IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 13-688 (GMS) CONSOLIDATED
CIPLA LTD., CIPLA USA, INC., EUROHEALTH INTERNATIONAL SARL, WEST-WARD PHARMACEUTICAL CORP., and MYLAN INSTITUTIONAL LLC,	)	
Defendants.	)	

PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

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Plaintiffs Helsinn Healthcare S.A. and Roche Palo Alto LLC commenced this patent-infringement action under the Hatch-Waxman Act based upon Defendants'[1] respective ANDAs seeking approval to market generic versions of Plaintiffs' Aloxi® product. In accordance with the Court's Scheduling Order, Plaintiffs submit this opening claim construction brief in support of their proposed, plain-meaning constructions of the four claim terms in the patents-in-suit[2] for which Defendants have sought a *Markman* ruling from this Court.

INTRODUCTION

As confirmed by the intrinsic evidence, each of the disputed terms has its ordinary and customary meaning. In a transparent attempt to manufacture a noninfringement argument, only Cipla argues that the term "said formulation is stable at 24 [or 18] months when stored at room temperature" somehow includes a pH "from 4.0 to 6.0" requirement. No such requirement appears anywhere in the claims at issue. In fact, claim 13 of the '094 patent ***expressly states that a pH limitation is merely "optional[]."*** This is consistent with the patent specification, which confirms that pH is just one of several variables that ***may*** be used to increase stability, as well as the prosecution history, which expressly states that the claims at issue "***lack*** . . . a pH limitation."

Cipla alone also erroneously contends that an isolated portion of the preamble of the '219 patent claims at issue — "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" — is not limiting. These words, however,

[1] In this brief, "Defendants" refers to Cipla Ltd. and Cipla USA, Inc. (collectively, "Cipla") and Mylan Institutional LLC ("Mylan"). Plaintiffs and the remaining defendants in this action, Eurohealth International Sarl and West-Ward Pharmaceutical Corp., previously briefed the "pharmaceutically stable" claim limitation addressed in Section III below. (D.I. 49-50, 58-59.) Plaintiffs' briefing relating to that claim term is incorporated by reference herein.

[2] Plaintiffs assert United States Patent Nos. 7,947,724 ("the '724 patent"), 7,947,725 ("the '725 patent"), 7,960,424 ("the '424 patent"), 8,598,219 ("the '219 patent"), and 8,729,094 (the '094 patent") against Mylan, and the '219 and '094 patents against Cipla. These patents, as well as the intrinsic evidence relied upon in the claim construction briefing, will be submitted in the Joint Appendix pursuant to the Court's Scheduling Order. (D.I. 110 at 2.)

are limiting at least because they (1) connote essential structure that provide antecedent basis for the body of the claims and (2) were clearly relied upon by the applicants in multiple prosecution history documents, including to distinguish the prior art.

Finally, Mylan and Cipla propose a construction of the claim term "pharmaceutically stable" that merely repeats the "pharmaceutically" portion of that limitation. Thus, it is actually a definition of only the word "stable." And because this partial definition is both inconsistent with the intrinsic evidence and indefinite, it should be rejected. To the extent the Court deems it necessary to provide any construction other than "plain meaning," Plaintiffs propose a construction that tracks the specification's elucidation of this meaning — "shelf stable for periods greater than 24 months at room temperature."

BACKGROUND

Palonosetron is a serotonin subtype 3 ($5\text{-}HT_3$)-receptor antagonist that reduces nausea and vomiting by blocking the attachment of serotonin to this receptor, thereby preventing the brain from receiving signals that would otherwise trigger a nausea and vomiting response. Palonosetron was developed as an injectable solution by both Helsinn and Roche (through the work of Roche's predecessor, Syntex USA, Inc.), and is marketed in the United States as a formulation with various excipients under the brand name Aloxi®. Aloxi® is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy, as well as the prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. (Ex. 1, Aloxi® Prescribing Information, at 1.)[3] Aloxi® is also indicated for the prevention of acute postoperative nausea and vomiting. (*Id.*)

[3] "Ex. __" refers to the exhibits attached to the December 5, 2014 Declaration of A. Ni, submitted herewith.

