UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

AVENTIS PHARMA S.A., AND AVENTIS PHARMACEUTICAL, INC.,
Plaintiff,

v.

AMPHASTAR PHARMACEUTICALS, INC., AND TEVA PHARMACEUTICALS USA, INC.,
Defendant.

AND RELATED COUNTERCLAIMS

CASE NO. EDCV03-887 MRP (PLAx)
CASE NO. EDCV04-333 MRP (PLAx)

MEMORANDUM OF DECISION FINDING IN FAVOR OF DEFENDANTS AMPHASTAR PHARMACEUTICALS, INC. AND TEVA PHARMACEUTICALS USA, INC. ON THE RELATED ISSUES OF INTENT TO DECEIVE THE PATENT AND TRADEMARK OFFICE AND INEQUITABLE CONDUCT

I. INTRODUCTION

This case was commenced before District Judge Robert J. Timlin. Aventis Pharma S.A. and Aventis Pharmaceuticals, Inc. (collectively, "Aventis"[1]) brought suit against Amphastar Pharmaceuticals, Inc. ("Amphastar") and Teva Pharmaceuticals USA, Inc. ("Teva")

[1] Pharmuka, Rhone-Poulenc, and Phone-Poulenc Rorer are predecessor corporations to Plaintiff Aventis. At various times, each of these entities was responsible for the enoxaparin product. The Court uses "Aventis" generally to refer to whichever entity was in existence at the time.

924

(collectively, "Defendants") for infringement of Aventis' patent, U.S. Patent No. 5,389,618, and its replacement, U.S. Reissue Patent No. 38,743 (collectively, "the '618 patent"). The case was transferred to this Court for all further proceedings on June 27, 2006. A bench trial on inequitable conduct was held December 4 through December 8, 2006. The Court limited its inquiry to Aventis and its agents' intent in failing to disclose highly material information to the United States Patent and Trademark Office ("PTO"). Based on consideration of the evidence adduced at trial and the post-trial arguments made by counsel, the Court concludes as follows:

II. BACKGROUND

Heparin is an anticoagulant used to decrease the clotting ability of the blood. Chemically, it is a heterogeneous mixture of straight-chain anionic mucopolysaccharides having anticoagulant properties. Low molecular weight heparin ("LMWH") is synthesized by various methods of heparin fractionation or depolymerization. These methods break down heparin's long, heavy polysaccharide molecules, yielding smaller, less massive chains in more homogenous proportions. The resulting mixtures consist of shorter chains of polysaccharides having lower average molecular weights.

The '618 patent claims a range of defined LMWH mixtures. These encompass the drug formulation, enoxaparin, approved by the United States Food and Drug Administration ("FDA") as an anticoagulant in diseases featuring venous thromboses. Aventis is the international pharmaceutical company that manufactures enoxaparin, which it markets under the brand name Lovenox®. Enoxaparin was approved in France in 1987. By 1989, it had "taken the French market by storm" and achieved commercial success throughout Europe. Aventis exerted a monopoly position in the European market for enoxaparin in the 1980s by virtue of European

Patent 40,144 ("EP '144"), which issued in 1984 and broadly claimed undefined LMWH mixtures invented by J. Mardiguian.

Serious challenges to EP '144 soon threatened this position. Opposition proceedings initiated in the mid-1980s before the European Patent Office to revoke EP '144 as devoid of novelty had, by 1989, proved successful -- the opposition was allowed, and the revocation of EP '144 became effective in October 1990. Enoxaparin did not have patent coverage in the U.S. at this time. Aventis had been forced to abandon its U.S. counterpart application to EP '144 in 1984 when it had no argument to oppose the PTO's prior-art rejections. Notwithstanding this deficit, Aventis filed its New Drug Application ("NDA") with the FDA in July 1991 to obtain marketing approval for enoxaparin in the U.S. In concert, Aventis sought to protect enoxaparin in the U.S. with an EP '144 successor: a formulation of enoxaparin invented by Roger Debrie (the "Debrie" or "'618" product).[2] This was the subject of the '618 prosecution. The high cost of FDA approval generated substantial pressure on Aventis to succeed. Internal Aventis documents reveal its commitment of "significant financial and human resources" to the "enoxaparin USA-patent situation."

The '618 prosecution involved successive rounds of rejection and appeal. The Patent Examiner ("PE") issued three Office Actions dated April 2, 1992 ("First Office Action"), October 16, 1992 ("Second Office Action"), and March 2, 1993 ("Third Office Action"). Each rejected the Debrie formulation under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious in light of Mardiguian EP '144. The keystone of Aventis'

[2] Aventis filed U.S. Patent Application Serial No. 721,315 ("the '315 application") on June 26, 1991 in the PTO, claiming a priority date of June 26, 1990 based upon an earlier French application. On July 16, 1993, Aventis filed a continuation of the '315 application, United States application No. 92,577, which ultimately issued as the '618 patent.

strategy for overcoming the PE's rejections was to distinguish the Debrie LMWH based on its purportedly superior pharmacokinetic properties -- particularly, its longer plasma half-life. The '618 patent discloses that "[t]he processes described in the prior art, and especially in EP '144, do not permit the production of mixtures possessing the requisite pharmacological properties for improved therapeutic applications, namely, a sufficiently long plasma half-life, a fairly high absorption rate, a high bioavailability or alternatively, a low clearance." In support of these assertions, Aventis directed the PE's attention to Example 6 of the '618 patent ("Example 6") and the half-life analysis presented therein.[3] Aventis also submitted two expert declarations from its employee, French scientist Dr. Andre Uzan ("Dr. Uzan"), who was responsible for the data underlying Example 6.[4]

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[3] Example 6 of the '618 patent provides as follows (emphasis added):

> This example illustrates the increase in stability, in vivo, of the mixtures of the invention, expressed by their plasma half-life.
>
> A first pharmacokinetic study was carried out on volunteers between 21 and 30 years of age. Subcutaneous injections of doses ranging from 20 to 80 mg/ml were performed. At intervals of time, samples were drawn (4.5 ml) and stored at approximately 4°C. The samples were then centrifuged for 15 minutes at 2,300 g and the platelet-poor plasma was separated and frozen prior to analysis. The half-life of the mixtures was then determined by measuring the anti-Xa activity. The results obtained were as follows:
>
> (1) From the mixtures produced in Examples 3 and 4:
>
> 40 mg dose: in 75% of the cases, the half-life was longer than 4 hours, and was even longer than 4 1/2 hours in approximately 45% of the cases;
>
> 60 mg dose: in 75% of the cases, the half-life was longer than 3.7 hours.
>
> (2) Under identical dosage conditions, intact heparin injected intravenously possessed a half-life of approximately 0.6 hours.
>
> (3) When the product was prepared according to the process described in European Patent EP 40,144, the half-life was longer than 4 1/2 hours in 17% of the cases.
>
> (4) A second study carried out under similar conditions on 20 patients provided the following results for the mixtures according to the present invention:
>
> 40 mg dose: in 80% of cases, the half-life was longer than 4 hours, and it was longer than 4 1/2 hours in approximately 40% of the cases;
>
> 20 mg dose: in 60% of the cases, the half-life was longer than 3.9 hours.

[4] The first was submitted on March 29, 1993 ("First Declaration"), the second on May 17, 1994 ("Second Declaration").

Throughout the prosecution, Aventis and Dr. Uzan affirmatively represented that Example 6 "clearly demonstrate[d]" a significantly longer plasma half-life for the Debrie LMWH compared to Mardiguian EP '144. At no time, however, did Aventis or Dr. Uzan disclose at what dosage the half-life comparisons in Example 6 had been made. Subparagraph (3) of Example 6 omitted the experimental dose of EP '144. In his Second Declaration, Dr. Uzan presented five tables: Tables I, X, and XI referred to the '618 product, while Tables A and III referred to Mardiguian EP '144. Again, Table III failed to disclose the dose. In fact, Dr. Uzan had compared a 60 mg dose of Mardiguian EP '144 to a 40 mg dose of the Debrie product. However, comparing the 60 mg dose amount of Mardiguian EP '144 to the 60 mg dose amount of the Debrie product results in a far closer mean half-life.[5] The difference is not statistically significant.

III. PRIOR PROCEEDINGS

Amphastar moved for summary judgment on its affirmative defense and counterclaim of inequitable conduct, arguing that Aventis and Dr. Uzan's withholding of the EP '144 dosage constituted a failure to disclose material information to the U.S. PTO and rendered the '618 patent-in-suit unenforceable. Judge Timlin agreed, finding that: (1) the EP '144 dose information was highly material, because Aventis made half-life the centerpiece of its argument for patentability, and a reasonable PE would have considered the experimental dose important in deciding whether to allow Aventis' application on that basis; and (2) the omission of the dose information supported a strong inference of intent to deceive, because the Debrie product's half-

[5] This is evident by comparing Table III with Table XI. Table III reported the half-life for Mardiguian EP '144 at a 60 mg dose as 3.33 hours, with a standard deviation of 0.2. Table XI reported the half-life for the '618 product at a 60 mg dose as 3.70 hours, with a standard deviation of 0.82.

life was not significantly different from EP '144 at the same dose. Accordingly, Judge Timlin granted summary judgment in favor of Amphastar and held the '618 patent and the '743 reissue patent unenforceable. *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 390 F. Supp. 2d 936 (C.D. Cal. 2005).

