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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ALLERGAN, INC., and ALLERGAN SALES, LLC., Plaintiffs, v. ALCON INC., ALCON LABORATORIES, INC., and ALCON RESEARCH, LTD., Defendants.	**Civil Action No: 04-968-GMS** **CONFIDENTIAL** **FILED UNDER SEAL**

DEFENDANTS ALCON INC., ALCON LABORATORIES, INC., AND ALCON RESEARCH, LTD.'S REPLY MEMORANDA OF LAW IN FURTHER SUPPORT OF MOTIONS *IN LIMINE*

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I. MEMORANDUM IN FURTHER SUPPORT OF MOTION *IN LIMINE* TO PRECLUDE PLAINTIFFS FROM PRESENTING EVIDENCE OF ALLEGED SUPERIORITY OR COPYING[1]

Alcon respectfully submits this reply memorandum of law in further support of its motion *in limine* to preclude Plaintiffs from presenting evidence or argument for non-obviousness based upon either of the following propositions: (1) that Allergan's 0.15% brimonidine product (Alphagan®P) is commercially successful based on patented features not present in Allergan's 0.2% brimonidine product (Alphagan®), or generic versions thereof; and (2) that Alcon "copied" Allergan's formula for Alphagan P in formulating its proposed 0.15% brimonidine product.

This is not a matter of "weighing" the evidence, as Allergan suggests, because evidence of commercial success or copying is simply not relevant here and therefore is inadmissible. See Fed. R. Evid. 401. Any alleged commercial success of Alphagan P would not permit an inference as to non-obviousness, given that Allergan chose as a marketing strategy to withdraw Alphagan from the market after switching patients over to Alphagan P – preventing competition between Alphagan P and generic 0.2% generic brimonidine products, which cannot be substituted for Alphagan P at the pharmacy level (the essential predicate for generic competition) . Additionally, because this is a Hatch-Waxman case, any alleged "copying" by Alcon would reflect merely Alcon's conduct consistent with the statutory and regulatory framework for bringing generic drugs to market, rather than any inherent novelty in Alphagan P.

FACTS

The FDA approved Allergan's 0.2% brimonidine product, Alphagan, on September 6, 1996, granting Allergan five years of market exclusivity for that product. Before the period of market

[1] Defined terms used herein have the meanings set forth in Alcon's opening memoranda of law in support of its motions *in limine*, except as otherwise indicated.

exclusivity on Alphagan expired, the FDA approved Allergan's 0.15% Alphagan P product (on March 16, 2001) and granted three years and six months of market exclusivity for that product – which represents Congress's judgment as to the appropriate period of exclusivity to reward the company that conducts safety and efficacy trials in bringing an NDA product to market. In 2002, as part of a marketing strategy to maintain the "Alphagan franchise," Allergan adopted a program to switch patients over to Alphagan P, in connection with its announced intention to withdraw Alphagan 0.2% from the market.[2]

The Hatch-Waxman Act provides a mechanism to permit a generic drug manufacturer -- after a branded drug manufacturer's period of market exclusivity has expired -- to substitute bioequivalence data for the extensive and costly safety and efficacy studies that must accompany a full new drug application ("NDA"). In April 2004, Alcon submitted to the FDA an abbreviated "paper NDA" under that Act, applying for approval of its own proposed 0.15% brimonidine product as a modified, bioequivalent, version of Allergan's Alphagan product.[3] Shortly thereafter, Allergan commenced this suit.

ARGUMENT

As set forth in Alcon's opening brief, the mere presence of an alleged secondary consideration of obviousness does not mean it is in fact relevant to obviousness. For example, commercial success is relevant to obviousness "only if there is proof that the sales were a direct result

[2] Allergan stopped selling Alphagan. Allergan also filed a citizen petition with the FDA asking it to deny approval of any new application for a 0.2% brimonidine product, because, Allergan alleged, its new 0.15% Alphagan P product was safer and more effective. The FDA denied Allergan's petition and, in doing so, noted that the fact that physicians were prescribing Alfaghan P did not demonstrate its superiority over Alphagan, because physicians overwhelmingly preferred Alphagan before its withdrawal from the market. Opening Br. Ex. 1 at 10.

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of unique characteristics of the claimed invention – as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." In re Huang, 100 F.3d 135, 140 (Fed. Cir. 1996). The authorities Allergan cites for the general proposition that secondary considerations of non-obviousness should be considered do not alter the black letter rule that they should not be considered if not relevant. See Huang, supra.