Aloxi® is a commercial embodiment of the patents-in-suit. One of the central purposes of those patents was to provide sufficiently stable palonosetron formulations. Based upon their confidential research, however, the inventors discovered that developing a suitable pharmaceutical formulation of palonosetron was difficult because of "shelf-stability issues." ('219 patent,[4] at col. 1:49-51.) For example, the specification explains that the prior-art palonosetron formulations disclosed in Example 13 of U.S. Patent No. 5,202,333 ("the '333 patent"), which contained different amounts of palonosetron and excipients compared to the claimed palonosetron formulations, did not have sufficient shelf stability to meet regulatory standards. (*Id.* at cols. 1:49-1:67, 2:33-34.)

In addressing these issues, the inventors discovered that, by adjusting the formulation's pH, ingredients, ***and/or*** concentrations of those ingredients, they could increase the stability of the formulation. (*See e.g., id.* at col. 3:4-6 (emphasis added), 3:19-21.) For example, the patent specification explains that the use of lower doses of palonosetron facilitates increased shelf stability. (*See e.g., id*. at col. 2:60-65, 4:39-43.) The specification also discloses several embodiments in which certain excipients are included in particular amounts to enhance stability. (*See, e.g., id*. at col. 3:11-17, 5:20-47, 5:50-6:3.) For example, excipients such as EDTA, citrate buffer, and mannitol, either individually or collectively, could be used in differing amounts to further increase the formulation's stability. (*See, e.g., id.* at cols. 3:11-17, 5:48-6:3.) Moreover, the specification explains that, in yet another, separate embodiment, "adjusting the formulation's pH" can provide additional stability increases. (*See, e.g., id*. at col. 5:1-3.)

The common specification also notes the existing need, at the time of invention, for an improved antiemetic treatment, particularly with respect to "delayed nausea and vomiting" that

[4] Because the relevant portions of the specifications of the patents-in-suit are identical, Plaintiffs cite only the '219 patent when referring to this common specification.

can occur after chemotherapy (*i.e.*, nausea and vomiting that occurs more than roughly 24 hours after chemotherapy). (*Id.* at col. 1:12-43.) The patent explains that, as a result of "recent[] clinical investigations," it was discovered that the inventive formulations containing low doses of palonosetron are "effective to reduce delayed-onset nausea induced by chemotherapeutic agents." (*Id.* at col. 1:43-49; *see also id.* at col. 2:53-55.)

PLAINTIFFS' PROPOSED CONSTRUCTIONS

I. "said formulation is stable at 24 [18] months when stored at room temperature"[5]

Claim Term	Plaintiffs' Construction	Cipla's Construction
said formulation is stable at 24 [18] months when stored at room temperature (claims 1 and 8 of the '219 patent; claim 13 of the '094 patent)	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

As can be seen from the above, Cipla's proposed construction of the term "said formulation is stable at 24 [18] months when stored at room temperature" consists of: (1) the words of the claim re-written (in red, green, and blue); and (2) additional text (in black). Thus, the parties' dispute concerning this claim term is straightforward: whether the "pH that enables" and "pH . . . from 4.0 to 6.0" requirements that Cipla attempts to import into a claim limitation

[5] The parties' proposed constructions for the separate terms "said formulation is stable at 24 months when stored at room temperature" and "said formulation is stable at 18 months when stored at room temperature" are the same, except for the "24 months" and "18 months" portions thereof. For efficiency, Plaintiffs therefore address these two disputed terms together.

that does not refer at all to pH is proper. Because it is not, Cipla's construction should be rejected in favor of Plaintiffs' construction of "plain meaning."[6]

A. The Claim Language Confirms That the "Plain Meaning" Applies

It is a cardinal principle of claim construction that "the context in which a term is used . . . can be highly instructive." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc). Here, the express language of the claims alone warrants rejecting Cipla's proposed importation of a "from 4.0 to 6.0" pH limitation.

The relevant claims of the '219 and '094 patents do not impose any specific pH requirement, let alone a precise range of "from 4.0 to 6.0." In fact, claim 13 of the '094 patent expressly provides that a pH limitation is merely ***optional***:

> 13. A method for reducing the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising intravenously administering to a human in need thereof a pharmaceutical single-use, unit-dose formulation comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:
>
> . . .
>
> wherein said solution optionally comprises a citrate buffer and ***optionally*** has a ***pH of from about 5.0±0.5***,
>
> wherein said formulation is stable at 24 months when stored at room temperature . . . .

('094 patent, at col. 10:50-64 (emphases added).) The language "optionally" indicates that a pH limitation is not required,[7] and, as such, Cipla's construction should be rejected. *See, e.g.*, *In re Johnston*, 435 F.3d 1381, 1384 (Fed. Cir. 2006) ("As a matter of linguistic precision, ***optional*** elements ***do not narrow the claim*** because they can always be omitted."); *Santarus, Inc. v. Par*

[6] Notably, none of the other defendants support Cipla's proposed claim construction.

