2)(A)(vi). This section requires an ANDA applicant to submit with its application "the items specified in clauses (B) through (F) of subsection (b)(1)." 21 U.S.C. § 355(j)(2)(A)(vi). Clauses (B) through (F) of subsection (b)(1) require the ANDA applicant to submit basic descriptive information:

> (B) a full list of the articles used as components of such drug;
>
> (C) a full statement of the composition of such drug;
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> (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;
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> (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; and
>
> (F) specimens of the labeling proposed to be used for such drug.

21 U.S.C. § 355(b)(1). In other words, clauses B through F require the ANDA applicant to tell FDA how the generic drug is made.

FDA argues that section 505(b)(1)(D), in particular, authorizes it to require immunogenicity testing. Section 505(b)(1)(D) requires 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 such drug." 21 U.S.C. § 355(b)(1)(D). FDA's interpretation is unreasonable because safety testing is not a means of *describing* methods, facilities and controls used for manufacturing, processing, and packing. Rather, safety testing is a means of analyzing *the effects* of such methods, facilities or controls. In other words, subparagraph D requires an applicant to describe its manufacturing process and identify the product (including impurities) this process produces. It does not, however, require the applicant to test that product to see if it

is safe. The requirement of such basic safety testing as a condition for approval of an ANDA is not contemplated by section 505(b)(1) and is thus barred by section 505(j)(2)(A).[4]

FDA argues in the alternative that it could order the testing under section 505(j)(4)(A). Section 505(j)(4)(A) states that FDA must approve an ANDA unless it finds, *inter alia*, that "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." 21 U.S.C. § 355(j)(4)(A). FDA claims that this section requires the Agency to "evaluate the purity of an ANDA product," and thus permits it to require ANDA applicants to submit information the Agency deems necessary to make that evaluation. FDA Br. at 5.

FDA's interpretation is barred by the unambiguous language of the FDCA, and in any event is certainly not a "reasonable" interpretation for purposes of *Chevron* step two. FDA's interpretation would read section 505(j)(2)(A)'s clear mandate—"[t]he Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) though (viii)"—entirely out of the statute. It is well-established, however, that when two provisions "are capable of co-existence, it is the duty of the courts, absent a clearly expressed congressional intention to the contrary, to regard each as effective." *Morton v. Mancari*, 417 U.S. 535, 551 (1974). Here, sections 505(j)(2)(A) and 505(j)(4)(A) are perfectly consistent and speak to two quite distinct subjects. Whereas section 505(j)(2)(A) specifies the information FDA

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[4] FDA also points to 21 C.F.R. § 314.94(a)(9), under which ANDA applicants must submit the information required in 21 C.F.R. § 314.50(d)(1), as support for its authority to require immunogenicity testing. FDA Br. at 6. Section 314.50(d)(1), however, does not purport to permit FDA to require additional testing specifically barred by Congress. Rather, this regulation simply parallels FDA's authority under sections 505(b)(1)(B)-(F) to establish the identity, strength, quality, purity, potency, and bioavailability of the drug product. For the reasons set forth above, the immunogenicity testing FDA required of Sandoz was not intended for this limited purpose.

may require of an ANDA applicant, section 505(j)(4) specifies the approval standards that FDA must apply. Under FDA's interpretation, the approval standards of section 505(j)(4)(A) would expand the types of information that FDA may require an ANDA applicant to submit beyond the categories of information that Congress specifically delineated in section 505(j)(2)(A). FDA's interpretation thus cannot be squared with Congress's unambiguous prohibition.

The structure of 505(j) is no mere accident or formality. Rather, it is a reflection of Congress's intent through the Hatch-Waxman framework to strike a compromise between the competing societal interests represented by the pioneer and generic drug companies—namely, the development of innovative cures to new diseases and the availability of low cost generics for existing drugs. *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1358 (Fed. Cir. 2003) (explaining that the Hatch Waxman Act was "a compromise between two competing sets of interests"); *Mylan Pharm., Inc. v. Thompson*, 268 F.3d 1323, 1326 (Fed. Cir. 2001) (noting that Hatch-Waxman "emerged from Congress's efforts to balance two conflicting policy objectives: to induce name brand pharmaceutical firms to … research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market").

