

Clarithromycin is a macrolide antibiotic used to treat bacterial infections, particularly those of the skin and upper respiratory system. Abbott held a patent on the immediate release version of clarithromycin, marketed as BIAXIN ®, until the patent expired on May 23, 2005. Abbott began marketing BIAXIN ® in the United States in approximately 1991. In 2000, Abbott was issued two formulation patents (the '616 and the '718 patents) on an extended release formulation of clarithromycin. Abbott began marketing this extended release formulation under the name BIAXIN ® XL in 2000. As of May 2005, Abbott estimated that BIAXIN ® XL accounted for approximately 70% of the sales in the BIAXIN ® market. Generic competitors entered the market for immediate release clarithromycin on May 24, 2005.

Abbott filed for separate preliminary injunctions against Andrx Pharmaceuticals, Inc. ("Andrx") and Teva Pharmaceuticals USA, Inc. ("Teva") in this Court. This Court held hearings and entered preliminary injunction orders against Teva and against Andrx. The Federal Circuit Court of Appeals, in an opinion authored by Circuit Judge Prost, vacated the preliminary injunction order against Teva on June 22, 2006. Teva and Abbott subsequently entered into a settlement agreement. Andrx also appealed the preliminary injunction order entered against it. The Federal Circuit, in an opinion again authored by Circuit Judge Prost, affirmed that preliminary injunction against Andrx on January 5, 2007.

Sandoz has brought to market a generic version of an extended release clarithromycin product that undoubtedly will cause Abbott some loss of market position. Thus, Abbott here seeks to stop Sandoz's intrusion upon the market for extended release clarithromycin products. Abbott previously moved this Court for a temporary restraining order against Sandoz. This Court denied Abbott's motion because of the practical effect of the Federal Circuit's holding in

the Teva case, this Court could not issue a temporary restraining order based on the limited record before it. *Abbott Laboratories v. Sandoz, Inc.*, No. 05 C 5373, 2006 WL 3718025 (N.D.Ill. Dec. 15, 2006); *see also Abbott Laboratories v. Andrx Pharmaceuticals, Inc.*, 452 F.3d 1331 (*vacating Abbott Laboratories v. Andrx Pharmaceuticals, Inc., et. al.*, 2005 WL 1323435 (N.D.Ill. June 3, 2005)). Now, after having the benefit of a full hearing, this Court is able to better decide the merits of enjoining Sandoz from further selling or marketing its extended release formulation of clarithromycin.

II. STANDARD FOR PRELIMINARY INJUNCTION

A party seeking a preliminary injunction must make a four-part threshold showing that (1) the movant has some likelihood of success on the merits of the underlying litigation; (2) immediate irreparable harm will result if the relief is not granted; (3) the balance of hardships to the parties weighs in the movant's favor; and (4) the public interest is best served by granting the injunctive relief. *Polymer Techs., Inc. v. Bridwell*, 103 F.3d 970, 973 (Fed. Cir. 1996).

III. DISCUSSION

The '718 and '616 patents at issue here, have already been analyzed by both this Court and the Federal Circuit Court of Appeals, most recently in upholding this Court's grant of a preliminary injunction in a separate but related case. In the Teva case, Abbott secured a preliminary injunction against another generic drugmaker, Teva, that was trying to come to market with its own extended release clarithromycin product. 452 F.3d at 1332. For purposes of the motion, Teva conceded that its generic extended release clarithromycin product infringed upon the '718 patent. *Id.* at 1333. However, Teva raised the defense that Abbott's '718 patent claims 2, 4 and 6 were invalid for obviousness under 35 U.S.C. § 103. *Id.* This Court found that

Teva had failed to raise a substantial question as to the validity of Abbott's claims 2, 4 and 6. *Id.* On appeal, the Federal Circuit vacated the Order of this Court. *Id.* It held that this Court erred in assessing the content of prior art, which in the Federal Circuit's view, supported Teva's arguments and it held further that Teva had indeed demonstrated a substantial question regarding the validity of the '718 patent's claims 2,4 and 6. *Id.* at 1348.

In the Andrx case, Abbott also obtained a preliminary injunction against a generic drugmaker, Andrx, who was trying to come to market with yet another extended release clarithromycin product. *Abbott Laboratories v. Andrx Pharmaceuticals, Inc.*, 473 F.3d 1196, 1198 (Fed. Cir. January 5, 2007). Andrx argued that its product did not infringe any claims of Abbott's asserted patents, either literally or under the doctrine of equivalents. *Id.* at 1199. Furthermore, Andrx asserted that the '718, '616 and '407 patents were invalid because of indefiniteness under 35 U.S.C. § 112; and the '718 and '616 patents were invalid as anticipated under 35 U.S.C. § 102(b) and invalid for obviousness 35 U.S.C. § 103. *Id.* This Court held that Abbott had shown a likelihood of success on its claims that Andrx infringed claims 1, 4, and 6 of the 718 patent under the doctrine of equivalents; induced and contributed to infringement under the doctrine of equivalents of claim 2 of the '616 patent; and literally infringed claims 8 and 16 of the '407 patent. 473 F.3d at 1200. This Court also held that Andrx did not meet its burden of raising a substantial question of invalidity as to any of the patents in suit. *Id.* On appeal, the Federal Circuit affirmed the Order of this Court. *Id.* at 1213. However, it held that this Court erred in construing the claims of the '718 patent by narrowing the scope of the claim term "pharmaceutically acceptable polymer." *Id.* Now Abbott seeks a preliminary injunction against

Sandoz for manufacturing and selling a generic extended release product that infringes on its patents' claims.

A. Likelihood of Success on the Merits

In order to demonstrate a likelihood of success on the merits, the movant (Abbott) must show, in light of the presumptions and burdens that will be present at any eventual trial on the merits, that it is likely to prove that the non-movant (Sandoz) infringed the patents in suit, and that any of the non-movant's challenges to the validity and enforcement of its asserted patents lack substantial merit. *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350-51 (Fed. Cir. 2001). Patents are presumed to be valid, 35 U.S.C. § 282 (2002), and at trial, the party raising a validity challenge must prove invalidity by clear and convincing evidence. *Gemmy Indus. Corp. v. Chrisha Creations Ltd.*, 452 F.3d 1353, 1358 (Fed. Cir. 2006). This presumption does not relieve a patentee who moves for a preliminary injunction from carrying its normal burden of demonstrating a likelihood of success on all disputed liability issues at trial, including validity. *See Canon Computer Sys., Inc. v. Nu-Kote Intern., Inc.*, 134 F.3d 1085, 1088 (Fed. Cir. 1998).

A validity challenge at the preliminary injunction stage can succeed on evidence that would not support a judgment of validity at trial. 239 F.3d at 1359. "Vulnerability is the issue at the preliminary injunction stage, while validity is the issue at trial." *Id.* The alleged infringer must identify at least some persuasive evidence of invalidity at this early stage to overcome the presumption of validity. *Pharmacia & Upjohn Co. v. Ranbaxy Pharmaceuticals, Inc.*, 274 F. Supp. 2d 597, 601 (N.D. Ill. 2003). The patentee also is held to a less stringent standard and must only present a "clear case supporting the validity of the patent in suit." *Id.* A patentee can

make such a case by showing, for example, that the patent in suit has withstood previous validity challenges in other proceedings or benefitted from a long period of industry acquiescence in its validity.

Abbott asserts that it is likely to succeed on the merits because at trial it will likely prove infringement of one or more of the claims of the '718 and '616 patents in suit. Abbott also contends that it likely will demonstrate that Sandoz's challenges to the validity of the patents in suit lack substantial merit.

1. Inequitable Conduct

Sandoz alleges that Abbott engaged in inequitable conduct when prosecuting the '718 and '616 patents. This Court will analyze Sandoz's claim that Abbott engaged in inequitable conduct before addressing the issues of infringement and validity. A finding of inequitable conduct that would warrant holding the patents at issue to be unenforceable would render this dispute moot. *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 877 (Fed. Cir. 1998).

a. Standard for Inequitable Conduct

Inequitable conduct occurs when a patent applicant violates his or her "duty of candor and good faith..., which includes a duty to disclose to the Office all information known to that individual to be material to patentability...." 37 C.F.R. §1.56(a) (2007); *Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1350-1 (Fed. Cir. 2005). A court will hold a patent unenforceable due to inequitable conduct if there is clear and convincing evidence that the applicant while prosecuting the patent at issue, (1) made an affirmative misrepresentation of material fact, failed to disclose material information, or submitted false

material information, and (2) intended to deceive the U.S. Patent and Trademark Office (“PTO”).
Impax Labs., Inc. v. Aventis Pharm. Inc., 468 F.3d 1366, 1374 (Fed. Cir. 2006).

b. Sandoz’s Allegations

(1) ‘718 Patent

Sandoz contends that during the prosecution of the ‘718 and the ‘616 patents, Abbott failed to disclose material information, selectively withheld information that contradicted assertions made in its patent claims, and submitted information to the PTO that contained material misrepresentations of fact. In particular, Linda Gustavson submitted a declaration to the PTO in support of the ‘718 patent prosecution. In this declaration, Gustavson claimed a statistical test demonstrated the maximum plasma concentration (“C-max”) of the extended-release clarithromycin (the claimed composition) was statistically significantly lower than the C-max of the immediate-release clarithromycin (a prior art composition). Sandoz contends that Abbott breached its duty of candor by submitting the Gustavson declaration because (1) it did not assert what Gustavson declared it did and (2) the data on which the declaration was based was improper, and Abbott should have disclosed the nature of the data. Sandoz asserts that the data on which Gustavson relied did not in fact show a “statistically significant” difference in C-max for the extended-release and immediate-release formulations and that Gustavson did not perform any such statistical test nor did she even know how to perform one. Also, Sandoz claims that the data was derived from an improper cross-study involving *different* study participants instead of the *same* study participants.

Sandoz also claims Abbott withheld information from the PTO that contradicts Abbott’s claims that BIAXIN® XL has a statistically significantly lower mean fluctuation index (“DFL”)

in the plasma than an immediate release composition. Specifically, Abbott claimed that the mean DFL values for a modified release version of clarithromycin claimed by a prior patent, the '190 patent, were substantially equal to the mean DFL values for the immediate release version of clarithromycin. However, while the '718 patent was pending, Abbott and more specifically, Gustavson, became aware that the mean DFL values for a modified release version of clarithromycin claimed by '190 patent were actually statistically significantly lower than the immediate release composition. Thus, Sandoz concludes, this evidence tends to show that BIAXIN ® XL has the same pharmacokinetic (“PK”) properties as the modified release formulation covered by the prior art patent; a material fact according to Sandoz.