[7] Instead, this is a requirement in claim 18 of the '094 patent, which depends from claim 13 and is directed to "[t]he method of claim 13, wherein said solution is buffered at a pH of about 5.0±0.5." ('094 patent, at col. 11:9-10.) The same is true of dependent claim 6 of the '219 patent, which adds only a "wherein said solution is buffered at a pH of 5.0±0.5" limitation to independent claim 1 of that patent. ('219 patent, at col. 10:21-22.)

Pharm., Inc., No. 07-551 (GMS), 2008 WL 5736587, at *1 (D. Del. Nov. 5, 2008) (construing the claim phrase "at least one ***optional*** Secondary Essential Buffer" as "a buffering agent that is ***not required in every formulation*** . . . .") (emphases added).

Indeed, if Cipla's proposed construction were adopted, the result would be illogical. Specifically, claim 13 of the '094 patent would first include an *optional* pH requirement (*i.e.*, "about 5.0±0.5"), and then be followed by a *mandatory* pH requirement (*i.e.*, "from 4.0 to 6.0"):

> wherein said solution optionally comprises a citrate buffer and ***optionally*** has a pH of from about 5.0±0.5,
>
> wherein said formulation ***has a pH that enables*** said formulation to be stable for 24 months when stored at room temperature, ***wherein the pH is from 4.0 to 6.0***

Such a nonsensical proposed construction should be rejected because it neither "stays true to the claim language" nor "most naturally aligns with the patent's description of the invention." *Phillips*, 415 F.3d at 1316.

B. The Intrinsic Evidence Supports a "Plain Meaning" Construction

Because there can be no legitimate dispute that the plain meaning of the disputed claim language does not include a pH requirement, the specification and prosecution history can compel departure from the plain meaning only through "lexicography" or "disavowal." *Thorner v. Sony Computer Entm't Am., LLC*, 669 F.3d 1362, 1365-66 (Fed. Cir. 2012); *see also Williamson v. Citrix Online, LLC*, 770 F.3d 1371, 1377 (Fed. Cir. 2014) ("[C]laims must not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction.") (internal quotations omitted). Neither exception applies here. In fact, both sources of evidence confirm that the plain meaning governs.

The ’219 and ’094 patent specification confirms that the formulation’s stability is not contingent on a specific pH range. As noted above, the specification explains that, “by adjusting the formulation’s pH ***and/or*** excipient concentrations it is possible to increase the stability of palonosetron formulations.” (’219 patent, at col. 5:1-3) (emphasis added).) Similarly, the specification describes a method of storing palonosetron for “24 months or more” at room temperature, which includes a list of five different options for achieving the claimed stability, all of which are separated by the word “or.” (*Id.* at col. 6:25-48.) Having a pH between 4.0 and 6.0 is ***only one*** of those options. (*Id.* at col. 6:41-42.)[8] The use of the disjunctives “and/or” and “or” demonstrates that the inventors viewed pH as merely ***one*** of ***several options*** to achieve the claimed stability of the inventive palonosetron formulations. *See, e.g.*, *Pragmatus AV, LLC v. Yahoo! Inc.*, No. 11-902, 2014 WL 1961980, at *24 (D. Del. May 15, 2014) (finding the use of “and/or” to “include one ‘and’ the other, or it can include one ‘or’ the other”); *see also Thorner*, 669 F.3d at 1366 (“It is . . . not enough that the only embodiments, or all of the embodiments,

[8] Indeed, the specification is replete with embodiments in which the stability of the formulation is not tied to pH. Rather, excipients may be selected, and concentrations of ingredients varied, to achieve optimal stability. (*See, e.g.*, ’219 patent, at cols. 2:60-3:3, 3:11-18, 4:38-53, 4:53-58, 5:50-56.) Therefore, Cipla’s attempt to read a preferred embodiment into the claims (*see id.* at col. 9:36-37) is contrary to well-established principles of claim construction. *See, e.g.*, *Phillips*, 415 F.3d at 1323 (“[A]lthough the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments.”); *Cephalon Inc. v. Mylan Pharm. Inc.*, 962 F. Supp. 2d 688, 700-01 (D. Del. 2013) (“Even if it is highly preferred . . . such a preference is an embodiment that is not properly read into the limitation.”).

contain a particular limitation. We do not read limitations from the specification into the claims; we do not redefine words.").[9]

Nor was there any clear and unmistakable disavowal in the prosecution history. Instead, the exact opposite occurred. In an examiner interview summary in the '219 prosecution, the Examiner expressly noted "the ***lack of a pH limitation in the claims***" at issue. (9/30/13 Examiner-Initiated Interview Summary, at 2 (emphasis added).) In response, the applicants' attorney "highlighted the limitations that ***[a]re in the claims***" (*id.* (emphasis added)), which did not include the pH limitation sought to be imported by Cipla.