To give effect to these dual and sometimes competing objectives, the Hatch-Waxman Amendments set forth a carefully circumscribed pathway for approval of generic drugs under section 505(j). As part of the Hatch-Waxman compromise, that pathway is a limited one, which can be used only if the generic (via the submissions specified in section 505(j)(2)(A)) can be demonstrated to be a *copy* of the reference listed drug such that safety testing (e.g., immunogenicity testing) is not, and indeed cannot, be required. *See Warner Lambert Co. v. Shalala*, 202 F.3d 326, 327 (D.C. Cir. 2000) ("[G]eneric *copies* may be approved using the far simpler, abbreviated new drug application (ANDA)." (emphasis added)). As sanofi previously

explained in its opening memorandum, generic applicants that are required to produce safety data beyond that contained in the file of the reference listed drug must use the section 505(b) pathway.[5] Mem. at 5.

Again, in contrast to FDA's (and Sandoz's) assertions, *Serono* is not to the contrary. First, as discussed above, the D.C. Circuit focused exclusively on the information FDA can properly consider if it is voluntarily submitted to the Agency. The Court was not presented with the separate question of whether FDA can require safety testing as a condition of approval of an ANDA. This point alone is sufficient to render FDA and Sandoz's reliance on that decision inappropriate.

Putting aside this basic distinction, in describing what FDA may consider in approving an ANDA, *Serono* did not go nearly as far as FDA and Sandoz suggest. The *Serono* court did not hold that FDA may consider anything it wants to in ruling on an ANDA. In fact, *Serono* assessed what FDA may consider (again, assuming the information was not required) in two specific circumstances: active ingredient sameness, and the safety of inactive ingredients. *See Serono*, 158 F.3d at 1316 ("Two aspects of the ANDA process, corresponding to two kinds of drug ingredients, are relevant to this case."). The immunogenicity testing that FDA required in this case had nothing to do with either active ingredient sameness, nor inactive ingredient

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[5] Sandoz asserts that FDA's approval should not be enjoined because "even if Sandoz had filed a 505(b) application, its application *would have been* approved and *would have been* awarded therapeutic equivalence." Sandoz Br. at 22-23 (emphasis added). Although sanofi disagrees with Sandoz's views on the applicability of therapeutic equivalence ratings to 505(b)(2) applications, this determination is, of course, not one for Sandoz to make. FDA, moreover, takes a different position in its brief, noting that "approval of any competitor by the [505(b)(2)] pathway … could result in a non-substitutable – and less competitive – drug product." FDA Br. at 26 n.13.

safety.[6] Thus, far from "dispos[ing] of every significant argument made by sanofi-aventis," Sandoz Br. at 7, *Serono* says nothing whatsoever about what the Agency can consider (let alone require) to establish the safety of impurities in an ANDA product.

B. FDA's Attempt To Reconcile Its Approval of Sandoz's ANDA With Its Prior Precedent is Unavailing

FDA argues that its approval of Sandoz's ANDA is consistent with Agency precedent. FDA Br. at 28-34. However, even a cursory examination of FDA's arguments demonstrates that the arguments in sanofi's opening brief remain in large part unanswered.

1. Calcitonin

FDA claims that its requirement that Sandoz provide immunogenicity testing with its enoxaparin ANDA is consistent with its previous positions regarding generic versions of salmon calcitonin. *Id.* at 24. Yet FDA's argument as well as Sandoz's "surprise" at sanofi's reliance on the calcitonin Citizen Petition response (Sandoz Br. at 15) miss the mark because they focus exclusively on how FDA establishes sameness. FDA and Sandoz fail to address the wholly inconsistent manner in which FDA dealt with basic safety issues such as immunogenicity in salmon calcitonin where, as here, standard characterization of impurities was not feasible.

