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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

SHIRE LLC, SUPERNUS PHARMACEUTICALS, INC., AMY F.T. ARNSTEN, PH.D., PASKO RAKIC, M.D., and ROBERT D. HUNT, M.D.,

Plaintiffs,

v.

IMPAX LABORATORIES, INC., WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC.—FLORIDA, WATSON PHARMA, INC., and ANDA, INC.,

Defendants.

Case No. 10-CV-05467-RS

DEFENDANTS WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC.-FLORIDA, WATSON PHARMA INC., AND ANDA, INC.'S OPPOSITION TO PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF

Date: **May 30, 2012**
Time: **10:00 AM**
Courtroom: **3, 17th Floor**
Judge: **Hon. Richard Seeborg**

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I. INTRODUCTION

Defendants Watson Pharmaceuticals, Inc., Watson Laboratories, Inc.-Florida, Watson Pharma, Inc. and Anda, Inc. (collectively "Watson") hereby submit their responsive claim construction brief for the Court's consideration. Watson's constructions best define the metes and bounds of the pH-independent formulations disclosed in the patents-in-suit by most closely tracking the claims' language, properly interpreting the patents' data, and adding clarity where possible. The patents' disclosures are limited, and Plaintiffs misinterpret them to support constructions that contradict the patentee's stated goal for the claimed technology. Because Watson's proposed constructions most closely align with the patents' disclosures, Watson respectfully asks the Court to adopt them.

II. PLAINTIFFS ARE LITIGATING IN FOUR VENUES AND TAKING DIFFERENT POSITIONS IN CLAIM CONSTRUCTION

Plaintiffs currently are asserting infringement of the same patents-in-suit in this case as in five other actions in three other courts. These actions are: *Shire LLC, et al. v. Teva Pharms. USA, Inc., et al.*, No. 10-cv-329-SD (D. Del.); *Shire LLC, et al. v. Actavis Elizabeth LLC, et al.*, No. 10-cv-397-SD (D. Del.); *Shire LLC, et al. v. Anchen Pharms., Inc. et al.*, No. 10-cv-484-SD (D. Del.);[1] *Shire LLC, et al. v. Mylan Pharms. Inc., et al.*, No. 11-cv-55-IMK (N.D.W.Va.);[2] and *Shire LLC, et al. v. Sandoz Inc.*, No. 11-cv-1110-RJB-KMT (D. Col.). The parties have submitted claim construction briefing in the consolidated Delaware action and in the Colorado action. In both Delaware and Colorado, Plaintiffs have taken positions that are different than, and even contradict, positions they now take in this litigation.[3]

[1] The three Delaware cases have been consolidated into the one case, *Shire LLC et al. v. Teva*

[2] Only Shire LLC and Supernus Pharmaceuticals, Inc. are Plaintiffs in the Northern District of West Virginia action.

[3] *See, e.g.*, Ex. 1 to Olinger Decl., April 15, 2011 Plaintiffs' Opening Brief on Claim Construction, *Shire LLC, et al. v. Teva Pharms. USA, Inc., et al.*, No. 10-cv-329-SD (D. Del.), Dkt. No. 95 at 21-27 (discussing pH-dependent agent); Ex. 2 to Olinger Decl., February 3, 2012 Plaintiffs' Opening Brief on Claim Construction, *Shire LLC, et al. v. Sandoz Inc.*, No. 11-cv-1110-RJB-KMT (D. Col.), Dkt. No. 89 at 24-31 (discussing pH-dependent agent).

On March 22, 2012, the District of Delaware issued a memorandum opinion on claim construction in that action. (Ex. 3 to Olinger Decl., March 22, 2012 Memorandum Opinion ("Del. Op."), *Shire LLC, et al., v. Teva Pharms. USA, Inc. et al.*, 1:10-cv-00329-RGA, Dkt. No. 228.) Courts are split as to whether a claim construction ruling is issue preclusive prior to the entry of a final judgment. *See TM Patents, L.P. v. IBM Corp.*, 72 F. Supp. 2d 370, 377 (S.D.N.Y. 1999) (holding that a *Markman* ruling from a prior case was "sufficiently final" to apply issue preclusion in a subsequent case); *see also Curtiss-Wright Flow Control Corp. v. Z & J Techs., GmbH*, 563 F. Supp. 2d 1109, 1122 (C.D. Cal. 2007) (applying issue preclusion based on prior claim construction rulings). *But see Kollmorgen Corp. v. Yaskawa Electric Corp.*, 147 F. Supp. 2d 464, 469-70 (W.D. Va. 2001) (holding that a *Markman* ruling from a prior case did not have issue preclusive effect).

Watson believes that the better-reasoned authority counsels that Plaintiffs should be precluded from re-litigating claim construction issues they already have raised and lost in another court. However, even if the Court does not apply issue preclusion, the inconsistencies in Plaintiffs' claim construction positions in the various litigations provide strong evidence in support of the 35 U.S.C. § 112-based invalidity arguments raised by Defendant Impax. Not even the patentees can agree on what their patents disclose.