Cipla largely ignores the prosecution histories of the '219 and '094 patent, the latter of which it ***does not even cite*** in the Final Joint Claim Chart. (D.I. 102 at 8-12 ("Joint Chart").) Cipla instead cites select documents from the prosecutions of certain applications that are related to the '219 and '094 patents. (*Id.*) Each of the documents cited by Cipla, however, were filed in applications containing claims that expressly recited a pH of 4.0 to 6.0 limitation. If anything, these earlier prosecution documents evidence that, when the inventors wanted to limit the claimed formulations to a pH of 4.0 to 6.0, they knew how to do so. *See, e.g.*, *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1333 (Fed. Cir. 2010) (concluding that it was inappropriate to impose a limitation on the claims at issue based upon, *inter alia*, the express inclusion of the same limitation in related patent claims). Because, as explained above, the inventors intentionally chose not to so limit the claims of the '219 and '094 patents, Cipla's transparent attempt to manufacture a noninfringement argument should be rejected accordingly.

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[9] Plaintiffs' proposed construction of plain meaning is further consistent with industry standards. A POSA would have understood that the claimed formulation could be intravenously tolerated over a pH range broader than from 4.0 to 6.0. (*See* Ex. 2, Joanne Broadhead, *Parenteral Dosage Forms, in* PHARMACEUTICAL PREFORMULATION AND FORMULATION 331, 333 (Mark Gibson ed., 2001) (When dosing is via the IV route, "pHs ranging from 2 to 12 can be tolerated . . . . [T]he vast majority of licensed products have a pH between 3 and 9.").)

II. "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting"

Plaintiffs and Cipla do not dispute that the preambles of claims 1 and 8 of the '219 patent have their "plain meaning." Nor do Plaintiffs and Cipla dispute that the preamble of those claims, at least in part, serves to limit the claims. Instead, the parties' dispute centers on Cipla's contention that an isolated portion of that preamble language — "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" — does not limit the claims.[10]

A claim's preamble is limiting "if it recites essential structure or steps, or if it is necessary to give life, meaning, and vitality to the claim." *Poly-America, L.P. v. GSE Lining Tech.*, 383 F.3d 1303, 1309-10 (Fed. Cir. 2004) (internal quotations omitted). "No litmus test defines when a preamble limits claim scope." *Id.* at 1309. The Federal Circuit has explained, however, that preamble language should be found limiting when "limitations in the body of the claim rely upon and derive antecedent basis from the preamble." *Proveris Sci. Corp. v. InnovaSystems, Inc.*, 739 F.3d 1367, 1372 (Fed. Cir. 2014) (quotations omitted). "[C]lear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art" also "transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention." *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1370 (Fed. Cir. 2003).

As explained below, the intrinsic evidence conclusively demonstrates that the preamble language at issue serves to limit the asserted claims of the '219 patent.

[10] Notably, Cipla is once again alone in its position that this portion of the preamble is not limiting, as no other defendant in this consolidated action is advancing this argument.

A. The Disputed Preamble Language Connotes Essential Structure That Provides Antecedent Basis for the Body of the '219 Patent Claims

The language of the claims themselves alone demonstrates the limiting nature of the preamble language at issue. Specifically, the body of claim 1 of the '219 patent refers to "said formulation," but the ***only*** description of that "formulation" appears in the preamble:

> 1. A ***pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting***, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:
>
> palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;
> from 0.005 mg/mL to 1.0 mg/mL EDTA; and
> from 10 mg/mL to 80 mg/mL mannitol,
> wherein ***said formulation*** is stable at 24 months when stored at room temperature.

('219 patent, at col. 10:2-12 (emphasis added).) Such reliance on the preamble language for antecedent basis supports treating the prepositional phrase "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" as a limitation. *See, e.g.*, *Proveris*, 739 F.3d at 1372-73; *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1357-58 (Fed. Cir. 2012).