Sanofi's opening memorandum demonstrated that, where FDA was able to rule out impurity-related immunogenicity problems by identifying the impurity profile and comparing

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[6] First, the Administrative Record makes clear that FDA did *not* require immunogenicity in an effort to establish sameness. *See, e.g.*, CP Response at 41-42 ("*[I]n addition to demonstrating sameness* …, sponsors should submit a comparative assessment of their generic enoxaparin and Lovenox for potential impurities that may have an adverse impact with respect to immunogenicity." (emphasis added)). Nor can an impurity be considered an "inactive ingredient." *See, e.g.*, 21 C.F.R. §§ 210.3(b)(3) & (8) (defining "inactive ingredients" as "any component other than an 'active ingredient'" and "components" as "any ingredient *intended for use* in the manufacture of a drug product, including those that may not appear in such drug product." (emphasis added)).

that profile to the pioneer drug's profile (synthetic calcitonin), the Agency concluded that an ANDA was appropriate.[7] Mem. at 21. Where, however, due to the complexity of the product, actually identifying and comparing the impurity profiles was not feasible (recombinant calcitonin), FDA concluded that immunogenicity testing was required and therefore concluded that an ANDA *was not appropriate*. *Id.* This is precisely the situation with enoxaparin. Because of the complexities of enoxaparin, it is not possible to identify and quantify the impurities in Sandoz's product and compare them to those in Lovenox. As a result, FDA required Sandoz to test its product to see what immunogenic responses it might create. Once it did so, approval of an ANDA was no longer appropriate.

2. Heparin

FDA's invocation of other precedents fares no better. FDA and Sandoz both claim support in the Agency's prior approval of generic versions of heparin. FDA Br. at 30; Sandoz Br. at 18. According to Sandoz, "[g]eneric heparin is particularly relevant because heparin is the 'parent' of both Lovenox and generic enoxaparin." Sandoz Br. at 18.

Heparin is irrelevant to the issues surrounding approval of generic enoxaparin, for one simple reason: the manufacture of heparin does not involve a depolymerization process. AR 2882. FDA has acknowledged that it is the depolymerization process, central to converting heparin into LMWH, that gives enoxaparin its structural "fingerprints" and process dependent nature. AR 2885. FDA's past practice with heparin therefore is not germane to a discussion of LMWH.

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[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.

3. Hetastarch

Similarly, FDA contends in its litigation brief that its approval of several generic versions of hetastarch also serves as a precedent for approval of generic versions of enoxaparin because enoxaparin and hetastarch are similar. FDA Br. at 30. However, some of FDA's own experts appear to take the opposite view. For example, in an internal FDA memorandum from Dr. Ali Al-Hakim dated April 18, 2004, Dr. Al-Hakim states that "Hetastarch cannot be compared to Enoxaparin because these two substances are completely different chemical entities with very different characteristics." AR 3714. Dr. Al-Hakim goes on to note several important differences between hetastarch and enoxaparin that render this precedent inapposite, including that, unlike hetastarch, "LMWH products are generated using specific depolymerization agents [and] [e]ach process yields a different LMWH product with different biological activity and/or clinical efficacy." AR 3715; *see also* AR 3798-00 (Internal FDA memorandum from Dr. Moheb M. Nasr noting, *inter alia*, that chemical and manufacturing differences make the two products incomparable).

C. FDA Has Failed to Supply A Sufficient Explanation For Disregarding the Scientific Evidence Contained in Sanofi's Citizen Petition And Supplements

FDA's approval of Sandoz's ANDA is improper for the additional reason that the Agency has not made a proper finding of active ingredient "sameness" as required by section 505(j)(4).[8] FDA repeatedly invokes *Serono* in support of its current position. *See, e.g.*, FDA Br.