III. FACTUAL BACKGROUND

A. pH Independent Pharmaceutical Compositions

When the effectiveness of an active agent depends on maintaining a certain concentration of the agent in the body, it can be desirable to obtain a constant rate of release of the active agent from a pharmaceutical composition. Fluctuations in the amount of the active agent in the body can impact the effectiveness of the agent as well as the side effects associated with the administration of the agent. The rate of release of the active agent depends, in part, on the solubility of the active agent in the surrounding medium.

Weakly basic active agents, including guanfacine hydrochloride, are less soluble in media having higher pH values. The human gastrointestinal tract exhibits a range of pH values that vary from the very acidic environment of the stomach (pH of about 1.2) to the less acidic and even slightly basic environment of the intestines (pH reaching as high as about 7.8). Therefore, as a

pharmaceutical composition containing a weakly basic active agent travels through the gastrointestinal tract from the lower pH environment of the stomach to the higher pH environment in the intestines, less of the active agent dissolves and the rate of release decreases.

Pharmaceutical formulators have addressed the delivery of weakly basic active agents from a controlled-release pharmaceutical composition by incorporating various inactive ingredients (also known as excipients), including swellable polymers, enteric agents, and/or organic acids, into the pharmaceutical composition to offset the decrease in solubility of the pH-dependent active agent at higher pH values. These formulations have achieved minimized pH-dependent or a pH-independent release of the active agent. The patents-in-suit apply these well-known techniques to guanfacine formulations.

B. The Patents-in-Suit

The patents-in-suit are U.S. Patent No. 6,287,599 ("the '599 patent") and U.S. Patent No. 6,881,794 ("the '794 patent").[4] The inventions claimed in these patents are similar, pertaining generally to sustained release technologies for pharmaceutical products. (Sustained release has been known in the pharmaceutical arts for decades). Both patents claim pharmaceutical formulations that provide a pH-independent rate of release for their active agents. The goal of these formulations is to balance the pH-dependent release profile of the active agent through the use of various inactive excipients. To compensate for the slower release rate of the active agent, the allegedly inventive formulations contain non-pH-dependent sustained release agents and a pH-dependent agent that increases the rate of release of the drug above a pH of 5.5.

1. The '599 Patent

The '599 patent claims sustained release compositions with pH-independent or minimized pH-dependent dissolution profiles. (Ex. 4 to Olinger Decl., '599 patent at col. 1, ll. 6-8.) The patent claims the use of three primary elements to reduce pH-dependent release: (1) at least one

[4] U.S. Patent No. 5,854,290 ("the '290 patent") remains in the case for now, but Watson agrees with Plaintiffs that the Court need not construe its claims. After bringing suit on the '290 patent against Watson and filing a failed motion challenging the sufficiency of Watson and Impax's counterclaims on the '290 patent, Plaintiffs abruptly dedicated the '290 patent to the public. Should the Court determine that construction of any of the '290 patent's claim terms is required, Watson would seek leave to supplement its claim construction briefing.

pharmaceutically active agent that is pH-dependent;[5] (2) at least one non-pH-dependent sustained release agent; and, (3) at least one pH-dependent agent that increases the rate of release of at least one pharmaceutically active agent from the tablet at a pH in excess of 5.5. (*Id.* at col. 1, ll. 32-38.)

The patent contains brief descriptions of these three elements. First, the patent indicates that the pH-dependent active agents covered by the patent include active agents that have weakly basic dissolution profiles. (*Id.* at col. 1, ll. 40-43.) The specification states that these weakly basic active agents are more soluble in an acidic medium than in a basic medium, meaning that the active agent dissolves faster in pHs under 5.5 than at higher pH levels. (*Id.* at col. 1, ll. 14-16.) Second, the patent provides an exemplary list of non-pH-dependent sustained release agents without explaining their method of action or other identifying characteristics. (*Id.* at col. 1, l. 58 to col. 2, l. 1.) Presumably, because these excipients were well-known in the art by the time the patentees filed the application that resulted in the '599 patent, the patent merely lists them by name and not by any unifying characteristics or method of action. Finally, the patent identifies three categories of excipients that it labels as pH-dependent agents. (*Id.* at col. 2, ll. 8-15.) For two of these categories of excipients, swellable polymers and enteric agents, the patent merely provides a list of excipients that fall within these categories. (*Id.* at col. 2, ll. 19-27.) The patentees identify a third category of pH-dependent agents, which they describe functionally as agents that increase the solubility of the active agent at a pH greater than 5.5. The patentees assert that this third category includes a group of well-known organic acids used to create an acidic microenvironment inside the tablet. (*Id.* at col. 2, ll. 28-34.)

There is not a single indication in the '599 patent that the manner in which the listed excipients are formulated in a pharmaceutical composition will affect the function of the excipients, *e.g.*, whether an agent will act as a non-pH-dependent sustained release agent or pH-dependent agent.

[5] The patent contemplates formulations that contain multiple pharmaceutically active agents present in the composition, but that situation is not present in this case with Shire's Intuniv product or Watson's proposed guanfacine hydrochloride product.