On appeal, the Federal Circuit reversed and remanded, *Aventis Pharma S.A. v. Amphastar Pharmaceuticals, Inc.*, 176 Fed. Appx. 117 (Fed. Cir. 2006), concluding that, although there were no genuine issues as to high materiality, a finding of deceptive intent was inappropriate on summary judgment. The panel conceded that Judge Timlin's inference of intent by Aventis to deceive the PTO was "reasonable," observing that "by failing to disclose that the EP 40,144 data was at a 60 mg dose, Aventis may have been painting the rosiest picture possible as to the half-life improvement of its claimed compounds in an attempt to deceive the examiner." *Aventis*, 176 Fed. Appx. at 123. This concession ratified Amphastar's *prima facie* case of intent. *See Paragon Podiatry Lab., Inc. v. KLM Lab., Inc.*, 984 F.2d 1182, 1192 (Fed. Cir. 1993) ("A party charging inequitable conduct may make a *prima facie* case by showing an unexplained violation of the duty of candor.").

The panel also agreed with Aventis, however. The case for deceptive intent "hinge[d] on an assessment of Dr. Uzan's credibility and an examination of the scientific rationale and facts justifying Dr. Uzan's half-life comparison at different doses." (Fed. Cir. Reply Br. 21-22.) Aventis had stated facts supporting a "plausible justification" for its material omission, but Judge Timlin had denied Dr. Uzan an opportunity to testify to it at trial. Thus, because "there [was] another reasonable inference [than intent to deceive] -- namely, as Aventis argue[d], if the comparison between different doses was reasonable, the failure to disclose may have been partly due to inadvertence" -- the finding of intent was premature.

Upon remand and transfer, the Court entertained pre-trial motions,[6] considered the trial briefs of the parties, and conducted the bench trial on intent to which the present decision relates.

IV. LEGAL STANDARD

"Inequitable conduct occurs when a patentee breaches his or her duty of 'candor, good faith, and honesty,'" *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1342 (Fed. Cir. 2005) (quoting *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995)), by affirmatively misrepresenting or failing to disclose material information to the PTO. *Pharmacia Corp. v. Par Pharm., Inc.*, 417 F.3d 1369, 1373 (Fed. Cir. 2005). "The inequitable conduct analysis is performed in two steps comprising 'first, a determination of whether the withheld reference meets a threshold level of materiality and intent to mislead, and second, a weighing of the materiality and intent in light of all the circumstances to determine whether the applicant's conduct is *so culpable* that the patent should be held unenforceable.'" *Dayco Prods., Inc. v. Total*

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[6] In the Court's pretrial conference and resultant Minute Order of November 14, 2006, the Court ruled that certain opinions of Aventis' medical expert, Dr. Weitz, regarding the common practice in the industry with respect to doses used to compare LMWHs would be excluded unless Aventis consented to hear certain opinions from Amphastar's patent law expert, Mr. Goolkasian. Aventis agreed not offer expert opinion testimony on industry practice from paragraph 2 of Dr. Weitz's supplemental report, and Amphastar agreed not to present Mr. Goolkasian. During the bench trial, however, Aventis repeatedly sought to introduce industry practice testimony through Dr. Uzan. Aventis also sought to avoid its agreement to restrict Dr. Weitz's testimony on industry practice by reference to paragraphs 3 and 4, which are claimed also to deal with industry practice and stand independently of paragraph 2. Amphastar has made a post-trial motion to strike all testimony going to industry practice. The Court finds Aventis agreed with Amphastar to withhold all expert opinion testimony by Dr. Weitz on the subject matter of industry practice, regardless of the paragraphs from which that testimony might derive. No other conclusion obviates the need, from Amphastar's perspective, for Mr. Goolkasian's testimony. Dr. Uzan was not covered by Amphastar's agreement. Dr. Uzan was also not a testifying expert under Fed. R. Civ. P. 26(a)(2). He was a percipient fact witness accused of intending to deceive the PTO, and the focal point of the trial. However, the Court finds that the actual practice in LMWHs, even if established, is irrelevant to the reasonableness of Aventis' and Dr. Uzan's non-disclosures in this case. Accordingly, Amphastar's December 4, 2006 motion to strike is denied.

Containment, Inc., 329 F.3d 1358, 1362-63 (Fed. Cir. 2003) (emphasis added) (quoting *Purdue Pharma L.P. v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1366 (Fed. Cir. 2001)).

The quantum of proof required to show intent is tied to materiality; the "more material the omission or the misrepresentation, the lower the level of intent required to establish inequitable conduct." *Semiconductor Energy Lab. Co., Ltd. v. Samsung Elecs. Co., Ltd.*, 204 F.3d 1368, 1375 (Fed. Cir. 2000). "Materiality does not," however, "presume intent, which is a separate and essential component of inequitable conduct." *GFI, Inc. v. Franklin, Corp.*, 265 F.3d 1268, 1274 (Fed. Cir. 2001) (quoting *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 552 (Fed. Cir. 1990)). Although "a lesser quantum of proof is needed to establish the requisite intent" in this case, *Aventis Pharma*, 176 Fed. Appx. at 119, Amphastar and Teva must still prove the predicate facts by clear and convincing evidence. *Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1187 (Fed. Cir. 2006).

Satisfying this burden does not require "smoking gun" evidence. *Paragon*, 984 F.2d at 1189. The Federal Circuit has "repeatedly said that direct evidence of intent is unavailable in most cases and unnecessary in any event." *Frazier v. Roessel Cine Photo Tech, Inc.*, 417 F.3d 1230, 1235 (Fed. Cir. 2005); *see also Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs. Ltd.*, 394 F.3d 1348, 1354 (Fed. Cir. 2005) ("'Intent need not, and rarely can, be proven by direct evidence.'" (quoting *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1422 (Fed. Cir. 1989)); *Ulead Sys., Inc. v. Lex Computer & Mgmt. Corp.*, 351 F.3d 1139, 1146 (Fed. Cir. 2003) ("[d]irect evidence of deceptive intent is not required"). Rather, "in the absence of a credible explanation, intent to deceive is generally inferred from the facts and circumstances surrounding a knowing failure to disclose material information." *Bruno Indep. Living*, 394 F.3d at 1354; *see also Digital Control, Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1319 (Fed. Cir.

2006) ("Intent...may be inferred from the totality of the evidence."); *Ulead Sys.*, 351 F.3d at 1146 ("deceptive intent is...usually inferred from the patentee's overall conduct"). Such an inference is commonly supported "by a showing of acts the natural consequence of which were presumably intended by the actor." *Paragon*, 984 F.2d at 1189.

Proving intent does not require showing that an individual involved in the prosecution "subjectively believed the [] submission was deceptive." *Frazier*, 417 F.3d at 1235-36. It does require that "the involved conduct, viewed in light of all the evidence, including evidence of good faith, [] indicate sufficient culpability to require a finding of intent to deceive." *Paragon*, 984 F.2d at 1189 (quoting *Kingsdown Med. Consultants Ltd. v. Hollister, Inc.*, 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc)). Circumstances indicative of good faith must be considered. *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1580 (Fed. Cir. 1997). But a "patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead." *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997). "[M]erely conclusory statements or completely insupportable, specious or conflicting explanations or excuses will not suffice" to establish good faith, *Paragon*, 984 F.2d at 1190, nor will "[a] mere denial of intent to mislead (which would defeat every effort to establish inequitable conduct)." *GFI*, 265 F.3d at 1275 (quoting *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1416 (Fed. Cir. 1987)). Furthermore, where a patentee "has not proffered a credible explanation for the nondisclosure...an inference of deceptive intent may fairly be drawn in the absence of such an explanation." *Bruno Indep. Living*, 394 F.3d at 1354.

V. THE EXPLANATIONS AND JUSTIFICATIONS OFFERED BY AVENTIS AND DR. UZAN

(A.) The Reasonableness Of Comparing Half-Lives Of LMWHs At Dissimilar Doses.

Aventis contends that Dr. Uzan had scientifically valid reasons for not making his half-life comparison at equivalent doses. Specifically, Aventis contends: (1) that Dr. Uzan used clinical benchmarks derived from scientific literature to select doses for the compounds he compared; (2) that this was the only appropriate method for Dr. Uzan to employ given his objective of comparing the clinical properties of a new drug to an old drug; (3) that it was standard practice in the industry to perform dose-ranging comparisons when studying the properties of different LMWHs; and (4) that it was reasonable for Dr. Uzan to select a 40 mg experimental dose of the Debrie product because that dose was approved for a use that presented the greatest challenge in terms of balancing safety and efficacy.