[8] Sandoz suggests that this court must disregard the declarations of Drs. Christian Viskov and Marc Cohen because the declarations were not before FDA at the time the Agency rendered its decision. Sandoz Br. at 8-11. Sandoz's suggestion is erroneous. The D.C. Circuit has recognized that a party may supplement the Administrative Record with "background information" in order to assist the Court in determining "whether the agency considered all of the relevant factors." *Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1002 (D.C. Cir. 2008) (internal quotation marks omitted). That is just what sanofi has done here. This dispute has little practical (continued…)

at 28. In *Serono*, FDA contended that for complex products, it is impractical to require generic versions to be absolutely identical down to the last detail. Instead, FDA asserted that such a product must at least demonstrate that the basic chemical structure of its product is the same as that of the pioneer drug, and that slight differences that may exist between the two products are not "clinically significant" for the product's intended uses. *Serono*, 158 F.3d at 1319. The court found FDA's interpretation of the statute to be reasonable under *Chevron* step two. *Id.*

Under FDA's own interpretation of the statute, as articulated in *Serono*, the Agency cannot approve an ANDA for enoxaparin unless its basic structure is determined to be the same as enoxaparin, and it is determined that any small differences that exist between the products would not have clinically significant consequences. Sandoz's ANDA for generic enoxaparin has not met this standard. Although FDA asserts that its "five criteria" demonstrate sameness, FDA acknowledges that it has not fully analyzed the structure of enoxaparin or compared that structure to Sandoz's product. *See, e.g.*, AR 2897. Instead, it has analyzed and compared only parts of that structure and is extrapolating (i.e., assuming) that the rest of enoxaparin will be similarly comparable. *Id.* In other words, FDA has determined that parts of Sandoz's product are the same as enoxaparin. For the rest, FDA is making an assumption. Several examples illustrate this point.

First, FDA states in its third criteria that, for a finding of active ingredient "sameness," it is necessary, among other things, to directly sequence enoxaparin's polysaccharide chains. This allows one to confirm that the sequences of disaccharide building

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import for this litigation, however, because many of the exact same scientific points made by Drs. Viskov and Cohen were set forth in sanofi's Citizen Petition, Supplements, and materials in support and are thus part of the Administrative Record.

block units in the polysaccharide chains of the generic are the same as those in Lovenox. AR 2896. Sandoz, however, did not actually sequence all of enoxaparin's polysaccharide chains. Instead, Sandoz sequenced only a very small subset of these polysaccharide chains—namely the shortest chains. *Id.* at 2897. Thus, rather than actually requiring Sandoz to demonstrate sameness, FDA is merely extrapolating sameness from analysis of a small subset of enoxaparin's polysaccharide chains.[9]

Second, FDA asserts that criteria four and five "ensure that the generic enoxaparin product has the same degree of anticoagulant activity as Lovenox. *See* FDA Br. at 12. Both of these last two criteria approach this task by measuring traditional anticoagulant factors including anti-Xa activity and anti-IIa activity. *Id.* FDA has acknowledged, however, that other factors, such as enoxaparin's effect on tissue factor plasma inhibitor (TFPI) may contribute to enoxparin's overall anticoagulant activity. *See, e.g.*, AR 2883. Thus, factors four and five, which are supposed to "ensure that the generic product has the same degree of anticoagulant activity as Lovenox," FDA Br. at 12, do not even take into account all of the ways FDA has acknowledged that enoxaparin generates its anticoagulant effect. Once again, FDA has extrapolated from what it knows to fill in the blanks of what it does not know.