Abbott also claimed in its patent prosecutions that its extended release formulation provided reduced taste perversion¹ compared to its immediate release formulation. Sandoz alleges that Abbott failed to disclose relevant data to the PTO from two of its own studies that cast doubt on this assertion: the double-blind Acute Bacterial Exacerbation of Chronic Bronchitis study (the “bronchitis study”) and the Acute Maxillary Sinusitis study (the “sinusitis study”). The prosecution history reveals that Abbott supported its assertions about improved taste perversion by citing the results of a 24-subject pilot study which allegedly showed a two- to three-fold improvement in taste perversion of the extended release product over the immediate release formulation. The bronchitis and sinusitis studies, by contrast, involved 910 subjects and were described as “two well-controlled, double-blind clinical trials” “conducted to compare the

¹ Taste perversion is defined in the '718 patent as “the perception of a bitter metallic taste normally associated with the erythromycin derivatives, particularly, with clarithromycin.” U.S. Pat. No. 6,010,718, at 3:53-55. “Taste profile,” a related term which the patent specifications at issue use as an apparent synonym for taste perversion, is not defined in the specification.

safety and efficacy of extended release clarithromycin and immediate release clarithromycin.”
See, e.g., U.S. Pat. No. 6,872,407, at 11:27-30. Generally, larger study samples produce statistically more reliable results. Abbott collected data about a wide range of reported side effects in the bronchitis and sinusitis studies, including both gastrointestinal side effects and taste perversion. Yet only the gastrointestinal side effects data was reported to the PTO. Sandoz avers that the taste perversion data from the clinical studies failed to support Abbott’s contention that extended release clarithromycin had improved taste perversion over immediate release. Further, Sandoz states that Abbott was aware of the taste perversion results, that the results were material to Abbott’s patent application, and that Abbott intentionally withheld the results in order to receive the patent.

Sandoz states the final reports on the two clinical studies was completed in April 1999. Yet, according to Sandoz, the BIAXIN® XL label submitted to the FDA in May of 1999 stated that three percent of patients taking immediate release BIAXIN® reported incidences of taste perversion while six percent of patients taking extended release BIAXIN® XL reported incidences of taste perversion. Thus Sandoz alleges that Abbott had evidence that its taste perversion claims of BIAXIN® XL were incorrect and it intentionally withheld this information from the PTO.

(2) ‘616 Patent

Sandoz also alleges that the ‘616 patent is unenforceable because it is a continuation-in-part of the ‘718 patent. Sandoz contends that the unenforceability of a parent patent for inequitable conduct infects the later-issued descendants of that patent. However, unenforceability of a parent patent for inequitable conduct does not automatically render the

later-issued descendants of that patent unenforceable. *Cordis Corp. v. Boston Sci. Corp.*, 188 Fed. Appx. 984, 986 (Fed. Cir. 2006). In fact, when determining whether later-issued descendants of a parent patent that has been found to be unenforceable are themselves unenforceable, a court must determine whether inequitable conduct occurred during the prosecution of the descendant patents or “whether the ‘inequitable conduct in prosecuting the [parent] patent had immediate and necessary relation to the . . . enforcement of the [child] patents.’” *Id.* (quoting *Consol. Aluminum Corp. v. Foseco Int’l Ltd.*, 910 F. 2d 804, 810-811 (Fed. Cir. 1990). Sandoz does not address the ‘616 patent’s immediate and necessary relation to the ‘718 patent. Sandoz does, however, contend that the prosecution of the ‘616 patent was tainted by its own inequitable conduct.

Sandoz alleges that Abbott had data from its studies showing no reduction in the incidences of adverse gastrointestinal (“GI”) events after taking extended release clarithromycin, contrary to the claims of the ‘616 patent. Sandoz contends that Abbott withheld this information from the PTO, choosing only to present data on the reduced number of patients who dropped out of the studies due to incidences of adverse GI events. Use of such drop-out data instead of the data showing no reductions in the number of incidences of adverse GI events was improper and misleading.

Sandoz also alleges inequitable conduct on the part of Abbott in filing its ‘616 application with claims of improved taste profile even though it had evidence from its two clinical studies that allegedly contradicted those then-pending claims. A month before filing the ‘616 patent application, the same inventors who co-authored the clinical study reports attended a

conference where they publicized only certain elements of their data, not the taste-perversion data that contradicted the then-pending claims.

c. Abbott's Response

(1) '718 Patent

Abbott contends that its actions during the prosecution of the '718 and '616 patents did not amount to inequitable conduct. Abbott first states that Gustavson's declaration of a "statistically significant" difference in C_{max} for the extended-release and immediate-release formulations and the admission that Gustavson did not perform any such statistical test nor did she even know how to perform one is immaterial. Abbott asserts that no claim of the '718 patent requires the ER formulation to have a statistically significant lower C_{max} than the IR formulation. Furthermore, Abbott argues that Sandoz has failed to allege any evidence that Gustavson made the statement with an intent to deceive, rather than out of a simple mistaken belief.

Regarding the propriety of the data Gustavson used to reach her conclusions that there was a "statistically significant" difference in C_{max} for the extended release and immediate release formulations, Abbott concedes that crossover comparisons are generally more reliable than cross-study comparisons. However, Abbott has provided evidence that such cross-study comparisons are fairly common and not indicative of fraud; especially in the instant case given that Gustavson declared that "pharmacokinetics studies were conducted in similar groups." Thus, by declaring to the PTO that she used multiple studies, instead of a single study, using similar groups, as opposed to the same subjects, Abbott satisfied its duty of candor to the PTO.

Abbott also regards Sandoz's argument that it withheld information that contradicted its claim that the extended release version of clarithromycin have a statistically significantly lower DFL than the immediate release version of clarithromycin to be specious. According to Abbott, its internal study W98-268 showed that the extended release version did in fact have a statistically significantly lower DFL than the immediate release version. The results from study W98-268 showed the modified release version's DFL was lower than the DFL of immediate release version of clarithromycin (1.94 \ll 2.22). At that time Dr. Gustavson was aware of other studies that showed the modified release version did not have a statistically significantly lower DFL than the immediate release version. Thus, one showing of a lower DFL did not suggest to Gustavson that a statistically significantly lower DFL was a property of the modified release version of clarithromycin.

Abbott also claims that it satisfied its duty to candor with regard to its claims of reduced incidence of taste perversion. Abbott states that the information it presented to the PTO adequately supported its claim for reduced incidence of taste perversion and was found to be acceptable by the PTO. Next, Abbott contends that neither the prosecuting attorney nor the inventors were aware of the taste perversion data from the bronchitis and sinusitis studies during the prosecution of the '718 patent. Semla and Gustavson testified at deposition that they never saw the clinical study reports and did not know of the taste perversion results. Abbott asserts that Semla, who was the lead formulator on the '718, had no responsibilities for clinical studies and did not receive phase III clinical study reports such as these. Gustavson was a pharmacokineticist who performed PK analyses, but in clinical studies, her duties were limited to interpreting blood concentration data only; she had no involvement with clinical studies that

measured side effects. Three of the remaining four inventors on the '718 patent also were formulators with no responsibilities for phase III clinical studies. Sheri Crampton, the final inventor, was the only one with any responsibilities for clinical trials, but she left Abbott on August 18, 1998, seven months before the reports on the sinusitis and bronchitis studies were completed.

Lastly, Abbott asserts that the Biaxin ® label, which states that the taste perversion incidence rate of the immediate-release formulation is 3% while that of the extended release formulation is 6%, is not actually relevant to its claims of reduced incidence of taste perversion. Abbott explains that the 3% rate was derived from a combination of 500 milligram (“mg”) and 1000 mg dosage studies whereas the 6% rate was based on studies utilizing 1000 mg dosages only. Furthermore, Gustavson claims she never reviewed this part of the label as it dealt with side effects; not pharmacokinetics, her speciality.

(2) '616 Patent

With respect to the '616 patent, Abbott contends that it did not withhold taste perversion data with the requisite intent to deceive. Abbott emphasizes that the '616 patent was a continuation-in-part of the '718 patent, whose application originally included the taste perversion claim originally filed in the '718 application. According to Abbott, that claim was withdrawn contemporaneously with the submission of the signed inventor oaths with the '616 application. Thus, Abbott contends that for this Court to find inequitable conduct based upon the withdrawn claim would be inconsistent with Federal Circuit precedent that states that references that are material only to withdrawn claims cannot form the basis of a finding of inequitable

conduct. *Scripps Clinic & Research Found. v. Genetech, Inc.*, 927 F.2d 1565, 1583 (Fed. Cir. 1991).

Abbott explains that the claims of the '616 patent refer to the clarithromycin formulation as producing a "method for reducing adverse gastrointestinal side effects." According to Abbott, the side-effect improvements discussed in the '616 patent include both the most severe GI side effects and the patient discontinuations due to GI side effects, not the overall incidence rates of GI side effects. The incidence data provided in the patent specification actually shows the two formulations of clarithromycin to have similar overall GI side effect incidence rates. Thus, since the incidence data from the two studies merely corroborated data that was already present in the patent, the data was cumulative and not material. *See* 37 C.F.R. §1.56(b).

In response to Sandoz's argument that it improperly submitted data on the severity of the GI side effects, Abbott first states that this data has no relevance to the prosecution of the '616 patent claims. Second, Abbott asserts that the rating scale it used is not misleading and is commonly used in clinical studies.

d. Analysis

In evaluating materiality, this Court refers to the definition provided in 37 C.F.R. §1.56. *See, e.g., Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1352 (Fed. Cir. 2005) (citing *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997)). The rule defines information as material to patentability when:

[I]t is not cumulative to information already of record or being made of record in the application, and
 (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
 (2) It refutes, or is inconsistent with a position the applicant takes in:

- (I) Opposing an argument of unpatentability relied on by the Office, or
- (ii) Asserting an argument of patentability.²

37 C.F.R. §1.56(b).

(1) '718 Patent

Cmax data

Sandoz contends that Abbott breached its duty of candor when it submitted the Linda Gustavson declaration stating that the Cmax of the claimed extended release composition of clarithromycin was statistically significantly lower than the Cmax of a prior art composition (immediate release pediatric suspension formulation) of clarithromycin, when in fact it was not statistically significantly lower. Abbott asserts that the statement was immaterial because it had no bearing on any claim of the '718 patent. Claim 4 of the '718 patent claims in relevant part that "... maximum peak concentrations of the erythromycin derivative are lower than those produced by an immediate release pharmaceutical composition..." This Court finds that the Gustavson declaration that the Cmax of the extended release clarithromycin was statistically significantly lower than the Cmax of the prior-art composition of clarithromycin was not material to patentability.

The PTO had rejected the claims of the '718 application and had issued Abbott a challenge to show that its product did not have the same PK properties of the prior art product. Abbott made clear that the purpose of the Gustavson declaration was to clarify to the PTO that

² The rule continues: "[i]n any continuation-in-part application, the duty under this section includes the duty to disclose to the Office all information known to the person to be material to patentability, as defined in paragraph (b) of this section, which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-art application." 37 C.F.R. § 1.56(e) (2007).

the prior art of the '411 patent was different from the '718 patent. So, the statement obviously had relevance on the difference between the extended release formulation and the prior art formulation. However, neither party disputes that the extended release formulation was indeed pharmacokinetically different from the prior art immediate release suspension formulation, just as Abbott had asserted to the PTO. Given the accuracy of the ultimate conclusion- that the extended release formulation was indeed different from the immediate release suspension formulation, Gustavson's declaration of a "statistically significantly lower" Cmax is immaterial despite the fact that it satisfies the definition of "material" provided by 37 C.F.R. §1.56(b). There still must be a showing of a substantial likelihood that a reasonable examiner would consider the statement important in deciding whether to allow the application to issue as a patent. *See Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1364 (Fed.Cir. 2007).

Abbott has submitted evidence that the Cmax of the extended release formulation was in fact lower than the Cmax of the immediate release suspension formulation. *Declaration of Linda Gustavson in Support of Abbott Laboratories' Motion for a Preliminary Injunction*, ¶31. Sandoz has not submitted any evidence to the contrary. Since 1) no claim of the '718 patent requires the extended release formulation to have a statistically significant lower Cmax than the immediate release formulation; 2) the data in fact shows the Cmax of the extended release formulation to be lower (albeit not statistically significantly lower) than the Cmax of the immediate release formulation; and 3) the extended release formulation was in fact pharmacokinetically different from the immediate release suspension formulation, it is more likely than not that the PTO would not have found the "statistically significantly lower" statement to be important. Therefore, this

Court declines to find that the statement was material to the PTO's decision to issue the '718 patent.