Dr. Uzan's testimony was consistent with these contentions. Dr. Uzan testified that his objective in propounding Example 6 was to compare the LMWHs at their "clinically relevant dose[s]," which he defined as the "dose[s] presenting the best efficacy-safety ratio." He clarified that "for the clinicians there is a balance between efficacy and side effects, mainly bleeding, and so the therapeutic dose, clinically relevant, is a dose for which this safety ratio, including bleeding, is the best." According to Dr. Uzan, "[c]omparing the identical dose is not an appropriate comparison" because a "gravimetric comparison...has no clinical relevance." The reason that a "comparison in the field of heparin is only valued when you compare clinically relevant dose," Dr. Uzan explained:

> is that the low molecular weight heparins are mixtures containing million of saccharides and a very complex composition. And the consequence is that those compounds have, according to this composition, pharmacological, pharmacokinetic, and clinical effects

> which are composition related. And so clinically it has no sense to compare qualimetric dose...equal quantities, equal amounts in milligram. You cannot do that.

Dr. Uzan further testified to his understanding that, for these reasons, "all the people involved in low molecular heparin compare clinically relevant dose," and 40 mg was the clinically relevant dose for the indication Dr. Uzan claims to have been focused on -- namely, the prevention of deep vein thrombosis ("DVT") in high-risk patients undergoing orthopedic surgery. Dr. Weitz, Aventis' biology expert, testified in support of Dr. Uzan's approach. Although Dr. Weitz condemned Dr. Uzan's failure to identify the Mardiguan EP '144 dose, even suggesting it to have been an unreasonable omission, Dr. Weitz testified that the omission did not affect the validity of Dr. Uzan's half-life comparison. In Dr. Weitz's opinion, Dr. Uzan's "comparison was reasonable because those were the preferred doses of the drugs," and "as clinicians, as doctors, we are only interested in comparing drugs at the doses that have that appropriate benefit-to-risk ratio that -- the right efficacy, and the acceptable safety." "As a doctor," Dr. Weitz explained, "I want to know the half-life of a drug at a dose that I am going to use in my patients." Dr. Weitz further testified that "the preferred dose for the high-risk surgical patients [was] 40 mg."

Aventis maintains that Dr. Uzan finds additional support for his clinical justification for selecting 40 mg in scientific articles that compare the pharmacokinetic properties of various LMWHs at their respective -- and different -- therapeutic doses. Coupled with the fact that no contemporaneous publication studied enoxaparin at 60 mg, Aventis further maintains that these articles prove that Dr. Uzan's clinical rationale comports with the practice of those skilled in the art of LMWHs.

Amphastar and Teva dispute Dr. Uzan and Aventis' contentions, arguing three points: (1) that Dr. Uzan's professed reliance on clinical benchmarks to select an experimental dose is a

litigation-inspired pretext fabricated in order to portray the 40 mg dose as reasonable; (2) that Dr. Uzan and Aventis employed an arbitrary and statistically flawed analytical method in order to cherry-pick the best data and create an artificial impression of significance; and (3) that Aventis adduced insufficient evidence at trial to permit the Court to find any standard practice in the industry to compare LMWHs at their therapeutic, different doses.

It is, however, unnecessary for the Court decide the merits of Amphastar and Teva's particular arguments. Whether selecting the "clinically relevant" dose was scientifically valid given Dr. Uzan's stated objective of comparing the therapeutic properties of a new drug versus an old drug is irrelevant. Whether it is standard practice in the industry of LMWHs to perform dose-ranging comparisons when studying the properties of different LMWHs is irrelevant. Even if the Court accepts both propositions as true, Dr. Uzan's clinical justifications -- as he and Aventis have stated them -- are implausible under the circumstances of the '618 prosecution and, in that context, fail to persuade the Court that the comparison between different doses was reasonable.

At the heart of Aventis' case for reasonableness is the proposition that Dr. Uzan's objective before the PTO was limited to demonstrating that the claimed LMWH, the Debrie '618 formulation, exhibited superior therapeutic properties over a prior art LMWH, the Mardiguian EP '144 formulation, which was known to be compositionally different. The presumption of compositional difference pervades Aventis' case. It was treated as established fact by every Aventis witness and referenced as such by every Aventis argument.[7] In post-trial briefing,

[7] For example, the objective of each scientific publication Aventis invites the Court to consider for the industry practice was to compare the biochemical properties of various LMWHs known by prior investigation to be compositionally distinct. Similarly, Dr. Weitz testified that his own research involved, and he has himself personally performed, comparisons of the pharmacological properties of different

Aventis argued that "it only makes sense to focus on the clinical dose" when the "objective is to compare the clinical properties of a new drug to an old drug." Dr. Uzan himself testified that "[c]omparing the identical dose is not an appropriate comparison, because ... you cannot compare one kilogram of potatoes to one kilogram of mushrooms."

This metaphor reveals that Dr. Uzan presupposed the very conclusion his half-life analysis sought to prove. Certainly, the use of equal weights of potatoes and mushrooms tells you nothing you do not already know about the properties of potatoes and mushrooms; potatoes taste different than mushrooms, no matter how many of either you eat. The problem for Aventis is that the PE was concerned precisely with the open question of compositional difference: had Aventis claimed a potato or a mushroom, and how ought she to tell the difference?

(1.) The Central Objection To Patentability Throughout The '618 Prosecution.

In the First Office Action, the PE observed that EP '144 taught the "instantly claimed sulfated heparinic polysaccharide admixture" and relied on an inherency argument in rejecting the Debrie LMWH as anticipated by EP '144. In addition, because the Oestergaard reference taught that LMWH mixtures are "substantially equivalent regardless of the process by which they are obtained," the PE concluded that "it would have been obvious to one of ordinary skill in the art at the time [Debrie invented the '618 product] to select any of the well known prior art methods for obtaining a low molecular weight fraction of heparin for the advantage of increased biological activity."

Aventis responded in two ways, first by defining the composition, then by emphasizing its properties. Aventis stated that "[t]he admixture comprises from 9% to 20% of polysaccharide

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heparin-based products, including enoxaparin, at different experimental doses because those doses were the preferred clinical doses.

chains having a molecular weight greater than 2,000 daltons and from 5% to 20% of polysaccharide chains having a molecular weight greater than 8,000 daltons, the ratio between the weight average molecular weight and the number average molecular weight thereof ranging from 1.3 to 1.6." Because Mardiguian did not disclose or suggest this particular compositional makeup, and because the properties of LMWHs were said to be highly composition dependent, Aventis argued that Mardiguian did "not permit the production of mixtures possessing the requisite pharmacological properties [to achieve] improved therapeutic applications, namely a sufficiently long plasma half-life." Aventis explained the reason as follows:

> Given the fact that the inventive formulations and those of the European patent exhibit different properties, such as half life, it necessarily follows that the formulations of the invention could not possibly be the same as those of the European patent. As is notoriously well established, compounds and their properties are inseparable and thus, when two compounds exhibit different properties it follows that they must necessarily be of different structure. Here, therefore, it should be apparent that formulations as claimed, having significantly improved half lives as compared to the formulations of the European patent, are necessarily different from those of the European patent.[8] (emphasis added)

Clearly, then, Aventis was well-aware of the PE's concern that the inventive formulation was inherent in EP '144, which is say, that Debrie and EP '144 were essentially the same. But Aventis could not successfully distinguish Debrie merely by appealing to Debrie's ratio of number average and weight average molecular weights. The EP '144 patent is not limited by a specific ratio of constituents. Rather, it employs open claim language "comprising various proportions of particular molecular weight products." Therefore, Aventis attacked sameness

[8] Aventis argued in closing that Aventis' U.S. patent counsel, Mr. Schulman, went too far here in arguing that the compositions must be different if their properties are different. The Court is at a loss to understand this retreat. It contradicts Dr. Uzan's testimony that the properties of LMWHs are highly composition dependant. More important, if different compositions may not be inferred from different properties, and Aventis could not disprove inherency by virtue of compositional differences alone, then the '618 patent could not be distinguished from EP '144 or overcome the PE's inherency objections.

based on a difference in properties. It also relied on Debrie's properties to rebut obviousness. Foreshadowing Dr. Uzan's trial testimony, Aventis maintained that a LMWH mixture's properties vary with its ratio of chemical constituents, and "the crucial step lies in the selection of the combination of lengths which will provide a final product having the combination of desirable properties." Accordingly, because the ratio identified by Debrie's LMWH exhibited superior properties over EP '144, the inventive formulation could neither be inherent nor obvious.

The PE was not persuaded. In the Second Office Action, she maintained her rejections. The EP '144 LMWH, she wrote, is "inherently the same as" the claimed invention, as its "composition is so close to the instantly claimed admixtures as to be considered the same, or having differences which are within experimental error." Because the PTO lacks "facilities for testing and comparing various products," she noted that it was incumbent on Aventis to "convincingly demonstrate that the claimed product provides some unexpected or unobvious property not demonstrated by the prior art." The PE further noted that the half-life assertions in Example 6 were not convincing because "the *half life for the EP 40144 product appears to be essentially the same as that for the instant mixtures*," and "[n]o statistically significant or convincing data which clearly establishes Applicant's assertions has been provided" (emphasis in original).