2. The '794 Patent

Similar to the '599 patent, the '794 patent relates to sustained release pharmaceutical compositions with pH-independent or minimized pH-dependent dissolution profiles. (Ex. 5 to Olinger Decl., '794 patent at col. 1, ll. 28-30.) The asserted claims in the '794 patent are directed to methods of administering guanfacine in such compositions: (1) a method for treating attention deficit disorder or attention deficit hyperactivity disorder by using a sustained release guanfacine composition (claims 3 and 4) and (2) a method of reducing the likelihood of side effects associated with guanfacine administration by using a sustained release guanfacine composition (claims 8 and 9). (*Id.* at col. 15, l. 5 to col. 16, l. 27.)

IV. LEGAL STANDARD

Claim construction is an issue of law exclusively for the Court. *See Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372 (1996). "Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). Accordingly, a claim should be construed in a manner that "most naturally aligns with the patent's description of the invention." *Id.* The Federal Circuit's opinion in *Phillips* provides the proper framework for claim construction.

Claim construction begins with the words of the claim itself. "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Id.* at 1312. Claim terms should be given their ordinary and customary meaning, which "is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application." *Id.* at 1313. Because claim terms are often used "consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims." *Id.* at 1314.

In addition to the claims, the court must consider the remainder of the intrinsic evidence, including the specification and prosecution history.[6] *Id.* at 1313-1314. In explaining the importance

[6] Watson agrees with Plaintiffs that the prosecution histories of the patents-in-suit do not inform the claim construction inquiry in this case.

of the specification, *Phillips* states that "the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.* at 1313. The specification is always relevant to claim construction and is usually the single best guide to the meaning of disputed terms. *Id.* at 1315 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Further, where the specification "reveal[s] a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess . . . the inventor's lexicography governs." *Id.* at 1316.

Although *Phillips* underscores the importance of first considering the intrinsic evidence, it allows a court to consult extrinsic evidence, including dictionary definitions, technical treatises, and expert testimony. *Phillips*, 415 F.3d at 1317-18. Courts may use the extrinsic evidence to resolve any ambiguity in a disputed claim term that was not resolved by consulting the intrinsic evidence. *Vitronics*, 90 F.3d at 1583. Courts may also consult extrinsic evidence to help understand general technology involved in the patent claims at issue, but may not use extrinsic evidence to vary or contradict the patent claims. *See Phillips*, 415 F.3d at 1316. "In most situations, [however], an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term." *Vitronics*, 90 F.3d at 1583.

Claim construction is of the utmost importance in any patent case, because it is the first step in both the patent infringement and patent invalidity analysis. *See Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1362 (Fed. Cir. 1998) ("The first step in any invalidity or infringement analysis is claim construction.") Only after claims have been properly construed can a court then move to the separate questions of whether the accused product infringes or whether the prior art renders a patent claim invalid. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 997 n.7 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996) ("A claim must be construed before determining its validity just as it is first construed before deciding infringement.").

V. TERMS IN DISPUTE

The parties have identified five terms that they believe are the most significant to resolution of this case. Of these five terms, Watson believes that the most important terms are "non-pH-

dependent sustained release agent" and "pH-dependent agent that increases the rate of release of said at least one pharmaceutically active agent from the tablet at a pH in excess of 5.5."

A. The Five Most Significant Terms

1. "Non-pH-dependent sustained release agent" [7]

Watson's proposed construction of the term "non-pH-dependent sustained release agent" is a ***"substance, which does not function as a pH-dependent agent in the formulation, that slows the rate of release of the drug from the composition regardless of the pH of the surrounding media."***[8]

a. Sustained Release Agent Should be Construed as Slowing "the Rate of Release"

Watson contends that the phrase "sustained release" should be understood to "slow[] the rate of release" of a pharmaceutically active agent, whereas Plaintiffs use the phrase "slows release." Watson does not discern a substantive distinction between the two phrases, but believes that its construction is preferable because it is consistent with the patent's usage of the phrase "increases the rate of release" in the pH-dependent term and the agreed upon portions of Plaintiffs' and Watson's proposed constructions of the pH-dependent term. (*See, e.g.*, Ex. 4 to Olinger Decl., '599 patent at col. 1, ll. 35-39; Joint Claim Construction Statement, Dkt. No. 143, Ex. D at 8.) To the extent there is no substantive difference, the consistent phrasing should be used; if there is a substantive difference, Plaintiffs have not yet explained what distinction they are attempting to achieve through their proposed construction.

While general agreement exists regarding what the phrase "sustained release" means, Watson does not agree with Plaintiffs' representations that the data set forth in Tables 1 and 2 provide support for its construction and offers some brief comments as to why it disagrees because the topic may become a substantive issue in the case. (Pls.' Opening Claim Construction Brief ("Pls.' Brief"), Dkt. No. 148 at 10-11.)

[7] The '599 and '794 patents share substantially similar specifications. For purposes of this brief, Watson cites only to the '599 patent for claim terms appearing in both patents.

[8] Watson does not object to Impax's proposal to include a non-exclusive list of excipients for this term.

As an initial matter, the patent inaccurately describes Formulations PD0052-22A and PD0052-22B as "controls" for comparison with the allegedly inventive formulations. (Ex. 4 to Olinger Decl., '599 patent at Table 1). For each allegedly inventive formulation, more than one excipient is varied (added or removed) from the control formulation. Thus, one cannot determine the impact of any particular excipient that is present in the allegedly inventive formulation but is not present in the "controls," because the patent never actually controls for any one specific excipient.