Sandoz has failed to explain why a reasonable examiner would assign any importance to Gustavson's statement in evaluating whether the C_{max} of the extended release formulation was indeed lower than the C_{max} of the immediate release formulation. Since this Court finds the Gustavson statement to be immaterial, the specifics of how she arrived at the statement are also immaterial.

DFL Data

Sandoz takes issue with Gustavson's use of a cross-study comparison instead of a crossover comparison study. Sandoz has presented evidence that generally, crossover comparisons yield more accurate results than cross-study comparisons. Abbott submitted evidence that Gustavson disclosed the nature of the cross-study data to the PTO, thus leaving the PTO to freely accept or reject her conclusions drawn from the data. This Court finds that Gustavson, and thus Abbott, did not breach the duty of disclosure here because Gustavson's Rule 132 declaration explicitly stated that she drew her conclusions from data gathered from "pharmacokinetic studies" that were conducted "in similar groups of subjects." Thus, Abbott had informed the PTO of the origin of the data even though it did not explicitly state: "This data was derived from a cross-study comparison."

The final problem with Gustavson's declaration regarding C_{max} values is that she did not actually perform a statistical test to verify her assertion of statistical significance. While it is obviously troublesome that Gustavson made her assertion without having actually performed the statistical test, it does not amount to a material omission or misrepresentation for the same

reasons outlined above. The extended release formulation is different from the immediate release suspension formulation. The data suggested to Gustavson that the Cmax of the former was actually lower than that of the latter. Simply put, the fact that Gustavson did not perform a statistical test was not material to the patentability of the '718 application.

Sandoz also claims Abbott intentionally withheld material information regarding the DFL of the extended release clarithromycin formulation from the PTO while the '718 patent was being prosecuted. Abbott responds that the information was not material. Claim 1 of the '718 patent states in relevant part that "the [extended release] composition induces statistically significantly lower mean fluctuation index in the plasma than an immediate release composition of the erythromycin derivative" Abbott claimed that the mean DFL values for a modified release version of clarithromycin claimed by a prior patent, the '190 patent, were substantially equal to the mean DFL values for the immediate release version of clarithromycin. However, while the '718 patent was pending, Abbott and more specifically, Gustavson, became aware that the mean DFL values for a modified release version of clarithromycin claimed by '190 patent were actually statistically significantly lower than the immediate release composition through an internal Abbott study, Study W98-268.

The final report of Study W98-268 states that the modified release formulation exhibited a statistically significantly lower mean DFL than that for the immediate release formulation. Similarly the extended release formulation also exhibited a statistically significantly lower mean DFL than that for the immediate release formulation. The specification of the '718 patent states in relevant part that "[t]he mean DFL values for the controlled release formulation and for the IR

are substantially equal in value...”³ U.S. Patent No. 6,010,718 col.11:1.18-19 (filed Apr. 11, 1997). Abbott knew of the report of Study W98-268 but did not disclose it to the PTO. Abbott basically treated the result of modified release being nearly equal to immediate release as an aberration since it chose to rely on the results of several other studies that showed differing mean DFL values. The situation can be summarized as follows:

‘718 patent specification	MR = IR; implies MR \neq ER
‘718 patent claim 1	ER \ll IR
Study W98-268 final report	MR < IR ER \ll IR
Three other studies	MR > IR MR < IR MR \gg IR
Gustavson’s Conclusion	MR \approx IR despite results of Study W98-268

Simply put, this Court fails to see the relevance of Sandoz’s argument. Sandoz claims that the results of Study W98-268 contradict the claim 1 requirement that the extended release formulation have a statistically significantly lower DFL than the immediate release formulation and that is why Abbott did not disclose it to the PTO. But claim 1 speaks of the PK relationship of extended release and immediate release formulations, not of modified release and immediate release formulations. Undisclosed information is material if it satisfies 37 C.F.R. §1.56(b) and if there is a substantial likelihood that a reasonable examiner would have considered the undisclosed information important in deciding whether to allow the patent to issue. *See Cargill,*

³ Here, the term “controlled release” is identical to the term “modified release”.

Inc., 476 F.3d at 1364 . Abbott has submitted evidence demonstrating the Study W98-268 results differed from the results of three other studies. Furthermore, Abbott also submitted evidence showing a mean DFL value consistently lower than the mean DFL value for the IR formulation is not a static characteristic of the MR formulation. Abbott has also demonstrated that the totality of the evidence suggests the DFL of the MR formulation is not consistently lower than the DFL for the IR formulation. Yet there is no evidence showing the DFL of the ER formulation to be anything but consistently statistically significantly lower than the DFL of the IR formulation. Thus, contrary to Sandoz’s assertion, Study W98-268 does not demonstrate that the prior art MR formulation has the same broad PK properties as those claimed for the ER formulation. Therefore, Study W98-268 is not material to the patentability of the ‘718 patent.

Taste Perversion Data

Sandoz’s first argument regarding the taste perversion data found in Table VI of the ‘718 patent is without merit. Sandoz does not allege that the data is false or misleading, but rather that it simply does not demonstrate what Abbott purported. Specifically, Sandoz alleges Abbott committed inequitable conduct because it did not tell the PTO that there was no difference statistically in the adverse events of the extended and immediate release clarithromycin. Since this data was before the PTO, this Court presumes the PTO had every opportunity to review it when prosecuting claim 6. Claim 6 of the ‘718 patent states the extended release formulation has “an improved taste profile as compared to the immediate release formulation.” Sandoz submitted the declaration of an expert biostatistician, Dr. Pagano, concluding that the data of Table VI does not provide any support for claim 6. Declaration of Dr. Marcello Pagano, ¶11. However, Dr. Pagano’s own analysis reveals that five out of twenty-three patients experienced

taste perversion under the immediate release regimen only, while one patient out of twenty-four experienced taste perversion under the extended release regimen A only and one patient out of twenty-three experienced taste perversion under the extended release regimen B only, respectively. When comparing the ratio of 5/23 to the ratios of 1/24 and 1/23, it is readily apparent that some improvement is a justifiable conclusion. Abbott was not under any obligation to show a statistical difference to support claim 6, just some improvement.

Sandoz is correct in asserting that the results of the two clinical studies were material to the patentability of the '718 patent.⁴ First, the results directly refute Abbott's claims that extended release clarithromycin results in reduced taste perversion. *See* 37 C.F.R. §1.56(b)(2)(ii) (2007). By contrast, they indicate that the extended release formulation offers no improvement over the immediate release formulation. The results were not cumulative of other evidence before the PTO; the only other evidence relating to taste perversion was the 24-subject pilot study discussed in the specification of the three patents. These results were material to the prosecution of the '718 patent because it contained a claim for improved taste perversion over immediate release clarithromycin.

With respect to intent, this Court previously found that Ranbaxy had not demonstrated a substantial question that it could show intent to deceive the PTO in the prosecution of the '718 patent under the same facts as presented here. *Ranbaxy Labs. Ltd. v. Abbott Labs., Abbott Labs. v. Andrx Pharms. Inc.*, Nos. 04 C 8078, 05 C 1490 (N.D.Ill. Nov. 10, 2005) The prosecution of the patent and the clinical studies occurred contemporaneously. This Court accepted Abbott's explanation that the difference between its submissions to the FDA and the PTO was that the

⁴ These results were also material to the patentability of the '616 patent.

“submission of studies to the FDA [was] of no moment, given that the ‘718 inventors’ roles with respect to the FDA submission, to the extent they were involved at all, had nothing to do with adverse event data.” Sandoz has not offered any new evidence supported an inference of intent to deceive. Abbott has submitted declarations of the ‘718 inventors and prosecuting attorney, each stating that she was unaware of the data at the relevant times. Since Sandoz has not yet demonstrated a substantial question that it can show intent to deceive the PTO in the prosecution of the ‘718 patent, this Court declines to find Abbott engaged in inequitable conduct by withholding the results of the two clinical studies.

Lastly, Sandoz argues that Abbott withheld material labeling data from the PTO. Sandoz contends that the label is material because it contains information that contradicts claim 6 of the ‘718 patent of an improved taste profile. The label states that the taste perversion incidence rate of the immediate-release formulation is 3% while that of the extended-release formulation is 6%. Abbott claims the label is not material because these incidence rates came from different tests involving different dosages and that incidence of side effects is related to dosage. Sandoz retorts that there is no dosage limitation contained in claim 6.

Through Gustavson’s declaration and the supplemental declaration of Professor Stanley Davis, Abbott contends that given the differences in dosages, a person of ordinary skill in the art would find a comparison of the two percentages to be useless in determining whether the extended release formulation results in an improved taste profile over the immediate release formulation. Gustavson declares that the Biaxin ® IR was administered in dosages of 500mg and 1000mg per day. Davis declares that the Biaxin ® IR was administered primarily in dosages

of 250mg BID.⁵ Both declare that the Biaxin ® XL was administered in 1000mg dosages per day. The labeling data is material under 37 C.F.R. §1.56(b). It was not cumulative to information already of record or being made of record in the application, and it is (at least superficially) inconsistent with a position the applicant took in asserting an argument of patentability. Again, the relevant inquiry is whether a reasonable examiner would have found the data to be important in determining whether the patent should have issued.

Sandoz is correct that claim 6 contains no limitation on dosage. However, Abbott asserts (and Sandoz does not disagree) that the dosage of the drug affects the incidence of side effects. Taste perversion is a side effect. Thus, Abbott contends that because these incidence rates derive from studies based on different dosages of the two formulations, a person of ordinary skill would not have found a comparison of the two incidence rates important in the prosecution of the claim of an improved taste profile. Although this Court disagrees with Abbott's use of a "person of ordinary skill", it nonetheless finds that the labeling data was not material to patentability.

Materiality is determined from the point of view of the reasonable examiner, not the subjective view of the patentee. *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1238 (Fed. Cir. 2003). Although the labeling information deals with the incidence rates of taste perversion, Abbott has submitted evidence that demonstrates that the data is not actually probative of whether or not the extended release formulation has an improved taste over the immediate release profile. While information may be material even if its disclosure would not have rendered the invention unpatentable, *Digital Control, Inc. v. Charles Mach. Works*, 437 F.3d 1309, 1318 (Fed. Cir. 2006), information is not material if there is not a substantial

⁵ BID is an abbreviated term that means the dosage was administered twice a day.

likelihood that a reasonable examiner would consider the statement important in deciding whether to allow the application to issue as a patent. *See Cargill, Inc.*, 476 F.3d at 1364. Therefore, this Court finds that the information regarding the incidence rates on the label submitted to the FDA was not material to patentability.

After considering the evidence, this Court declines to find persuasive evidence of inequitable conduct in the prosecution of the '718 patent.

(2) The '616 Patent

Taste Perversion Data

The '616 patent, as originally filed, included a claim for taste perversion. The results of the two clinical studies were therefore material to the patentability of that claim at the time of filing. The fact that the taste perversion claim was deleted shortly after filing, as Abbott asserts, does nothing to diminish the materiality of these results to the patent application at the time of filing. The abstract and specification for all three patents contain references to improved taste perversion and/or taste profile (a term Abbott uses synonymously with "taste perversion").⁶ However, Abbott argues that a finding of materiality is not warranted where claims have been withdrawn. *See Scripps Clinic & Research Fund. v. Genetech, Inc.*, 927 F.2d 1565, 1583 (Fed. Cir. 1991) (citing *Kimberly-Clark Corp. v. Johnson & Johnson Co.*, 745 F.2d 1437, 1457 (Fed.Cir. 1984)). Despite the fact that it withdrew the claim, Abbott filed the '616 application with knowledge of the results of the two studies. Those results were highly material to the claim at issue. These actions are enough to support an inference of an intent to deceive.