That "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" is limiting is confirmed by Cipla's concession that similar use language found in a portion of the preamble, "[a] pharmaceutical single-use, unit dose" is limiting. (*See* D.I. 102, at 5 (identifying only "for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" as non-

limiting).) There is no rational basis to treat certain portions of the preamble — but not others — as limiting.[11]

B. The Prosecution History Confirms That the Disputed Term Is Limiting

The relevant prosecution history removes any doubt as to whether the preamble language at issue is limiting. During the prosecution of U.S. Patent Application No. 11/186,311, a parent application of the '219 patent ("the '311 parent application"),[12] the Examiner rejected the then-pending claims as unpatentable in light of certain oral formulations disclosed in the prior art "Berger" and "Gambhir" references. (10/6/08 Office Action, at 5-6 ("Berger . . . teach[es] an oral formulation for reducing emesis comprising palonosetron (100 mg/100ml = 0.1 mg/ml) . . . . Gambhir teaches an anti-emetic liquid formulation . . . .").) To overcome this rejection, the applicants added the word "intravenous" to the preamble of independent claim 32, and deleted "adapted for oral administration" from dependent claim 41.[13] (4/6/09 Amendment and Response

[11] Under Cipla's reading of the claims, a formulation that includes the ingredients set forth in the body of claim 1 of the '219 patent, but does not have the ability to reduce chemotherapy-induced nausea and vomiting, would nevertheless be covered by the claims. This nonsensical reading of the claims that ignores "a fundamental characteristic of the claimed invention" should be rejected. *See, e.g.*, *Vizio, Inc. v. ITC*, 605 F.3d 1330, 1340-41 (Fed. Cir. 2010) ("[A] construction that required only receipt and storage of the channel map information, and not the ability to decode using that information, could effectively broaden the claims to cover all devices and methods of decoding an A/65 compliant digital broadcast.").

[12] This application, which issued as the '724 patent, can be considered in construing the claim term. *See, e.g., Masco Corp. v. United States*, 303 F.3d 1316, 1324 (Fed. Cir. 2002) ("When multiple patents derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain the same claim limitation.") (citation omitted).

[13] The applicants also replaced the phrase "adapted for intravenous administration" from dependent claim 40 with the word "intravenous" in the preamble to address the Examiner's objection to the use of the word "adapted." (4/06/09 Amendment and Response, at 3; *see also* 12/29/08 Amendment After Final, at 2, 9 in the prosecution of the '424 patent (replacing language in response to the Examiner's rejection under 35 U.S.C. § 112 (10/29/08 Office Action, at 4-5) that "the phrase 'adapted for intravenous administration' is not found in the specification as originally filed. There is [a] formulation for intravenous administration but not adapted as claimed").)

to Office Action, at 3.) In explaining these amendments, the applicants represented that "[t]he ***present claims are drawn towards*** pharmaceutically stable ***intravenous*** solutions of palonosetron." (*Id.* at 5 (emphases added).)

After the Examiner maintained her rejection, the applicants appealed, emphasizing again that the pending claims "describe[] an intravenous liquid formulation" that "is ***limited by*** the following features: "(1) an intravenous solution." (5/24/10 Appeal Brief, at 2 (first emphasis added); *see also id.* at 6-7 ("The claimed formulation is defined by numerous features, including: (1) an intravenous solution.").) Moreover, in distinguishing the prior art relied upon by the Examiner, the applicants explicitly stated that:

> [t]he Office's rejection ignores the fact that ***the claimed formulations are intravenous formulations***, and there would be no reason to include a sweetener from Gambhir's ***oral*** formulation in an intravenous formulation. The Office seems to be arguing that the dosage form is a mere statement of use, and that the claimed formulations include oral liquids, but that argument ***ignores the requirement of the claims for isotonicity***, which in turn ***is a requirement only for intravenous formulations.***

(*Id.* at 13-14 (emphases added).) Shortly thereafter, the Examiner relented, issuing a Notice of Allowance. (3/4/11 Notice of Allowance.)[14]

Similarly, during the prosecution of the '424 patent,[15] the Examiner rejected the then-pending claims for obviousness based upon, *inter alia*, a "100 mg/100ml" formulation in the prior art, and further issued an enablement rejection relating to the phrase "adapted for

[14] A similar rejection was made by the Examiner during the prosecution of the '725 patent. (*See, e.g.*, 3/29/10 Office Action, at 8-9.) In response, the applicants explained that the pending claims "describe an intravenous liquid formulation," and "require[]," *inter alia*, "an intravenous solution," (10/11/10 Appeal Brief, at 3), and thereafter, a Notice of Allowance was issued (*See* 12/22/10 Notice of Allowance).