Finally, FDA has failed to take into account the voluminous scientific evidence provided in the Citizen Petition. Through the Citizen Petition and its supplements, sanofi provided rigorous scientific evidence demonstrating numerous ways in which a product

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[9] FDA claims that if sameness can be demonstrated in the shorter polysaccharide chains, one can assume that the longer chains will also be the same because the shorter chains "have resulted from the most cleavage reactions and are therefore most dependent on the chemical selectivity of the depolymerization process." AR 2896-97. FDA fails to take into account, however, the fact that the longer enoxaparin polysaccharide chains are the most biologically active (i.e., they do most of the work in the body). *See, e.g.*, AR 14, 1314-1317.

manufactured with a different manufacturing process will have a different pharmacological profile with potentially clinically significant consequences. FDA's overarching response to these data is to reject sanofi's claims because sanofi has not supported them with data from clinical trials. AR 2910. Of course, it is not medically ethical to administer a drug to patients when you expect the drug to be less than safe and effective. Thus, sanofi could not conduct a clinical trial comparing Lovenox to a drug that sanofi believed was substandard.

An overall review of FDA's comparison of enoxaparin to Sandoz's generic product leads to one inescapable conclusion: FDA has satisfied itself that Lovenox and Sandoz's product are highly similar. It has not, however, demonstrated sameness. FDA admittedly has not even analyzed large portions of enoxaparin that are the most biologically active. AR 2897, 3844. It has reviewed and compared only some of the mechanisms by which FDA acknowledges that enoxaparin derives its anticoagulant effect. And many aspects of its five criteria, *see, e.g.*, AR 2891-92, are designed not to demonstrate sameness, but only to demonstrate that the two products "will be at least similar," *id.* FDA's approval is improper because it falls short of FDA's own standard for complex products, endorsed by the *Serono* court, which requires ANDA applicants to demonstrate that the basic chemical structure of its product is the same as that of the pioneer drug, and that any slight differences that may exist are not "clinically significant" for the product's intended uses. *Serono*, 158 F.3d at 1319.

II. FDA AND SANDOZ HAVE FAILED TO REBUT SANOFI'S EVIDENCE THAT IT WILL SUFFER IRREPARABLE HARM IN THE ABSENCE OF PRELIMINARY RELIEF

In its opening memorandum, sanofi set forth in detail the substantial and irreparable losses it will incur if FDA's unlawful approval decision remains in place pending a decision on the merits. Specifically, whereas annual domestic sales for Lovenox in 2009 were approximately $2.5 billion, if interim relief is not granted, sanofi can either maintain its existing

prices and consequently lose a huge portion of its sales, or reduce prices and lose a minimum of 50 percent of its Lovenox revenue. *See* Mem. at 38; Durso Decl. ¶¶ 14, 26.

This future injury is plainly "certain," not "speculative." *See, e.g.*, *Chaplaincy of Full Gospel Churches v. England*, 454 F.3d 290, 298 (D.C. Cir. 2006). Sandoz will undoubtedly continue to ship its generic product if FDA's approval remains in place, and it cannot plausibly be denied that generic competition will lead to a considerable drop in sanofi's Lovenox sales. FDA does not now seriously dispute this evidence.[10] Rather, FDA insists that, even if sanofi is deprived of most of its Lovenox revenue while awaiting a decision on the merits, resulting in hundreds of millions or perhaps billions of dollars in losses, such injury is not irreparable unless it constitutes hardship that would threaten sanofi's continuing existence. *See* FDA Br. at 40-43.

In support of this argument, FDA relies on a doctrine of irreparable harm developed in *Wisconsin Gas Company v. FERC*, 758 F.2d 669 (D.C. Cir. 1985), and subsequent decisions. This line of cases has no application here. In *Wisconsin Gas*, the D.C. Circuit held that "*[r]ecoverable* monetary loss may constitute irreparable harm only where the loss threatens the very existence of the movant's business." *Id.* at 674 (emphasis added). The *Wisconsin Gas* decision thus stands for the unremarkable proposition that preliminary relief is not warranted in response to injuries that can be remedied after a trial on the merits.

