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.	Case No. 1:10-cv-01255-EGS

SANDOZ INC.'S MEMORANDUM OF POINTS AND AUTHORITIES IN OPPOSITION TO PLAINTIFF SANOFI-AVENTIS US LLC'S APPLICATION FOR TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

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MISCELLANEOUS

GLOSSARY

ANDA:	Abbreviated New Drug Application, submitted to the FDA under 21 U.S.C. § 355(j)
Bioequivalence:	Showing of the absence of a significant difference in the rate and extent to which an active ingredient in a pharmaceutical equivalent becomes available at the site of drug action when administered at the same dose under similar conditions in an appropriately designed study
Characterize:	Conduct a scientific analysis (or a variety of analyses) to determine the physical and chemical characteristics of a compound
Cleavage:	Process by which the heparin long chains are split (broken) into smaller chains, resulting in a low molecular weight heparin ("LMWH"), such as enoxaparin; also referred to as "depolymerization"
Compendial standards:	Standards such as the USP and the EP that provide testing standards for individual drug products
Crude heparin:	Unpurified heparin extracted from the mucosa layer of pig intestines
Enoxaparin injection USP:	Final finished drug product for injection, which contains enoxaparin sodium USP as the active ingredient and which satisfies USP standards
Enoxaparin USP:	Enoxaparin sodium USP, the sodium salt form of enoxaparin, a low molecular weight form of heparin that satisfies USP standards
EP:	European Pharmacopeia, like the U.S. Pharmacopeia for the U.S., sets the public standards for prescription medicines in Europe
FDA:	Defendant United States Food & Drug Administration (the "Agency")
Heparin:	A complex, heterogeneous mixture of polysaccharide chains that, as extracted from pig tissue, vary in length and contain various chemical groups (and other modifications) along the polysaccharide backbone of the chains; used as an active ingredient in prescription injectable drugs as an anti-clotting agent (*i.e.*, an anticoagulant)[1]
Heparin EP:	Heparin sodium EP, sodium salt form of a purified form of heparin that satisfies EP standards
Immunogenicity:	Potential of a drug substance or product to elicit an immune response, such as an allergic reaction, when introduced to the body

[1] *See* FDA citizen petition response regarding generic enoxaparin for description. (CP Dec. at 5-9.)

LMWH:	Low molecular weight heparin that results from cleavage of heparin (or UFH)
Lovenox:	Brand drug product for injection that contains enoxaparin sodium USP as the active ingredient, owned by sanofi-aventis
Momenta:	Momenta Pharmaceuticals, Inc., collaboration partner of Sandoz, Inc.
NDA:	New Drug Application, under 21 U.S.C. § 355(b)(1)
Polysaccharide:	A sugar chain consisting of a number of building blocks; in heparin each so-called building block is predominantly a disaccharide, which consists of two monosaccharide
Reproducibility:	Measure of the ability of an analytical test to produce the same results when the test is conducted by different individuals
Robustness:	Measure of the ability of an analytical test to produce reliable results under varying test conditions
Saccharide:	A carbohydrate consisting of one or more simple sugar units; a "monosaccharide" is so-named because it contains one sugar unit, a "disaccharide" contains two units
Sandoz ANDA Enoxaparin:	Finished final injection drug product containing enoxaparin sodium as the active ingredient, as described in the Sandoz ANDA
Sandoz GmbH:	Affiliate of Sandoz based in Austria
Sandoz:	Intervenor-Defendant Sandoz, Inc., owner of ANDA 77-087 for generic Lovenox
Sanofi-aventis:	Plaintiff sanofi-aventis US LLC, owner of NDA for Lovenox
Specificity:	Measure of the correlation between the results of an analytical test and the specific test components used
UFH:	Unfractionated heparin, another term for "heparin" that refers to the fact that it has not been cleaved into smaller chains
USP:	U.S. Pharmacopeia, a non-governmental, official public standards-setting authority for prescription medicines and other healthcare products manufactured or sold in the United States

PRELIMINARY STATEMENT

FDA's decision to approve the generic enoxaparin developed by Sandoz Inc. ("Sandoz") was amply supported by extensive scientific data, and under the law of this Circuit should be upheld. Sandoz joins, and incorporates by reference, the arguments set forth in FDA's memorandum.[2]

Sandoz wishes to emphasize one point at the outset: that the D.C. Circuit's decision in *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998), a decision that sanofi-aventis barely mentions in its papers, is directly on point and disposes of every significant argument made by sanofi-aventis. Among other things, *Serono* rejects the contention that "sameness," as used in section 355(j) of the Federal Food Drug and Cosmetics Act ("FDCA"), means exact chemical identity between the active ingredients of a brand and its proposed generic. *Id.* at 1320. *Serono* also emphasizes the "high level of deference" accorded FDA in making scientific judgments concerning sameness, based on the kind of drug at issue, the data presented to the Agency, and the Agency's scientific experience and expertise. *Id.* at 1319-25. Finally, it holds that FDA has broad discretion both to assess whether impurities in a proposed generic pose a safety risk greater than that of the brand, and to determine what studies, including animal studies, to require so it can make that assessment. *Id.* at 1324. The same "high level of deference" applicable to FDA's decision in *Serono* applies to FDA's decision here and compels the identical result – upholding the Agency's decision.

Sanofi-aventis fails all four prongs of this Circuit's test for preliminary injunctive relief.

[2] Mindful of the Court's admonition against duplication, we have endeavored to avoid repeating arguments and authority set forth in FDA's memorandum of law. In order to assist the Court, we aim to supplement certain points made by the government and present the irreparable harm and public interest arguments from Sandoz' perspective.

First and most importantly, it cannot demonstrate a likelihood of success on the merits. FDA was well within its authority to consider studies going to the purity of the Sandoz generic in relation to the brand. FDA's approach to evaluating sameness – imposing a rigorous five-criteria test, rather than requiring full characterization of every molecule – was well within its scientific discretion, consistent with prior Agency practice, and amply supported by data and scientific reasoning. FDA's decision on the citizen petition and the Administrative Record make this clear. FDA's judgment that Sandoz has satisfied the five-criteria test is also amply supported in the Administrative Record.[3]

Sanofi-aventis' suggestion that there is some kind of consensus of "independent" individuals and organizations supporting its position is belied by the fact that the individuals and entities it identifies receive funding from sanofi-aventis and thus, can hardly be viewed as independent. The real consensus of the medical community is reflected in the demand for Sandoz' generic. Sandoz has received orders for huge quantities of its generic enoxaparin, including from major hospital and long-term care networks – entities that have medical professionals actively managing the medications dispensed to their patients. (Picard ¶¶ 7-8, 10.)[4]

[3] Sanofi-aventis improperly relies on declarations which were not before FDA during the citizen petition proceeding. Sandoz also believes that sanofi-aventis may submit more such declarations with its reply. The law is clear that, absent extreme circumstances not present here, a court's review of agency action is limited to the administrative record that was before the agency at the time the decision was made. (*See infra* pp. 8-12.) The Court should not consider the sanofi-aventis declarations. If the Court does elect to consider them, however, Sandoz respectfully requests that the Court consider rebuttal declarations from Sandoz, submitted herewith for the Court's convenience.

[4] Citations appearing herein are in the following forms: Citations to "Milne" refer to the Robert M. Milne Declaration, dated August 6, 2010, and the exhibits attached thereto; to "Wheeler" refer to the Craig Wheeler Declaration, dated August 6, 2010; to "Crawford" refer to the Thomas C. Crawford, Ph.D. Declaration, dated August 6, 2010; to "Picard" refer to the David Picard Declaration, dated August 6, 2010; to "May" refer to the Declaration of Jeffrey May, a Senior Vice President at Medco Health Solutions, Inc., dated July 22, 2010; and to "Kostis" refer to the Dr. John Kostis Declaration, dated August 6, 2010.