[15] Because U.S. Patent Application No. 11/388,270, which issued as the '424 patent, is a related application that claims priority to the same provisional application as the '219 patent, it can be considered in determining the scope of the claims in that patent. *See, e.g.*, *Masco,* 303 F.3d at 1324.

intravenous administration" because the Examiner found that the specification discloses a "formulation ***for intravenous administration***, but not adapted as claimed." (10/29/08 Office Action, at 4-5 (emphasis added).) In response, the applicants introduced the term "intravenous" to the preamble of the independent claims and specifically relied upon this language in distinguishing their invention over the prior art:

> It is also notable that the 100mg/100ml formulation from Example 13 of the Berger '333 patent, as cited by the Office, is an oral formulation. ***In contrast, the pending claims are limited to intravenous formulations***.

(12/29/08 Amendment After Final, at 2, 4 (emphasis added).)

Later in the same prosecution, in providing a "Summary of Claimed Subject Matter" in an appeal brief, the applicants explicitly stated that "[t]he claimed formulation is ***limited by***," *inter alia*, "an intravenous solution." (11/13/09 Appeal Brief, at 2 (first emphasis added).) Further, in distinguishing prior art in their Appeal Brief, the applicants stated that, "[n]one of the secondary references is specific for . . . an aqueous ***intravenous*** solution of palonosetron HCl defined by the pending claims." (*Id.* at 12, 15 ("Nothing in the cited publications specifically describes or suggests an ***intravenous*** aqueous solution made up of palonosetron HCl, EDTA, and mannitol at a pH from 4.0 to 6.0.") (emphases added).) In her next communication, the Examiner allowed the claims to issue. (*See* 1/26/10 Notice of Allowance).)

All of the above statements demonstrate that the term "for intravenous administration" is a fundamental characteristic of the invention that limits the claims. *See, e.g.*, *W.E. Hall Co. v. Atlanta Corrugating, LLC*, 370 F.3d 1343, 1351-52 n.3 (Fed. Cir. 2004) (finding "little disagreement" that the preamble is limiting when the applicant used it to distinguish prior art during prosecution); *Invitrogen Corp.*, 327 F.3d at 1370 (finding applicant's statements relying

on preamble language "improved competence" to distinguish prior art rendered the preamble limiting). This language should accordingly be found to limit the claims.

In any event, the "isotonic" limitation in the *body of the claims* makes clear that "intravenous" limits the claims at issue. (*See* 5/24/10 Appeal Brief, at 13-14 ("The Office seems to be arguing that the dosage form is a mere statement of use, and that the claimed formulations include oral liquids, but that argument ignores the requirement of the claims for ***isotonicity***, which in turn ***is a requirement only for intravenous formulations***.") (emphases added).) Indeed, Cipla itself acknowledges this. (*See* Ex. 3, Cipla's Responses to Plaintiffs' First Set of Interrogatories, at 25 ("A person of ordinary skill would understand that an intravenous solution should be isotonic.").) Thus, irrespective of how the Court rules on the parties' dispute with respect to the preamble language, the "isotonic" limitation in the body of the '219 patent claims independently supports an "intravenous" requirement.

Finally, the prosecution of the application that directly issued as the '219 patent further confirms that the applicants and Examiner continued to understand the preamble to breathe life, meaning, and vitality into the claims. For example, "to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting" was expressly identified as an exemplary claim limitation during an interview with the Examiner discussing the "prior art." (9/30/13 Examiner-Initiated Interview Summary, at 2 ("In response, Mr. Sullivan highlighted the ***limitations*** that were in the claims, ***including . . . cancer chemotherapy-induced nausea and vomiting***.") (emphases added).) The Court should therefore reject Defendants' attempt to read out of the claims language that was clearly and repeatedly explained to limit them.

III. "pharmaceutically stable"

Plaintiffs' position is that a construction of "plain meaning" is sufficient. *See, e.g.*, *Finjan, Inc. v. Secure Computing Corp.*, No. 06-369, 2007 U.S. Dist. LEXIS 100215, at *3 n.1,

*5-*8 (D. Del. Dec. 11, 2007), *aff'd*, 626 F.3d 1197, 1207 (Fed. Cir. 2010). To the extent the Court determines that a more detailed construction is necessary, however, Plaintiffs' exemplary definition is consistent with the intrinsic evidence.