This signaled to Aventis that its reliance on biochemical properties held promise for overcoming both the PE's inherency and obviousness objections. Aventis relied heavily on Example 6 to respond:

> ...Example 6 of the originally filed application [] clearly demonstrates that the preparations of Mardiguian are not inherently the same as those currently claimed. In particular, Example 6 clearly demonstrates that the claimed compounds exhibit improved

> pharmacokinetic properties and, in particular, the products of the invention were found to have a plasma half-life longer than 4-1/2 hours in 40-45% of the cases where such half-life was observed in accordance with Mardiguian in only 17% of cases. This represents an increase in 250% in half-life. This is very important for a pharmaceutical because such increased half-life enables use of lower dosages of the preparations in accordance with the invention.

In his First Declaration, Dr. Uzan echoed this position, claiming Example 6 "represents an increase in 250% in half-life and is very significant because it enables the same effect to be achieved with lower dosages."

Aventis also used Dr. Uzan's First Declaration to resurrect its argument that compositional differences themselves, rather than the properties asserted by Aventis to be composition dependent, rendered the Debrie formulation patentably distinct from EP '144. Dr. Uzan recounted the preparation of a LMWH product using the process disclosed by Mardiguian. He claimed that the resulting LMWH had "21% of chains having a molecular weight lower than 2,000; 6% of chains having a molecular weight greater than 8,000 and 73% of chains having a molecular weight between 2,000 and 8,000." Accordingly, Dr. Uzan concluded that "the formulations of Mardiguian [were] clearly outside the scope of the present invention."

The PE remained skeptical. In the Third Office Action, she observed that "the differences in composition between the instant product and the Mardiguian formulation are minimal." Aventis had "failed to demonstrate that such minor differences render the instant invention patentably distinct over the prior art," especially "because [Aventis] ha[d] not provided evidence of any unexpected results." Rejecting Aventis' and Dr. Uzan's respective assertions about the import of Example 6, the PE concluded that Aventis had still:

> ...failed to provide evidence that the alleged difference between the half life of the Mardiguian product and that of the instant mixture is statistically significant. Specifically, with regard to Example 6, [Aventis] states neither the number of volunteers

> in the first study nor their overall physical condition. No data which clearly and convincingly establishes [Aventis'] assertions in a statistically significant way.

Thus, by this point in the prosecution, the Debrie formulation stood rejected both as anticipated by, and obvious in light of, Mardiguian EP '144. Aventis had yet to successfully rebut either objection. The PE had required Aventis to come forward with clear evidence that the compositions were different, but Aventis' second attempt to prove the Debrie LMWH was chemically distinct from EP '144 based on their compositional differences had failed. The PE had flagged her willingness to accept evidence of statistically significant differences in pharmacokinetic properties as indirect proof of compositional difference sufficient to disprove inherency, but Aventis had not made the requisite showing.

Aventis argues that by the time of Dr. Uzan's Second Declaration, the PE had acknowledged that the Debrie product was different from EP '144 by dropping her anticipation rejection under 35 U.S.C. § 102. In a Supplemental Response following the Third Office Action, but preceding Dr. Uzan's Second Declaration, Aventis claims that, "as the Patent Office makes only a rejection under 35 U.S.C. § 103 [in the Third Office Action], it is beyond dispute that the Patent Office does not view the claimed preparations as being inherent." Aventis went on: "Indeed, the [First] Declaration previously submitted by applicant refutes such inherency … [and] … [i]t being a given, therefore, that the claimed preparations are not inherent, the next questions is whether they would have been obvious…." In effect, Aventis simply declared victory on inherency and proceeded to argue nonobviousness. This strategic shift is reflected in Dr. Uzan's Second Declaration. Whereas Dr. Uzan repeatedly asserted in his First Declaration that the data presented in Example 6 and elsewhere conclusively established a patentable difference, he interpreted the same data in his Second Declaration solely in terms of the Debrie composition's properties.

There is no need to debate the PE's references to the Patent Act.[9] The Third Office Action explicitly rejects Aventis' attempt to prove its claimed LMWH was chemically distinct from EP '144 based on compositional differences. The PE wrote that "[t]he recited properties of bioavailability and antithrombotic activity are considered to be inherent in the prior art," while "[n]o evidence has been presented which clearly and convincingly demonstrates that the instant compounds would provide any properties or activities not necessarily inherent to the prior art compounds." Moreover, the PE's handwritten Interview Summary Record, dated several months after the Third Office Action, records that "[a]nother declaration will be submitted...to further indicate how the claimed invention distinguishes over the Mardiguian reference." These statements would make little sense if, by this stage, the PE had already concluded that the claimed preparations were not inherent. Thus, the central question throughout the prosecution of the '618 patent was whether the Debrie and Mardiguian EP '144 LMWH products were compositionally different.[10] Even if the Court were to accept as true Aventis' unlikely

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[9] *But see* the Third Office Action, in which the PE restated her rejections over Mardiguian under 35 U.S.C. § 103 without expressly restating them under 35 U.S.C. § 102, but at no time actually withdrew her rejections over Mardiguian under 35 U.S.C. § 102. Not having been withdrawn, those anticipation rejections over Mardiguian were technically still pending. Thus, Aventis' argument based on the PE's citations to the Patent Act is specious.

[10] Here, the issue of obviousness necessarily folds into, and is subsumed, by inherency. Evidence of statistically significant differences in pharmacokinetic properties between Debrie and EP '144 sufficient to disprove sameness would also be sufficient to prove nonobviousness. In addition, when dealing with LMWHs, the concept of obviousness presents conceptual difficulties. Aventis maintains that a LMWH's ratio between weight average molecular weight and number average molecular weight defines its properties, and the inventive insight comes in recognizing when a specific ratio promises improved therapeutic properties over the prior art. The dilemma arises because, as argued *infra*, a LMWH's therapeutic properties may not always be determinable until the LMWH has been identified as compositionally distinct from the prior art. Obviousness, in such a case, presupposes a determination, one way or another, about inherency. Yet, this may render obviousness impossible in every case: a beneficial property can never be obvious to a person of ordinary skilled in the art when a LMWH is invented if that skilled person cannot know the property is beneficial until after the LMWH is invented. Accordingly, it is more helpful to examine this case through the lens of inherency.

contention that, by the time of Dr. Uzan's Second Declaration, the PE had conceded that the Debrie and EP '144 products were different, there can be no question that inherency was the central, dispositive question up to that point.

(2.) The Adequacy Of Dr. Uzan's Method For Demonstrating Compositional Difference: Composition-Effect Indistinguishable From Dose-Effect.

Aventis' and Amphastar's experts agreed that, where the objective of a pharmacokinetic analysis is to establish that two LMWH products, or any chemical compounds, are compositionally different, a dose-ranging experimental design is inappropriate. The reason is that, if prior experimentation has not conclusively established the two formulations as chemically distinct, any observed differences in pharmacokinetic properties, including half-life, could be explained either by a difference in experimental dose or a difference in the compositions.

Amphastar's pharmacology expert, Dr. Boons, testified that valid experimental design asks one scientific question at a time and keeps all other parameters the same. That way "one can arrive at conclusions whether [the] two preparations have different or the same pharmacokinetic properties." Dr. Boons observed: "[I]f one has two heparinic preparations and one wants to establish that they were not the same, that one is different and has superior properties in this case as measured by anti-X_a activity, one has to keep everything the same except the two preparations. If one then observes a difference, that can then be attributed to the two different preparations."

Aventis' own medical expert, Dr. Weitz, corroborated Dr. Boon's view. When asked on cross examination why he would not want to control all the experimental confounds -- or "noise," as he put it -- in his experimental design, Dr. Weitz at first hesitated, then responded:

> I mean, I think it depends. If you are trying to compare a pharmacokinetic parameter of two different drugs when they are used at the clinically relevant doses, then you don't care about that control [of holding the dose constant]. What you want to do is you want to see what that parameter is at the dose that you are going to use in the clinic. (emphasis added)

In other words, Dr. Weitz understood Dr. Uzan's different-dose comparison to be directed at a much narrower scientific question than the PE had actually posed to Aventis and Dr. Uzan. Dr. Weitz testified that Example 6 "wasn't being offered for the purpose of showing that the two drugs were different." Rather, Dr. Weitz understood Example 6 and Dr. Uzan's representations to the PTO about its significance to have been directed at the question whether the half-life of the Debrie product at 40 mg was more effective for the prevention of DVT in patients undergoing high-risk orthopedic surgery than the half-life of the Mardiguian product at 60 mg when used for the same purpose.

Dr. Weitz testified that "there was evidence that [the Debrie and Mardiguian products] were different compositions." For justification, he referred to Dr. Uzan's statement in the First Declaration "that the molecular weight distributions of the claimed product are different from the molecular weight distribution of the prior art product." Dr. Weitz further admitted that his entire testimony was based on this assumption of chemical compositional difference. Therefore, the validity of the testimony of Aventis' sole expert is by his own admission predicated on evidence Dr. Uzan offered to the PE to establish a proposition (compositional difference) that the PE found insufficient to support that proposition.[11]

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[11] Note that the Court is not now considering the question of whether the compositions used in the various studies underlying Example 6 are, in fact, chemically different from each other. Nor is the court concluding whether, as a matter of law before the PTO, Aventis submitted sufficient evidence to establish the same. Rather, the Court makes two observations: (1) because of the chemical nature of LMWHs as heterogeneous mixtures of polysaccharide molecules of varying lengths and weights in defined ratios, the question of compositional difference between two LMWH's is question of law for the PTO--which is to say, the issue is not compositional difference but patentable compositional difference; and (2) whether Dr.