In fact, Medco Health Solutions Inc. ("Medco"), the country's largest pharmacy benefit manager, with approximately 60 million patients under management, takes the extraordinary step of submitting a declaration here in opposition to sanofi-aventis' motion. (*See* May ¶ 2.) Among other things, the Medco declaration states that it views entry of the generic as in the public interest and makes clear that "especially after [FDA's] lengthy review," Medco is "confident in using [generic equivalents to Lovenox] in [its] generic education and substitution programs as safe, effective and lower-cost equivalents to the brand." (*Id.* ¶ 7.)

Further, AARP, representing millions of senior citizens in this country (major users of drugs such as Lovenox), has submitted an amicus brief to oppose sanofi-aventis' effort to undo FDA's judgment and extend its monopoly. Neither Medco nor AARP (nor any of the myriad healthcare providers purchasing the generic) is receiving compensation from Sandoz. (*Id.* ¶¶ 2-3.) Even if viewed as proper, the speculation of sanofi-aventis' declarants is far outweighed by the actions of medical professionals around the country who are in the process *right now* of using the generic with their patients. There is no likelihood of success on the merits.

As to irreparable harm, sanofi-aventis must show that its claimed economic loss threatens its very existence – something it cannot come close to doing here. It cannot credibly claim a need for emergency relief to protect its market share when it allowed that share to be substantially eroded for almost four full days without applying for relief. Nor can sanofi-aventis deny the clear harms that Sandoz will suffer if its hard-won FDA approval is reversed, including, among others, the loss of reputation and goodwill associated with having to stop sales of the generic, and customer doubts about the safety or efficacy of the generic that will be impossible to eradicate even after the injunction is lifted. As to the public interest, granting the requested injunction would harm the well-recognized public interest in favor of competition, lower prices

for medicine, and allowing FDA to do its job. These concerns are reflected in the amicus submission from AARP and the declaration from Medco.

Finally, sanofi-aventis' action must be seen for what it is: yet another last-ditch effort by a branded drug manufacturer to extend its monopoly after all else has failed, in this case a monopoly on Lovenox that has persisted for 17 years; a monopoly that in 2009 alone generated $2.5 billion – almost $7 million *per day* – in the United States. (Pl's Mem. at 37.)[5]

Sandoz respectfully submits that the requested injunction must be denied.

FACTUAL BACKGROUND

I. SANOFI-AVENTIS' CAMPAIGN TO BLOCK GENERIC COMPETITION AND TO PRESERVE MONOPOLY PROFITS

Sanofi-aventis received marketing approval for Lovenox (NDA No. 020164) in March of 1993, and, as noted, has been the only game in town for 17 years. From 1999 through 2009, Lovenox generated more than *$26 billion* worldwide in sales for sanofi-aventis. In 2009, sales of Lovenox totaled more than *$2.5 billion* in the United States alone, with sales of *$4.1 billion* worldwide. (Pl's Mem. at 37.)

Sanofi-aventis has been fighting for years to eliminate or delay generic competition to Lovenox. It has adopted a multi-pronged approach in this effort, the last vestiges of which are being played out through this lawsuit.

A. Sanofi-Aventis Secured Patent Protection by Intentionally Deceiving the Patent and Trademark Office ("PTO")

The first prong of sanofi-aventis' strategy to avoid competition was to bring patent lawsuits. But in 2007, the patent that it was relying on to support its monopoly through 2012

[5] Citations appearing herein to "Pl's Mem." refer to the Memorandum in Support of Application of Plaintiff Sanofi-Aventis for a Temporary Restraining Order and a Preliminary Injunction, Dkt # 3-18; to "FDA Mem." refer to the Federal Defendants' Memorandum in Opposition to Plaintiff's Motion for a Temporary Restraining Order and a Preliminary Injunction, Dkt # 16; and to "AARP Mem." refer to AARP's Brief *Amicus Curiae* in Support of Defendants, Dkt # 12.

was held to be unenforceable because sanofi-aventis had deliberately misled the PTO in order to obtain it, and therefore was guilty of inequitable conduct. *Aventis Pharma v. Amphastar Pharms.,* 525 F.3d 1334, 1349 (Fed. Cir. 2008) (affirming district court conclusion that sanofi-aventis provided data to patent examiner "in a very misleading way" and that "there is sufficient evidence of concealment to warrant a determination that the dose information was intentionally withheld"), *cert. denied*, 129 S. Ct. 2053 (2009).

B. Sanofi-Aventis Commenced a Citizen Petition Campaign Seeking to Block Generics

The second line of sanofi-aventis' defense against generic competition was to launch the citizen petition campaign with FDA that culminated in the Agency decision at issue here. This campaign commenced in 2003 with sanofi-aventis' original petition, which was followed by four supplements filed between Feb. 12, 2004 and June 29, 2007.[6]

In its submissions, sanofi-aventis claimed, among other things, that certain structural features of Lovenox "may" have clinical (*i.e.*, patient) effects and therefore, would have to be replicated in any generic. To take just one example (out of many), sanofi-aventis' original petition speculated that "[d]istinctive fingerprints with pharmacological relevance *presumably exist* in those [uncharacterized] chains above 3,600 Da." (AR 1-26 (emphasis added).) Yet sanofi-aventis has submitted no data in the seven intervening years to turn this speculation into actual evidence of biologic effect, *e.g.*, by actually identifying new fingerprints and conducting

[6] The use of citizen petitions to delay the approval of generics is a tactic that has been adopted by many branded drug companies. As an FTC Commissioner (and current Chair) recently noted, "the FDA uses citizen petitions to learn of potential problems before a product enters the market. For many years, however, there have been complaints about companies seeking to use this process to delay generic entry." (Remarks of FTC Comm'r Leibowitz, Milne Ex. 2.) "[W]hen the cost of filing an improper petition is trivial compared to the value of securing even a brief delay in a rival's entry, there's certainly an incentive to misbehave." (*Id.*)

clinical trials. The same is true for sanofi-aventis' other speculative assertions,[7] which FDA analyzed extensively and rejected in its citizen petition decision. (CP Dec. at 30-36, Milne Ex. 3; *see also* FDA Mem. at 9 for more on sanofi-aventis' citizen petition.)

C. Sanofi-Aventis Commenced This Action

By seeking an emergency injunction to block generic competition, sanofi-aventis is taking a last desperate shot at extending its Lovenox monopoly. Yet an analysis of sanofi-aventis' arguments demonstrates that FDA fully addressed each point.

II. THE SANDOZ ANDA DEMONSTRATES "SAMENESS"

Sandoz submitted its ANDA on August 26, 2005. The ANDA explains in extensive detail the methods Sandoz used to characterize Lovenox and, ultimately, to show that its generic satisfies FDA's sameness requirements.[8] (*See generally* AR 4320-4431 (FDA Chemistry Review, analyzing Sandoz' methods and results).)

Since Lovenox is a complex, heterogeneous mixture of oligosaccharide chains (AR 4326-28; CP Dec. at 7-9), Sandoz used a combination of overlapping, advanced analytical techniques to thoroughly compare the active ingredient in both the brand and the generic. (*E.g.*, AR 4353-94; CP Dec. at 11-23.) Sandoz employed these overlapping methods to examine the enoxaparin mixture at multiple levels, including identifying and quantifying the building blocks present within the mixture, measuring the structure of longer fragments either intact or generated after

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[7] For similar speculation, *see, e.g.*, Feb. 19, 2003 Submission (AR 13); Feb. 12, 2004 Supplement (AR 633); Sept. 1, 2004 Supplement (AR 1006); Sept. 26, 2005 Supplement (AR 1314); Sept. 14, 2006 Supplement (AR 1653); June 29, 2007 Supplement (AR 2314).