⁶ In the Abstract of the '718, the '616, and the '407 patents, the invention is described as having "an improved taste profile and reduced gastrointestinal side effects as compared to those for the immediate release composition." *See, e.g.*, the '616 patent, at (57).

“Intent need not be proved by direct evidence; it is most often proven by a showing of acts, the natural consequence of which are presumably intended by the actor.” *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1180 (Fed. Cir. 1995). Proof that non-disclosed information was highly material and that the patent applicant knew or should have known of that materiality makes it “difficult to show good faith to overcome an inference of intent to mislead.” *Semiconductor Energy Lab. Co., Ltd. v. Samsung Elecs. Co., Ltd.*, 204 F.3d 1368, 1375 (Fed. Cir. 2000) (citing *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997)). The clinical study results were highly material to the patent at issue. Moreover, the results were Abbott’s own proprietary information, at least until Abbott began to publish the results more broadly. Further complicating Abbott’s position is the fact that it submitted the complete results of the two clinical studies to the FDA in May 1999. Three of the named inventors on the ‘616 and ‘407 patent, Hom, Zhang, and Palmer, approved the reports of the two clinical studies, signing their names under a statement that they had read the reports and that the reports accurately stated the results of the studies. Two of the ‘616 inventors, Devcich and Zhang, were named authors on a 2001 journal article reciting the taste perversion results of the studies.

This Court finds, as a preliminary matter, that Sandoz has raised a substantial likelihood that it can show intent to deceive as to the ‘616 patent based upon the withholding of the results of the two studies. But this is not the end of the analysis; Sandoz has asserted other grounds for finding the ‘616 patent unenforceable.

GI Incidence Rates

Sandoz alleges that Abbott had data from its studies showing no actual reduction in the incidences of adverse GI events after taking extended-release clarithromycin. The '616 patent claims a method of reduction of "gastrointestinal adverse side effects". Sandoz contends that Abbott withheld this information from the PTO, choosing only to present data on the reduced number of patients who dropped out of the studies due to incidences of adverse GI events. According to Abbott, the improvements in "gastrointestinal adverse side effects" discussed in the '616 patent referred to 1) the most severe GI side effects and 2) the patient discontinuations due to GI side effects, not the overall incidence rates of GI side effects. The incidence data provided in the patent specification actually shows the two formulations of clarithromycin to have similar overall GI side effect incidence rates. *See* U.S. Patent No. 6,551,616 col. 11:l. 55- col. 12:l. 36 (filed Oct. 13, 1999). Thus, since the incidence data from the two studies merely corroborated data that was already present in the patent, the data was cumulative and not material. *See* 37 C.F.R. §1.56(b).

Abbott claims that the '616 patent invention provides a "method of reducing gastrointestinal adverse side effects". In a memorandum filed by Abbott on March 20, 2006, Abbott took the following position regarding construction of claim 1 of the '616 patent:

"[R]educing gastrointestinal adverse side effects," as used in claim 1 of the '616 patent, should be construed to mean a reduced incidence of gastrointestinal adverse side effects following ingestion of the ER clarithromycin formulation compared to an immediate release formulation, *including* reduced incidence of severe gastrointestinal adverse side effects and/or a reduced incidence of gastrointestinal side effects severe enough to cause patient or subject discontinuance of treatment. "Gastrointestinal adverse side effects" means those physiological effects to the gastrointestinal system which cause pain and discomfort to the individual subject.

The parties do not dispute the meaning of “gastrointestinal adverse side effects.” As Ranbaxy, Teva, Andrx, and Sandoz all note, examples of such effects *include* abdominal pain, constipation, diarrhea, dyspepsia, flatulence and nausea, all of which are listed in Table VI of the ‘616 patent.

Abbott Laboratories’ Memorandum in Support of Its Proposed Claim Construction, p. 26 (emphasis added). Sandoz’s own proposed construction did not differ very much from Abbott’s.

One of ordinary skill in the art would understand the term “gastrointestinal adverse side effects” to include adverse events in the digestive system, abdominal pain, constipation, diarrhea, dyspepsia, flatulence and nausea. (Ex. D at ¶15.) These are the adverse side effects listed in Table VI of the patent specification.

Memorandum of Law in Support of Defendant Sandoz, Inc.’s Construction of Claim Terms of the Patents In Suit, p. 10-11.

This Court declines to find that the term “reducing gastrointestinal adverse side effects” only refers to the most severe GI side effects and the patient discontinuations due to GI side effects. However, it is clear from both Table VI and Table VIII that some data demonstrating no change in the subcategories of GI adverse side effects of abdominal pain, constipation, diarrhea, dyspepsia, flatulence and nausea were in fact disclosed to the PTO. The data Sandoz claims was withheld demonstrates the exact same conclusion as the data that was disclosed. Therefore, such data was cumulative under 37 C.F.R. §1.56, Abbott was not under a duty to disclose it and Sandoz’s argument fails.

Severity Data

Sandoz alleges that Abbott used a rating system that mischaracterized the severity of the adverse GI side effects. Sandoz states that while Abbott did disclose data from the two clinical studies and an Integrated Summary of Safety to the FDA, it did not disclose this data to the PTO. Pagano’s Declaration, ¶ 48-50. Despite the fact that this data was not submitted to the PTO,

Sandoz nonetheless complains that Abbott engaged in inequitable conduct by categorizing the data in a deceitful manner. Given that Sandoz concedes this data was not submitted to the PTO, it is difficult to understand how the manipulation of the data was an act of fraud upon the patent examiner. Sandoz does state that Abbott was improper to “report the number of discontinuations due to gastrointestinal adverse side effects to the PTO.” Pagano’s Declaration, ¶ 49.

Submitting the number of discontinuations due to gastrointestinal adverse side effects to the PTO was not an act of inequitable conduct. The information was highly relevant to Abbott’s contention that use of the ER formulation reduced the number of patient discontinuations. Sandoz has not submitted any evidence that the number is false or misleading while Abbott has produced evidence through the declaration of Dr. Daniel Weiner, (Supplemental Declaration of Weiner, Exhibits A and B.) that demonstrates the common usage of the disputed rating system in the pharmaceutical industry in measuring symptom severity. Therefore, even if this argument is relevant, this Court finds that it fails.

e. Conclusion

Having found that Sandoz has shown a substantial likelihood of materiality and intent to deceive only in regard to the ‘616 patent application on Abbott’s failure to disclose the taste perversion data at the time of filing, the Court must now engage in a balancing of the evidence to determine whether the scales tilt towards finding inequitable conduct.

Despite its previous ruling in the Ranbaxy case, this Court now declines to preliminary find the ‘616 patent unenforceable because of inequitable conduct. Although this Court found the taste perversion data to be material at the time of filing and Abbott probably had an intent to deceive the PTO at the time of filing, Abbott nonetheless on its own volition, abandoned the

claim. According to *Kimberly-Clark*, it is inappropriate to find a patentee committed inequitable conduct based on a claim that was abandoned during prosecution where the PTO rejected the claim for reasons unrelated to the abandonment. 745 F.2d at 1457. Here, the PTO rejected the '616 application as non-conforming because it lacked signed inventor roles. Abbott then provided the signatures and that very same day withdrew the taste perversion claim.

Redemption is one of the core principles of the American ethos. Thus in addition to being contrary to the spirit of *Scribbs*, *Kimberly-Clark* and the Code of Federal Regulation,⁷ it seems wholly inequitable to hold a patent to be invalid for fraudulent conduct in the prosecution of a claim that was withdrawn before actual prosecution had even begun. Based on the evidence presented at this juncture, this Court preliminarily finds both the '616 and the '718 patents are not invalid over Abbott's alleged inequitable conduct in intentionally failing to disclose highly material information to the PTO.

2. *Infringement Analysis*

An infringement inquiry proceeds in two steps. *MBO Laboratories, Inc. v. Beckton, Dickinson & Co.*, 474 F.3d 1323, 1329 (Fed.Cir. 2007). First, a court will determine, as a matter of law, the correct scope and meaning of the disputed claim term(s). *Id.* Then, the court will compare the properly construed claim to the accused device and ascertain whether that device contains *every* limitation of the claim or a substantial equivalent thereof. *Id.*

⁷ See 37 C.F.R. §1.56(a) (The duty to disclose information exists with respect to each pending claim until the claim is cancelled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is cancelled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application.)

Despite upholding the preliminary injunction order against Andrx, the Court of Appeals for the Federal Circuit held that this Court's claim construction was flawed. 473 F.3d at 1213. Therefore, this Court will again construe the relevant claims of the patents at issue.

a. '718 Patent

There is a "heavy presumption" that a claim term carries its ordinary and customary meaning." *CCS Fitness Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002). Claim terms should therefore be accorded their ordinary meaning unless the patentees "clearly set forth a definition of the disputed claim term in either the specification or prosecution history." *Id.* The ordinary and customary meaning of a claim term refers to that meaning a person of ordinary skill in the art in question would attach to the term. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). Even though a term may have a distinct ordinary meaning to a person of ordinary skill in the art, a patentee may still "expressly define terms used in the claims." *Phillips*, 415 F.3d at 1321. When interpreting an asserted patent claim, the court should look first to the intrinsic evidence of record, which is the patent itself, including its claims, specification, and complete prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*). This intrinsic evidence is the primary and most significant source of the legally operative meaning of any claim language that is in dispute. *Vitronics Corp. v. Conceptoronic, Inc.* 90 F.3d 1576, 1583 (Fed. Cir. 1996). The court may also consider extrinsic evidence such as expert declaration evidence provided for the parties. *Pharmacia*, 274 F. Supp. 2d at 602.

As a threshold matter, the court must determine what constitutes a person of ordinary skill in the art for the purposes of the patent. Previously, this Court defined a person of ordinary

skill in the art as someone with “a Ph.D. in pharmaceutical chemistry or a related field and at least two years experience in formulating drugs” or a skilled artisan with “a Bachelor’s or Master’s Degree in an appropriate field and substantially more practical experience in formulating drugs.” *Teva*, No. 05-1490, 2005 WL 1323435, at *7, n.3. Neither party has suggested that the Court should modify its previous definition and therefore, that definition is hereby adopted and will be used in construing the claims below.

(1) Claim 1 Construction

First, “the claims themselves provide substantial guidance as to the meaning of particular claim terms.” *Phillips*, 415 F.3d at 1314. Claim 1 reads as follows:

A pharmaceutical composition for extended release of an erythromycin derivative in the gastrointestinal environment, comprising an erythromycin derivative and from about 5 to about 50% by weight of a pharmaceutically acceptable polymer, so that when ingested orally, the composition induces statistically significantly lower mean fluctuation index in the plasma than an immediate release composition of the erythromycin derivative while maintaining bioavailability substantially equivalent to that of the immediate release composition of the erythromycin derivative.

U.S. Patent No. 6010718 col.11 ll.28-38 (filed Apr. 11, 1997).

