IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC, Plaintiffs, v. AUROBINDO PHARMA LTD. and AUROBINDO PHARMA LLC, Defendants.	1:13-cv-00688-GMS CONSOLIDATED
HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC, Plaintiffs, v. CIPLA LTD. and CIPLA USA, INC. Defendants.	1:14-cv-00427-GMS (All documents filed in 13-688)

DEFENDANTS CIPLA LTD. AND CIPLA USA, INC.'S
CORRECTED[*] OPENING CLAIM CONSTRUCTION BRIEF

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[*] Defendants Cipla Ltd. and Cipla USA, Inc. submit this Corrected Brief to correct citations to conform to the exhibits referenced in the Joint Appendix of Intrinsic Evidence (D.I. 128).

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I. INTRODUCTION

Defendants Cipla Ltd. and Cipla USA, Inc. (collectively, "Cipla") submit this claim construction brief to address the disputed terms of the patents-in-suit, i.e., U.S. Patent Nos. 7,947,724 ("the '724 patent"), 7,947,725 ("the '725 patent"), 8,598,219 ("the '219 patent"), and 8,729,094 ("the '094 patent").

Cipla asks this Court to construe the term "said formulation is stable at 24[18] months when stored at room temperature" to require that the formulation claimed in the asserted claims of the '219 and '094 patents has a pH of 4.0 to 6.0, which enables the formulation to have the recited stability. This Court should construe the term according to Cipla's proposed construction because throughout the prosecution of ancestor applications to the '219 and '094 patents, the patentees repeatedly informed the United States Patent and Trademark Office ("PTO"), and hence, the public, that they discovered the allegedly improved stability of palonosetron formulations *only* in formulations having a pH of 4.0 to 6.0. To permit the claims to encompass palonosetron formulations having a pH outside the range of 4.0 to 6.0 would run afoul of the public notice function of the patent system, and would allow the patentees to enforce claims that exceed the scope of what they actually invented. Cipla also requests that the preamble "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting," which appears in the claims of the '219 patent, be found not to be limiting because it is not necessary to render the claims structurally complete and there is no exception which justifies interpreting it as a limitation. Lastly, Cipla joins Ben Venue Laboratories, Inc. in arguing that the phrase "pharmaceutically stable," which appears in all of the claims of the '724

and ’725 patents, be construed to mean “without significant change in chemical and physical integrity for pharmaceutical use.”[1]

II. FACTUAL BACKGROUND

The present action is a patent infringement lawsuit arising under the Hatch-Waxman Act involving four Orange Book listed patents, i.e., the ’724 patent, the ’725 patent, the ’219 patent, and the ’094 patent. The drug in dispute is a palonosetron hydrochloride injection sold under the brand name Aloxi®. Intravenous formulations of palonosetron hydrochloride were known in the prior art, having been disclosed in U.S. Patent No. 5,202,333, filed in 1991. The ’724 patent, the ’725 patent, the ’219 patent, and the ’094 patent, along with several other Orange Book listed patents, including U.S. Patent Nos. 7,960,424 (“the ’424 patent), 8,518,981 (“the ’981 patent”), and 8,598,218 (“the ’218 patent”), which are no longer asserted in this case, are derived from a single family of patents, each of which allegedly covers a shelf-stable liquid formulation of palonosetron having particular pH and excipient concentration requirements.

The claims of the ’724 and ’725 patents are directed to “pharmaceutically stable” solutions of palonosetron hydrochloride having a pH of from 4 to 6.[2] The asserted claims of the ’219 patent (i.e., claims 1-5 and 8) are directed to pharmaceutical formulations of palonosetron hydrochloride that are stable for 18 or 24 months at room temperature. The asserted claims of the ’094 patent (i.e., claims 13-17 and 19-21) are directed to methods for reducing the likelihood

[1] With respect to this term, Cipla incorporates by reference herein the arguments set forth in Ben Venue Laboratories, Inc.’s Opening Claim Construction Brief (D.I. 47), Ben Venue Laboratories, Inc.’s Answering Claim Construction Brief (D.I. 57), and the Declaration of Michael S. Chang and Exhibits 1-20 thereto (D.I. 48).