[8] Sandoz and Momenta Pharmaceuticals, Inc. ("Momenta") entered into a collaboration agreement in 2003 for the development and commercialization of generic enoxaparin. The collaboration combined Momenta's technology to sequence and analyze complex polysaccharide mixtures with Sandoz' global capabilities for developing, manufacturing, and marketing complex generic pharmaceuticals. The collaboration partners are referred to in this memorandum collectively as "Sandoz."

enzymatic digestion, and detecting intact oligosaccharide chains. (*E.g.*, AR 4354-56; CP Dec. at 11-23.) Importantly, the analytical tests were validated to determine the reliability of the data. (*E.g.*, AR 4329, 4388-91; CP Dec. at 23, 36.) Among many other things, Sandoz' methods captured important data on the shorter chains in the enoxaparin mixture; such information was critical since the shorter chains are most sensitive to subtle changes in the chemical mode used for splitting the longer heparin chains into smaller chains, *i.e.*, cleaving. (*See, e.g.*, AR 3748-49, 4385-88; CP Dec. at 20)

Sandoz compared its generic with Lovenox across the full range of parameters captured by its testing protocols, including building blocks, chain fragments, and full chains. (*E.g.*, AR 4353-94.) The results showed that the generic was equivalent to the brand, as FDA concluded. (*E.g.*, AR 4329-30, 4353-94; CP Dec. at 11-22.) The finding of equivalence across all such dimensions makes the likelihood of a difference in some unforeseen dimension extremely unlikely. (Crawford ¶ 37.)

Beyond testing of the finished products, Sandoz ensured that its proposed generic would satisfy FDA's "sameness" requirement in multiple ways: for example, by using the same source material that sanofi-aventis uses for its Lovenox (*e.g.*, AR 4341-42, 4355, 4391), by employing sophisticated tests on the heparin source material to ensure that it produces an equivalent finished product (*e.g.*, AR 4338-43, 4350-53), and by employing the same basic chemistry to cleave the heparin chains (*e.g.*, AR 4343-53, 4391; CP Dec. at 13-15). Because the process of cleaving does not change the basic chain sequences, using the same type of starting material and mode of cleavage is an important element in ensuring that the basic sequences and structure of Sandoz' product are the same as Lovenox. (*E.g.*, AR 4355; CP Dec. at 13-16.)

In addition, Sandoz analyzed numerous batches of both Lovenox and its generic to assess the batch-to-batch variability of the brand and to ensure that the generic fell within that range across all parameters. (*E.g.*, AR 4356-93.) Sandoz also established that its enoxaparin has the same stability profile as Lovenox over time. (*E.g.*, AR 4401-04.) Thus, the Sandoz enoxaparin was, and is, equivalent to Lovenox not only at one time point but also over time. (*E.g.*, AR 4320-4431.)

The Sandoz methodologies established equivalence consistent with FDA's five criteria. (*E.g.*, AR 4329-30; CP Dec. at 7 n.24.)

ARGUMENT

As detailed in FDA's memorandum, the emergency relief sanofi-aventis seeks is "extraordinary and drastic," and should be granted only sparingly – particularly where, as here, the injunction would disrupt the *status quo*, not maintain it. (FDA Mem. at 15.) The Sandoz generic has been on the market for two full weeks, a lifetime when it comes to the introduction of a new generic; over 5 million units have been shipped around the country and are being used with patients as a more affordable equivalent to Lovenox. (Picard ¶¶ 7, 8, 10.) To disrupt the flow of the product would cause chaos and consternation throughout the country.

Sanofi-aventis has not and cannot satisfy any of the four prongs necessary to support injunctive relief.

I. SANOFI-AVENTIS IS NOT LIKELY TO SUCCEED ON THE MERITS

A. Sanofi-Aventis Improperly Relies on Declarations That Were Not before FDA at the Time Its Decision Was Rendered and Therefore Should Not Be Considered by This Court

"It is a widely accepted principle of administrative law that the courts base their review of an agency's actions on the materials that were before the agency at the time its decision was made." *IMS, P.C. v. Alvarez*, 129 F.3d 618, 624 (D.C. Cir. 1997); *see also, e.g., Camp v. Pitts*,

411 U.S. 138, 142 (1973); *Citizens to Preserve Overton Park v. Volpe*, 401 U.S. 402, 420 (1971), *abrogated on other grounds by Califano v. Sanders*, 430 U.S. 97, 99 (1977).

Accordingly, courts have consistently rejected efforts by litigants challenging agency actions to submit new evidence – in the form of affidavits, declarations or documents – that was not before the agency at the time its decision was made. *See, e.g., IMS*, 129 F.3d at 624 ("The [proferred] affidavits contain information that should have been submitted to the agency before this dispute reached the courts. To allow the affidavits to be considered now would be to permit *ex post* supplementation of the record, which is not consistent with the prevailing standards for agency reviews."); *Texas Rural Legal Aid, Inc. v. Legal Servs. Corp.*, 940 F.2d 685, 698 (D.C. Cir. 1991) ("Ordinarily, judicial review of informal agency rule-making is confined to the administrative record; neither party is entitled to supplement that record with litigation affidavits or other evidentiary material that was not before the agency."); *Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 177 (D.D.C. 2000) (declining to consider affidavits that were not part of the administrative record from scientific experts concerning safety of recombinant DNA technology.).[9]

Sanofi-aventis has submitted two litigation declarations, and may submit at least one more, that were not before FDA when it rendered its decisions on the citizen petition and Sandoz' ANDA. (Pl's Exs. A and B.) Both declarations offer opinions on possible differences between the brand and a hypothetical generic and the potential for clinical differences between the two. (Viskov ¶¶ 18-32, Pl's Ex. A; Cohen ¶¶ 11-19, Pl's Ex. B.) Counsel for sanofi-aventis

[9] *See also, e.g., Walter O. Boswell Mem'l Hosp. v. Heckler*, 749 F.2d 788, 793-94 (D.C. Cir. 1984) (refusing to consider extra-record affidavits); *Calloway v. Harvey*, 590 F. Supp. 2d 29, 36-39 (D.D.C. 2008) (same); *Alexander & Alexander Servs., Inc. v. SEC*, No. 92-1112 (JHG), 1993 WL 439799, at *12 (D.D.C. Oct. 19, 1993) (affidavits "specifically prohibited as a post-hoc rationalization").

has also indicated that it wishes to make confidential information in the Administrative Record available to Jerry Turnbull, a professor at the University of Liverpool, England (Milne ¶ 2), which suggests that sanofi-aventis plans to offer on reply an "expert" declaration from Dr. Turnbull.[10] These declarations should be disregarded by the Court consistent with the authority above.

Sanofi-aventis cannot appeal to any exception to the general rule precluding this Court's consideration of material outside the administrative record. Just two weeks ago, the D.C. Circuit warned that "[t]he APA limits judicial review to the administrative record except when there has been a strong showing of bad faith or improper behavior or when the record is so bare that it prevents effective judicial review." *Theodore Roosevelt Conservation P'ship v. Salazar*, Nos. 09-5162, 09-5193, 2010 WL2869778, at *13 (D.C. Cir. July 23, 2010) (internal quotations omitted).[11] Neither circumstance is present here: there is no claim of improper behavior or bad

[10] Sanofi-aventis also submits the declaration of Jerome Durso, addressing sanofi-aventis' purported harm. (Pl's Ex. C.) Sandoz does not object to this declaration. Likewise, Sandoz submits the declarations of David Picard and Craig Wheeler on the irreparable harm to Sandoz and Momenta, respectively, if an injunction were entered. In addition, as noted above, Sandoz submits the declaration of Jeffrey May of Medco addressing the public interest issues from Medco's perspective.