None of the following elements are disputed and each term is assigned its plain and ordinary meaning as understood by a skilled artisan. The term “pharmaceutical composition” means an aggregated product formed from two or more substances for use as a drug in medical treatment. The term “gastrointestinal environment” means the organs that make up the GI tract, including the stomach, intestines, and to a lesser extent the mouth, pharynx, esophagus and the anus. The term “mean fluctuation index” means the average degree of fluctuation $((C_{max} - C_{min})/C_{avg})$ over a specified period of time (usually twenty-four hours) by which pharmacokineticists can distinguish rates of release into the plasma.

The term “bioavailability” in the context of the ‘718 patent means the total exposure of the erythromycin derivative in the bloodstream as measured by the logarithm-transformed area under the plasma concentration-time curve (“AUC”), which is a mathematical and visual representation of the aggregate amount of the drug reaching systemic circulation over a given period of time. Bioavailability does not encompass both the rate and effect of release because extended release and immediate release formulations have different rates of release by definition. That is also why the claim calls for a lower mean fluctuation index for the extended release formulation versus the immediate release formulation- to highlight the importance of changing the rate of release without changing the overall amount of erythromycin derivative in the plasma. Both parties agree that in claim 1, the term “substantially equivalent to that of the immediate release composition” means the extended release composition AUC values must be between 80% to 125% within a 90% confidence level as compared to the immediate release composition AUC values.

The parties do not dispute that clarithromycin is an “erythromycin derivative.” The extended release composition at issue is designed for release in the gastrointestinal environment (e.g., oral administration). The patent specification defines “erythromycin derivative” as meaning “erythromycin having no substituent groups, or having conventional substituent groups, in organic synthesis, in place of a hydrogen atom of the hydroxy groups and/or a methyl group of the 3'-dimethylamino group, which is prepared according to the conventional manner.” U.S. Pat. No. 6,010,718, at col. 3:ll. 34-39. The patent specification further states that the “pharmaceutically active compound” of the composition “is an erythromycin derivative.” *Id.*, at ll. 58-61. It goes on, “[p]referably, the erythromycin derivative is 6-O-methoxy erythromycin A,

known as clarithromycin.” *Id.* The language of the claim is definite (“an erythromycin derivative”) but not closed. It does not specify that the pharmaceutically active compound “is a member selected from the group consisting of A, B, and C.” Thus, clarithromycin is an erythromycin derivative under this meaning.

Sandoz’s product uses clarithromycin as its pharmaceutically active compound. As noted in an earlier decision, Abbott defined “erythromycin derivative” in the ‘718 patent in such a way as to leave out azithromycin. Azithromycin is the name for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A. Pfizer, the patent holder on azithromycin, describes azithromycin as a “broad spectrum antimicrobial compound derived from erythromycin A.” WO 95/30422 (the “422 patent”). It is likely that Abbott consciously defined “erythromycin derivative” as it did to avoid infringing Pfizer’s existing ‘422 patent.

The primary dispute in this matter is over the meaning of the term “pharmaceutically acceptable polymer.” The term is not defined in the claim. Even the claims of a patent that are not at issue in an infringement suit are nonetheless part of intrinsic evidence to be considered during claim construction. Claim 1 of the ‘718 patent requires a composition that includes a “pharmaceutically acceptable polymer.” col. 11:ll. 31-32. Claim 2, not at issue here, depends from claim 1 and further requires that the pharmaceutically acceptable polymer “is a hydrophilic water-soluble polymer.” *Id.*, col. 11 ll. 39-40. Claim 3, also not asserted in this case, depends from claim 2 and more specifically requires that “the polymer is selected from the group consisting of polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures thereof.” *Id.*, col. 11 ll.

42-47. “The presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim.” *Phillips*, 415 F.3d at 1315. Furthermore, independent claims are generally given broader scope so as to avoid rendering corresponding dependent claims redundant. *Id.* at 1324 (citing *Dow Chem. Co. v. United States*, 226 F.3d 1334, 1341 (Fed. Cir. 2000)). Therefore, the language of the claims and the doctrine of claim differentiation imply that the “pharmaceutically acceptable polymer” limitation in claim 1 is most likely broader than the “hydrophilic water-soluble polymer” limitation described in claim 2 and involves more compounds than those contained in claim 3.

When the claim does not define a term, a court will turn to the specification. The claims “ ‘must be read in view of the specification, of which they are a part,...’ because “it is the single best guide to the meaning of a disputed term.” *Phillips*, 415 F.3d at 1315 (citing *Vitronics*, 90 F.3d at 1582). Here, the patent specification provides as follows:

The pharmaceutically acceptable polymer is a water-soluble hydrophilic polymer selected from the group consisting of polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures thereof. Preferably, the polymer is selected from hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and methyl cellulose. More preferably, the polymer is hydroxypropylmethyl cellulose. Most preferably, the polymer is a low viscosity hydroxypropylmethyl cellulose with viscosity ranging from about 50 cps to about 200 cps. The most preferred low viscosity polymer is a hydroxypropylmethyl cellulose with a viscosity of about 100 cps, commercially available under the Tradename Methocel™ K 100 LV from The Dow Chemical Company.

‘718 patent, col. 3 l. 65-col. 4 l. 14.

Previously, this Court found that the phrase “selected from the group consisting of” in the specification signaled a Markush group, which limited the term “pharmaceutically acceptable

polymer” to the polymers listed. Claim drafters often use the term “group of” to signal a Markush group, which lists specified alternatives in a patent claim. The typical form of a Markush group is “a member selected from the group consisting of A, B, and C.” See *Manual of Patent Examining Procedure* § 803.2 (2004) (quoted in *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1372 (Fed. Cir. 2005)). The Federal Circuit explained that while a Markush group can be used to limit a claim to a list of specified alternatives, a Markush group has no “meaning within the context of a written description of a patent” and a court should not rely on Markush group language to limit the construction of a claim term to certain items listed in the written description.

The presence of the “hydrophilic water-soluble” and the “group consisting of ...” limitations in dependent claims 2 and 3 implies that Abbott intended the “pharmaceutically acceptable polymer” limitation of claim 1 to be broader than the limitations of claims 2 and 3. But Sandoz explains the appearance of the polymer limitation in claims 1, 2 and 3 differently. According to Sandoz, the specification’s description of “pharmaceutically acceptable polymer” merely teaches one skilled in the art that this limitation appearing in claims 1, 2 and 3 is the same limitation. If the “pharmaceutically acceptable polymer” limitation meant the same thing in claim 1 as it did in claims 2 and 3, then Abbott would have no need to include claims 2 and 3, as they would become superfluous. “The presumption [created by the doctrine of claim differentiation] is especially strong when the limitation in dispute is the only meaningful difference between an independent and dependent claim, and one party is urging that the limitation in the dependent claim should be read into the independent claim.” *Sunrace Roots Enter. Co., Ltd. v. SRAM Corp.*, 336 F.3d 1298, 1303 (Fed. Cir. 2003) (citation omitted).

This Court also focused on the phrase “the pharmaceutically acceptable polymer is” as a signal that Abbott was acting as its own lexicographer and defining the term to what followed- “a water-soluble hydrophilic polymer selected from the group consisting of...” In doing so, this Court ignored other intrinsic and extrinsic evidence relevant to the meaning of “pharmaceutically acceptable polymer” in claim 1.

First, in addition to claims 2 and 3 and the passage describing what a “pharmaceutically acceptable polymer is,” the specification unambiguously defines “pharmaceutically acceptable” as meaning “those compounds, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, in keeping with a reasonable benefit/risk ratio, and effective for their intended use in the chemotherapy and prophylaxis of antimicrobial infections.” ‘718 patent, col. 3:ll. 40- 47.

Second, as the Federal Circuit noted, the ‘718 patent explicitly defines other claim terms, which were susceptible to different meanings according to the ordinary understanding of a person of skill in the art, by stating that those terms have particular meanings within the patent. *See, e.g.* ‘718 patent, col. 3 ll. 34-35 (“‘Erythromycin derivative’ as used herein, means”); col. 3, ll. 40-41 (“‘Pharmaceutically acceptable’ as used herein, means”). Had Abbott intended the text that follows the phrase “the pharmaceutically acceptable polymer is” to be the term’s definition, it stands to reason that Abbott would have employed the same method of assigning a particular meaning to the term by stating that “pharmaceutically acceptable polymer, as used herein, means” Sandoz argues that this view of Abbott’s definitional format ignores long-standing Federal Circuit precedent that “the written description can provide guidance as to

the meaning of the claims, thereby dictating the manner in which the claims are to be construed, even if the guidance is not provided in explicit definitional format.” *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1344 (Fed. Cir. 2001). Sandoz is incorrect. This Court is (and the Federal Circuit advised) rejecting the assertion that the phrase “the pharmaceutically acceptable polymer is” signals the definition here, not because it is not explicit definitional language *per se*, but rather because Abbott used explicit definitional language elsewhere in the patent description to define terms susceptible to different meanings but did not use similar explicit language here.

Sandoz also incorrectly argues that Abbott’s use of “is” unambiguously identified the term “erythromycin derivative” as a “pharmaceutically active compound” such that its use of “is” should also unambiguously identify “a water-soluble hydrophilic polymer selected from the group consisting of...” as a “pharmaceutically acceptable polymer.” The term “pharmaceutically active compound” is not an element of any disputed claim so this analogy is not even a relevant one. Furthermore, the ‘718 patent is drafted in such a manner that there is no ambiguity as to what constitutes a “pharmaceutically active compound” whereas the same is not true for “pharmaceutically acceptable polymer.”

Third, Eudragit RS and Eudragit RL are water-insoluble methacrylic acid co-polymers. Methacrylic co-polymers are specifically listed in the passage where Abbott describes the “group” from which the pharmaceutically acceptable polymer is selected. Sandoz contends that the existence of known water insoluble Eudragit polymers supports this Court adopting a narrow construction of “pharmaceutically acceptable polymer” that excludes polymers from the groups outlined in the passage that are not “water soluble” or “hydrophilic.” But given the evidence

already discussed, this Court finds that the existence of water-insoluble polymers from the specifically-mentioned methacrylic acid co-polymer subset actually militates towards a broader construction urged by Abbott that would encompass water-insoluble methacrylic acid co-polymers (such as Eudragit E, L and S, all three of which have powder or granule versions the Handbook of Pharmaceutical Excipients, 4th edition, regards as insoluble) instead of the narrow construction offered by Sandoz, which would exclude all water-insoluble polymers.

Abbott asserts that “pharmaceutically acceptable polymer” should be construed so as to include “any polymers, suitable for use in pharmaceutical compositions to be administered in humans that, alone or together with other polymers, are capable when mixed with the drug of forming a matrix to control and extend drug dissolution and release into the bloodstream.”

The Federal Circuit’s opinion at 452 F.3d 1331, at 1337-38 (June 22, 2006) and its later opinion at 473 F.3d 1196, 1209-11 (Jan. 5, 2007) are not in direct conflict as to the legal significance of Markush language, so this Court is not bound to afford precedential value to the first opinion as Sandoz argues. *See e.g. Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 765 (Fed. Cir. 1988). Only in the extremely unlikely situation where two opinions stand in direct contrast as to the legal significance of a certain element, the first opinion prevails. *Id.* In the first opinion, the Federal Circuit merely approved of turning to the specification in construing the claim; it made no mention of this Court’s specific reliance on Markush language. In short, the first opinion is no bar to this Court adopting a broader claim construction than it in previous rulings.