It is not possible for Allergan to prove that sales of Alphagan P directly resulted from patented or otherwise unique characteristics of that product, given that Allergan removed Alphagan from the market and substituted its new product, as to which the 0.2% products are not generic equivalents. Alphagan P inherited a customer base from its discontinued predecessor product. Yamanouchi Pharmaceutical Co. v. Danbury, 21 F. Supp. 2d 366, 385 (S.D.N.Y. 1998), where the court found that failed generic competition supported a finding of superiority, is distinguishable, because there the product covered by the patent-in-suit faced significant generic competition.

Second, in a Hatch-Waxman case such as this, "copying" is not relevant to obviousness, because such "copying" is motivated (as Congress intended) by a generic manufacturer's desire to avoid the expense of new safety and efficacy studies, rather than by any inherent contribution of the copied product to the art. Allergan was entitled to benefit from conducting the initial safety and efficacy trials, and it has received a period of exclusivity longer than Congress chose. It is not entitled to further benefit by using Alcon's permitted use of bioequivalency to prove patent infringement.

II. MEMORANDUM IN FURTHER SUPPORT OF MOTION *IN LIMINE* TO PRECLUDE DR. WILSON FROM OFFERING OPINION TESTIMONY REGARDING THE STATISTICAL ANALYSIS OF HIS STUDENT'S SOLUBILITY MEASUREMENTS

Alcon respectfully submits this reply memorandum in further support of its motion *in limine* to preclude Dr. Wilson from offering opinions regarding the statistical analysis of his student's solubility measurements. Alcon has moved to preclude such testimony on the ground that Dr. Wilson did not perform the analysis and freely admitted at his deposition that he is not qualified as an expert in statistics, biostatistics, or statistical methods. Opening Br. Ex. 2, Wilson Dep. 48:19-25.

Allergan opposes the motion by recasting the issue as one of "reliability," rather than qualification, and arguing that reliability is a fact-intensive inquiry that should be resolved at trial. Allergan then further asserts that the ANOVA method is reliable because it was purportedly used in certain in-house testing at Alcon.

The point of the instant motion, however, is not to obtain a ruling at this stage on the reliability of any particular statistical method. The point is that Dr. Wilson is not qualified to opine as to the validity, reliability, or appropriateness of any such method.[4]

Allergan's discussion of Alcon's in-house testing simply raises a red herring. Not only were Alcon's tests of a different type than those of Dr. Wilson, and amenable to a different type of analysis, but Alcon's tests have nothing whatsoever to do with the qualifications of Dr. Wilson – the only issue raised by this motion.

FACTS

In order to show that Alcon's proposed brimonidine product infringes the '337 patent, Allergan must demonstrate, among other things, that REDACTED Alcon's composition increases

[4] In its opening brief, Alcon additionally raised Allergan's failure to produce certain documents as a basis for this motion. As Allergan has since produced those documents, the only issue remaining is Dr. Wilson's qualification to offer the anticipated statistics testimony.

the solubility of the brimonidine in that composition relative to its solubility in a similar composition REDACTED Allergan retained Dr. Wilson to do certain testing, although – as Dr. Wilson concedes – he has no expertise in solubility studies. Dr. Wilson in turn enlisted his student, Hardik Shah, to make "equilibrium solubility" measurements, and Mr. Shah analyzed his results using a statistical method called "two-way ANOVA." Dr. Wilson opines on the basis of the "two-way ANOVA" analysis REDACTED solubility of the brimonidine in Alcon's proposed product.

Mr. Espino, an Alcon scientist, had previously done some in-house experiments to examine the behavior of Alcon's product with and without the viscosity enhancer, REDACTED Espino's tests were not designed to measure "equilibrium solubility," whereas Mr. Shah's tests were designed to make that measurement. Mr. Espino used a different laboratory methodology for his experiments than did Mr. Shah, and generated a different type of data from Mr. Shah. Unlike Mr. Shah's measurements, Mr. Espino's results were neither readily amenable to curve-fitting and regression analysis, nor properly analyzed in that manner. A statistician then analyzed Mr. Espino's results using "one-way ANOVA" and t-testing – not the "two-way ANOVA" analysis that Mr. Shah used.

One of Alcon's expert witnesses, Dr. Amidon, who taught statistical methods at the University of Wisconsin for approximately ten years, reviewed the "two-way ANOVA" analysis reported by Dr. Wilson and concluded that it is not a standard or reliable method for analyzing the particular type of measurements made by Mr. Shah.