[11] *See also, e.g.*, *Am. Wildlands v. Kempthorne*, 530 F.3d 991, 1002 (D.C. Cir. 2008) (administrative record can be supplemented only under "unusual circumstances"); *Menkes v. Dep't of Homeland Sec.*, 662 F. Supp. 2d 62, 69 (D.D.C. 2009) ("Only in narrow circumstances when a party makes a 'strong showing of bad faith or improper behavior' can the record be supplemented."); *Calloway*, 590 F. Supp. 2d at 37 ("Courts grant motions to supplement the administrative record only in exceptional cases."); *Cnty. of San Miguel v. Kempthorne*, 587 F. Supp. 2d 64, 78 (D.D.C. 2008) (same); *City of Williams v. Dombeck*, 151 F. Supp. 2d 9, 18 n.6 (D.D.C. 2001) (finding exception did not apply where plaintiffs failed to make a specific showing "that effective judicial review will be thwarted without an extra-record inquiry"); *Oceana, Inc. v. Locke*, 674 F. Supp. 2d 39, 48 (D.D.C. 2009) (noting extra-record evidence is not appropriate to challenge the *manner* in which agency considered the relevant factors); *Nat'l Wilderness Inst. v. U.S. Army Corps of Eng'rs*, No. 010273 (TFH), 2005 WL 691775, at *10 (D.D.C. 2005) ("[T]here 'is no occasion for a judicial probe beyond the confines of a record which affords enough explanation to indicate whether the agency considered all relevant factors.'") (quoting *Envtl. Def. Fund, Inc. v. Costle*, 657 F.2d 275, 286 (D.C. Cir. 1981)).

faith on the part of FDA; nor can the record be viewed as "bare" in any sense – the Administrative Record produced by FDA consists of thousands of pages and the citizen petition decision explains the Agency's reasoning at length.[12] This is the classic case for the Court to limit itself to the Administrative Record. Accordingly, the Court should disregard the declarations of Drs. Viskov, Cohen and (if proffered) Turnbull.

Sandoz emphasizes, however, that sanofi-aventis has not carried its burden even if the Court considers the above declarations – in a nutshell, they consist of the same speculation that infects sanofi-aventis' overall position. The argument that follows in this memorandum assumes that the Court does not disregard the sanofi-aventis declarations. If the Court does elect to consider the sanofi-aventis declarations, Sandoz respectfully requests that the Court also consider two declarations it submits in response. The declarations focus on information that was before the Agency and show that the arguments of sanofi-aventis' declarants are without merit. The declarants are:

- John Kostis, M.D., Chief of Medical Service and Professor of Medicine and Pharmacology at the Robert Wood Johnson University Hospital and Medical School, and long-time practicing cardiologist. Dr. Kostis rebuts the contention that there is some kind of medical consensus against the use of FDA-approved generic enoxaparin and responds to various claims made by Dr. Cohen. (Kostis ¶¶ 17-18.)

[12] While dicta from an earlier Court of Appeals decision, *Esch v. Yeutter*, 876 F.2d 976, 991 (D.C. Cir. 1989), noted other possible exceptions, these exceptions have since been narrowed substantially, if not repudiated altogether, by the Court of Appeals. *See, e.g.*, *Peterson Farms I v. Espy*, No. 92-5243, 1994 WL 26331, at *3 (D.C. Cir. 1994) (noting "the probative value of [the *Esch*] dicta is limited"); *Saratoga Dev. Corp. v. United States*, 21 F.3d 445, 457-58 (D.C. Cir. 1994) (stating that additional administrative discovery is permissible only if necessary "for effective judicial review" or if the existing "record cannot be trusted."); *Axiom Res. Mgmt., Inc. v. United States*, 564 F.3d 1374, 1380 (Fed. Cir. 2009) ("*Esch*'s vitality even within the D.C. Circuit is questionable in light of more recent opinions by that court which demonstrate a more restrictive approach to extra-record evidence.").

- John Crawford, Ph.D., an organic chemist and expert in pharmaceutical process development and controls with over 35 years of experience in developing pharmaceuticals of all types, including nearly six years as the leader of the global chemical research and development group at Pfizer, one of the world's leading innovator pharmaceutical companies. Dr. Crawford rebuts the speculation of Drs. Viskov and Cohen about potential differences between Lovenox and a hypothetical generic by reviewing the scientific data Sandoz actually submitted to FDA and concluding that it amply supports a finding that the Sandoz generic is the same as Lovenox. (Crawford ¶¶ 4, 21-40.) Dr. Crawford would also rebut a declaration from Dr. Turnbull, if one is submitted.

As noted, Sandoz submits these declarations herewith.[13] If the Court elects to disregard the sanofi-aventis declarations, however, the Court need not review the proposed Sandoz declarations and can limit its consideration to the Administrative Record produced by FDA. Either way, sanofi-aventis' motion should be denied.

B. FDA's Approval of the Sandoz ANDA Is Entitled to the Highest Deference

The standard of review of agency actions involving scientific decisions, under *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984), is familiar to the Court and is discussed at length in FDA's brief. (FDA Mem. at 16-18.) While there are many cases applying this standard, the one that is particularly relevant here is *Serono,* for reasons noted above and in FDA's memorandum. (FDA Mem. at 21-22, 24, 28-30.)

As the Administrative Record forcefully illustrates, FDA's determination of the five "sameness" criteria and its ultimate approval of Sandoz' ANDA were comprehensive and well-

[13] Sandoz recognizes that, given the tight schedule, it does not have the luxury to await the Court's ruling on the declarations before submitting its opposition.

reasoned scientific decisions – each entitled to the highest levels of deference from this Court.[14] An agency decision does not need to be indisputably correct to be upheld under *Chevron* – it just needs to be reasonable. *See Young v. Cmty Nutrition Inst.*, 476 U.S. 974, 980-81 (1986) (applying *Chevron* analysis to FDA's interpretation of the FDCA and concluding that FDA's interpretation was "a sufficiently rational one to preclude a court from substituting its judgment for that of [the agency]").[15] Here, FDA's decision should be upheld under any standard, and there can be no question that it should be upheld under the deferential test announced in *Chevron* and applied in *Serono* on facts strikingly similar to those here.[16]

C. FDA's Decision to Require Additional Data about Impurities/Immunogenicity Is Consistent with the Statute and Is Plainly within the Agency's Discretion under *Serono* and Other Cases

FDA's memorandum covers its clear authority – indeed its obligation – under sections 355(j)(4)(A) and 355(j)(2)(A)(vi) of the FDCA, to evaluate the purity of a proposed generic product, and points out that the D.C. Circuit in *Serono* rejected the same argument sanofi-aventis

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[14] FDA's decision was rendered with great care and deliberation over a period of almost ten years, as reflected in the Administrative Record. Such care and attention, standing alone, counsel deference. *See, e.g., Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218-19 (D.D.C. 1996) (challenge to FDA scientific judgment denied where agency "made a comprehensive review" of relevant scientific tests and presented a "reasonable scientific basis" for its decision); *Somerset Pharms. v. Shalala*, 973 F. Supp. 443, 454 (D. Del. 1997) ("Whether [FDA's] conclusion was scientifically correct is not a matter within the purview of this court . . . . Considering the care with which this decision was apparently made, it does not seem likely that plaintiff will succeed on the merits.").

[15] *See also, e.g.*, *Int'l Fabricare Inst. v. FDA*, 972 F.2d 384, 400 (D.C. Cir. 1992) ("[O]ur task [in reviewing agency scientific determinations] is to assure that they be reasoned, not that they be right."); *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (courts have a "narrowly defined duty" to "hold[] agencies to certain minimal standards of rationality."); *Serono*, 158 F.3d at 1321 ("[U]nder *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.").

[16] In addition to ignoring *Serono*, sanofi-aventis also ignores the unbroken line of authority, cited by FDA, rejecting brand challenges to FDA sameness decisions in cases like this. (FDA Mem. at 1 n.1.) All apply here.

makes here; namely, that FDA exceed its authority.[17] (FDA Mem. at 21-24.) Sandoz will not repeat that discussion and makes only three brief, additional points.