This Court finds that a person of ordinary skill in the art of this invention who read the entire ‘718 patent would read the term “pharmaceutically acceptable polymer” in claim 1 and

construe it to mean any polymer, which within the scope of sound medical judgment is suitable for use in pharmaceutical compositions for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, in keeping with a reasonable benefit/risk ratio, and effective for their intended use in the chemotherapy and prophylaxis of antimicrobial infections, and is capable of forming a matrix to extend drug release into the bloodstream. Such a “pharmaceutically acceptable polymer” must constitute 5 to 50% by weight of the product.

(2) Claim 4 Construction

Claim 4 repeats the description of the pharmaceutical composition from claim 1 and adds that “upon oral ingestion, maximum peak concentrations of the erythromycin derivative are lower than those produced by an immediate release pharmaceutical composition, and AUC and the minimum plasma concentration are substantially equivalent to that of the immediate release pharmaceutical composition.” ‘718 patent, at col. 11:ll. 48-58.

This means that the concentration-time curve representing the concentration of drug in blood plasma will be flatter and lower for the extended release formulation than for the immediate release formulation, but will have an AUC that is substantially equivalent to that of its immediate release corollary. At the same time, the minimum plasma concentration for the extended release formulation will be substantially the same as that of the immediate release formulation, meaning that the drug will be present in the blood at the same minimum level at all times for both the immediate release and extended release formulations.

The parties disagree as to the proper construction of the term “substantially equivalent to that of the immediate release composition” with regard to C_{min} values in this claim. Sandoz

argues that it should be construed to encompass the FDA definition of bioequivalence (measured by the use of 90% confidence levels) as applied to the term “bioavailability” in claim 1. Abbott argues that here “substantially equivalent” with respect to Cmin values simply means not statistically significantly different. Abbott responds that FDA guidance does not call for bioequivalence in terms of Cmin values, only in overall AUC values and usually in respect to Cmax values. What is persuasive here is that Abbott provides evidence showing that Sandoz’s definition of “substantially equivalent” in this claim would exclude Abbott’s own preferred embodiments from the scope of claim 4 if the 90% confidence levels advised by the FDA. A claim construction that excludes preferred embodiments from the scope of the claim “is rarely, if ever, correct and would require highly persuasive evidentiary support.” *Vitronics Corp.*, 90 F.3d at 1583. Sandoz lacks such support. Indeed, in discussing the comparison of Cmin values of the claimed formulation versus the immediate release formulation, only statistical significance is discussed, not the use of the FDA guideline bioequivalent 90% confidence levels.

(3) Claims 1 and 4 Infringement Analysis

Literal Infringement

A court must compare the properly construed claim to the accused device and ascertain whether that device contains *every* limitation of the claim or a substantial equivalent thereof. *Pharmacia*, 274 F. Supp. 2d at 601. Abbott alleges that Sandoz’s product infringes every element of claim 1. Sandoz argues that its product does not literally infringe upon claim 1 because 1) the release-extending ingredient in its product, glycerol behenate, is a non-polymer wax; and 2) silicified microcrystalline cellulose (“SMCC”) and maltodextrin, which are

polymers and are found in Sandoz's product, do not control or extend release, rather they speed up release.

Claim 1 explicitly limits the invention to pharmaceutically acceptable polymers.

Glycerol behenate is a wax not a polymer. Abbott does not dispute that glycerol behenate is not a pharmaceutically active polymer. However, Abbott asserts and has submitted evidence that SMCC and maltodextrin, both independently and in combination, have the capacity to extend release. So the relevant question then is whether Abbott has shown a substantial likelihood that SMCC and maltodextrin either alone or together *have the capacity* to extend the release of the drug in Sandoz' formulation. While Sandoz admits that the SMCC and the maltodextrin "fine tune" drug release, it maintains that neither polymer has the capability to extend drug release.

SMCC is comprised of 98% of microcrystalline cellulose ("MCC"), a polymer that is capable of forming a matrix to extend drug release. SMCC makes up about 31.5% of Sandoz's product. Given that 1) SMCC is comprised of 98% MCC; 2) SMCC has very similar physical and chemical properties as MCC and; 3) substitutions of SMCC for MCC in formulations have shown no effect on the dissolution rate of the drug from the formulation, Abbott's expert, Dr. Davis, opines that SMCC would also be capable of forming a matrix to extend drug release.

Fifteen percent of Sandoz's product is maltodextrin, a water soluble hydrophilic polymer that scientific literature has shown can be used as part of a matrix to control drug release. In support of its argument, Abbott offers the patent application of a Dr. Mulye, who invented the formulation in use in Sandoz's product. That patent application states that maltodextrin has been found to have drug retarding capabilities. Later, it states that maltodextrin in combination with a water insoluble cellulose can effectively control the release of a drug. The application explicitly

states “the maltodextrin used in the present invention [Sandoz’s product] is to counteract the accelerated rate of release of the drug attributable to the addition of the water insoluble or partially insoluble cellulose.” U.S. Pat. App. Pub. No. 2004/0224017 ¶52.

In addition, Abbott offers the ‘803 and ‘531 patents as evidence that maltodextrin can be used to form a polymer matrix to control release. The ‘803 patent claims maltodextrin as a possible polymer that swells and slows the release of a drug. U.S. Patent 6,102,803 col. 30: l. 6 (filed Aug. 10, 1998). The ‘531 patent claims that “the powdered cellulose and the maltodextrin act to slow the disintegration of the orally administered specimen to provide a sustained release....” U.S. Patent 7,056,531 col. 30: l. 6 (filed May 4, 2001).

Sandoz relies on a description of maltodextrin in a recognized industry treatise as evidence that maltodextrin does not extend drug release. It states that maltodextrin appears to have no adverse effect on the rate of dissolution of tablet and capsule formulations...” Ainley Wade & Paul J. Weller, *Handbook of Pharmaceutical Excipients* 289 (2d ed. 1994). This evidence is simply not persuasive when viewed along with the plethora of Abbott’s evidence.

Abbott also submits industry literature as evidence that maltodextrin is known to have release-extending capabilities and to be used as part of a matrix to control release. One article describes how matrix tablets using a combination of waxes starches, including maltodextrin, can control release. Zhou, et. al, *Matrix Pellets Based on the Combination of Waxes, Starches and Maltodextrins*, 133 Int’l J. Phar. 155 (1996). Sandoz replies that the maltodextrin referred to in this article is actually “waxy maltodextrin,” which is different from maltodextrin because it derives from waxy starches whereas maltodextrin does not. The Court finds that this article and

the other articles presented are not persuasive as to maltodextrin's use as a release-extending ingredient.

As for SMCC, Abbott submits U.S. Patent 6,641, 840, which describes a matrix-based sustained formulation where the matrix can be formed by MCC and identifies SMCC as interchangeable with MCC (albeit in its role as an excipient). Col. 4: 1. 13 (filed Aug. 27, 2001). Abbott also submitted various articles demonstrating that MCC could form a matrix to slow release. Other than the '840 patent reference, none of Abbott's material clearly demonstrates that SMCC is capable of forming a matrix to extend release.

After weighing all of the evidence, this Court finds that Abbott has demonstrated a substantial likelihood that maltodextrin is a polymer that alone or in combination with other polymers, is capable of forming a matrix to extend drug release. Although Sandoz has shown why several pieces of Abbott's evidence was not persuasive, it has not presented any evidence that negates Abbott's affirmative showing that these maltodextrin polymers can indeed be used to extend release and were envisioned by the inventor of Sandoz's product to do so. Maltodextrin is a pharmaceutically acceptable polymer that makes up 15% of Sandoz's product.

Sandoz's product is a pharmaceutical composition containing an erythromycin derivative at about 15% by weight of a pharmaceutically acceptable polymer. Abbott offers Sandoz's ANDA as preliminary evidence that its product's dosage maintains an AUC substantially equivalent to the comparable immediate release dosages over a 24 hour period. The ANDA also contains evidence that Sandoz's product induces a statistically significantly lower mean DFL than the immediate release formulation because it contains a graph showing that its extended release formulation produces a flatter PK profile than the immediate release formulation, which

indicates a lower DFL. Thus Sandoz's generic extended release product preliminarily satisfies every single element of claim 1 and therefore literally infringes upon claim 1.

Sandoz's product likely infringes claim 4 because it likely infringes claim 1's structural elements and its pharmaceutical limitations. The graph found in Sandoz's ANDA shows that its extended release formulation produces lower Cmaxs than the immediate release formulation, which satisfies one of claim 4 additional limitations. Abbott already demonstrated that Sandoz's product maintains an AUC substantially equivalent to the comparable immediate release dosages over a 24 hour period. Lastly, Abbott has also demonstrated that graph found in Sandoz's ANDA and the data upon which the graph is based, both show that Sandoz's product produces a Cmin substantially equivalent to that of the immediate release formulation. Therefore, Abbott has succeeded in demonstrating to the Court that it has a substantial likelihood of proving Sandoz's product infringes upon claims 1 and 4 of the '718 patent. Since this Court has found that Sandoz has failed to establish a substantial question as to the validity of those claims, there is no need to discuss the construction, infringement and validity of claim 6 of the '718 patent and the '616 patent claims in this decision.

(3) Infringement Defenses to Claim 1

After finding a likelihood of success on the merits of at least one claim, the court must determine whether the alleged infringer has raised sufficiently persuasive evidence of patent invalidity to overcome the presumption that the patent is valid. *Pharmacia & Upjohn v. Ranbaxy Pharms, Inc.*, 274 F. Supp. 2d 597, 601 (N.D. Ill. 2003). The patentee can overcome such a showing by demonstrating that the invalidity defense lacks sufficient merit to defeat the patentee's likelihood of success on the merits. *Oakley, Inc. v. Sunglass Hut Int'l*, 316 F.3d 1331,

1339 (Fed. Cir. 2003). Sandoz argues that it can raise a substantial question as to the validity of claim 1. It contends that claim 1 is invalid as anticipated and/or obvious over the prior art.

'571 Publication

Sandoz argues that Eli Lilly's European Patent Publication 0280571 B1 ("the '571 publication") anticipates claims 1 and 4 of the '718 patent. Sandoz contends that the '571 publication expressly discloses the compositions of claims 1 and 4; specifically, it teaches pharmaceutical formulations that combine a drug, including erythromycin, with a hydrophilic polymer to provide extended release compositions. '571 publication, at 3:1-14, claim 1. A patent claim is invalid by reason of anticipation if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent" 35 U.S.C. §102(a) (2001). For anticipation based on a printed publication, such as Sandoz alleges here, each and every limitation of the claimed invention must be present in the prior art. *Adv. Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). But "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing feature is necessarily present, or inherent, in the single anticipating reference." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005) (citation omitted). To be anticipatory, prior art must also be enabling, such that a person of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. *Id.* at 1342. Anticipation "only requires that ... suggestions [in the prior art] be enabled to one of skill in the art." *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001) (citation omitted).

The '571 publication discloses the hydrophilic polymer as being about 5% to about 29% of the composition by weight, with HPMC as the most preferred polymer. *Id.* The '571 publication also discloses an acrylic polymer, including those sold as Eudragit, which comprises from about 0.5% to about 25% of the composition by weight. *Id.* at 3:41-54. The patent limits the total weight of the hydrophilic and acrylic polymers to "less than 30% by weight of the formulation." *Id.* at 2:49. The '571 publication also discloses the method for making sustained release compositions as the method disclosed in the '718 patent. Sandoz's expert, Dr. Chambliss, states that because the '571 publication discloses the same structural limitations and method of manufacture as the '718 patent, it would certainly permit one of ordinary skill in the art to produce analogous extended release tablet formulations if erythromycin were used in place of the drug substances reported in the examples (and importantly, such a composition would inevitably possess the same functional (PK) limitations of claim 1). Chambliss Declaration, ¶¶ 24-29.