[2] Cipla asserts that it does not infringe the claims of the ’724 and ’725 patents, because Cipla’s palonosetron formulation does not have a pH of from 4 to 6. Similarly, Cipla asserts that it does not infringe the claims of the ’219 and ’094 patents because when the claims are properly construed, they require that the formulation have a pH of from 4 to 6, which pH limitation is not met by Cipla’s palonosetron formulation.

of cancer chemotherapy-induced nausea and vomiting comprising the administration of pharmaceutical formulations of palonosetron hydrochloride that are stable for 24 months at room temperature. Unlike the claims of the '724 patent and the '725 patent, the claims that issued in the '219 patent and the '094 patent, which claims were pursued only after the commencement of litigations involving the '724 patent and '725 patent, do not expressly recite any pH limitation.

III. ARGUMENT

A. The '219 and '094 Patentees Represented to the PTO and to the Public that Stable Palonosetron Formulations of the Invention Were Achieved Only With a pH From 4.0 to 6.0

Plaintiffs and Cipla disagree on the construction of the term "said formulation is stable at 24[18] months when stored at room temperature," which appears in all of the asserted claims of the '219 and '094 patents. Each party's proposed construction is as follows:

Claim Language	Plaintiffs' Construction	Cipla's Construction
said formulation is stable at 24[18] months when stored at room temperature	plain meaning	said formulation has a pH that enables said formulation to be stable for 24[18] months when stored at room temperature, wherein the pH is from 4.0 to 6.0 "stable" means without significant change in chemical and physical integrity[3]

The Federal Circuit has recognized that when, during prosecution, "the patentee explicitly characterizes an aspect of his invention in a specific manner to overcome prior art," such statements may limit the meaning of a claim term. *Purdue Pharma L.P. v. Endo Pharms., Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006). The Federal Circuit directs that the prosecution history of a patent should be reviewed because it "constitutes a public record of the patentee's representations concerning the scope and meaning of the claims, and competitors are entitled to

[3] Cipla's proposed construction of the term "stable" corresponds with Cipla's proposed construction of the term "pharmaceutically stable," as discussed in footnote 1, *supra*.

rely on those representations when ascertaining the degree of lawful conduct, such as designing around the claimed invention." *Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc.*, 222 F.3d 951, 957 (Fed. Cir. 2000); *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005). Statements made during prosecution "that describe the invention as a whole . . . are more likely to support a limiting definition of a claim term." *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 864 (Fed. Cir. 2004). This ensures that the patentee cannot enforce claims that extend beyond the scope of what he actually invented. *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001).

The Federal Circuit has also recognized that the prosecution histories of related applications are relevant to interpretation of the scope of a claim. *See Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1350 (Fed. Cir. 2004) ("Any statement of the patentee in the prosecution of a related application as to the scope of the invention would be relevant to claim construction, and the relevance of the statement made in this instance is enhanced by the fact that it was made in an official proceeding in which the patentee had every incentive to exercise care in characterizing the scope of its invention."); *Realtime Data, LLC v. Morgan Stanley*, 554 Fed. Appx. 923, 934 (Fed. Cir. 2014) ("In connection with patents that are part of an extended family of patents, a patentee's disclaimers made during prosecution are 'relevant' both as a statement made with regard to the patent at issue and with regard to related 'sibling' patents."); *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1306 (Fed. Cir. 2007).

A review of the prosecution histories of the numerous ancestor patent applications of the '219 and '094 patents makes clear that the patentees explicitly and repeatedly represented to the PTO, and to the public, that the claimed stability of their allegedly inventive palonosetron formulation was due to the formulation's pH of 4.0 to 6.0 and that it was this feature that

distinguished the invention from the prior art. As discussed herein, the prosecution histories are replete with statements in which the patentees represent that the pH range of 4.0 to 6.0 is a necessary, inter-cooperative element required to achieve a stable palonosetron formulation of the invention, and that the discovered beneficial effects of mannitol and EDTA on stability were only found within a pH range of 4.0 to 6.0.