First, FDA did not require Sandoz to conduct any specific tests as part of the Agency's purity inquiry; instead FDA suggested certain approaches by which Sandoz might make the required showing of sameness between the generic and brand as to impurity and immunogenicity profiles, but made clear that "other approaches might also be acceptable." (AR 4170-74.) The studies conducted by Sandoz (detailed in FDA's memorandum at 19-21) are entirely consistent with the FDCA. These studies were not at the core of a New Drug Application's required showing that a drug product is safe and effective in its own right. Rather, the impurity studies performed by Sandoz were *comparative*, that is, they established that the impurity/immunogenic properties of the Sandoz generic were equivalent to those of the brand. (FDA Mem. at 23-24.)[18]

Sanofi-aventis is wrong when it suggests that Sandoz conducted a clinical study involving healthy human volunteers in connection with FDA's immunogenicity inquiry (Pl's Mem. at 12-13, n.17), although Sandoz plainly could have submitted, and FDA could have relied on, such a study under either of the rationales in *Serono*. The only human study conducted by Sandoz was conducted in 2005 (two years before FDA initiated its impurity/immunogenicity

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[17] The Third Circuit has also held that FDA has wide "discretion to determine what tests or studies would provide it with appropriate information from which to determine bioequivalence." *Serono*, 158 F.3d at 1319 (citing *Schering Corp. v. FDA*, 51 F.3d 390, 399-400 (3d Cir. 1995)).

[18] The two mouse studies Sandoz conducted were fully consistent with the approach in *Serono*, 158 F.3d at 1324. They were comparative and, even if viewed as not comparative, they were plainly "limited and confirmatory," which FDA (57 FR 17958), sanofi-aventis (Pl's Mem. at 18-19) and the court in *Serono* (158 F.3d at 1324 n.6) have stated may be included in an ANDA. FDA also made clear to Sandoz that the mouse studies were only suggested: they "depend[ed] on the outcome of the [other] suggested studies." (AR 4170-74.) Sandoz ultimately submitted more than one dozen physicochemical and *in vitro* studies, such as the level of impurities and their effect on particular binding reactions, which established equivalence in respect of immunogenic issues. (AR 4433,4194.) The two mouse assays confirmed these results. (AR 4433, 4194.)

inqiury), and was used to support FDA's fifth sameness criterion (CP Dec. at 22-23); it has nothing to do with impurities or immunogenicity.

Sanofi-aventis also makes the specious argument that FDA would not have required immunogenicity testing if it were confident that Sandoz had adequately demonstrated that its active ingredient was the same as that of Lovenox. (Pl's Mem. at 21.) This is wrong, as demonstrated by FDA's calcitonin decision, surprisingly relied on by sanofi-aventis, where FDA makes clear that the evaluation of impurities is distinct from that of active ingredient sameness. (Calcitonin CP at 10-11, Pl's Ex. P.) As noted, impurities are evaluated pursuant to section 505(j)(2)(A)(vi) and 505(j)(4)(A); active ingredient sameness pursuant to sections 505(j)(2)(ii) and (j)(4)(C).[19]

In short, FDA had clear authority to rely on the immunogenicity testing submitted by Sandoz in support of its application. Indeed, it would be ironic if such additional confirmation that the generic version did not present any additional risk as compared to Lovenox could serve as a basis to bar the new generic from the market.

D. FDA's Determination That the Sandoz Active Ingredient Is the Same as the Lovenox Active Ingredient Was Plainly within Its Discretion

1. FDA's Scientific Judgment on Sameness Was Correct

FDA's approval of Sandoz' ANDA took almost five years, and the basis for that approval is set forth in the comprehensive, 45-page Agency decision denying sanofi-aventis' citizen petition. There can be no question that the approval should be upheld under *Serono*. Indeed, application of even the least deferential standard of review would still result in upholding FDA's decision here.

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[19] Sandoz incorporates by reference FDA's discussion of why its calcitonin decision is fully consistent with its actions here. (FDA Mem. at 24-25.)

FDA relied on Sandoz' use of a host of overlapping approaches to ensure that its generic is the same as Lovenox. (AR 4353-94.) These include using equivalent heparin source material to Lovenox; using the same chemical mode for splitting the long chains of the starting heparin into the shorter chains of enoxaparin; deploying a battery of cutting edge analytical techniques to show equivalence of the generic with Lovenox at the composition, building block, chain fragment and full-chain levels; using sophisticated analytical tests of the heparin source material to ensure that it will produce equivalent finished product; and showing sameness in respect of anticoagulant activity. (*Id.*; CP Dec. at 3, 11-23.) In its consideration of Sandoz' ANDA, FDA noted that with recent progress in structural analysis of complex carbohydrates such as enoxaparin, it is possible to thoroughly characterize the heterogeneity of composition, sequence, and chain length of enoxaparin sodium at a molecular level using overlapping high-resolution analytical methods. (AR 4355.) That is exactly what Sandoz did here.

As FDA detailed in its citizen petition decision, Sandoz' analytical methods are so sensitive that, when applied to enoxaparin manufactured by third parties outside the U.S., they were able to detect differences with Lovenox not revealed by standard compendial measures. (CP Dec. at 18 n.72, 21 n.82.) Sandoz agrees that the structure of a low molecular weight heparin can vary with process conditions (temperature, pH level, time of reaction, etc.); however, the sensitivity of Sandoz' analytical tests ensure that the conditions it has adopted for its process will produce a product equivalent to the brand, as FDA found. (*See, e.g.*, AR 4340-42, 4385-86, 4388; CP Dec. at 17, 18, 20, 35.)

Likewise, FDA's five-criteria test for assessing sameness reflects a careful analysis of the chemistry and biological mechanisms of enoxaparin, the collective power of the above-noted overlapping analytical techniques, and the data from those techniques submitted by Sandoz. The

methods are analogous to the tailored criteria that the Agency adopted and the D.C. Circuit affirmed in *Serono*.[20] 158 F.3d at 1318-19.

Notably, sanofi-aventis does not contest any of the scientific conclusions embedded in any of the five criteria, or the utility of the criteria themselves. To take just one example, sanofi-aventis does not suggest that FDA is wrong when the Agency concludes (in its discussion of criterion three) that

> If there is equivalence in physicochemical properties, heparin source material, and mode of depolymerization together with this sensitive marker of equivalent chemical selectivity (*i.e.*, based upon data showing equivalence of disaccharide compositional analysis, fragment mapping and sequences of short-chain oligosaccharides), this information provides evidence that the manufacturing process for generic enoxaparin will cleave heparin polysaccharide chains at sites equivalent to those for Lovenox's enoxaparin.

(CP Dec. at 20.) This crucial finding, and all of the others embodied in FDA's analysis of the criteria for sameness, stand unquestioned. Instead, sanofi-aventis focuses on a fictitious absolute rule against generic approval where full characterization is not possible – a rule squarely rejected in *Serono* and inconsistent with FDA practice.[21]

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[20] Although the Court need not consider it if it excludes the sanofi-aventis declarations, Dr. Crawford reviewed Sandoz' showing to FDA together with the citizen petition record and, applying his 35 years of experience in drug development, concluded that the Agency was entirely justified in determining that Sandoz has shown equivalence. (Crawford ¶¶ 2, 5, 37.)

[21] Nor does the presence of disagreements among FDA employees over issues involved in the review (a common occurrence) warrant second-guessing FDA's judgment, as the D.C. Circuit made clear in *Serono*. 158 F.3d at 1321 ("*Chevron* deference is owed to the decisionmaker authorized to speak on behalf of the agency, not to each individual agency employee."); *see also, e.g., San Luis Obispo Mothers for Peace v. NRC*, 789 F.2d 26, 33 (D.C. Cir. 1986) ("The position of an agency's staff, taken before the agency itself decided the point, does not invalidate the agency's subsequent application and interpretation of its own regulation."); *Homemakers N. Shore, Inc. v. Bowen*, 832 F.2d 408, 413 (7th Cir. 1987) ("Although Homemakers observes that the Secretary's minions have taken different views of § 405.460(f)(7), this demonstrates only that the Department of Health and Human Services is a mammoth bureaucracy with seemingly endless layers of internal review, and that reasonable people disagree about the meaning of the 1979 regulation."); *Alliance for Bio-Integrity*, 116 F. Supp. 2d at 177-78 ("Nonetheless, Plaintiffs, pointing to the critical comments of lower-level FDA officials[,] insist that even the administrative record reveals a lack of general recognition of safety among qualified experts. . . .

