

# United States Court of Appeals for the Federal Circuit

2007-1300

ABBOTT LABORATORIES,

Plaintiff-Appellee,

v.

SANDOZ, INC.,

Defendant-Appellant.

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Appealed from: United States District Court for the Northern District of Illinois

Judge David H. Coar

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ABBOTT LABORATORIES,

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Appeal from the United States District Court for the Northern District of Illinois in case no. 05-CV-5373, Judge David H. Coar.

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DECIDED: October 21, 2008

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Before NEWMAN, Circuit Judge, ARCHER, Senior Circuit Judge, and GAJARSA, Circuit Judge.

Opinion for the court filed by Circuit Judge NEWMAN, in which Circuit Judge ARCHER concurs in the judgment and joins except as to Parts I and VI. Dissenting opinion filed by Circuit Judge GAJARSA.

This appeal is from the grant of a preliminary injunction, pending final resolution of the several challenges raised by Sandoz, Inc. to the validity, enforceability, and infringement of the Abbott Laboratories patents in suit.<sup>1</sup> We conclude that abuse of

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<sup>1</sup> Abbott Laboratories v. Sandoz, Inc., 500 F. Supp. 2d 807 (N.D. Ill. 2007) (grant of preliminary injunction); 500 F. Supp. 2d 846 (N.D. Ill. 2007) (denial of stay pending appeal); 529 F. Supp. 2d 893 (N.D. Ill. 2007) (grant and denial of various motions for summary judgment).

discretion has not been shown in the district court's decision to grant the injunction pendente lite. That decision is affirmed.

## BACKGROUND

This suit concerns two Abbott Laboratories patents on extended release formulations of the antibiotic drug clarithromycin, sold by Abbott with the brand name Biaxin®XL. The patent on clarithromycin itself expired in 2005; only extended release formulations are at issue. The purpose of the extended release formulation is to extend the period of drug effectiveness after ingestion and thereby to reduce the requisite frequency of dosage. Sandoz filed an Abbreviated New Drug Application (ANDA) for its extended release formulation of clarithromycin; the Food and Drug Administration approved the ANDA on August 25, 2005, and on September 16, 2005 Abbott filed suit in the United States District Court for the Northern District of Illinois, charging Sandoz with infringement of United States Patent No. 6,010,718 (the '718 patent) and Patent No. 6,551,616 (the '616 patent). Abbott also charged infringement of Patent No. 6,872,407, but has withdrawn this patent from suit.

The '718 patent claims an extended release pharmaceutical composition comprising an erythromycin derivative and a pharmaceutically acceptable polymer, whereby after ingestion certain specified parameters of drug bioavailability are met. Claims 1, 4, and 6 of the '718 patent are in suit:

1. 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.

4. 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 upon oral ingestion, maximum peak concentrations of the erythromycin derivative are lower than those produced by an immediate release pharmaceutical composition, and area under the concentration-time curve and the minimum plasma concentrations are substantially equivalent to that of the immediate release pharmaceutical composition.

6. An extended release pharmaceutical composition comprising an erythromycin derivative and a pharmaceutically acceptable polymer, the composition having an improved taste profile as compared to the immediate release formulation.

The '616 patent is a continuation-in-part of the '718 patent, with claims directed to the method of reducing gastrointestinal side effects. Claim 2 is in suit, shown with claim 1 from which it depends:

1. A method of reducing gastrointestinal adverse side effects comprising administering an effective amount of extended release pharmaceutical composition comprising an erythromycin derivative and a pharmaceutically acceptable polymer.
2. The method according to claim 1, wherein the erythromycin derivative is clarithromycin.

In response to the charge of infringement Sandoz presented the defenses of invalidity based on anticipation and obviousness, unenforceability based on inequitable conduct, and noninfringement. This appeal is from the district court's grant of Abbott's motion for a preliminary injunction, preserving the status quo during the pendency of this litigation. Sandoz challenges the district court's rulings on all issues.

## VALIDITY ISSUES

The district court reviewed the factors relevant to the grant or denial of a preliminary injunction, viz., (1) likelihood of success on the merits of the underlying litigation, (2) whether irreparable harm is likely if the injunction is not granted, (3) the balance of hardships as between the litigants, and (4) factors of the public interest. See Oakley, Inc. v. Sunglass Hut Int'l, 316 F.3d 1331, 1338-39 (Fed. Cir. 2003); H.H. Robertson Co. v. United Steel Deck, Inc., 820 F.2d 384, 387-88 (Fed. Cir. 1987). At the stage of the preliminary injunction, before the issues of fact and law have been fully explored and finally resolved, "[t]he purpose of a preliminary injunction is merely to preserve the relative positions of the parties until a trial on the merits can be held." University of Texas v. Camenisch, 451 U.S. 390, 395 (1981).

On appellate review of the grant of a preliminary injunction, the question "is simply whether the issuance of the injunction constituted an abuse of discretion." Doran v. Salem Inn, 422 U.S. 922, 932 (1975). "It is well settled that the granting of a temporary injunction, pending final hearing, is within the sound discretion of the trial court; and that, upon appeal, an order granting such an injunction will not be disturbed unless contrary to some rule of equity, or the result of improvident exercise of judicial discretion." Deckert v. Independence Shares Corp., 311 U.S. 282, 290 (1940). Abuse of discretion is established "by showing that the court made a clear error of judgment in weighing relevant factors or exercised its discretion based upon an error of law or clearly erroneous factual findings." Novo Nordisk of North America, Inc. v. Genentech, Inc., 77 F.3d 1364, 1367 (Fed. Cir. 1996). See Cybor Corp. v. FAS Technologies, Inc., 138 F.3d 1448, 1460 (Fed. Cir. 1998) (*en banc*) ("A district

court abuses its discretion when its decision is based on clearly erroneous findings of fact, is based on erroneous interpretations of the law, or is clearly unreasonable, arbitrary or fanciful.”).