For example, during the prosecution of the application that gave rise to the '725 patent, the Examiner rejected claims to a stable liquid palonosetron formulation not containing a pH limitation under 35 U.S.C. § 103(a), arguing the claimed excipients EDTA and mannitol in the particular claimed amounts were obvious to a skilled person because such excipients and amounts were disclosed in the prior art and/or could be obtained through routine optimization. In response, the patentees amended the claims to include the limitation that the formulation has a pH of 4 to 6. In addition, the patentees distinguished their invention from the prior art arguing that the elements of their allegedly inventive formulation (i.e., the excipients and their concentrations, and the pH of the formulation) "cooperate in an interdependent manner to produce a highly stable formulation." J.A.152. Similar arguments were made during the prosecution of the applications that gave rise to the '424 patent and '724 patent, respectively. *See, e.g.*, J.A.241 ("While the various features of the claims can be found individually in the prior art, the claimed invention is premised on the combination and *inter-cooperation* of several features."); J.A.259 ("The number of elements in this combination—and their inter-dependency—is also significant. . . . The record demonstrates . . . that all the elements must be carefully balanced to arrive at a stable formulation."). Thus, the patentees repeatedly represented to the PTO that the allegedly inventive stability of palonosetron formulations was not due merely

to the inclusion of certain excipients at specific concentrations, but was due to the inter-cooperation of those excipients with the formulation's pH of 4.0 to 6.0.

In making these statements, the patentees explained to the PTO, and to the public, that "the [claimed] formulation was discovered after a sequence of experiments, each building on the prior experiment like a series of building blocks to arrive at the claimed invention," and that "Applicant extensively investigated the appropriate pH of the molecule, the appropriate tonicity agent, and excipient interactions at various concentrations." J.A.240; *see also* J.A.113- J.A.114. This is reflected in the examples included in the specifications of the '219 and '094 patents. Example 1 of the '219 patent found that palonosetron hydrochloride is most stable at a pH of 5.0, and the patentees used this pH to subsequently determine concentrations of both EDTA and mannitol that allegedly further stabilized the formulations. J.A.031 at 7:1-38. *See also* J.A.089-J.A.090 at ¶¶ 10-13.

Over and over, the patentees unequivocally stated to the PTO, and to the public, that their alleged discovery that mannitol imparts improved stability when included in palonosetron formulations was made only in formulations having a pH of 4.0 to 6.0: "Applicant has discovered that mannitol results in a more stable formulation, *but this discovery was only made in the context of an aqueous formulation at a pH of 4-6* using palonosetron HCl." J.A.152-J.A.153 (emphasis added); *see also* J.A.241-J.A.242. Also during the prosecution of the '725 and '424 patents, the patentees made identical statements concerning their alleged discovery that EDTA imparts improved stability when included in palonosetron formulations: "Applicant has discovered that EDTA stabilizes the formulation, but *it only does so* at low concentrations of palonosetron HCl *in an aqueous formulation of palonosetron hydrochloride having a pH of 4-6*." J.A.152-J.A.153 (emphasis added); *see also* J.A.241-J.A.242.

Thus, the patentees' explicit and repeated statements make clear that any alleged discovery concerning the stability of palonosetron hydrochloride formulations was only made in formulations having a pH of 4.0 to 6.0. This supports and necessitates that the term "said formulation is stable at 24[18] months when stored at room temperature" be construed as proposed by Cipla—"said formulation has a pH that enables said formulation to be stable for 24[18] months when stored at room temperature, wherein the pH is from 4.0 to 6.0."

Plaintiffs may point to language in the specifications of the '219 and '094 patents suggesting that formulations having a pH of 4.0 to 6.0 are only embodiments of the alleged invention, and that excipients such as mannitol and EDTA can also be used to impart stability, regardless of the pH of the formulation. *See, e.g.*, J.A.029 at 3:4-6 and J.A.030 at 5:1-3. However, this language must be interpreted in light of the patentees' repeated and explicit statements to the PTO that, while it may be possible to improve stability of a formulation by including mannitol and EDTA, this alleged discovery is true *only* in the context of a palonosetron formulation having a pH of 4.0 to 6.0. Indeed, as discussed above, the patentees repeatedly stressed that their findings were "interdependent" on one another, and the result of a series of building blocks that built on one another, beginning with a determination of the appropriate pH for the formulation.

Thus, while Cipla readily recognizes that one should use caution when importing limitations from the specification into the claims, in view of the patentees' clear statements to the PTO, and to the public, concerning what they viewed to be the invention, a person of ordinary skill in the art would conclude that, for the formulations claimed in the '219 and '094 patents to be "stable at 24[18] months when stored at room temperature," such formulation must have a pH of 4.0 to 6.0. Accordingly, any construction of this term that would give the patentees broader

claim scope than what they repeatedly represented to the PTO and the public to be their alleged invention must be rejected.