More importantly, Plaintiffs misrepresent the data set forth in Table 2. Plaintiffs argue that the data presents dissolution information for both non-sustained release "control" formulations and the allegedly inventive sustained release formulations. (Pls.' Br. at 11 ("formulation[s] of the present invention sustained release . . . of the active agent independent of pH").) Plaintiffs are incorrect. Not only does the table identify every formulation as "Guanfacine Sustained Release Tablets," but both "control" formulations also contain excipients that the patent expressly identifies as non-pH-dependent sustained release agents. (Exh. 4 to Olinger Decl., '599 patent at Table 2; col. 1, ll. 60-62 (identifying polyethylene oxide and cellulose acetate, excipients contained in the "controls," as non-pH-dependent sustained release agents).) Therefore, any variation in dissolution data set forth in Table 2 cannot be attributed to the presence of a sustained release excipient, because each formulation disclosed contains a sustained release agent.

In summary, Watson generally agrees with Plaintiffs' regarding the meaning of "sustained release," but cannot agree that the specification, including Tables 1 and 2, provides a comparison that would support the construction of sustained release.

b. The Non-pH Dependent Sustained Release Cannot Also Function as a pH Dependent Agent in the Formulation

Watson asserts that the non-pH-dependent sustained release agent cannot also function as a pH-dependent agent in the same formulation. This issue was briefed and argued in the guanfacine litigation occurring in the Delaware federal district court. That court adopted a construction of non-pH dependent that incorporated this portion of Watson's proposed construction and rejected Plaintiffs' arguments to the contrary. (Ex. 3 to Olinger Decl., Del. Op. at 7.)[9]

[9] Plaintiffs filed a motion for reconsideration of the Delaware Court's claim construction order on April 5, 2012. (Ex. 6 to Olinger Decl., April 15, 2012 Pls.' Mot. for Recons., *Shire LLC, et*

The language of the '599 patent supports Watson's proposed construction. Claim 1 covers a composition comprising "at least one" pH-dependent pharmaceutically active agent, "at least one" non-pH-dependent sustained release agent, and "at least one" pH-dependent agent. (Ex. 4 to Olinger Decl., '599 patent at col. 7, ll. 33-41). The use of "at least one" before each element and the use of the conjunction "and" between each element demonstrate that the inventors sought to describe three distinct elements performing three distinct functions in the claimed composition. Furthermore, no formulation embodied in the patent contains only one excipient serving as both the non-pH-dependent sustained release agent and the pH-dependent agent.[10]

Additionally, the proposed constructions in this case support a ruling that the two terms must be mutually exclusive. Plaintiffs, Watson, and Impax uniformly agree that the non-pH-dependent sustained release agent slows the rate of release of the pharmaceutically active agent from the composition at any pH. (Joint Claim Construction Statement, Dkt. No. 143, Ex. D at 7.) Conversely, both Plaintiffs' and Watson's proposed constructions agree that the pH-dependent agent must increase the rate of release at a pH above 5.5. An agent cannot both slow the rate of release at any pH and also increase the rate of release at a pH above 5.5 simultaneously. Even if it could, the specification provides no insight into how this could be done. Thus, the specification and the parties' proposed constructions support this portion of Watson's proposed construction.

Further, nothing in the specification prohibits the mutual exclusivity of the pH-dependent and non-pH-dependent agents in a single formulation. The specification identifies carrageenan, alginic

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al., v. Teva Pharms. USA, Inc. et al., 1:10-cv-00329-RGA (D.Del.), Dkt. No. 237.) In their brief in support of this motion, Plaintiffs ask the Delaware Court to modify its construction for this term to remove the clause "and that is not the pH dependent agent," and modify its construction of "pH dependent agent" by removing the clause "that is neither the non-pH dependent sustained release agent nor the pharmaceutically active agent." (Ex. 7 to Olinger Decl., April 10, 2012 Redacted Public Version of Pls.' Br. in Supp. of Its Mot. for Recons. ("Recons. Br."), *Shire LLC, et al., v. Teva Pharms. USA, Inc. et al.*, 1:10-cv-00329-RGA, Dkt. No. 241 at 1.) Watson believes Plaintiffs' motion for reconsideration is meritless and that the Delaware Court's original construction of these terms will stand.

[10] PD0052-28B contains sodium alginate, which is identified as both a non-pH-dependent sustained release agent and a pH-dependent agent. (Ex. 4 to Olinger Decl., '599 patent at Table 1; col. 1, l. 63; col. 2, l. 20.) However, this formulation also contains ethylcellulose (Ethocel FP), which is identified solely as a non-pH-dependent sustained release agent. (*Id.* at col. 1, l. 60.) By process of elimination, sodium alginate must function as the pH-dependent agent in this formulation for the formulation to embody the allegedly inventive technology. *See Vitronics*, 90 F.3d at 1583-84 (holding that a construction that would cause a preferred embodiment to fall outside of the scope of the patent claims is strongly disfavored).

acid salts, and sodium carboxymethyl cellulose as both non-pH-dependent and pH-dependent agents. (Ex. 4 to Olinger Decl., '599 patent at col. 1, ll. 3-66 and col. 2, ll. 20-22.) Plaintiffs likely will argue that this limited overlap in lists for non-pH-dependent agents and pH-dependent agents means that one excipient can serve multiple functions. Watson's proposed construction is not inconsistent with the overlap in the exemplary lists. The possibility[11] that an excipient may function differently in different formulations does not mean that the excipient can serve both functions at the same time. Further, the specification does not explicitly disclose that this is the case.