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[10] FDA criticizes sanofi for "[r]elying on unspecified 'past examples'" to establish a loss range in the event FDA's approval decision is permitted to stand. FDA Br. at 42. FDA, however, does not specify any particular problems associated with sanofi's methodology. Sanofi provided clear explanations as to the quantum of loss that could reasonably be expected, if it lowered prices in response to FDA's approval decision *and* if it did not. Mem. at 38; Durso Decl. ¶¶ 14, 26. Sanofi, of course, is not required to distill the harm it will incur into a precise numeric figure, *see, e.g.*, *Brady Campaign to Prevent Gun Violence v. Salazar*, 612 F. Supp. 2d 1, 25 (D.D.C. 2009), *appeal dismissed per stipulation*, 2009 WL 2915013 (D.C. Cir. Sept. 8, 2009), and FDA makes no attempt to rebut the self evident proposition that sales of a pioneer drug like Lovenox will inevitably fall as a result of generic approval.

For the reasons explained by Judge Walton, that general principle is inapplicable where no subsequent damages remedy is available because of the defendant's sovereign immunity:

> The defendant argues that monetary loss is not irreparable harm unless it threatens the very existence of the plaintiff's business. The Court agrees with this proposition as a general matter. But where, as here, the plaintiff in question cannot recover damages from the defendant due to the defendant's sovereign immunity, any loss of income suffered by a plaintiff is irreparable *per se*.

Feinerman v. Bernardi, 558 F. Supp. 2d 36, 51 (D.D.C. 2008) (internal quotation marks and citations omitted).

Numerous recent decisions of this court reiterate this common-sense conclusion. In *Smoking Everywhere, Inc. v. U.S. Food and Drug Admin.*, 680 F. Supp. 2d 62, 77 n.19 (D.D.C. 2010), for example, this court explained that "even if the claimed economic injury did not threaten plaintiffs' viability, it is still irreparable because plaintiffs cannot recover money damages against FDA." Similarly, in *Alf v. Donley*, 666 F. Supp. 2d 60, 70 (D.D.C. 2009), this court found that the plaintiff demonstrated irreparable harm because, among other reasons, "by virtue of the government's sovereign immunity, the plaintiff will be unable to recoup his lost income." In stark contrast to these decisions, virtually all of the cases cited by FDA do not so much as *mention* sovereign immunity or the Eleventh Amendment.[11]

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[11] *See Wisconsin Gas*, 758 F.2d 669; *Astellas Pharma U.S., Inc. v. Food and Drug Admin.*, 642 F. Supp. 2d 10, 21-24 (D.D.C. 2009); *Hi-Tech Pharmacal Co., Inc. v. U.S. Food and Drug Admin.*, 587 F. Supp. 2d 1, 11-12 (D.D.C. 2008); *Mylan Laboratories, Inc. v. Leavitt*, 484 F. Supp. 2d 109 (D.D.C. 2007); *Sandoz, Inc. v. Food and Drug Admin.*, 439 F. Supp. 2d 26, 31 -32 (D.D.C. 2006); *American Association for Homecare v. Leavitt*, 2008 WL 2580217 (D.D.C. June 30, 2008); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp 212 (D.D.C. 1996). While some of these cases appear to have been litigated against agencies *generally entitled* to sovereign immunity, the decisions simply did not address or consider this issue. It is, of course, axiomatic that "[i]n order for a decision to be given stare decisis effect with respect to a particular issue, (continued…)

Consistent with this court's decisions, numerous U.S. Courts of Appeal have recognized that monetary losses are properly characterized as irreparable harm where the defendant would be shielded by sovereign immunity in a subsequent suit.[12] There is no dispute that this critical factor is present here, *see* Mem. at 39, and FDA barely addresses it. FDA insists that its own sovereign immunity is "inconsequential" to the irreparable harm inquiry given sanofi's supposed "failure to demonstrate, or even allege, that such losses would cause it serious harm." FDA Br. at 43 n.26. As a threshold matter, FDA's premise is incorrect. Sanofi did allege and proffer evidence that it "would suffer very substantial economic loss if generic sales could continue until a merits ruling issued." Mem. at 37-39. More fundamentally, FDA does not even attempt to address *Feinerman* and *Smoking Everywhere*, *supra*, in which this court made clear that *any* economic loss qualifies as irreparable *per se* if it cannot be recovered due to the defendant's sovereign immunity. FDA claims that *Astellas* "reject[ed a] similar argument" but the *Astellas* court did not even mention sovereign immunity, and nor did the other two cases on which FDA relies for support. *See supra* note 11.