ARGUMENT

Federal Rule of Evidence 702 provides for a witness qualified as an expert to offer opinion testimony where it would assist the trier of fact. See Fed. R. Evid. 702. The proponent of an

expert witness must establish the witness's qualification as an expert by a preponderance of the evidence. See Daubert v. Merrell Dow Pharms., 509 U.S. 579, 592 n.10 (1993). In this case, Dr. Wilson has expressly disclaimed any expertise in statistics (see Opening Br. at 9) and therefore should not be permitted to offer opinions as to the appropriate statistical methodology for analyzing Mr. Shah's data.

In its opposition brief, Allergan concedes that Dr. Wilson is not an expert in statistics; asserts that Dr. Wilson is being offered only as an expert in pharmaceutical formulations; and notes that he has often used statistics in his work as a formulator. Allergan Opp. Br. at 9. Allergan, however, is offering Dr. Wilson not to testify as a formulator about the desirability of any particular formulation, but instead to testify concerning the alleged effects of REDACTED product based on the statistical analysis of Mr. Shah's data. Having no expertise in that area, Dr. Wilson should be precluded from offering testimony specifically concerning the validity, reliability, or appropriateness of particular forms of statistical analysis – including any testimony as to the relative merits of "two-way ANOVA" and "regression" analysis. Such a limitation on the scope of Dr. Wilson's testimony is appropriate in light of the conceded bounds of his expertise. Moreover, the fact that Alcon may have used "one-way ANOVA" to analyze some of its in-house data not only has no bearing on the reliability or propriety of the use of "two-way ANOVA" to evaluate a different type of experiment, but, more important, is utterly irrelevant to Dr. Wilson's qualifications to offer statistical opinions.

III. MEMORANDUM IN FURTHER SUPPORT OF MOTION *IN LIMINE* TO EXCLUDE OPINIONS OF DR. VALENTINO STELLA PERTAINING TO THE ALLEGED INFRINGEMENT OF CLAIM 6 OF THE '337 PATENT

Alcon respectfully submits this reply memorandum of law in further support of its motion *in limine* to preclude Dr. Stella from offering opinions regarding the alleged infringement of claim 6 of the '337 patent. As set forth in Alcon's opening brief, claim 6 of the '337 patent describes an ophthalmic composition containing an SEC that is effective to increase the solubility of brimonidine "in a biological environment." '337 patent, col. 16, ll. 65-67. Accordingly – notwithstanding Allergan's assertion in its opposition brief that Alcon has articulated no explicit basis for its motion – Alcon submits that, "[b]ecause Dr. Stella offers no opinion as to whether Alcon's proposed product contains an SEC effective to enhance the solubility of brimonidine under the sum of surrounding conditions that actually constitute the 'biological environment' of the human eye, his opinions with respect to the alleged infringement of claim 6 of the '337 patent are unhelpful and inadmissible." Opening Br. at 11-12.

In its opposition brief, Allergan does not dispute that Dr. Stella offers no opinion as to whether Alcon's proposed product contains an SEC that increases the solubility of brimonidine in the actual "biological environment" of the human eye. Rather, Allergan contends that "Dr. Stella's focus on pH in showing infringement of claim 6 is the product of what one of ordinary skill in the art would understand claim 6 to encompass." Allergan Opp. Br. at 12. Thus, Allergan concedes that Dr. Stella's infringement opinion with respect to claim 6 of the '337 patent depends on construing the term "biological environment" to be nothing more than a pH range – a claim limitation that the inventors could have, but did not, set forth in claim 6. The '337 patent contains no pH limitation in any claim, and excerpts of the specification that Allergan cites out of context do not show that "biological environment" means a pH range.

FACTS

Dr. Stella proposes to testify that (1) REDACTED Alcon's proposed brimonidine product acts as an SEC in compositions formulated at a pH range of about 7.0-7.3; (2) a pH range of about 7.0-7.3 is representative of the pH range of the human eye; and (3) REDACTED acts as an SEC in a "biological environment." Claim 6 of the '337 patent, however, requires an SEC that is effective in a "biological environment," and makes no reference to pH. The specification places the term "biological environment" in the context of the "human eye" and, specifically, the "cornea of the human eye." E.g., '337 patent, col. 1, ll. 57-64; col. 4, ll. 47-51). The plain meaning of "biological environment" is clearly something more than pH.[5]

ARGUMENT

Expert testimony may not be used to alter the plain meaning of patent claims, and may properly be excluded from evidence to the extent that it would do so. See Markman v. Westview Instruments, Inc., 52 F.3d 967, 979, 983 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996). Moreover, in construing patent claims, the words of a claim are presumed to carry their ordinary meaning, and that presumption may be rebutted in favor of a different or restricted meaning only by intrinsic evidence clearly disavowing the claim's ordinary meaning and scope. Texas Digital Sys., Inc v. Telegenix, Inc., 308 F.3d 1193, 1204 (Fed. Cir. 2002).