Finally, in their brief in support of the motion for reconsideration in the Delaware action, Plaintiffs contend that the use of the modifier "pH-dependent" with respect to the word "agent" is not in conflict with the use of "non-pH-dependent" as it modifies "sustained release agent," because that "agent" and "sustained release agent" are different classes of excipients. (Ex. 7 to Olinger Decl., Recons. Br. at 5.) Plaintiffs here have not yet made such an argument, but the argument is meritless. In both instances, an "agent" is identified based on its response to variations in pH: one is pH-dependent and one is not pH-dependent. Furthermore, both agents are characterized based on their impact on the rate of release of the pharmaceutically active agent: one agent slows the rate of release and the other agent speeds the rate of release. As discussed above, an agent cannot decrease the rate of release at any pH, while simultaneously increasing the rate of release above a specific pH.

Despite Plaintiffs' protestations otherwise, a single agent cannot perform both as a non-pH-dependent sustained release agent and a pH-dependent agent in a single formulation.

c. No Support Exists for Including the Phrase "When the Claimed Composition is Formulated"

Plaintiffs further suggest adding the phrase "when the claimed composition is formulated" to the construction, but the specification does not support this addition.

Nothing in the specification suggests that an excipient's function only can be determined when the entire composition is formulated. Plaintiffs admit as much because they do not cite to such a disclosure. Instead, based on nothing more than rhetoric, Plaintiffs contend that the patent claims "formulations, not isolated components, and the properties or effects of a single component can

[11] Watson does not concede that these excipients can in fact perform both functions.

change from pH-dependent to pH-independent depending on its amount, its environment, and on the other components of the formulation." (Pls.' Br. at 9.) However, the patent is silent as to how the properties of a single component can vary based on its amount, its environment, or other components in the formulation. Further, despite Plaintiffs' argument otherwise, the mere overlap of three excipients on both the non-pH-dependent sustained release agent list and the pH-dependent agent list does not mandate that one must look to the formulation as a whole to determine an excipient's role. This is especially true when one considers that the patent identifies 19 non-overlapping non-pH-dependent sustained release agents or groups of agents, and 18 non-overlapping pH-dependent agents or groups of agents.

Because the patent provides no information regarding how the contents of the formulation can influence a component's behavior in the formulation, adding the phrase "when the claimed composition is formulated" provides no clarity to the meaning of this claim term and finds no support in the intrinsic record.

d. No Support Exists for Including the Phrase "Gastrointestinal pH"

Plaintiffs' inclusion of "gastrointestinal pH" in their proposed construction is unsupported by the patent claims and the specification.

While the patent generally relates to pharmaceutical compositions, the patentees never expressly limited their claimed technology to gastrointestinal pH in the patent specification or file history. The term "gastrointestinal" does not appear anywhere in the '599 specification. Additionally, Plaintiffs can identify only a single sentence in the specification to support their construction that the relevant pH should be limited to gastrointestinal pH; however, the cited support merely identifies a potential problem that may occur when formulating basic drugs in compressed matrix tablets. (Ex. 4 to Olinger Decl., '599 patent at col. 1, ll. 25-27 ("Compressed matrix tablets containing a basic drug often give a faster dissolution profile in simulated gastric fluid, having a pH about 1.0, than in simulated intestinal fluid (pH 6.8 to 7.4).").) Identifying a potential problem that may occur in a subset of the allegedly inventive formulations hardly rises to the express statement required to limit the scope of the claims. *See Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004) (*quoting Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir.

2002)) ("Even when the specification describes only a single embodiment, the claims of the patent will 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.'"). Further, the patent uses the term pH extensively throughout the specification, but only once references a specific medium. The patentees had every opportunity during prosecution to limit the pH to be considered to "gastrointestinal pH," but they did not. Plaintiffs should not be allowed to do so at this stage.

Finally, including this phrase does not clarify the meaning of this claim term. Neither the patent nor Plaintiffs' brief indicates if this phrase defines the pH over the entire range of fluids in the gastrointestinal tract, if this phrase means a particular range of pHs, or if this phrase has some other meaning. Construing this term to include the undefined phrase "gastrointestinal pH" does not clarify what the claim term means, and instead adds confusion. Doing so contradicts the purposes of claim construction; therefore, "gastrointestinal pH" has no place in the proper construction of the claim term.