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that issue must have been actually decided by the court." 18 JAMES WM. MOORE, ET AL., MOORE'S FEDERAL PRACTICE § 134.04[5] (3d ed. 1999); *see also U.S. v. Garcia-Caraveo*, 586 F.3d 1230, 1234-35 (10th Cir. 2009); *Moore v. Campbell*, 344 F.3d 1313, 1319 (11th Cir. 2003); *Beacon Oil Co. v. O'Leary*, 71 F.3d 391, 395 (Fed. Cir. 1995). In *Coalition For Common Sense In Government Procurement v. U.S.*, 576 F. Supp. 2d 162 (D.D.C. 2008), this court briefly addressed sovereign immunity but stated that, although "an unrecoverable financial loss can constitute irreparable injury under some circumstances," it did not in that case because the harm involved (at most approximately 1/100th of one percent of the plaintiffs' revenues), was truly negligible. *Id.* at 169-70 & n.3.

[12] *See, e .g.*, *Dominguez v. Schwarzenegger*, 596 F.3d 1087, 1097-98 (9th Cir. 2010); *Chamber of Commerce of U.S. v. Edmondson*, 594 F.3d 742, 770-71(10th Cir. 2010); *Rosario-Urdaz v. Rivera-Hernandez*, 350 F.3d 219, 222 (1st Cir. 2003); *Murray v. Silberstein*, 882 F.2d 61, 63-64 (3d Cir. 1989); *U.S. v. State of N.Y.*, 708 F.2d 92, 93-94 (2d Cir. 1983); *Chu Drua Cha v. Noot*, 696 F.2d 594, 599 (8th Cir. 1982); *cf. Hillhaven Corp. v. Wis. Dept. of Health and Soc. Servs.*, 733 F.2d 1224, 1226 (7th Cir. 1984).

FDA's cursory responses to sanofi's additional examples of irreparable harm are similarly unavailing. As this court has recognized, "injury to reputation or goodwill is not easily measurable in monetary terms, and so often is viewed as irreparable." *LG Elecs. U.S.A., Inc. v. Dep't of Energy*, 679 F. Supp. 2d 18, 35 (D.D.C. 2010). FDA does not dispute this general proposition. Nor does FDA challenge sanofi's claim that consumers and physicians will lose faith in both Lovenox and Sandoz's generic if the generic causes adverse health consequences. Rather, FDA simply cites to particular instances in which courts rejected claims of reputational harm based on introduction of a generic drug. FDA Br. at 43. In all these cases, however, the court rested its conclusion that no loss of goodwill would result on its previous finding that the plaintiff was unlikely to demonstrate that FDA had wrongfully approved the generic. *See, e.g.*, *Astellas*, 642 F. Supp. 2d at 23; *Somerset Pharms., Inc. v. Shalala*, 973 F. Supp 443, 454-55 (D. Del. 1997); *Bristol-Myers*, 923 F. Supp. at 221. Thus, the examples cited by FDA are inapposite.

In its initial memorandum, sanofi also highlighted several additional examples of irreparable harm sanofi would incur if injunctive relief were denied. Specifically, sanofi explained that generic competition could cause it to lose its preferred position on some hospital pharmacy and managed care formularies, would lead to an irreversible loss in sales volume and a price erosion, and would result in layoffs of sanofi employees. Mem. at 39-40; Durso Decl. ¶¶ 29-30, 36. All of these examples unquestionably describe injury that is properly considered under the irreparable harm prong, yet neither FDA nor Sandoz even address them. *See, e.g.*, *Purdue Pharma L.P. v. Boehringer Ingelheim*, GMBH, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (acknowledging that price erosion and loss of market position can support finding of irreparable harm); *Abbott Labs. v. Sandoz, Inc.*, 500 F. Supp. 2d 807, 843 (N.D. Ill. 2007) (holding that

plaintiff had demonstrated irreparable harm by pointing to probability of layoffs, loss of market share, goodwill, and erosion of formulary position).