Dr. Weitz's testimony is still relevant, however, insofar as it goes to the reasonableness of Dr. Uzan's comparison for the scientific purpose Dr. Uzan was actually making it. When Teva's counsel clarified her question as directed at the intrinsic pharmacokinetic properties of the claimed formulation, not its relative efficacy in the clinic for a particular purpose at a particular dose, Dr. Weitz hesitated again, then retreated:

> I think if you were trying to show that one product was different in composition from the other, and you want to show whether that difference in composition -- you know, whether -- sorry. If you want to show that a product is different from another, you might -- you might compare them head to head at the same dose.

Even the inventor of the '618 patent, Mr. Debrie, confirmed that a head-to-head comparison is essential when it is the nature and not the uses of a compound being studied.[12]

Accordingly, the Court finds that Dr. Uzan's clinical justification for his different-dose comparison is unreasonable, because Dr. Uzan's experimental design is unconnected to and inconsistent with his true experimental purpose. Aventis cannot disprove sameness broadly with a methodology calculated only to show utility narrowly. Dr. Uzan's comparison cannot show that enoxaparin is compositionally different than Mardiguian at any dose. Nor can it show that enoxaparin, *per se*, as opposed to "enoxaparin-at-40-mg-for-DVT," is superior to Mardiguian, *per se*, as opposed to "Mardiguian-at-60-mg-for-DVT." At best, Dr. Uzan's comparison can

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Weitz was correct to believe that the Debrie and Mardiguian products are compositionally different, or even that they are in fact patentably compositionally different, is irrelevant. Dr. Weitz's testimony is contingent on the PE's acceptance of Debrie and Mardiguian as patentably compositionally different based on Dr. Uzan's First Declaration. This the PE did not do. Thus, Dr. Weitz's testimony on the reasonableness of Dr. Uzan's comparison at different doses can be disregarded.

[12] He testified that "[i]f the tests performed and reported under Subparagraph 3 were not done under the same conditions as those referred to in Paragraph 1, this has no meaning" and "is worthless." Dr. Uzan faults Mr. Debrie for being a chemist who is "not aware about biology," but Mr. Debrie's discipline is immaterial. A professional chemist studying LMWHs certainly knows the importance of holding all parameters constant except the independent variable (the formulation) and the dependant variable (half-life).

illustrate -- and the Court here makes no finding that it does -- that enoxaparin at 40 mg is superior to Mardiguian EP '144 at 60 mg for preventing DVT in high-risk orthopedic surgery. The uncontrolled, confounding variable of dose renders any more expansive conclusions based on Dr. Uzan's comparison meaningless.

(3.) The Adequacy Of Dr. Uzan's Methodology Presuming Dose-Independence: Uncontrolled Variability.

Aventis argues that because the half-lives of the LMWHs are dose-independent -- i.e., as dosage varies, half-life does not vary in a statistically significant way -- it was reasonable for Dr. Uzan to select any dose from the Duchier study, from which he drew the 40 mg half-life data for Example 6. However, any composition-effect remains indistinguishable from a possible dose-effect in this case, because the evidence did not establish dose-independence. Aventis never attempted to convince the PTO or argue to the Court on this point, either for the '618 or the EP '144 products. The Duchier study suggests but does not prove dose-independence because, as Dr. Boons reported, a study including a much larger subject group than twelve could reveal statistically significant differences in the mean half-lives between different doses. The Fouquet study, from which Dr. Uzan drew the EP '144 data for Example 6, tested only 60 mg doses of EP '144. As designed, Fouquet was incapable of showing dose-independence of the EP '144 LMWH. Thus, assuming *arguendo* that the Court finds credible Aventis and Dr. Uzan's contention that Dr. Uzan had no choice but to use 60 mg data for the Mardiguian EP '144 LMWH because the Fouquet study tested only 60 mg doses and that was the only study Dr. Uzan was aware of reporting half-life data for an EP '144 LMWH, it would still not have not have justified Dr. Uzan's belief that the half-life of EP '144 was dose-independent.

This uncertainty rules out a 40 mg to 60 mg comparison; as testified to by Dr. Boons, only a 60 mg to 60 mg comparison could have possibly been reasonable. However, even if the LMWHs do, in fact, have dose-independent half-lives, and even if Dr. Uzan knew this to be true, his dose-ranging comparison was still unreasonable.

(a.) Dose-Independence Of The '618 LMWH. The Duchier study involved measuring the half-life of enoxaparin in 12 individuals at four doses: 20, 40, 60, and 80 mg. In theory, and other things being equal, if the half-life of the '618 enoxaparin was dose-independent, the observed half-lives at each dose should have been virtually identical. Aventis' position is essentially that Dr. Uzan was reasonable in picking the 40 mg dose because dose-independence renders the data from each dose interchangeable. If so, Aventis does not explain how, if 40 mg could be substituted for 60 mg, the half-life improvement over EP '144 was significant at 40 mg but not at 60 mg. The reason is that, in practice, variability between subjects (between the 12 subjects at a given dose) ("inter-subject variability") and variability within each subject (within the four doses tested in every subject) ("intra-subject variability") results in differences in the observed half-life values along Duchier's 20 to 80 mg dose range. Aventis did not give the PE sufficient information to assess the impact of this variability, a fact about which she complained in the Third Office Action, observing that Aventis "state[d] neither the number of volunteers in the first study nor their overall physical condition."[13]

Although the half-lives exhibited by each of Duchier's subjects along the full 20 to 80 mg dose range were insignificantly different in themselves, they were not interchangeable. The

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[13] In his Second Declaration, Dr. Uzan responded by attempting to reduce the influence of inter-subject variability on his comparison. He averaged the half-lives of Duchier's twelve subjects at the 40 mg dose, and, separately, he averaged the half-lives of Fouquet's twelve subjects at the 60 mg dose. It is undisputed, however, that Dr. Uzan, in using only the Duchier 40 mg dose, never accounted for intra-subject variability.

Duchier data revealed a relatively high intra-subject variability. Because the Duchier study used a cross-over model, this cannot easily be explained as a subject effect.[14] Rather, the noise within subjects may have been random or caused by uncontrolled factors of which the Court is unaware: e.g., off- or on-protocol differences in the manner or time of the application of the investigational drug, variations in the site of injection, changing medical personnel giving the injection, or behavior changes in individual subjects from one administration to the next. Although the slope of this noise was effectively flat across individual subjects, suggesting the absence of a dose effect, it was nevertheless large enough to overwhelm a composition effect when the '618 and EP '144 LMWHs were compared. This explains how, notwithstanding dose-independence, the mean of the 40 mg dose of the '618 product compared to the mean of the 60 mg dose of EP '144 could appear statistically significantly different, while the 60 mg dose of the '618 product did not. Put simply, the noise in the Duchier system swallowed the signal in the Duchier-Mardiguian comparison. Accordingly, even were the half-life of the Debrie enoxaparin dose-independent, Dr. Uzan's different-dose comparison was still incapable of distinguishing between differences in the plasma half-life of the Debrie and Mardiguian products caused by differences in their chemical compositions, as opposed to uncontrolled intra-subject variability.

The experts offered by Amphastar, Teva, and Aventis each advocated different methods by which this intra-subject variability might have been controlled.[15] The Court finds that the

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[14] This is because intra-subject variability is a function of geno- and phenotypic differences between individuals. Different people respond differently to the same drug; however, without knowing more, the same individuals would not be expected to respond differently to different administrations of the same drug over a short period of time.

[15] Dr. Buller favored incorporating all the data points from each of Duchier's twelve subjects at each of the four experiment doses: 20, 40, 60, and 80 mg. Where half-life is independent of dose, the real obstacle to controlling this variability is simply insufficient numbers of observations; thus, Dr. Buller would have used as many observations as were available. Neither Dr. Weitz nor Dr. Boons, by contrast, believe it is necessary or appropriate to consider all the data points; however, if this was to be done, each

methods of Drs. Buller and Boons target and, theoretically, ought to arrive at approximately the same result. Dr. Weitz's method should control intra-subject variance somewhat less well. But, whether Drs. Buller, Boons, or Weitz is ultimately correct is not dispositive, because the problem of intra-subject variability affects experimental efforts to determine the plasma anti-X_a activity and half-life curves of the Mardiguian LMWH just as it does the Debrie enoxaparin.