2. "pH-dependent agent that increases the rate of release of said at least one pharmaceutically active agent from the tablet at a pH in excess of 5.5"[12]

Watson's proposed construction of the term "pH-dependent agent that increases the rate of release of said at least one pharmaceutically active agent from the tablet at a pH in excess of 5.5" is a ***"substance, which does not function as a non-pH-dependent agent in the formulation, that increases the rate of release of the drug from the composition in surrounding media having a pH above 5.5."***

a. Watson's Proposed Construction Most Closely Follows the Claim Language

Watson's proposed construction most closely mirrors the claim language, clarifies the claim term, and stays true to the patentee's teachings in the specification. The claim's plain language

[12] Watson agrees with Impax that Plaintiffs' inconsistent positions and the specification's bare disclosures with respect to this term show that this term is indefinite under 35 U.S.C. § 112. If the patentees cannot consistently interpret their own patent, it would be impossible for the public to do so. However, to the extent the Court determines that this term can be construed, Watson offers that its proposed construction is the only construction possible based on the limited disclosures in the patent.

requires that this agent increase the rate of release of the pharmaceutically active agent at pHs above 5.5. Further, as discussed above, the pH-dependent agent cannot function as a non-pH-dependent sustained release agent in a single formulation. The specification provides no additional information regarding this claim term. Plaintiffs incorporate additional aspects into their construction of the term, but the additional aspects are unsupported by the specification and are litigation-guided.

Should Plaintiffs contend that Watson has not defined what about the pH-dependent agent depends on pH, Watson asserts that this is because the patent specification provides no information on this issue. In describing the pH-dependent agent, the patent merely identifies three classes of agents that are included within the scope of this claim term: (1) polymers that swell at a pH in excess of 5.5; (2) enteric agents; and, (3) agents that increase the solubility of the pharmaceutically active agent at a pH greater than 5.5, by maintaining an acidic microenvironment in the tablet. The patent is silent as to how these three classes of agents behave at pHs at or below 5.5 and what impact these agents have on the rate of release of the pharmaceutically active agents at pHs at or below 5.5. Thus, the specification does not explain how these agents depend on pH. Further, because the patent explicitly states that agents that satisfy the term pH-dependent agent, "include, but are not limited to" these three broad categories of agents (Ex. 4 to Olinger Decl., '599 patent at col. 2, l. 10), a broad universe of agents could exist that qualify as pH-dependent agents, but for which the specification provides no information.

b. The pH-Dependent Agent Cannot Also Function as a Non-pH-Dependent Sustained Release Agent

For the reasons discussed *supra* in Section V.A.1.b, the pH-dependent agent necessarily cannot also function in the same formulation as a non-pH-dependent sustained release agent.

c. No Support Exists for Including the Phrase "When the Claimed Composition is Formulated"

For the reasons discussed *supra* in Section V.A.1.c, including the phrase "when the claimed composition is formulated" is not supported by the specification.

d. Comparing the Rate of Release Above 5.5 and Below 5.5 Is Unsupported by the Specification

Plaintiffs' argument that the pH-dependent agent "increases the rate of release of the active agent . . . in an environment having a pH above 5.5 over when the composition is . . . (i) in an environment having a pH of 5.5 or less" is unsupported by the specification.

The stated goal of the patents-in-suit is to provide pharmaceutical compositions with pH-independent or minimized pH-dependent active agent dissolution profiles. (*Id.* at col. 1, ll. 7-8.) Plaintiffs' construction of pH-dependent agent contradicts the patent's stated goal. Under Plaintiffs' proposed construction, the pH-dependent agent must increase the rate of release of the active drug at a pH above 5.5 such that the rate of release would be higher than the rate of release at a pH at or below 5.5. Such a dissolution profile would not be pH-independent or minimally pH-dependent. Accordingly, the resulting formulation would not be within the asserted scope of the invention.

e. The pH-Dependent Agent Must Cause the Increase in the Rate of Release at a pH above 5.5

The specification and claim 1 of the '599 expressly state that the pH-dependent agent must increase the rate of release of the active agent at a pH above 5.5. A pH-dependent agent must actually cause the increased release rate. Any construction that makes it optional for the pH-dependent agent to be responsible for increasing the release rate renders that claim language meaningless, and therefore, should not be permitted.

Yet under clause (ii) of their proposed construction, Plaintiffs propose exactly that. Plaintiffs offer that the pH-dependent agent "increases the rate of release of the active agent . . . from the composition in an environment having a pH above 5.5 over when the composition is either (i) in an environment having a pH of 5.5. or less, or (ii) when the composition is formulated without the pH-dependent agent." (Joint Claim Construction Statement, Dkt. No. 143, Ex. D at 8.) Watson believes that clause (ii) of Plaintiffs' proposed construction reflects the necessary result of including this agent in the formulation. Including the clause in the proposed construction is redundant.

According to the patent, the pH-dependent agent increases the rate of release of the active agent above a pH of 5.5. Patentees should not be allowed to claim an agent based on its function and

then propose a construction that makes the claimed function optional. Such a result would render the patentee's chosen claim language meaningless. Watson believes the proper course is not to include this clause, because it is understood that the agent must perform its designated function to satisfy the claim limitation. To the extent that the Court agrees with Plaintiffs that both clauses (i) and (ii) are proper claim limitations, Watson contends that the conjunction between the clauses should be "and" instead of "or." This reflects that the pH-dependent agent must cause the increase in rate of release.