The '571 publication does not disclose, however, any PK characteristics of the invention, the so-called functional limitations of claims 1 and 4. It provides *in vitro* drug dissolution profiles about cephalosporin drugs but gives no information about *in vivo* performance of any formulation under the patent. Further, the '571 publication discloses erythromycin among a list of active pharmaceutical ingredients which it suggests "might benefit from this type of delivery system." '571 publication, at 3:9-10. But Sandoz contends that the '571 publication discloses all the elements of the '718 patent and that the PK limitations were inherent in the formulation disclosed because a chemical composition and its properties are inseparable. *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). Thus, Sandoz argues that Abbott's '718 patent simply covers

properties of a known invention which are necessarily present, which is impermissible.

Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985). Sandoz also cites to *Atlas Powder Co. v. Ireco, Inc.*, where the Federal Circuit held that “when a patent claims a chemical composition in terms of ranges of elements, any single prior art reference that falls within each of the ranges anticipates the claim.” 190 F.3d 1342, 1346 (1999) (citation omitted).

Sandoz also argues that the ‘517 publication renders claim 1 invalid as obvious under 35 U.S.C. § 103 (2004). Section 103 denies patents to those devices where “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” The “person ... of ordinary skill” is not the inventor but rather someone “who ... is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights” *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). Obviousness must be evaluated not by reference to each individual part claimed, but rather by reference to the invention as a whole. *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 724 (Fed. Cir. 1990). To avoid the temptation of what the Federal Circuit has termed the “hindsight trap,” courts require some motivation or teaching that would lead a person of ordinary skill in the art to arrive at the claimed invention. *See In Re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998).

In Sandoz’s opinion, since the ‘571 publication discloses the same structural limitations and method of manufacture as the ‘718 patent, it would certainly motivate a person of ordinary skill in the art seeking to create an extended release erythromycin composition with the same limitations as the ‘718 patent. In turn, FDA requirements would have naturally motivated such a

person to make an extended release composition that was bioequivalent to the immediate release composition. Bioequivalence meaning that the AUC would have been substantially equivalent over a given time period for the two compositions. Further, according to Sandoz, such a person would expect to achieve a C_{max} that was significantly lower than the C_{min} for an immediate release composition because of the presence of the hydrophilic polymer. Lastly, such a person would also be motivated to maintain the C_{min} of the extended release formulation substantially the same as the C_{min} for the immediate release formulation so as to maintain the antibiotic effect of the erythromycin derivative in the plasma. This would lead to a statistically lower DFL as a natural consequence of its mathematical relationship to the relative plasma concentration measures.

Abbott responds that the '571 publication does not disclose all of the limitations of the '718 patent. Specifically, the '571 publication is directed to beta-lactams, rather than macrolide antibiotics such as erythromycin and clarithromycin. In addition, Abbott emphasizes that the '571 provides no *in vivo* data about the performance of the invention. The inclusion of the acrylic polymer Eudragit L 500 in the '571 demonstrates that the '571 does not anticipate the '718. Abbott notes that Eudragit L-500 is pH-dependent and slows or prevents release of the active pharmaceutical ingredient in more acidic environments, like the stomach, and therefore should not be used to achieve the PK profile claimed in the '718 patent. Other forms of Eudragit, however, do not have pH dependent solubilities. Abbott seeks to distinguish *Titanium Metals* on the basis that the Federal Circuit construed the disputed claim as being limited to the structural properties previously disclosed in the prior art. By contrast, Abbott contends that the

claims in the '718 were not previously disclosed and that they were not discoverable without significant experimentation.

This Court has reviewed the record, including the submissions from both Abbott and Sandoz's experts, and finds that Sandoz has failed to meet its burden. Sandoz has not presented sufficient evidence that the '571 publication's teachings would enable Abbott to create an extended release of an erythromycin derivative drug simply based on the structural limitations. *See Titanium Metals*, 778 F.2d. at 781. Although the separate elements of the '718 patent are disclosed in the '571 patent, the specific PK limitations of the '718 patent are not present. These limitations are more than merely properties that were undiscovered or unrecognized. *See Atlas Powder*, 190 F.3d at 1347.

Generally, a showing that there is an established structural relationship between a prior art composition and the claimed composition demonstrates a *prima facie* case of obviousness. However, a patentee can rebut such a showing by demonstrating unobvious claimed properties. Abbott has sufficiently demonstrated (preliminarily) that the specific PK properties embodied in claims 1 and 4 of the '718 patent are in fact the unobvious product of the specific claimed formulations performed to achieve those specific properties. Supplemental Davis Declaration, ¶44. They are not the necessary by-products of utilizing the '571 publication art to formulate an extended release composition as Sandoz argues. The '718 patent is directed to the PK performance of extended release clarithromycin. The '571 publication does not offer any formulations that include erythromycin. It does not offer any *in vivo* dissolution data. It does not even offer the pharmacokinetic profile of its own formulations. The claims, on their face and as construed by this Court, are not limited to the formulation structural parameters disclosed in

the '571 but rather to the PK characteristics of a formulation not specifically disclosed therein. This Court therefore preliminarily declines to find the claim 1 (and claim 4 for the same reasons) invalid as anticipated or obvious by the '571 patent.

WO '422 Publication in Combination with U.S. Patent No. 5,705,190

Sandoz argues that claims 1 and 4 would have been obvious in light of PCT Application WO 95/30422 (the "WO '422 publication") in combination with U.S. Patent No. 5,705,190 (the "'190 patent"). The WO '422 publication discloses sustained release dosage forms of azithromycin in general and discloses a sustained release formulation created from combining azithromycin with HPMC in particular. While the '190 patent does not disclose the claimed polymers of the '718 patent it does disclose the use of an alginate polymer in making sustained release formulations and discloses the use of clarithromycin.

First, Abbott has demonstrated that the Federal Circuit did not have the benefit of ceratin evidence demonstrating that the '190 patent did not in fact disclose compositions with substantially bioequivalent PK properties as the PK properties of claim 1 of the '718 patent. This Court has already explained that the PK limitations of claim 1 (and claim 4) are distinct and no less important than the structural limitations. To succeed on its obvious claim, Sandoz must produce evidence indicating that the PK limitations were disclosed in the prior art or were at the very least inherent to the structural limitations of the prior art compositions. Dr. Weiner, an expert statistician for Abbott, submits evidence that it was not possible for a person skilled in the art to utilize DFL from the '190 patent formulations to create the '718 invention because of the differences in which the underlying variables used to calculate DFL (Cmax, Cmin, and AUC) were themselves calculated. Weiner Declaration, ¶¶10-23. Also, subsequent studies conducted

by Abbott demonstrate that the commercial embodiment of the '190 patent formulation does not in fact have a statistically significantly lower DFL than the immediate release formulation, a necessary element of claim 1. *Id.* at ¶¶ 24-31. Lastly, Abbott also demonstrated that even accepting Sandoz's definition of "minimum plasma concentration substantially equivalent to" as having the meaning the FDA assigns to bioequivalence, the '190 patent does not teach that its extended release C_{min} is substantially equivalent to the correlating immediate release C_{min} because the '190 patent's C₂₄ value is simply not equivalent to the '718 patent's C_{min} value. This Court also finds that a person skilled in the art would not treat those different C values as interchangeable. In short, Abbott has shown not only that the PK profile of the clarithromycin-metabolite data of the '190 patent formulation was not the same as the PK profile of the clarithromycin-only data utilized by the '718 patent, but also that those skilled in the art would not have been motivated to apply the '190 pharmacokinetic profile to clarithromycin.

Furthermore, Abbott has demonstrated through its presentation of U.S. Patent 6,068,859, the domestic counterpart of the WO '422 publication, that many of the controlled release formulations of that patent were found to exhibit less bioavailability than their respective immediate release formulations once *in vivo* data was gathered. This fact supports Abbott's assertion that a person of ordinary skill in the art could not simply use *in vitro* data from the WO '422 publication and be motivated to try to utilize HPMC matrices with clarithromycin, a drug with substantial dissimilarities to azithromycin. Abbott correctly asserts that because the '190 prior art does not disclose the PK profile of the '718 patent, a person skilled in the art would not be motivated to look at the WO '422 publication and interchange clarithromycin for

azithromycin. An important point to always keep in mind is that the claimed invention is scrutinized for obviousness “as a whole.”

In conclusion, Sandoz’s obvious argument based on the combination of the WO ‘422 publication and the ‘190 patent does not amount to a substantial question because 1) there is no indication that either prior art discloses the PK limitations of claim 1 (and 4) 2) there is no indication that either prior art would motivate a person of ordinary skill in the art to combine their teachings to arrive at the ‘718 patented invention.

WO ‘667 Publication

PCT patent publication WO 93/17667 (“the WO ‘667 publication”) discloses a method of preparing a pharmaceutical wax and polymer compositions for oral preparations, of which one example contains a functional polymer approximately 36% by weight comprised of Eudragit E, clarithromycin or azithromycin, and excipients. Sandoz claims the WO ‘667 publication discloses extended release compositions but even Sandoz’s expert does not claim that. *See* Sandoz Opposition Brief, p. 10; *but see* Chambliss Declaration, ¶¶ 31-34. Rather he claims that extended release properties are inherent, and thus anticipated, from the prior art composition of the WO ‘677 publication because it teaches the disclosed composition barely is removed by dissolution while exhibiting “excellent bioavailability.”

This argument fails. The WO ‘667 publication does not teach extended release formulations. The publication deals with oral preparations and it discusses elution in the context of occurring inside the mouth, not the stomach or intestines. “Bioavailability” outside of the meaning of the ‘718 patent refers to the “[e]xtent to which – and sometimes the rate at which – the active moiety [or drug] ... enters systemic circulation.” *Merck Manual of Diagnosis &*

Therapy 2559 (17th ed. 1999). Moreover, the WO '667 publication does not disclose any *in vivo* PK data. Sandoz's argument is based on an assumption that certain PK results will necessarily result from any extended release formulation. But this piece of prior art does not discuss extended release and Abbott has already demonstrated why that assumption is false in the context of PK limitations of the '718 patent. Sandoz provides no support for this assumption and Abbott argues that it is unfounded. Finally, Abbott asserts that Sandoz offers no more than a conclusory statement that the PK limitations are inherently met by the WO '667 publication. This suffices to demonstrate a lack of "substantial merit" to Sandoz's anticipation defense.

This Court declines to find that a person of ordinary skill would be motivated to utilize the taste-masking teachings of the WO '667 publication to derive a formulation that produced the PK values of the '718 patent. Thus, Sandoz's obviousness argument fails.

B. Irreparable Harm

The party seeking the preliminary injunction must not only show a likelihood of success on the merits but also that it will suffer irreparable harm in the absence of an injunction. If the movant establishes a clear showing of the validity of the patents in suit and infringement thereof, then a presumption of irreparable harm attaches. The burden then shifts to the non-movant to rebut the presumption. *Amazon.com v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350 (Fed. Cir. 2001). A successful rebuttal is a showing that the non-movant either has or shortly will cease its allegedly infringing activities; that the movant has a pattern of granting licenses for the patents in suit so that it is reasonable to believe money damages would be enough to satisfy any harm to the patentee; or that the movant unduly delayed in bringing suit on its patents. *Polymer Techs., Inc. v. Bridwell*, 103 F.3d 970, 974 (Fed. Cir. 1996).