(b.) Dose-Independence Of The EP '144 LMWH. Even if the EP '144 LMWH was also dose-independent and Dr. Uzan had, in fact, controlled for intra-subject variability in the Duchier data, the reasonableness of Dr. Uzan's methodology does not markedly improve. In Duchier, intra-subject variability was observed across four administrations. In Fouquet, it was unexpressed, because there was only a single administration of EP '144 per subject, but it was no less inherent in Fouquet than Duchier. Had Fouquet made multiple observations of EP '144 in every subject, even at the same dose, the same randomness or hidden confounds creating noise in the Duchier data may well have produced variable half-life values across observations within Fouquet's subjects. At that point, any of the methods proposed by the experts in this case could have been used to control this variability and increase confidence that any statistically significant differences in half-life observed when the '618 and EP '144 products were compared were signal, not noise, and could therefore be offered as valid indirect evidence of compositional difference between the LMWH products. Fouquet did not make multiple observations, however, and given the specter of unknown, unexpressed, and uncontrolled noise in the Fouquet data that the

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disagreed with Dr. Buller and favored an alternative method for doing so. Dr. Weitz would determine the mean half-life for each subject by averaging the half-life values observed along the full dose range and then taking the mean of those means. Dr. Boons, on the other hand, would weight the means of each subject's observed half-life along the dose range according to the standard deviations of those means, which attempts to account for the variability within each subject.

Duchier data raises, Dr. Uzan's total reliance on the Fouquet study would still have prevented the PE from separating signal from noise.

Thus, under the most favorable assumptions for Aventis possible, it may well have been scientifically impossible for Aventis to clearly and convincingly demonstrate compositional difference. To be certain, controlling intra-subject variability in the Duchier data might have been Aventis' best option for convincing the PTO of non-inherency. The PE may even have deemed this sufficient, notwithstanding the lingering worry about Fouquet. But there is still no dispute: both studies suffer from intra-subject variability, and Dr. Uzan compared them without even attempting to control the noise in the Duchier data, rendering his analysis all the more unreasonable.

(B.) The Credibility Of Dr. Uzan's Clinical-Relevance Justification.

Aventis does not dispute that there is no statistically significant difference between the two compounds' half-lives at the same dose (60 mg). Nor does it contest that there was no statistical difference between Debrie at 20 mg and 80 mg versus EP '144 at 60 mg. Only the 40 mg dose showed a statistically significant difference over EP '144. This gives rise to the natural inference that Aventis sought to achieve by hindsight the appearance of a statistically significant difference where none actually existed; that Aventis and Dr. Uzan engaged in a post-hoc analysis of the Duchier data, "cherry-picked" the one dose permitting a favorable comparison to Mardiguian, and developed in retrospect an analytical framework within which the use of this dose could be rationalized. Even if the Court is mistaken and a comparison at dissimilar doses is in some way scientifically capable of addressing inherency, the reasonableness of Dr. Uzan's comparison also depends on the credibility of his clinical-relevance justification. If it is credible,

Dr. Uzan's use of the only dose showing a difference in half-life is reasonable under the clinical relevance model only if 40 mg was the only clinically relevant dose. The evidence does not establish that it was.

First, clinical efficacy was rarely, if ever, the endpoint of Dr. Uzan's work. Dr. Uzan was not a practicing medical doctor regularly engaged in clinical research with human subjects. He testified to being a "pharmacologist and a biologist" primarily engaged in preclinical animal studies using rabbits and "*in vitro* test[s]."

Second, the '618 patent was not limited to the safe and effective doses for particular therapeutic indications. Claim 1 claims a chemical composition broadly. The '618 patent represents that beneficial properties, including a "sufficiently long plasma half-life, a fairly high absorption rate, a high bioavailability or, alternatively, a low clearance," inhere in the claimed composition *per se*, not according to clinical usage. It also represents that "the mixtures thereby obtained have a favorable ratio of the fractions of high to those of low molecular weights, which endows them with the requisite antithrombotic properties with but slight risk of hemorrhagic effect." Yet, Dr. Uzan's clinical rationale for the use of the 40 mg dose relies on unsafe and "excessive bleeding" caused by the 60 mg dose. Further, the title of the patent itself covers both treatment and prevention: "Mixtures of Particular LMW Heparinic Polysaccharides for the Prophylaxis/Treatment of Acute Thrombotic Events." Nowhere does the patent disclose that the claimed compound is unsafe or not useful at certain doses or for any of its claimed (or possible) indications.

Aventis maintains that it is irrelevant to Dr. Uzan's intent that the '618 patent covers all doses and indications other than the prevention of DVT in high-risk surgery, arguing that Dr. Uzan need not have been concerned with indications approved after he prepared Example 6

because his subsequent declarations merely "fleshed out that original comparison." This ignores the broad coverage of the '618 patent, fails to recognize that future approvals for additional indications were eminently foreseeable, and ignores the fact that Dr. Uzan's duty of disclosure extended not only through the filing of his First and Second Declarations, but throughout the '618 patent's entire prosecution history. *See Fox Indus., Inc. v. Structural Preservation Sys., Inc.*, 922 F.2d 801, 803 (Fed. Cir. 1990); *Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 34 F. Supp. 2d 1208, 1211 n.1 (C.D. Cal. 1998).

Aventis also contends that Dr. Uzan's focus on the "single breakthrough use of [its] new product" legitimately supported patentability, citing *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987), for the proposition that "[t]o be patentable, a compound need not excel over prior art compounds in all common properties." *Chupp* is inapposite. *Chupp* involved a claimed compound that exhibited superior herbicidal activity on only some of the crops with which it could be used. The Federal Circuit held that evidence of this unexpectedly but selectively superior performance was sufficient to rebut a *prima facie* case of obviousness. In this case, anticipation/inherency are at issue as much or more than obviousness. More substantively, although Dr. Weitz testified that the "big advance" enoxaparin "provided was in the high-risk patients, the patients undergoing orthopedic surgery," he described this as "a big advance over unfractionated heparin." Yet, whether the '618 patent was a breakthrough over the EP '144 prior art was the question before the PE. Under *Chupp*, Aventis could secure a patent on a LMWH even if that LMWH was only superior to the prior art in certain properties at certain doses for certain indications. But Aventis' reliance on *Chupp* begs the question of whether the '618 LMWH is, in fact, superior to the EP '144 LMWH prior art in any property at any dose for any

indication -- and is sufficiently so to prove both compositional difference and nonobviousness. The evidence suggests that only a same-dose comparison could have answered that question.

Because the '618 LMWH was not a breakthrough in preventing DVT in high-risk patients undergoing orthopedic surgery as compared to the prior art LMWHs that were blocking patentability, Dr. Uzan's exclusive focus on this indication is that much harder to explain and impossible to justify. Dr. Uzan's entire clinical-relevance rationale begins to collapse with evidence that there were a variety of preferred therapeutic doses at the time, depending on the indication. The record reflects, for example: (1) that a 20 mg dose was approved in France in 1987 for prophylaxis in general surgical patients; (2) that a twice-daily 30 mg dose for prophylaxis in high-risk surgical patients was commonly known to be under investigation in North America in the early 1990s, and it secured formal approval in 1993; (3) that a treatment dose of 1 mg/kg -- or 80 mg/175 lbs -- was approved in France in 1991[16]; and (4) that a 20 mg dose had been approved in 1987 in France for the prevention of DVT in general and orthopedic surgery. It is implausible that an animal biologist attempting to prove compositional difference focused on the clinical dose for an indication nowhere mentioned prior to trial to support a patent broader than this indication because the claimed invention was a breakthrough over a drug not blocking patentability.

Finally, Aventis offered no corroborating evidence of Dr. Uzan's clinical-relevance justification whatsoever. Neither the '315 application nor any document submitted to the PTO during the prosecution of the '618 patent anywhere refers to the concepts of "preferred therapeutic dose," "clinically relevant dose," or prophylaxis of DVT in high-risk orthopedic

[16] There can be no question that Dr. Uzan knew, at least, of the 1 mg/kg treatment dose; he himself authored the toxicology and pharmacology reports in 1990 supporting its approval.

surgery. Aventis also did not offer the testimony of a single percipient witness to verify Dr. Uzan's account.[17] The Court cannot escape the conclusion that Dr. Uzan's clinical-relevance justification for the Debrie 40 mg dose may find no corroboration because it cannot be corroborated, and Dr. Uzan's reliance on it may not have predated the present litigation.

(C.) The Implausibility Of Inadvertence.

Amphastar and Teva having established a *prima facie* case of intent, it fell to Aventis to come forward with facts supporting a plausible explanation or excuse justifying Aventis and Dr. Uzan's highly material omissions. The Federal Circuit tied the reasonableness of Dr. Uzan's comparison to Dr. Uzan's excuse of inadvertence. It held evidence of the former would be probative of the latter. This is why trial testimony dealt so extensively with the science behind Dr. Uzan's analysis: because even "gross negligence is not, in and of itself, sufficient to satisfy the intent element of inequitable conduct." *Ulead Sys.*, 351 F.3d at 1148. Because Dr. Uzan's testimony cannot explain his comparison as reasonable, the Court can now only look to Dr. Uzan's naked assertion that his failure to disclose the Mardiguian dose was inadvertent. He claims that the Mardiguian dose "did not come in [his] mind," that its omission was "pure

[17] The record establishes that patent agents, Michelle Morvan and Phillipe Becker, and their supervisor in the Aventis Patent Department, Jacques Savina, were involved in the '618 prosecution. Ms. Morvan was the Aventis Patent Department's heparin expert and the patent agent then in charge of heparin-based products. Mr. Becker drafted the French application which formed the basis for the '618 patent, and the evidence suggests he may have been the true author of Dr. Uzan's First Declaration. Ms. Morvan and Mr. Becker were both involved to differing degrees in documenting Mr. Debrie's alleged invention, drafting the '315 application, and prosecuting the '618 patent. Similarly, Mr. Savina was the head of the patent department with direct supervisory responsibility for the enoxaparin file. Each testified during their depositions that they failed to recall a single relevant detail concerning the prosecution history: not about Example 6; not about the doses used in the Fouquet study; not about the First or Second Declaration; and not about the half-life comparisons stressed to the PE.

inadvertence," and Aventis argues that inadvertence amounts to gross negligence, which cannot justify an inference of intent under *Kingsdown*. *See* 863 F.2d at 876.