Especially in light of sanofi-aventis' failure to offer meaningful criticism, these Agency findings can hardly be seen as irrational or an abuse of discretion.

2. Sanofi-aventis' Criticisms Are Unfounded

a. There is No "Full Characterization" Requirement for FDA to Approve a Generic

Sanofi-aventis wrongly asserts that, based on the FDCA and the Agency's past practice, FDA is required to refuse generic approvals whenever the brand product cannot be "fully characterized." (Pl's Mem. at 24.) The D.C. Circuit firmly established in *Serono* that full characterization is not necessary. 158 F.3d at 1320-22. FDA's memorandum discusses *Serono* and other authority on this issue, and that discussion will not be repeated here.[22] (FDA Mem. at 28-30.)

In addition to ignoring *Serono* (and FDA's flexible approach as to Pergonal, the product at issue in that case), sanofi-aventis ignores generic heparin and hetastarch, both examples of generic approvals where the brand was derived from natural sources and was not fully characterized. (CP Dec. at 23-25.) Generic heparin is particularly relevant because heparin is the "parent" of both Lovenox and generic enoxaparin. (CP Dec. at 5.) Sanofi-aventis also ignores FDA's decision on the citizen petition relating to Copaxone, a mixture of synthetic polypeptides constructed from four naturally occurring amino acids. (Copaxone CP at 2, Milne Ex. 4.) In responding to that citizen petition, FDA again rejected the contention of the brand

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However, lower-level comments on a regulation 'do[ ] not invalidate the agency's subsequent application and interpretation of its own regulation.'").

[22] In one of its citizen petition submissions, sanofi-aventis claimed that *Serono* was clear that the uncharacterized portions of the molecule at issue there did not have clinical significance. (Feb. 12, 2004 Supplement, AR 638.) But the plaintiff in *Serono*, like sanofi-aventis here, *claimed* that such uncharacterized portions *might* have clinical significance. *See* Brief for Appellee, 1997 WL 34643791, at *10 (arguing that uncharacterized portions "may result in serious side effects"). Exercising its scientific judgment, however, FDA rejected such speculation, and the Court of Appeals upheld that judgment.

manufacturer that generic approvals should be barred because Copaxone was not fully characterized and because of speculation as to clinical effects of potential differences between the brand and the generic. (*Id*. at 9-12.) FDA stated that it would "continue its practice of taking into account the 'kind of drug at issue' when making a determination of sameness. Any such determination would be based on current scientific data and information, the Agency's knowledge of the drug, its scientific experience and expertise, and the nature and extent of the data and information provided by an ANDA sponsor to support approval of its generic drug." (*Id*. at 5; *see also, e.g.*, Calcitonin CP at 3, Pl's Ex. P (reiterating Agency's "flexible approach" to sameness determination).)

Sanofi-aventis' attempt to depict FDA's actions as to hyaluronidase, Omnitrope and Premarin as inconsistent with "precedent" is similarly unavailing. None of these examples involved the kind of comprehensive, overlapping data that is present here. And, as detailed in FDA's memorandum, the facts and circumstances of these cases plainly were different than those here. (*See* FDA Mem. at 32-34.) The whole point of the Agency's consistent approach is that FDA may find sameness where the data supports it and find otherwise when it does not.

b. FDA Did Not Ignore Sanofi-Aventis' Arguments

Sanofi-aventis wrongly suggests that FDA ignored sanofi-aventis' showing that small differences in process conditions can have significant effects on the pharmaceutical activity of enoxaparin. (Pl's Mem. at 7-8, 34, 36.) In fact, FDA considered and rejected these contentions, and its well-reasoned judgment on these matters should be left undisturbed under *Serono* and *Chevron*.

First, FDA acknowledged repeatedly that enoxaparin is sensitive to the process conditions employed (*e.g.*, temperature, pH, time of reaction) (CP Dec. at 2 n.4, 14, 17-20, 30, 35) and explained how the sensitive analytical methodologies employed by Sandoz were able to discern

subtle process-dependent differences, thereby allowing Sandoz to adjust its process conditions to generate equivalent product. (*Id.*; AR 4329-30, 4353-94.)

Second, FDA addressed sanofi-aventis' claim that slight structural changes "can have significant effects on the pharmacological activity of the drug." (Pl's Mem. at 34.) In its citizen petition decision, the Agency reviewed sanofi-aventis' many assertions of *potential* clinical effect and found each claim speculative and unsupported by evidence. (CP Dec. at 30-33.) As noted above, on its face, sanofi-aventis' various claims of clinical impact are speculative – replete with statements like this: "Distinctive fingerprints with pharmacologic relevance *presumably exist* in those chains above 3,600 Da." (Original Petition, AR 19.) Although it filed the citizen petition seven years ago, sanofi-aventis has not submitted credible evidence that might convert its speculation into an argument that could be analyzed. In any event, FDA has found Sandoz' enoxaparin to be equivalent to Lovenox, thereby mooting sanofi-aventis' protests regarding such features.

Often, brand companies, playing on the natural inclination to be cautious where public health is concerned, invoke patient safety concerns in an effort to secure even a short delay in generic competition. But courts have not hesitated to deny emergency injunctions sought by branded monopolists offering dire predictions of health effects due to allegedly incorrect FDA decisions.[23] Though many dire predictions have been made by brand companies in these

[23] *See, e.g.*, *Serono*, 158 F.3d at 1327 (brand claimed that potential structural differences between brand and generic might lead to ineffectiveness and/or serious side effects); *Astellas*, 642 F. Supp. 2d at 23 (rejecting brand manufacturer claim that generic organ transplant drug might imperil transplant patients absent additional testing where evidence speculative); *see also Schering*, 782 F. Supp. 645, 652 (D.D.C. 1992) (immediate injunction denied where brand failed to offer "any affirmative evidence that there is reason for suspecting that the [approved generic] . . . would have *immediate* harmful effects on the public," and where FDA conducted "extensive review" of such issues) (emphasis added); *Bristol-Myers*, 923 F. Supp. at 221 ("[t]here is nothing before the court which would lead it to conclude that Prevalite *will cause* any harmful health

situations, we are aware of no example where the prediction was borne out when the generic was used with patients.

Sanofi-aventis refers to the views of so-called "independent" scientific/medical third parties supporting its position (the "sanofi supporters"). (Pl's Mem. at 6 n.7, 34, 36 n.31.) But each of these third parties is receiving funding – grants, sponsorships and the like – from sanofi-aventis (*see* Milne Decl. ¶ 11 for detail gleaned from public sources), and thus can hardly be considered "independent."[24] None have been privy to the showing of sameness actually made by Sandoz and none are sufficiently informed to criticize FDA's decision. FDA considered the statements of the sanofi supporters in connection with the citizen petition, but ultimately decided that Sandoz had demonstrated "sameness" (and thus safety and efficacy). This is precisely the type of scientific judgment to which this Court must give deference.

Moreover, the confidence of the medical community in the safety and efficacy of generic enoxaparin is shown by the fact that some of the largest health care providers in the country – entities with sophisticated drug evaluation and purchasing programs – are purchasing the generic for use with their patients. These entities include the St. Barnabas Health Care System, New

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effects") (emphasis added); *Somerset*, 973 F. Supp. at 455 ("Plaintiff has offered little more than a bare assertion that patients and physicians will confuse generic selegiline with Somerset's product.").