The "biological environment" of the human eye obviously encompasses components other than pH (e.g., Opening Br. at 15), and the specification of the '337 patent does not disclaim the full scope of the term "biological environment" or define it as limited to a pH range. Indeed, if anything, the specification confirms that the term carries its ordinary, broad, meaning. In an effort to

[5] Allergan incorrectly suggests that Alcon is trying to have the Court construe "biological environment" in a manner unsupported by the specification. Alcon seeks nothing more than a

find some disavowal of the plain meaning of "biological environment," Allergan improperly takes portions of the specification out of context. Specifically, Allergan notes that the specification does the following: (1) refers to "neutral and alkaline biological environments;" (2) teaches that "the biological environments into which present compositions are introduced have pHs ranging from about 7 to about 9;" and (3) explains that pH is important because "unionized forms of the adrenergic compounds facilitate their permeation across membrane lipid bilayers." Allergan Opp. Br. at 11-12. If the specification was simply as Allergan argues, Allergan would be guilty of reading a limitation from the specification into the claims. But, the facts are worse than that: Including the context, the specification states that "preferably, the alpha-2-adregenergic components are more soluble in present compositions having, for example, pHs of about 7 or greater . . . and in another embodiment . . . are more soluble in neutral, preferably alkaline, biological environments." '337 patent col. 2, ll 17-21 (emphasis added). Similarly, the specification states that "in one embodiment, the alpha-2-adrenergic components are unionized in the compositions. Preferably, the alpha-2-adrenergic components are also unionized in the biological environment into which the compositions are administered." Id. col. 2, ll. 48-52 (emphasis added). Thus, the specification distinguishes embodiments where brimonidine is solubilized in the composition (including at pHs of 7 and above) and embodiments where brimonidine is solubilized in a biological environment.

Dr. Stella would testify only as to the solubilization of brimonidine in laboratory compositions formulated within a pH range of 7.0-7.3. Such testimony simply does not address the limitation of claim 6 requiring an SEC that increases the solubililty of brimonidine in a biological environment.

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recognition that "biological environment" means more than a "pH range of interest" in a laboratory environment.laboratory environment.

IV. MEMORANDUM REGARDING MOOTNESS OF MOTION *IN LIMINE* TO EXCLUDE OPINIONS OF DR. VALENTINO STELLA PERTAINING TO THE EXPERIMENTAL DATA OF DR. CLIVE WILSON

Alcon respectfully submits this memorandum regarding its motion *in limine* to exclude opinions of Dr. Valentino Stella pertaining to the experimental data of Dr. Clive Wilson.

Alcon moved to exclude the opinions of Dr. Stella pertaining to Dr. Wilson's solubility data on the ground that Allergan had failed to produce a graph created by Dr. Stella from that data, or to respond in any way to Allergan's correspondence requesting that the graph be produced. After receiving Alcon's motions *in limine*, Allergan finally responded to Alcon's repeated requests for the production of that document. Specifically, Allergan has now produced what it represents is an accurate reproduction of the graph at issue, and has further represented that Dr. Stella has been unable to find, but continues to search for, the original.

Given these developments, Alcon hereby withdraws the instant motion as moot, without prejudice to its right to object to Dr. Stella's recreated graph, if offered into evidence by Allergan.

V. MEMORANDUM REGARDING MOOTNESS OF MOTION *IN LIMINE* TO REQUIRE ALLERGAN TO BRING THE INVENTORS ON THE PATENTS-IN-SUIT TO TESTIFY AT TRIAL

Alcon respectfully submits this reply memorandum regarding its motion *in limine* to require Allergan to bring the inventors on the patents-in-suit to testify at trial.

Allergan, in its response to the instant motion, has stated that it intends to bring the inventors on the patents-in-suit to testify at trial. In light of that response, this motion is moot and hereby withdrawn, without prejudice to Alcon's right to move anew to compel the inventors' appearance in the event of a change in circumstances.

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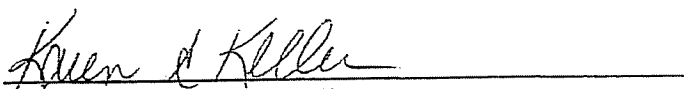
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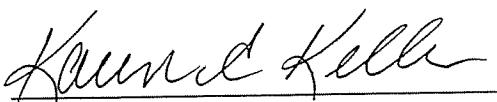
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