However, a bare declaration of gross negligence cannot evidence a lack of intent to mislead. *Paragon*, 984 F.2d at 1191; *Univ. of W. Va. v. Vanvoorhies*, 278 F.3d 1288, 1299 (Fed. Cir. 2002). Dr. Uzan has done little more than make a conclusory denial in a pleading. Certainly, if Dr. Uzan's failures of disclosure were unintentional, they could be nothing else but grossly negligent. But for the Court to find that Dr. Uzan's omissions were based on gross negligence, it must be plausible under the facts and circumstances of this case that Dr. Uzan could, in fact, have been grossly negligent. It is not -- entirely the opposite.

(1.) The Impressive Qualifications Of Dr. Uzan.

Aventis contends that Dr. Uzan is a world-class scientific mind whose reputation is wholly inconsistent with deceptive intent. The Court agrees that he is a world-class scientist but finds this fact irrelevant to his intent. Dr. Uzan's reputation is wholly inconsistent, not with deceptive intent, but with negligence -- especially negligence of the magnitude that would have had to have been committed here. The evidence shows that Dr. Uzan received training in numerous scientific fields, including but not limited to biological chemistry, coprology, parasitology, serology, hematology, microbiology, physiology, and Human Biological Research. The evidence reflects his current membership in numerous professional organizations, including but not limited to the French Society of Therapeutic and Clinical Pharmacology, France's National Academy of Pharmacy and Society of Biological Chemistry, the International Society of Biochemical Pharmacology, the American Society for Neurosciences, the European Neuroscience Association, the British Pharmacological Society, and The New York Academy of Sciences. Dr. Uzan is also a former member of France's National Center for Scientific Research

Commission No. 25. In his nearly fifty-year history with Aventis, Dr. Uzan has published, by his count, over 350 scientific articles, received frequent appointments as an expert, including by the Paris Court of Appeals, and held at least four separate CEO or Director-level posts in the company. In 1983, he received the International Prix Galien, an internationally recognized award within the pharmaceutical industry recognizing innovation in drug discovery. In addition, Dr. Uzan testified to having been recently elevated to the grade of Légion d'honneur, or Knight of the Honor Legion, by France's President, Jacques Chirac. Dr. Uzan explained that admittance is the highest honor in France, one conferred for outstanding achievements that improve the image of France domestically or abroad.

(2.) What Dr. Uzan Knew, Must Have Known, And Should Have Known.

Unsupported by more, it simply is not credible that a scientist of Dr. Uzan's caliber and distinction could have committed -- and then repeatedly failed to correct over such a long period of time -- errors as egregious as those in the '618 prosecution. The prosecution history of the '618 patent unambiguously reflects that evidence of a difference in properties sufficient to prove compositional difference and overcome the PE's inherency objections (and, necessarily, her obviousness objections, as well) was Dr. Uzan's goal. It is inconceivable that this fact was unclear to Dr. Uzan. The language of his First Declaration involves multiple assertions of compositional difference, and in it, Dr. Uzan declares his familiarity with the Second Office Action, which expressly rejected the '618 LMWH as anticipated by Mardiguian, stating that Aventis had not shown "any patentable distinction" between the two, and that the '618 product's claimed properties were "inherent since the prior art compounds [were] considered the same." The Second Declaration's abrupt shift in tone away from the language of difference supports the inference that Dr. Uzan was kept aware of the PTO's evolving objections throughout the

prosecution. It also demonstrates that Dr. Uzan knew the problem of insufficient proof of statistical significance was among those objections. Moreover, cases from *Ferring* to *Critikon* to *Brasseler* acknowledge that the Court may consider what he who failed to supply highly material information should have known about the information's materiality.[18] Even a deeply conservative account of what Dr. Uzan should have known must include knowledge of the PE's central objection to patentability. After all, Aventis can scarcely disagree that Dr. Uzan ought to have been aware of the nature of the questions he was called on to answer before the PTO.

Yet, Dr. Uzan still compared the half-lives of the '618 and EP '144 LMWH's at different doses. At trial, he admitted to doing this knowingly. (*See* 12/4 Tr. 85:8-86:19; 143:8-11.) Because Dr. Uzan must (and should) have known what experimental question he was answering, and because Dr. Uzan clearly did know what experimental design he was using to do so, it is inconceivable that a scientist of Dr. Uzan's abilities could have simply overlooked the fundamental scientific mismatch between what his comparison was required to show, to satisfy the PTO, and what it could show, scientifically. Dr. Uzan had no way of knowing if the EP '144 LMWH possessed a dose-independent half-life. His asserted subjective belief that the '618 product was so possessed was based on too few observations to be reliable. If either or both LMWHs do not, Dr. Uzan's comparison of half-lives at different doses is logically and statistically incapable of proving compositional difference. What is more, since it cannot distinguish a composition-effect from a dose-effect, his comparison is incapable of proving

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[18] Contrary to Aventis' arguments, it is well-established that proof of actual knowledge is not always necessarily required. *See Ferring*, 437 F.3d at 1191 (holding summary judgment on intent is appropriate where, among other things, "the applicant knew or should have known of the materiality of the information" not disclosed); *Brasseler, U.S.A. I, L.P. v. Stryker Sales Corp.*, 267 F.3d 1370, 1376 (Fed. Cir. 2001) ("intent may be inferred where a patent applicant knew, or should have known, that withheld information could be material to the PTO's consideration of the patent application"); *Critikon*, 120 F.3d at 1256-57 (holding that a patentee's failure to appreciate the legal significance of the facts that it failed to disclose did not absolve it of its duty to disclose).

anything at all about the relative half-lives of the '618 and EP '144 LMWHs, *per se*, despite the claim of the '618 patent to enoxaparin, *per se*. Even if the EP '144 and '618 LMWHs do, in fact, have dose-independent half-lives, Dr. Uzan's experimental design is no less handicapped, as it fails to control for high, random intra-subject variability in the Duchier data, and it ignores the risk of uncontrollable intra-subject variability lying dormant in the Fouquet data.

Notwithstanding such weaknesses, Dr. Uzan represented in his declarations to the PTO, in essence, that the claimed LMWH exhibited, at any dose, a statistically significant increase in half-life over the Mardiguian LMWH, at any dose. He further represented that this would enable the use of lower doses in the clinic compared to Mardiguian, and that it proved the Mardiguian LMWH was different from the '618 LMWH. Put simply, Dr. Uzan knowingly gave the PE a narrow answer to her broad question, and then represented that in so doing he had answered her question broadly. It strains credulity to suggest that a scientist of Dr. Uzan's skills and experience could have relied on logic so flawed purely by accident. That a figure such as Dr. Uzan also could have inadvertently failed to notice his error and taken steps to cure it over five years of involvement in the '618 prosecution is difficult for the Court to accept.

(3.) The Absence Of Clues To Negligence.

Had it truly been inadvertence causing Dr. Uzan's unreasonable comparison and related misstatements, the Court would expect to see clues to his negligence throughout the prosecution. Yet, virtually no red flags appear in the relevant history.[19] At no time did Aventis or Dr. Uzan

[19] Aventis argues that the submission of the Duchier study's 60 mg dosage information for the Debrie formulation was such a flag to the PE. This argument is of no moment. While the inclusion of Duchier data for two doses in subparagraph (1) might have spurred the PE to ask what dose was used in sub-paragraphs (2) and (3), Aventis' led the PE away from any inclination to do so by stating that both the 60 mg and the 40 mg dose in subparagraph (1) involved 75% of subjects exhibiting half-lives above four hours, thereby conveying the erroneous impression of practical equivalence between the 60 mg and 40 mg Duchier doses and irrelevance of dose to the comparison to EP '144. Moreover, as the Federal Circuit

disclose any fact to the PTO even reflecting that a 60 mg dose of the Mardiguian EP '144 LMWH was compared, or that a dose-ranging comparison had been made. Aventis' own expert testified that this was a scientifically unreasonable omission. His view is confirmed by every publication Aventis invites the Court to consider for the industry practice; each one fully discloses what doses are under investigation. Indeed, the Court would be most surprised if a single article among Dr. Uzan's three-hundred-plus publications survived peer review without extensive description of its experimental protocol and analytical methods, in addition to the inclusion of the basic summary statistics omitted from the First Declaration.