Claim Term	Plaintiffs' Proposed Construction	Mylan's Proposed Construction[16]
"pharmaceutically stable" (claim 1 of the '724 patent; claims 1 and 2 of the '725 patent; claim 1 of the '424 patent)	plain meaning, *i.e.*, shelf stable for periods greater than 24 months at room temperature	without significant change in chemical and physical integrity for pharmaceutical use

A. To the Extent the Court Determines That the Plain Meaning Requires Elucidation, Only Plaintiffs' Definition Is Consistent with the Specification

The common specification of the patents-in-suit explains that "an object of the present invention [is] to provide a formulation of Palonosetron hydrochloride with increased ***pharmaceutical stability*** for preventing and/or reducing emesis." ('724 patent, at col. 2:42-44 (emphasis added).) The specification further explains, in the "SUMMARY OF THE INVENTION," that this objective has been met through the discovery of "surprisingly effective and versatile formulation[s]" that "are ***shelf stable for periods greater than 24 months at room temperature***, and thus can be stored without refrigeration. . . ." (*Id*. at col. 2:57-61; *see also id*. at col. 1:13-15 ("The ***present invention*** relates to ***shelf-life stable*** liquid formulations of palonosetron that are especially useful in the preparation of injectable and oral medicaments."); Abstract ("The ***present invention*** relates to ***shelf-stable*** liquid formulations of palonosetron for reducing chemotherapy and radiotherapy induced emesis with palonosetron.") (all emphases

[16] Plaintiffs disagree with Cipla that the "pharmaceutically stable" claim term requires construction because, *inter alia*, it does not appear in any claim asserted against Cipla, and respond only to Mylan's proposed construction of this disputed term. To the extent that the Court allows Cipla to raise arguments concerning claims that are not asserted against Cipla, Plaintiffs' positions as set forth herein apply equally to Cipla's erroneous proposed construction.

added).) Accordingly, based upon the specification, the ordinary and customary meaning of "pharmaceutically stable" is "shelf stable for periods greater than 24 months at room temperature." *See, e.g., Netcraft Corp. v. eBay, Inc.*, 549 F.3d 1394, 1397-98 (Fed. Cir. 2008) (defining "ordinary meaning" of claim term based upon specification statements describing the invention because the common specification's repeated use of the phrase 'the present invention' describes the invention as a whole").

Plaintiffs' plain-meaning construction is also consistent with the specification's discussion of how the invention improved the prior-art palonosetron formulations by providing new palonosetron formulations that have the 1-2 years of pharmaceutical stability required by "health authorities in various countries." ('724 patent, at col. 1:52-2:3.) The patentees' goal of developing new palonosetron formulations with pharmaceutical stabilities that were comparable to other 5-HT_3 antagonists known at the time the application leading to the patents-in-suit was filed (*i.e.*, shelf stabilities greater than two years) is also reflected in Plaintiffs' proposed construction. This discussion in the specification of how the claimed invention overcame the deficiencies of the prior art further supports Plaintiffs' construction. *See Osram GmbH v. ITC*, 505 F.3d 1351, 1358 (Fed. Cir. 2007).

Despite its clear disclosure and guidance, Mylan proposes a construction that is not the plain meaning (D.I. 102, Joint Chart, at 13), and which conflicts with the specifications of the patents-in-suit. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (noting that the patent specification "is the single best guide to the meaning of a disputed term"). As a preliminary matter, Mylan's construction of "pharmaceutically stable" is, at most, a generic dictionary definition of the term "stable" that simply adds the words "for pharmaceutical use" at the end, rather than defining the term as a whole (*i.e.*, "stable" modified by the adjective

"pharmaceutically").[17] Not surprisingly, this ad hoc, extrinsic evidence-based definition finds no support in, and is divorced from, the specification's disclosure.

As explained above, the specification uses the term "pharmaceutically stable" to describe the novel palonosetron formulations that overcame the shortcomings of early prior-art solutions that were discovered to have a shelf life of "less than 1-2 year[s]." (*See, e.g.*, '724 patent, at col. 1:52-2:3.) Under Mylan's proposed construction, however, which does not provide any temporal guidelines, these prior-art formulations could be considered "pharmaceutically stable." Mylan's construction therefore ignores one of the central objectives of the patent, and should be rejected accordingly. *See Osram*, 505 F.3d at 1358. Moreover, without any temporal guidelines, Mylan's construction ignores the explicit disclosure in the "SUMMARY OF THE INVENTION": "These formulations are shelf stable for periods greater than 24 months at room temperature . . . ." ('724 patent, at col. 2:59-60.)