B. The '219 Patent Preamble Term "For Intravenous Administration to a Human to Reduce the Likelihood of Cancer Chemotherapy-Induced Nausea and Vomiting" is Not Limiting

Cipla believes that the preamble term "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" should not be construed as a limitation on the claims of the '219 patent.[4] Plaintiffs disagree:

Claim Language	Plaintiffs' Construction	Cipla's Construction
for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting	plain meaning	not a limitation of the claims; if found to be a limitation of the claims, plain meaning

As the Federal Circuit has repeatedly recognized, as a general rule, "a preamble does not limit the claims." *Allen Eng'g Corp. v. Barktell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002). Specifically, "[a] preamble is not limiting where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention." *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002); *see also Marrin v. Griffin*, 599 F.3d 1290, 1294 (Fed. Cir. 2010); *Altiris, Inc. v. Symantec Corp.*, 318 F.3d 1363, 1372 (Fed. Cir. 2003). This is because patentability depends on the claimed structure, not on the use or purpose of that structure. *Catalina*, 289 F.3d at 809.

The preamble language in claims 1 and 8 of the '219 patent states only a purpose or intended use for the invention—"for intravenous administration to a human to reduce the

[4] Plaintiffs and Cipla agree that, should the term "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" in the '219 patent be found as limiting on the claims, the term should be given its plain meaning.

likelihood of cancer chemotherapy-induced nausea and vomiting." The preamble language is not needed to render the claims structurally complete, because the limitations of claims 1 and 8 that follow the preamble, and all of the additional limitations that appear in dependent claims 2-7, form a complete set of structural limitations. Thus, according to the general rule set forth by the Federal Circuit, the preamble of claims 1 and 8 of the '219 patent should not be viewed as a limitation of the claims of the '219 patent. *Catalina*, 289 F.3d at 809.

The Federal Circuit has recognized only a few limited exceptions to this general rule whereby a preamble can be found to limit the claims, namely, when: (1) a later element of the claim relies on the preamble for antecedent basis; (2) the preamble recites additional structure or steps, which the specification identifies as important; or (3) the applicants clearly relied on the preamble during prosecution to distinguish the claimed invention over the prior art. *Id*. at 808. However, none of these exceptions applies in the present instance.

First, no later element of the claim relies on the preamble for antecedent basis. Indeed, there is no mention whatsoever in the body of claims 1 and 8, or in any of the claims that depend from claim 1, of "intravenous administration" or "cancer-chemotherapy induced nausea and vomiting." Second, the specification does not indicate that "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" is important to the claimed invention. Rather, the specification focuses on the stability of the alleged invention, and only briefly mentions the well-known use of the active ingredient, palonosetron hydrochloride, as an anti-emetic. Additionally, the specification of the '219 patent does not contain any clinical trial data concerning a reduction in the likelihood of cancer chemotherapy-induced nausea and vomiting upon intravenous administration.

Third, the patentees did not rely on the preamble phrase at all throughout prosecution of the ’219 patent to distinguish the claimed invention over the prior art. Indeed, nowhere in the prosecution history of the ’219 patent did the patentees attempt to argue that the intravenous administration of palonosetron hydrochloride or a reduction in the likelihood of cancer chemotherapy-induced nausea and vomiting due to the administration of palonosetron hydrochloride distinguished the claims of the ’219 patent over the prior art. Rather, the patentees focused solely on the claimed excipients and concentrations of those excipients recited in the bodies of claims 1 and 8 to overcome rejections based on prior art. This is likely because the patentees were well-aware that palonosetron hydrochloride had been known for decades to function as an anti-emetic, as acknowledged by the patentees in the “Background of the Invention” section of the ’219 patent, where the patentees discuss the prior art ’333 patent and state that palonosetron hydrochloride was known “to reduce delayed-onset nausea induced by chemotherapeutic agents.” J.A.028 at 1:43-49.

Because the body of the claims defines a structurally complete invention and none of the three enumerated exceptions above applies here or serves as a basis for interpreting the preamble as a limitation of the claims of the ’219 patent, Cipla’s proposed construction should be adopted.

IV. CONCLUSION

For all of the foregoing reasons, Cipla respectfully requests that this Court adopt Cipla’s claim constructions proposed herein.

Respectfully submitted,

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