[24] Indeed, many of these organizations and physicians have been criticized for failing to disclose their financial links to sanofi-aventis when they made submissions to FDA in support of sanofi-aventis' citizen petition. (*Letters Oppose Approval of Generic Heparin*, Milne Ex. 5.) Not surprisingly, the objectivity of these groups has been called into question. For example, as to the Society of Hospital Medicine ("SHM"), one commentator observed that: "it is hard to tell whether the [SHM] leadership is more concerned about the safety of anticoagulants, or the *financial interests of the drug companies that support it*." (*Sanofi-Funded Society of Hospital Medicine Stands Up for Lovenox*, Milne Ex. 6 (emphasis added).) "The problem with the funding of health care professional societies" by healthcare corporations with commercial interests in the medical specialty "is that it raises the suspicion that such societies may use their considerable influence to serve the corporations', not patients', interests, and so undermine the values of the societies' members." (*Id*.)

Jersey's largest integrated health care delivery system. (Picard ¶ 7.) In fact, Medco, one of the largest pharmacy benefit managers and mail order pharmacies in the country, has provided a declaration indicating that it intends to utilize generic enoxaparin with its 60 million patients on the basis of its confidence in FDA's review. (May ¶¶ 2-8.) AARP, the nation's largest organization of senior citizens, has submitted an amicus brief in opposition to sanofi-aventis' efforts to block the exercise of FDA's discretion. (*See generally* AARP Mem. at 1.) None of the above entities is receiving compensation. Moreover, as noted above, Dr. John Kostis, a long-practicing cardiologist and Professor and Chief of Medical Service at the Robert Wood Johnson Medical School and University Hospital, declares that he is perfectly comfortable prescribing generic enoxaparin for his patients. (Kostis ¶¶ 14, 16.)

Sanofi-aventis asserts that FDA's position on enoxaparin runs counter to that of the European Medicines Agency ("EMEA"), FDA's European counterpart. FDA addressed and rejected this contention in its citizen petition decision and in its memorandum. (FDA Mem. at 37-38; CP Dec. at 42-44.) Sandoz incorporates FDA's argument by reference.

FDA was well within its discretion in taking the approach that it took – which has already had the effect of making a more affordable option available to patients around the country.

3. Sanofi-aventis' Argument Regarding 505(b) Is without Merit and, in Any Event, Would Not Bar FDA from Approving Enoxaparin as a Therapeutic Equivalent to Lovenox

Sanofi-aventis argues that because of the allegedly improper impurity studies, Sandoz' ANDA for enoxaparin should have been filed as a New Drug Application under section 505(b) of the FDCA. (Pl's Mem. at 16, 23-24.) Sanofi-aventis is wrong: the Sandoz ANDA was properly evaluated under section 505(j), for the reasons discussed above and in the FDA's memorandum. (*See* FDA Mem. at 25-27.) But if sanofi-aventis was correct that FDA should have considered Sandoz' application under section 505(b), sanofi-aventis still cannot prevail.

Sanofi-aventis argues that drugs approved under section 505(b) cannot be deemed as therapeutically equivalent to, and therefore are not substitutable for, the referenced brand drug. (*See* Pl's Mem. at 16.) Sanofi-aventis is wrong in making this distinction between sections 505(b) and 505(j). In fact, according to FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the "Orange Book," a therapeutic equivalence rating is available for any FDA-approved drug product so long as it has made the necessary showing. Thus, the criteria by which FDA may assign therapeutic equivalence clearly does not depend on the regulatory pathway chosen, but rather on scientific determinations of equivalence that FDA can make. In this case, FDA has already determined that, as a matter of science and law, Sandoz' enoxoparin product is therapeutically equivalent to Lovenox and meets all other applicable regulatory requirements.

Therefore, under the law and under FDA's scientific decision, even if Sandoz had filed a 505(b) application, its application would have been approved, and it would have been awarded therapeutic equivalence because it would have demonstrated therapeutic equivalence. The relief sought by sanofi-avenitis in this case – enjoining FDA approval of enoxaparin under section 505(j) – would not bar Sandoz from marketing a therapeutically equivalent enoxaparin product approved by FDA under section 505(b). Thus sanofi-aventis can gain no meaningful relief even if it were correct on this issue, which provides an alternative basis for ruling that sanofi-aventis cannot succeed on the merits.

* * *

In short, given Sandoz' substantial scientific showing, FDA's careful evaluation thereof, and the substantial deference owed under *Chevron* and *Serono* to FDA's scientific determinations, there is no likelihood of success on the merits.

II. SANOFI-AVENTIS WILL NOT SUFFER IRREPARABLE INJURY ABSENT INJUNCTIVE RELIEF

Sanofi-aventis cannot come close to showing irreparable harm here, for all the reasons stated in FDA's memorandum. (FDA Mem. at 38-44.)

Sandoz notes the following in addition to the points made by FDA:

- As further confirmation that continued sales of generic enoxaparin will not threaten sanofi-aventis' very existence, sanofi-aventis management, on a call to investors just last week, expressed continued optimism in their company's financial condition and growth, with or without a monopoly on Lovenox in the U.S. (*See* Q2 2010 Earnings Call, Milne Ex. 7, at 2 (expressing satisfaction with second quarter profit growth despite generic competition, demonstrating "the resilience of the underlying business"), 7 (pointing out that almost half of Lovenox sales are outside the U.S. and that, even with U.S. generic entry, globally Lovenox "will remain [a] strong blockbuster product[]").)

- Rather than claim its existence is threatened, sanofi-aventis complains that it will suffer lost sales, price erosion and diminished market share due to the generic – in a word, it will suffer from competition. *See Biovail Corp. v. FDA*, 519 F. Supp. 2d 39, 48 (D.D.C. 2007) (rejecting argument that "market competition constitutes irreparable harm."). But such claims of feared harm from competition are routinely found not to constitute irreparable harm. *See, e.g.*, *Astellas Pharma v. FDA*, 642 F. Supp. 2d 10, 23 (D.D.C. 2009); *Biovail*, 519 F. Supp. 2d at 48-49; *Bristol-Myers*, 923 F. Supp. at 221; *TGS Tech. v. United States*, Civ. A. No. 92-0062 (JHG), 1992 WL 19058, at *4 (D.D.C. Jan. 14, 1992).[25]

[25] Moreover, sanofi-aventis' claim that it will suffer irreversible price and market share erosion is speculative. Sanofi-aventis cites the declaration of its Chief Commercial Officer, Jerome Durso, but the best he can say about price erosion is that "it *may* not be possible for sanofi-aventis to

- Having waited almost four full days to even seek an injunction – when sanofi-aventis itself concedes that large quantities of the generic are shipped immediately by a new entrant (*see* Durso Decl. ¶ 12) – sanofi-aventis is in no position to seek an emergency injunction to protect against loss of market share. Much of the lost sales sanofi-aventis fears already occurred while it sat on its hands. *See Graceway Pharms., LLC v. Perrigo Co.*, 697 F. Supp. 2d 600, 607 (D.N.J. 2010) (denying injunction barring drug launch where plaintiff delayed in seeking relief and defendant incurred substantial costs "associated with its putting its product in the stream of commerce").

- Finally, sanofi-aventis cites the district court decision in *Serono* for the proposition that it will suffer irreparable harm. (Pl's Mem. at 38.) It ignores, however, that in reversing the district court, the D.C. Circuit expressed doubts about the harm to plaintiff: "But even if [plaintiff's lost revenue] does constitute irreparable injury . . . that injury must be weighed against the next factor – the extent to which an injunction will substantially injure [the generic company]." *Serono*, 158 F.3d at 1326. Calling it a "draw" in that case, the court held that "[w]hatever sales [the brand] will lose to [the generic] in the absence of an injunction, [the generic] will lose to [the brand] in the presence of one." *Id*.