Aventis and Dr. Uzan also failed to disclose or represent to the PTO: (1) that the single-dose Fouquet study was the sole source of available data on the EP '144 LMWH; (2) that a dose-ranging analysis was used; (3) that Dr. Uzan's exclusive analytical focus was on the prevention of DVT in high-risk patients undergoing orthopedic surgery; (4) that Dr. Uzan selected his experimental dose of the '618 LMWH because it was the "preferred therapeutic dose" or the "clinically relevant dose" for that indication; (5) that the half-lives of the Debrie and Mardiguian products were believed to be dose-independent; or (6) that Example 6 was a not a well-controlled prospective trial, but a meta-analysis comparing data from three different studies performed for three different purposes at three different times, each more than four years before the filing of the patent application. Had Aventis or Dr. Uzan disclosed even one of these facts, it may well have ignited the PE's suspicion, increasing the probability that Dr. Uzan's flawed, dose-ranging study design would have been exposed. Had they all been stated, Dr. Uzan's gross negligence excuse could be viewed more credibly. Where, as here, none surfaced anywhere in the application,

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reasoned, the inclusion of this data might militate toward a finding of intent because it shows Dr. Uzan was aware of the importance of the 60 mg dose.

declarations, or written arguments, inadvertence is simply implausible. Consistently omitting so many references involves the application of diligence, not the commission of negligence.

In summary, the purpose of trying the issue of Dr. Uzan's intent was to afford Aventis the opportunity to substantiate factually the reasonableness of any excuse that Aventis claims for Dr. Uzan's material omissions. The state of the record in this regard is much improved over summary judgment. First, Defendants have clearly and convincingly established that Dr. Uzan's comparison at dissimilar doses was scientifically unreasonable. It could not prove anything the PE wanted to know. Second, Dr. Uzan's clinical-relevance justification did not withstand scrutiny. Dr. Uzan tested a clinically relevant dose for an important indication; however, 40 mg was not enoxaparin's only clinically relevant dose; the prevention of DVT was not its only important indication; and, in any event, the patent's reach was never limited by dose or indication. Third, other things being equal, the errors of omission in the '618 prosecution were errors that a "Dr. Uzan" simply would not have made. They were too egregious, too obvious, and too consistently committed over too long a period of time. The Court may not presume for Aventis' benefit that Dr. Uzan committed uncharacteristic errors of omission that concealed, purely coincidentally, experimental design mistakes that Dr. Uzan's training, skills, and experience strongly suggest he could have never accidentally made, but which were essential for him to make if Aventis was to overcome the PTO's objections to patentability.

VI. THE FACTS AND CIRCUMSTANCES SURROUNDING AVENTIS AND DR. UZAN'S FAILURE TO DISCLOSE MATERIAL INFORMATION

A *prima facie* case of deceptive intent has already been made. A strong inference that Dr. Uzan intended to deceive is reasonable. This is law of the case established by two prior courts. Having rejected Dr. Uzan's excuses, the Court need not revisit it a third time.

Nevertheless, because affirmatively proving intent is a burden that must lie with Amphastar and Teva at all times, the Court now separately finds that clear and convincing evidence adduced at trial independently reestablishes -- and substantially strengthens -- those earlier inferences of intent.

(A.) Clear And Convincing Evidence of Intent To Deceive.

(1.) The Elements Of Intent: Knowledge, Knowledge of Materiality, and No Credible Excuse.

A finding of deceptive intent is legitimate under the Federal Circuit's recent opinion in *Ferring*, 437 F.3d at 1191, because Defendants presented clear and convincing evidence that "there has been a failure to supply highly material information and [] the record establishes that (1) the applicant knew of the information; (2) the applicant knew or should have known of the materiality of the information; and (3) the applicant has not provided a credible explanation for the withholding." *See also Bruno Indep. Living*, 394 F.3d at 1354; *Critikon, Inc.*, 120 F.3d at 1257. The elements of nondisclosure and high materiality have been admitted, and no credible excuse demonstrated. Regarding knowledge, there is no debate that Dr. Uzan knew the doses used in the Duchier and Fouquet studies, and at trial, Dr. Uzan admitted to knowing that he was comparing the half-lives of the '618 and EP '144 LMWHs at different doses. Regarding knowledge of materiality, it was obvious that a reasonable PE would have considered dosage important. Depending on the dose tested, compositional difference was either possible to prove, or it was not; the difference in half-life either appeared significant, or it did not. Dosage was the fulcrum on which Aventis' entire case for patentability turned.

(2.) Dr. Uzan's Explanation: A Total Absence Of Indicia Of Credibility.

Here, the Court does not rely only on formal, mechanistic criteria to infer intent. Rather, the Court will step back and examine the overall credibility of Dr. Uzan's story on Dr. Uzan's terms -- asking: Is it complete? Is it consistent? Is it corroborated? Is it plausible? Is it explanatory? The Court's finding of deceptive intent is entailed by the negative answers it is forced to give for each question on the facts presented. Dr. Uzan's explanation suffers from a total absence of indicia of credibility. Where excusing a knowing nondisclosure of material information depends on believing a justificatory explanation that is coherent only if a sequence of statements are each true, and the evidence does not justify belief in the truth of any of those statements, then belief in the truth of the explanation cannot be justified. The Court is presented with just such a case. Believing Dr. Uzan's explanation requires the Court to accept, at a minimum, that Dr. Uzan was concerned with clinical relevance; that he was focused on DVT; that 40 mg was the therapeutically preferred dose; that Fouquet was the only known source of EP '144 data[20]; that the half-lives of the '618 and EP '144 LMWHs were dose-independent; that Dr. Uzan did not know, nor should he have known, that the PE's primary argument against patentability was based on inherency; that he subjectively believed the '618 and EP '144 LMWHs to be compositionally distinct; that it was mere coincidence that Dr. Uzan's methodology specifically called for the only dose of the '618 LMWH reflecting a statistically significant difference in half-life; that Dr. Uzan's omission of the EP '144 dosage information in Example 6 was inadvertent; that his omission of the EP '144 dosage information in Table III of the Second Declaration was inadvertent; and that the total absence, prior to litigation, of any reference to the

[20] This is improbable considering that enoxaparin as claimed and disclosed by the EP '144 patent had been widely prescribed in Europe prior to the '618 prosecution and studied in human volunteers as early as 1983. It was also disclosed in the 1989 Annual Report that clinical trials were ongoing in the United States.

DVT indication, to any scarcity of sources of EP '144 data, or to the concepts of clinical relevance of dose, therapeutically preferred dose, or dose-independence of half-life was also coincidence. That not one of these propositions is credible individually renders Dr. Uzan's explanation not credible globally.

(B.) Conclusion.

Negligence played no role in Aventis and Dr. Uzan's failure to disclose the EP '144 dose information. This is evident from the magnitude of the coincidence necessary to explain, as purely accidental, the convergence of Dr. Uzan's mistakenly narrow focus on clinical relevance; with his mistakenly narrow focus on DVT in high-risk orthopedics; with the memory loss of the Aventis Patent Department regarding both; with the incorporation of the only dataset supportive of patentability, into a flawed experimental design calculated to answer a question not asked; with the repeated omission over time, by both Aventis and Dr. Uzan separately, of precisely those bits of information capable, if disclosed, of arousing the PE's suspicions as to the negligence; with the consequent issuance of an urgently needed patent on a commercially valuable drug which has been argued, though not yet proven, to be chemically indistinct from unpatentable prior art.

This is a case involving a statistical analysis designed post-hoc and rationalized in hindsight to fit a hoped-for result. Legally and practically, Dr. Uzan stands before the Court in the same position as he would if no evidence of subjective good faith had been offered. Therefore, based on the totality of the facts and circumstances surrounding Dr. Uzan's repeated omissions, the Court hereby finds the Defendants have shown by clear and convincing evidence that Dr. Uzan intended to deceive the PTO.

VII. DISPOSITION

At this point, the Court must determine "whether the material misrepresentations or omissions in question are sufficiently serious in the light of the evidence of intent to deceive, to warrant the severe sanction of holding the patent unenforceable." *Hoffmann-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1372 (Fed. Cir. 2003). Balanced against the Federal Circuit's recognition of high materiality, the requisite showing of intent is proportionally less. *See Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1234 (Fed. Cir. 2003). The Court need not be detained by intricate questions of weight. But for Dr. Uzan's intentional omissions, the probability is high that the '618 patent would not have issued. The '618 patent must therefore be found to be unenforceable on the ground of inequitable conduct.

ACCORDINGLY, IT IS ORDERED:

(1.) United States Patent No. 5,389,618, and its replacement, United States Reissue Patent No. 38,743, are unenforceable by virtue of inequitable conduct before the U.S. PTO.

(2.) Defendant Amphastar Pharmaceuticals, Inc.'s MOTION TO STRIKE IMPROPER EXPERT OPINION TESTIMONY BY ANDRE UZAN is DENIED.

DATED: February 8, 2007

Mariana R. Pfaelzer

Hon. Mariana R. Pfaelzer
United States District Judge