As a threshold matter, Abbott is entitled to a presumption of irreparable harm regarding the '718 patent because this Court has found that it has made a clear showing of both infringement and validity of the '718 patent. Sandoz, therefore, bears the burden of rebutting that presumption.

Sandoz contends that Abbott's predicted loss of market share and profits is easily compensable with money damages, an amount that Abbott has allegedly already quantified in a previous matter involving the '718 patent. Sandoz also states that Abbott's delay in filing for this injunction demonstrates that there is no actual urgent need for injunctive relief. *See T.J. Smith and Nephew Ltd. v. Consol. Equip., Inc.*, 821 F.2d 646, 648 (Fed. Cir. 1987). Sandoz also argues that Abbott has previously given up a portion of its patent rights voluntarily by entering into settlement agreements with other generic extended release product makers. In Sandoz's view, voluntarily relinquishing patent rights is an act that is incompatible with the right to exclude and courts will not find irreparable harm when a patentee has engaged in such acts. *See id.* Lastly, Sandoz contends that Abbott's demonstration that it will suffer loss of market share, goodwill, and profits; will be constrained to lay off several hundred sales representatives; and will face losses that will never be fully compensable in money damages cannot constitute irreparable harm because they are merely economic ripple effects that are concomitant with business and necessarily quantifiable. *See Eli Lilly & Co. v. Am. Cyanamid Co.*, 896 F. Supp. 851, 860 (S.D. Ind. 1995), *aff'd* 82 F.3d 1568 (Fed. Cir. 1996).

First, Abbott filed its motion for a preliminary injunction four months after denial of its TRO request. Precedent shows that a delay of four months is not very long at all in the context of complex patent litigation. *See e.g. Consol. Equip., Inc.*, 821 F.2d at 648 (where the delay was

about fifteen months). Indeed, Sandoz ignores the fact that Abbott contended that it had an agreement with Sandoz that Sandoz would not come to market with its extended release product until a court could determine the merits of Abbott's claim to injunctive relief. Moreover, Abbott sought injunctive relief in the form of a TRO as soon as they became aware of Sandoz's product's launch.

Second, Sandoz discounts Abbott's complaints of lost good will, terminated or laid-off employees and lost market share and profits but it has not rebutted them. Abbott contends it has demonstrated irreparable harm because it has shown that it will suffer loss of market share, goodwill, and profits; will be constrained to terminate 190 sales representatives; and will face losses that will never be fully compensable in money damages. The Federal Circuit has stated that evidence on likelihood of price erosion and loss of market position resulting from competitor's entry in a pharmaceutical patent infringement case may support a finding of irreparable harm. *See Purdue Pharma L.P. v. Boehringer Ingelheim, GMBH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (noting that patentee was entitled to presumption of irreparable harm but analyzing sufficiency of patentee's proffered expert evidence). According to Dzvonic, Abbott's brand manager, after eight months of generic competition, Abbott will face a 90% decline in market share. Abbott reiterates the irreversible market share losses it will face as it loses its preferred position on pharmacy and insurance formularies.

Third, Sandoz asserts that Abbott voluntarily gave up some of its patent rights by entering into settlement agreements. Abbott responds that those settlements permit those specific two generic drugmakers to come to market in 2008, so they are not receiving any licensing proceeds now. Furthermore, the fact that they entered into settlement agreements does

not diminish the limitations of monetary damages in this case due to the substantial intangible losses that accompany market share and revenue erosion. Nor does the fact that competitors may enter the market next year automatically show that Abbott should not be able to reap the complete benefit of the power to exclude now.

The Federal Circuit instructs that “merely because a patentee is able to identify a monetary amount that it deems sufficient to avoid or end litigation does not necessarily mean that it automatically foregoes its right to seek a preliminary injunction or that any potential irreparable injury ceases to exist if infringement resumes.” Again, because it Sandoz’s duty to demonstrate to this Court why Abbott will not suffer irreparable injury because of Sandoz’s intrusion, merely discrediting Abbott’s evidence is not enough.

This court finds that Abbott has made a showing that it will suffer irreparable harm with respect to the ‘718 patent in the absence of a preliminary injunction. The very fact of this instant proceeding strongly suggests that the parties perceive a robust market remaining for the extended release formulation, even with generic competition on the immediate release level. Thus, as previously noted, this court concludes that entry of a generic extended release formulation competitor will likely crush the market.

C. Balance of Hardships

The third factor in determining whether a preliminary injunction should issue requires a court to examine the balance of the hardships between the two parties. *Hybritech*, 849 F.2d at 1457. A court weighs the hardship to the patentee if no injunction is entered against the harm to the alleged infringer if the injunction is granted incorrectly. *Id.*

The structure of the pharmaceutical market makes it difficult to determine the effect of generic competitor market entry. Most prescription drug purchases in the United States are paid for, at least in part, by employer-sponsored health insurance plans or by government programs like Medicaid. When a pharmaceutical enters the market, insurance companies, managed care organizations, and Medicaid plans decide whether to place the drug on their pharmaceutical formularies. The formulary is a list of approved medications for which the plan will pay some part of the cost. These formularies are, in many instances, divided into three tiers. The first tier comprises low cost generic products. The second tier comprises “preferred branded” products. The third tier comprises “non-preferred branded” products. Patients must pay more out-of-pocket for drugs listed on a higher tier than for a drug of the same price listed on a lower tier. The managed care provider typically pays more for drugs listed on a lower tier (e.g., Tier 1) than for a drug of the same price listed on a higher tier (e.g., Tier 3). The Medicaid formulary does not have tiers; either a drug is listed on the formulary (also known as the preferred drug list) or it is not. If the drug is not on the Medicaid formulary, the program will not cover any portion of its cost. If a doctor prescribes a non-formulary drug to a Medicaid patient, the patient must pay the entire cost out-of-pocket.

When a generic version of a branded product enters the market, managed care providers generally add the generic to their formulary on Tier 1. They will then move the branded product to a higher position (e.g., from Tier 2 to Tier 3). Some plans will remove the branded drug from their formulary altogether. If the generic product is AB rated, meaning that the FDA considers it therapeutically equivalent to the branded product, many pharmacies will substitute the generic product for the branded product unless the physician specifies on the prescription form

“Dispense as Written.” Medicaid programs typically remove branded products from their formularies altogether once a generic has entered the market.

Abbott argues that the balance of hardships weighs in favor of granting the preliminary injunction because it will face devastating loss of market share and other severe consequences. Abbott asserts that it has already lost about 70 percent of the clarithromycin market (although Abbott does not state how much of that loss is due to Sandoz’s current intrusion). Declaration of Frank Dzvonic, ¶ 14. Abbott also asserts that within eight months of Sandoz’s generic entry, it will have lost up to 90 percent of its market share that it would have otherwise retained except for Sandoz’ intrusion. *Id.*, ¶ 15. Abbott explains that an injunction and recall is the only remedy that will prevent it from losing all of its market share while simultaneously enabling it to recover some of its lost market share. Moreover, Abbott contends that its loss of market share will be permanent. Once a managed care organization moves a drug to a higher tier on its formulary or, in the case of Medicaid, removes the drug entirely, it is costly and difficult to regain a preferred position. Abbott contends that it will be unable to regain its position on the second tier of most managed care organization formularies and will be unable to be relisted on the Medicaid formulary. Competition from related antibiotics, the financial incentive to the prescription benefit providers of keeping a drug on a higher tier, and simple inertia on the part of the formulary administrators will combine to prevent Abbott from regaining more than a fraction of its current market share, even if a generic competitor subsequently exits the market.

In addition to losing market share, Abbott estimates it will be constrained to lay off several hundred members of its sales force and lose the good will of doctors who prescribe clarithromycin products.

Sandoz argues that the balance of hardships favors it because Abbott had a chance to license the allegedly infringing formulation at issue, but chose not to do so. It also argues that if the injunction were granted and Sandoz was forced to stop marketing its product it would suffer substantial hardship, and if it were forced to recall its product that would be an even greater hardship.

First, this Court regards Sandoz's argument about Abbott's failure to license the formulation when it had an opportunity to do so to be absolutely without merit. If Abbott really thought the product would infringe upon its own patented formulation, then agreeing to pay to license it would be similar to giving in to extortion. The potential licensor would be putting Abbott in a position where its choice would be to pay an amount to keep an infringing product of the market or suffer losses and litigation costs to rid the market of the intrusion, costs it should not have had to pay in the first place. Second, it should go without saying that one who infringes upon a patent cannot be heard to complain about the financial consequences of either ending its infringing conduct or being restored to its pre-infringement position. However, Sandoz has submitted detailed evidence that they would face severe hardship if it in fact turns out that this Court incorrectly granted a preliminary injunction and recall. *See* Declaration of Barbara Purcell, ¶¶ 9-12. Such hardship is reasonably quantifiable and capable of being protected against by a bond if need be. It barely requires noting that Sandoz chose to come to market with its product after this case was filed with full notice of Abbott's claims.

In conclusion, the evidence shows that Abbott will lose much more if this Court did not enjoin Sandoz's infringing conduct than if the Court enjoins Sandoz and it is subsequently found

that the '718 patent is invalid or unenforceable. To the extent that this Court has erred, Sandoz has offered an amount for a bond to protect it from losses.

D. Public Interest

The final factor a court should consider in determining whether to issue a preliminary injunction is the impact it will have on the public interest. *Hybritech*, 849 F.2d at 1458. “[I]n a patent infringement case, although there exists a public interest in protecting rights secured by valid patents, the focus of the district court’s public interest analysis should be whether there exists some critical public interest that would be injured by the grant of preliminary relief.” *Id.*

Abbott states that granting the preliminary injunction will serve the public interest by furthering the important public policy of encouraging innovation in pharmaceutical development. It emphasizes the value of the right to exclude inherent in a patent. *See, e.g., Smith Int’l, Inc. v. Hughes Tool Co.*, 718 F.3d 1573, 1578 (Fed. Cir. 1983). Abbott has previously stated that it invests a substantial percentage of its annual net sales revenue in research and development. If it cannot reap the full benefit of the twenty-year monopoly conferred by its patent, it argues that its incentive to invest such large amounts in a product would diminish because of the lower expected return from R&D investments. Thus, the public’s “strong interest in creating adequate incentives to innovate” outweighs its interest in allowing generic competition before patent expiration.

Sandoz explains that there is a substantial public interest in permitting competition and allowing companies offering low cost generic products to enter the market and ease the public’s burden of high prescription drug costs. In addition, the public interest is not served by the

enforcement of allegedly invalid patents or the extension of monopoly pricing by means of invalid patents over the distribution of low cost pharmaceuticals.

The Court recognizes the public interest in competition in the pharmaceutical market. It also recognizes, however, the public interest in creating beneficial and useful products and the cost involved in that process. To the extent that this Court has found a substantial likelihood that the '718 patent is valid and enforceable, there can be no serious argument that public interest is not best served by enforcing it.

Lastly, Abbott requests that Sandoz's product that has made it market be recalled. This Court agrees that a recall of Sandoz's market is appropriate, but only to the extent that an adequate bond is set that reflects an amount necessary to protect Sandoz from losses should it be determined on summary judgement or at trial that the '718 patent (and the other patents at suit) are invalid or unenforceable.

IV. CONCLUSION

For the foregoing reasons, this Court **GRANTS** Abbott's motion for a preliminary injunction.

Enter:

/s/ David H. Coar

David H. Coar

United States District Judge

Dated: **April 16, 2007**