III. A TEMPORARY RESTRAINING ORDER OR PRELIMINARY INJUNCTION WILL CAUSE IRREPARABLE INJURY TO SANDOZ

It is an "unwarranted use of the extraordinary writ of [injunction]" to "alleviate the hardship of one party by exposing the other party to great financial risk." *Dorfmann v. Boozer*, 414 F.2d 1168, 1173 (D.C. Cir. 1969). "Thus even where denial of a preliminary injunction will harm the plaintiff, the injunction should not be issued where it would work a great and

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later restore the price [of Lovenox] to its pre-generic level" if Sandoz' product is pulled from the market. Durso ¶ 27 (emphasis added).

potentially irreparable harm to the party enjoined." *Id.* As discussed in the FDA memorandum, injunctions that disrupt, rather than preserve, the *status quo* are especially disfavored. Sanofi-aventis seeks exactly that here.

Because Sandoz already has been selling its generic enoxaparin for 14 days, it will suffer substantial and irreparable harm if its approval is revoked and it is required to stop the sale of product to customers around the country. (Picard ¶¶ 7-8, 10, 17-20.) Sandoz would suffer not only the substantial cost of attempting to accomplish such a cessation, but also the incalculable impact to its goodwill and reputation with customers if they were asked to stop their use of the Sandoz generic in mid-stream. (*Id.*) As noted, millions of doses are already in the hands of customers and being used by patients. (*Id.*) Moreover, if sales of the generic are stopped because of sanofi-aventis' speculation about patient safety, customers likely will remain skeptical about the generic even after the injunction is lifted.[26] (*Id.* ¶ 20.)

Crucially, as the only ANDA approved for generic enoxaparin, Sandoz has a valuable "first mover advantage" as against subsequent generic entrants. The D.C. Circuit has recognized that the loss of such an advantage can create "severe economic impact" – an impact that is by definition irreparable. *Mova Pharm. v. Shalala*, 140 F.3d 1060, 1066 n.6 (D.C. Cir. 1998); *see also, e.g., Teva v. Sebelius*, 595 F.3d 1303, 1311 (Fed. Cir. 2010); Picard ¶ 15 (detailing harm to Sandoz). Indeed, one other ANDA applicant for generic enoxaparin already has indicated it

[26] Although sanofi-aventis states that it seeks only that future shipments of enoxaparin be suspended, its request for injunctive relief seeks an order directing FDA to "immediately suspend and withdraw approval of Sandoz' ANDA." (Relief Requested, ¶ b). Such an order would bar any healthcare supplier from selling or using product already in its possession – triggering chaos in Sandoz' distribution system, with customers seeking to return product, physicians frustrated at the changing landscape, and patients wondering about the efficacy of the generic they were taking.

believes it has satisfied the five criteria set by FDA for approval of generic enoxaparin, and expects that its ANDA will be approved soon. (Teva Press Release, Milne Ex. 8.)

Enoxaparin is expected to be Sandoz' biggest selling drug in 2010 – and the company's success this year depends heavily on its timely commercialization. Sandoz is expecting sales in the range of over $40 million in the next six weeks alone, sales which would be lost if the court were to enjoin it. (Picard ¶¶ 10-14; *see, e.g., Biovail*, 519 F. Supp. 2d at 50 ("Teva stands to forever lose millions of dollars even from a temporary interruption of its ongoing sales of the newly-approved generic product.").) Moreover, Sandoz has invested between $50 and $70 million in developing its enoxaparin process and working through the FDA review process. (Picard ¶ 5.) Even a temporary delay in sales would further erode the value of Sandoz' substantial investment and perpetuate sanofi-aventis' monopoly. (*Id.* at ¶¶ 11-13, 16.) And, even if Sandoz is allowed to relaunch following an injunction, it would suffer substantial and irreparable harm related to the costs of reestablishing its multi-step distribution system and the customer relationships it may have lost permanently (to sanofi-aventis or other generics) during the time it was held off the market. (Picard ¶ 21.) Sandoz' collaboration partner, Momenta, a much smaller company, will face substantial hardship if commercialization is delayed by injunction. (*Id*. ¶ 22; Wheeler ¶ 5.)

The Court in *Bristol-Myers* found that the balance of harms tipped decidedly in favor of defendants in circumstances strikingly similar to those here:

> The approval of [the generic] has entailed a significant investment of economic and other resources on the part of Upsher. Upsher has endured a seven year process to obtain FDA approval and has satisfied the FDA's testing protocol and established, to FDA's satisfaction, the bioequivalence of [its generic] and [the brand]. Moreover, the effect of an injunction on Upsher would be dramatically greater than the harm to [the brand manufacturer] . . . .

923 F. Supp. at 221. The same is true here. *See also, e.g., Dorfmann*, 414 F.2d at 1173.

At a minimum, as discussed above, the harm alleged by sanofi-aventis from denial of the preliminary injunction and the harm faced by Sandoz from a grant of the injunction are "a wash" and cancel each other out, meaning that sanofi-aventis has failed to carry its burden, given the weakness of its case on the merits.

IV. THE PUBLIC INTEREST FAVORS DENIAL OF INJUNCTIVE RELIEF

Sanofi-aventis has also failed to establish that the public interest would be better served if an injunction were issued by the Court. To the contrary, enjoining the sale of generic enoxaparin by Sandoz would deny patients an FDA-approved, high-quality, affordable alternative to Lovenox, and would frustrate the purposes of the Hatch-Waxman Amendments, whose aim is to increase competition in the drug industry by facilitating the approval of lower-cost generic drugs. *See, e.g.*, *Serono*, 158 F.3d at 1326 ("The purpose of the Hatch-Waxman Amendments was, after all, 'to increase competition in the drug industry by facilitating the approval of generic copies of drugs'") (citing *Mead Johnson*, 838 F.2d at 1333); *see also, e.g.*, *Bristol-Myers*, 923 F. Supp. at 221-22 (noting that delaying approval of generic manufacturer's ANDA would be contrary to the aims of Hatch-Waxman); *Hi-Tech Pharmacal v. FDAl*, 587 F. Supp. 2d 1, 12-13 (D.D.C. 2008); *Biovail*, 519 F. Supp. 2d at 50 (discussing the public interest in "'receiving generic competition to brand-name drugs as soon as possible'" (quoting *Boehringer Ingelheim Corp. v. Shalala*, 993 F. Supp. 1, 3 (D.D.C. 1997)) and "'in reduced prices'" (quoting *Schering*, 782 F. Supp. at 652)); *see also* AARP Mem. at 8-11.

Generic drugs have saved the U.S. healthcare system over $824 billion since 2000. (GPhA Study at 1, Milne Ex. 10.) The savings to be realized by the public here already have been huge and will only grow over time. (AARP Mem. at 4-5.) The generic sells at a substantial discount to Lovenox. And Lovenox represents the single largest pharmacy expenditure for most hospitals in the United States. (Picard ¶¶ 9, 19.) Substantial savings to community hospitals –

many of which are suffering greatly, particularly in these difficult economic times – would be a tremendous benefit to the public interest. (May ¶¶ 5, 8; AARP Mem. at 1-8.)

Moreover, granting an injunction in these circumstances – and thereby second-guessing FDA's thoroughly-considered scientific judgment – will only encourage other companies to mount challenges, however baseless, to generic drug approvals. (AARP Mem. at 3-4, 8-11.) The fact that entities such as AARP and Medco echo these concerns (Medco, through its declaration (May ¶¶ 5, 8), and AARP, through its amicus brief (AARP Mem. at 1-11)) only reinforces the public interest in denying sanofi-aventis' requested injunction.

CONCLUSION

For all the foregoing reasons, the Court should deny sanofi-aventis' motion for a temporary restraining order or preliminary injunction.[27]

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Respectfully submitted,

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[27] If the Court is inclined to order temporary injunctive relief (and Sandoz believes that there is no basis to do so), sanofi-aventis must be required to post an adequate bond, pursuant to Fed R. Civ. P. 65(c), as security for the damages Sandoz will suffer as a result of the injunction. Sandoz is prepared to make a showing as to the amount of such bond at the Court's request.