3. "polymer that swells at a pH in excess of 5.5"

Watson's proposed construction of the term "polymer that swells at a pH in excess of 5.5" is ***"a molecule with many units joined to each other through chemical covalent bonds, often in a repeating manner, which expands in surrounding media having a pH above 5.5."***[13]

a. The Relevant pH is That of the Surrounding Media

The primary area of dispute with respect to the construction of this term is Watson's inclusion of the phrase "in surrounding media" to describe the medium whose pH varies. Plaintiffs' proposed construction includes the phrase "expands at a pH above 5.5," but does not indicate what object or medium has a pH above 5.5. The polymer's action (i.e., swelling) occurs in response to a variation in the pH of "something." Watson asserts that this something must be that of the surrounding media. Nothing in the specification suggests that the polymer itself has a variable pH. Thus, for the polymer to swell in response to a changing pH, the variable pH must be that of the surrounding media.

b. No Support Exists for Including the Phrase "When the Claimed Composition is Formulated"

For the reasons discussed *supra* in Section V.A.1.c, the inclusion of the phrase "when the claimed composition is formulated" is not supported by the specification.

[13] Watson does not object to Impax's proposal to include a non-exclusive list of excipients for this term.

4. "agent that increases the solubility of said at least one pharmaceutically active agent at a pH of greater than 5.5"

Watson's proposed construction of the term "agent that increases the solubility of said at least one pharmaceutically active agent at a pH of greater than 5.5" is a "***substance that increases the amount of the drug that will dissolve when the surrounding media has a pH above 5.5."***[14]

a. Watson Does Not Dispute That For Purposes Of This Patent, Solubility Can Be Equated To The Amount Dissolved

Watson does not dispute Plaintiffs' position that the common definition of solubility can be used for purposes of interpreting this claim term. Thus, Watson's proposed construction defines solubility as "amount of the drug that will dissolve."

b. No Support Exists for Including the Phrase "When the Claimed Composition is Formulated"

For the reasons discussed *supra* in Section V.A.1.c, the inclusion of the phrase "when the claimed composition is formulated" is not supported by the specification.

c. Comparison of the Solubility Above 5.5 and Below 5.5 Is Unsupported by the Specification

For the reasons discussed *supra* in Section V.A.2.d, the specification does not support including language regarding a comparison of the solubility above a pH of 5.5 versus at or below a pH of 5.5.

d. The Agent Must Cause the Increase in Solubility at a pH Above 5.5

For the reasons discussed *supra* in Section V.A.2.e, this agent must perform its designated function and any construction that would make this optional should not be considered.

[14] Watson does not object to Impax's proposal to include a non-exclusive list of excipients for this term.

5. "reducing the likelihood of side effects"

Watson's proposed construction of the term "reducing the likelihood of side effects" is ***"decreasing the incidence of side effects compared to administering the same amount of guanfacine as an immediate-release composition."***

a. The Specification Demonstrates that Likelihood is Best Understood as Incidence Rate

The specification of the '794 patent makes no reference to Plaintiffs' "probability" language, as Plaintiffs tacitly admit, but instead supports Watson's proposal to construe "likelihood" to mean "incidence rate." Example 5 of the '794 patent discusses the results of bioavailability testing performed to compare the effectiveness of a prior art immediate release anagrelide hydrochloride formulation with three allegedly inventive anagrelide hydrochloride extended release formulations. (Ex. 5 to Olinger Decl., '794 patent at col. 11, ll. 61-64.)[15] This same study also evaluated the safety and tolerability of the allegedly inventive extended release formulations in healthy volunteers. (*Id.* at col. 11, ll. 66-67.) Tables 9 and 10 of the '794 patent summarize data regarding the "adverse events" experienced with the extended release formulations. This data consists of "count" information, or the number of instances when a patient experienced side effects. (*Id.* at Table 9). This testing supports Watson's proposed construction. The patentees collected and reported data about the incidence rate of the side effects—not their probability. This data is the only information in the specification regarding decreasing the likelihood of side effects, and therefore, is the best indication of the patentee's definition of this term.

Plaintiffs assert that "the patent distinguishes the 'likelihood' of side effects from the number of side effects." (Pls.' Br. at 18 (citing '794 patent at col. 3, ll. 50-55.).) Therefore, they contend that the claim language "likelihood" should be construed to mean something other than "incidence."

[15] The '794 patent identifies anagrelide hydrochloride as another pH-dependent pharmaceutically active agent. (Ex. 5 to Olinger Decl., '794 patent at col. 1, l. 44) Example 5 is the only data disclosed in the specification regarding the likelihood of side effects associated with the administration of a particular pharmaceutically active agent. Even though this data does not relate to guanfacine, Watson asserts that this data provides sufficient insight into the proper construction for the term "likelihood of side effects."