B. <u>The Remaining Evidence Fully Supports Plaintiffs' Construction</u>

The prosecution histories further support Plaintiffs' "plain meaning" construction. The inventors' declaration submitted during prosecution is consistent with Plaintiffs' proposed construction of "shelf stable for greater than 24 months at room temperature." For example, in their declaration, the inventors expressly represent that "pharmaceutically stable" formulations "can be stored for ***prolonged periods of time in a variety of conditions*** without significant degradation or loss of potency." (11/21/07 Statutory Declaration of G. Calderari, D. Bonadeo, R. Cannella, E. Braglia, and R. Braglia in the '311 application, at ¶ 6 (emphasis added).) This statement, referring to storage for "prolonged periods of time" under a "variety of conditions" in

[17] Cipla provides this exact definition of "stable," without the words "for pharmaceutical use," in its proposed construction of the "said formulation is stable at 24 [18] months when stored at room temperature" claim term. (D.I. 102, Joint Chart, at 8, 10.)

the context of the prior art, is consistent with the ordinary and customary meaning set forth in the specification, namely, shelf stability and storage "for greater than 24 months at room temperature."

Because the ordinary and customary meaning is clear from the intrinsic record, the Court need not look to extrinsic evidence. *See Phillips*, 415 F.3d at 1319. Nevertheless, Plaintiffs' plain-meaning definition of "pharmaceutically stable" is consistent with well-accepted industrial standards. Outside of the claimed invention, a POSA would understand that a "pharmaceutically stable" formulation should have a shelf life of at least two years. (*See, e.g*., Ex. 4, Howard C. Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems* 86 (7th ed. 1999) ("Under usual circumstances, most manufactured products require a shelf-life of 2 or more years to ensure their stability at the time of patient consumption.").) This general understanding of a necessary shelf-life of greater than 24 months at room temperature would be particularly recognized where, as here, the previously known products in the relevant field of treatment had shelf lives meeting this standard.[18]

[18] The inventors learned, though their confidential work, that the prior-art palonosetron formulations of the '333 patent did not compare favorably with other 5-HT_3 antagonists known at the time the application leading to the patents-in-suit was filed. These marketed formulations all had shelf stabilities of more than two years. (*See, e.g.*, Ex. 5, *Medicines Compendium* (2002), at NAV 1361, Navoban® (tropisetron) ("Shelf-Life: ***5 years***"); *id.* at KYT 1079, Kytril® (granisetron) ("Kytril ampoules have a shelf-life of ***three years***."); *id.* at ZOF 2205, Zofran® (ondansetron) ("Shelf Life" "***36 months***") (emphases added).)

C. Mylan's Proposed Construction Should Be Rejected as Impermissibly Indefinite

Mylan's proposed construction, "without significant change in chemical and physical integrity for pharmaceutical use," does not specify for how long a given formulation has to be "without significant change in chemical and physical integrity" to be considered "pharmaceutically stable." Thus, under Mylan's approach, the exact same palonosetron formulation could be both "pharmaceutically stable" and not "pharmaceutically stable" depending upon when Mylan's vague "without significant change" test is applied. Similarly, two formulations could be identical when manufactured, but only one considered "pharmaceutically stable" under Mylan's construction to the extent its identical twin was stored under harsher conditions.

The Federal Circuit has routinely rejected indefinite constructions like the one proposed by Mylan. *See, e.g., Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (2003) ("By GSK's proposed construction, a formulation … ***might infringe or not depending on its usage in changing circumstances*** . . . . That is the epitome of indefiniteness.") (emphasis added); *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1255 (Fed. Cir. 2008) ("When a proposed construction requires that an artisan make a separate infringement determination for every set of circumstances in which the composition may be used, and when such determinations are likely to result in differing outcomes (sometimes infringing and sometimes not), that construction is likely to be indefinite."). Because Mylan's proposed construction would raise new legal issues, instead of resolving them, this provides yet another independent basis to reject Mylan's construction.

CONCLUSION

For the foregoing reasons, Plaintiffs respectfully submit that their proposed claim constructions should be adopted by the Court.

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December 5, 2014

CERTIFICATE OF SERVICE

I hereby certify that on December 5, 2014, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on December 5, 2014, upon the following in the manner indicated:

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