In short, sanofi has made a clear showing of irreparable harm.[13] This factor militates strongly in favor of preliminary relief.

III. THE BALANCE OF EQUITIES TIPS IN FAVOR OF INJUNCTIVE RELIEF

In light of the substantial harm to sanofi discussed above, the balance of equities as between FDA and sanofi plainly tips in favor of injunctive relief. *Elzie v. Aspin*, 841 F. Supp. 439, 443 (D.D.C. 1993) (finding that the balance of equities favored the plaintiff because "[g]ranting a preliminary injunction . . . will result in no discernible injury to defendants"). FDA suggests, however, that "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" if relief is granted. FDA Br. at 45 n.28. Similarly, Sandoz details supposed harms it will suffer if it is forced to delay sales or if consumers must terminate their use of the Sandoz generic mid-stream. Sandoz Br. at 26-27. Yet sanofi does not seek recall of product already shipped by Sandoz, Mem. at 42 n.35, and Sandoz indicated at the scheduling conference on this matter that it has already shipped large quantities of its generic drug. It is simply not true, therefore, that Sandoz would lose the $40 million in sales it expects to earn over the next six weeks pending this Court's decision on the merits. Even if six months passes between a grant of preliminary relief and a decision on the merits, Sandoz will still be able to derive revenue from

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[13] Sandoz suggests that sanofi "is in no position" to vindicate its legal rights because it "sat on its hands" for "almost four full days" before filing its motion and supporting papers. Sandoz Br. at 25. Sanofi received FDA's decision on a Friday with no advanced warning and required time to review the FDA's 45-page response to its Citizen Petition before filing papers in this court on Monday. The case cited by Sandoz, *Graceway Pharmaceuticals, LLC v. Perrigo Co.*, 697 F. Supp. 2d 600, 606 (D. N.J. 2010), involving an unjustified delay of "one day short of a full calendar month" after a previous delay, has no application here.

product it has already shipped. Thus, while a preliminary injunction would at least mitigate the harm to sanofi described above, it would have a comparatively minor effect on Sandoz.

IV. THE PUBLIC INTEREST FAVORS GRANT OF INJUNCTIVE RELIEF

FDA claims that its "interest and the public's interest in generic drug approvals are the same." FDA Br. at 31. However, the public interest is vindicated when a reviewing court insists upon "meticulous compliance with the law by public officials." *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993). Thus, as applied to actions brought under the APA and FDCA, "[t]he public interest factor is inextricably linked with the merits of the plaintiff's claim." *Astellas*, 642 F. Supp. 2d at 23. As the Third Circuit has explained, the 1984 amendments to the FDCA reflected a congressional purpose "to aid generic drug competition not diminish the safety of commercial drugs" and "[t]he fact that actions by [pioneer manufacturers] may thwart the competing congressional purpose of easing the entry of generic drugs into the market is subsumed by the overriding necessity of ensuring public access to safe commercial drugs." *Schering Corp. v. Food and Drug Admin.*, 51 F.3d 390, 396 (3d Cir. 1995)).

Here, FDA acted contrary to law by approving an ANDA after requiring submission of additional safety data. It also departed from its own precedent without justification and failed to ensure that Sandoz's generic drug contains the same active ingredient as Lovenox. Accordingly, an injunction compelling FDA to withdraw its ANDA approval in light of these procedural and substantive improprieties is unquestionably in the public interest.

CONCLUSION

For all of the foregoing reasons, as well as those set forth in sanofi's initial memorandum, sanofi has satisfied all of the criteria for a preliminary injunction. Accordingly, sanofi's Application for a Preliminary Injunction should be granted.

Respectfully submitted,

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