Watson disagrees with the Plaintiffs' interpretation of this disclosure and the distinction being made. Watson interprets "number of side effects" to refer to the number of distinct side effects the formulation caused in a study whereas incidence rate refers to the number of times any side effect was reported. (*See* Ex. 5 to Olinger Decl., '794 patent at Example 5.) For example, instead of a patient experiencing three side effects (headaches, nausea, dizziness), the "number of side effects" could be reduced to two (headaches, nausea). This "number of side effects" is different from the "incidence rate," or how many times a side effect was experienced. Table 10 summarizes the testing results from Example 5 and shows that patients taking the claimed formulation suffered from a lower number of side effects (six, five, and four) when compared to patients taking the prior art immediate release formulation (ten). (*Id.* at Table 10.) These "numbers of side effects" associated with a formulation are distinct from those in the column "No. AEs Reported" in Table 10, where the patentees provide data on the incidence rate of side effects, *i.e.*, the number of times a specific side effect was reported. (*Id.*)

Thus, contrary to Plaintiffs' arguments, the specification demonstrates that "likelihood" should be construed to mean "incidence rate" and not "probability."

b. The Necessary Comparator is to Immediate Release Guanfacine Formulations

Watson also asserts that for side effects, the relevant comparison is between side effects experienced with guanfacine immediate release formulations and side effects experienced with guanfacine extended release formulations. Plaintiffs' proposed construction glosses over this issue. They construe this claim term to mean "reducing the probability of side effects resulting from guanfacine administration." However, in their opening brief, Plaintiffs concede that Watson's proposed comparison is appropriate. In describing the alleged benefits of the Intuniv product, Plaintiffs state:

> Guanfacine, prior to Shire's Intuniv product, had been sold by another pharmaceutical company in an immediate release formulation, called Tenex®, for the treatment of hypertension. However, Tenex® was ineffective in comparison to other hypertension drugs and was associated with various side effects that limited its suitability for some patients. . . . Shire's patented formulation, in addition to its sustained release of guanfacine, also reduces the probability of a patient suffering from guanfacine's side effect."

(Pls.' Br. at 5.) Plaintiffs thus implicitly agree that the reduction of side effects claimed by the '794 patent is a reduction in comparison to the immediate release guanfacine product, Tenex®. Watson asserts that its proposed construction is explicit about this comparison, and therefore is the proper construction of this term.

B. Additional Terms In Dispute

1. "agent that maintains an acidic microenvironment in the composition"

Watson's proposed construction of the term "agent that maintains an acidic microenvironment in the composition" is a ***"substance that keeps acidic, over a period of time, a region immediately around or in close proximity to the drug."*** [16]

The primary difference between Plaintiffs' proposed construction and Watson's proposed construction centers on the parties' description of microenvironment. Watson defines microenvironment as the "region immediately around or in close proximity to the drug." Watson's construction clarifies that microenvironment refers to the spatial area near the drug. Plaintiffs use the phrase "environment immediately around or in close proximity to the active agent," which fails to add clarity. "Environment" could refer to a spatial area, the medium in which the tablet is located, or some other unknown space. The purpose of claim construction is to add clarity to the meaning of claim terms. Watson's proposed construction provides this clarity, whereas Plaintiffs' proposed construction creates more ambiguity. Thus, Watson asserts that its proposed construction is the proper construction for this term.

2. "binding agent"

Plaintiffs and Watson agree that the term "binding agent" should be construed as a ***"substance that aids in the binding of ingredients in a tablet."*** [17]

[16] Watson does not object to Impax's proposal to include a non-exclusive list of excipients for this term.

[17] Watson does not object to Impax's proposal to include a non-exclusive list of excipients for this term.

3. "an amount effective to treat said attention deficit disorder or attention deficit with hyperactivity disorder in said patient"

Watson's proposed construction of the term "an amount effective to treat said attention deficit disorder or attention deficit with hyperactivity disorder in said patient" is ***"an amount of the composition sufficient to eliminate or reduce one or more symptoms of attention deficit disorder or attention deficit with hyperactivity disorder."***

The only issue in dispute is Plaintiffs' inclusion of the phrase "whether during a single application of the amount or repeated applications." Watson asserts that there is no support in the claim language or in the specification for including this phrase. In Claim 3 of the '794 where this term appears, the inventors specifically use the plain phrase "administering to said patient." This phrase connotes a single administration of guanfacine. Plaintiffs attempt to circumvent this claim's plain language by adding their suggested phrase, which would change "administering" to "administering or readministering." Because Plaintiffs' proposed construction would broaden the scope of the claim in direct contradiction to the claim's plain language, their proposal to include this phrase at the end of the term's construction should be rejected.

4. "a therapeutically effective amount of [the composition] comprising"

Watson's proposed construction of the term "a therapeutically effective amount of [the composition] comprising" is ***"an amount of the composition sufficient to eliminate or reduce one or more symptoms of one or more disease."***

Watson asserts that this term should be construed in a manner similar to "an amount effective to treat," because both claim terms address the "effective" treatment of a condition or disorder. Watson's proposed construction mirrors the agreed upon portions of the construction for "an amount effective to treat." Conversely, Plaintiffs' construction creates confusion and ambiguity, because one is left to guess what Plaintiffs mean by "improve" a condition. Plaintiffs identify no intrinsic or extrinsic evidence in support of their proposed construction that would clarify what it means to "improve" a condition. Because Watson's proposed construction is the only construction that adds clarity to this claim term and that is consistent with a similar claim term, Watson asserts that its

proposed construction is the proper construction of "therapeutically effective amount" of the composition.

VI. CONCLUSION

For the foregoing reasons, Watson respectfully requests that the Court adopt the constructions of claim terms Watson has proposed in the Watson's Defendants' proposed constructions attached as Exhibit G to the Joint Claim Construction and Prehearing Statement. (Dkt. No. 143.)

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s/ Laura Fahey Fritts
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