Sandoz assigns legal error to the district court's rulings that Abbott is likely to prevail on the issues of validity, infringement, and inequitable conduct, and states that the district court abused its discretion in balancing the equities and granting the injunction.

### ***Anticipation***

"Anticipation" in patent usage means that the claimed invention was previously known and described in a printed publication, explicitly or inherently. Anticipation is established by documentary evidence, and requires that every claim element and limitation is set forth in a single prior art reference, in the same form and order as in the claim. See In re Omeprazole Patent Litigation, 483 F.3d 1367, 1373 (Fed. Cir. 2007); Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1267 (Fed. Cir. 1991). An anticipating reference must enable that which it is asserted to anticipate. Omeprazole, 483 F.3d at 1378 (“To ‘anticipate,’ the identical subject matter must not only be previously known, but the knowledge must be sufficiently enabling to place the information in the possession of the public.”); Elan Pharmaceuticals, Inc. v. Mayo Found. for Medical Educ. & Research, 346 F.3d 1051, 1054 (Fed. Cir. 2003) (same).

Sandoz argued that the '718 patent is anticipated by European Patent Publication No. 0,280,571 B1 (the '571 Publication), which describes "a sustained release matrix formulation in tablet form comprising from 0.1% by weight to 90% by weight of an antimicrobial agent selected from . . . erythromycin . . . from 5% by weight to 29% by weight

of a hydrophilic polymer, and from 0.5% by weight to 25% by weight of an acrylic polymer . . ." The '571 Publication states that hydrophilic polymers such as hydroxypropylmethyl cellulose (HPMC) can be used to form a hydrophilic matrix which "respond[s] to increases in pH with a corresponding increase in the permeability of the dosage form." Sandoz argued in the district court that although the '571 Publication does not mention clarithromycin or the specific pharmacokinetic limitations in the '718 patent claims, the '571 Publication anticipates the '718 claims because clarithromycin is an erythromycin derivative and the claimed pharmacokinetic limitations are inherent in the extended release compositions of the '571 Publication. Sandoz also argued that enablement of the compositions in the '571 Publication must be presumed, because the compositions in the '718 patent are presumed to be enabled and, according to Sandoz, are identical.

Abbott responded that the '571 Publication cannot "anticipate" because it does not show the elements of the claims of issue; it does not mention clarithromycin, it does not disclose the pharmacokinetic criteria stated in the '718 claims, and it does not enable these limitations, either expressly or inherently. Abbott argued that significant experimentation would be required to ascertain the applicability of any release agent from the large number of release agents mentioned in the '571 Publication, particularly as applied to a different biological product having different dissolution and metabolic characteristics. Thus Abbott argued that the legal criteria of "anticipation" are not met by the '571 Publication.

The district court found that Sandoz did not present evidence sufficient to support its argument 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." Abbott, 500 F. Supp.2d at 840. The district court observed that the '571 Publication "does

not offer any in vivo dissolution data" nor state "the pharmacokinetic profile of its own formulations." Id. The court concluded that Sandoz would not be likely to succeed in establishing anticipation by this reference. We discern no clear error in this conclusion, for the '571 Publication neither describes the product of the '718 claims nor enables the pharmacokinetic properties that are set forth in the '718 claims. See Elan Pharmaceuticals, 346 F.3d at 1057 (an anticipating reference must disclose every element of the claims, and place a person of ordinary skill in possession of the claimed invention).

### ***Obviousness***

Sandoz also argued that the claims of the '781 and '616 patents are invalid on the ground of obviousness, in view of the combination of the '571 Publication with PCT Application WO 95/30422 (the PCT or '422 Application) and United States Patent No. 5,705,190 (the '190 patent).

In determining, for preliminary injunction purposes, the likelihood that patent invalidity would be established at trial, the district court evaluates the factual and legal arguments in light of the presumptions and burdens that will inhere at trial, viz., that "[a] patent shall be presumed valid. . . . The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. §282. This burden "exists at every stage of the litigation." Canon Computer Systems, Inc. v. Nu-Kote Int'l, Inc., 134 F.3d 1085, 1088 (Fed. Cir. 1998); see Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1374 (Fed. Cir. 2006) (taking into account the applicable presumptions and burdens in reviewing the grant of a preliminary injunction). Sandoz on this appeal relies on the Supreme Court's decision in KSR International Co. v. Teleflex, Inc., \_\_\_\_ U.S. \_\_\_, 127 S.

Ct. 1727 (2007), Sandoz arguing that the law of obviousness has been significantly changed, and that the district court did not give adequate recognition to the changed law. The district court had issued its initial decision granting the preliminary injunction shortly before the Court's decision in KSR. The court then requested supplemental briefing and argument, and issued a further opinion discussing the issues in light of KSR and continuing to conclude that Abbott was likely to prevail on the merits of the question of obviousness.

In its initial decision the district court discussed the references in detail. The court explained that the PCT Application, entitled "Controlled-Release Dosage Forms of Azithromycin," describes "[a] dosage form for oral administration comprising azithromycin and a pharmaceutically acceptable carrier, which releases not more than about 10% of its incorporated azithromycin into a mammal's stomach, and which releases not more than an additional 10% during the first 15 minutes after entering said mammal's duodenum," and exhibits decreased gastrointestinal side effects. The district court explained that the PCT Application shows hydroxypropylmethylcellulose (HPMC) and other polymers as "a hydrophilic polymer sufficient to provide a useful degree of control over the azithromycin dissolution," and contains in vitro data showing the amount and timing of dissolution of azithromycin in various conditions and sustained dosage forms.

Sandoz argued that these teachings should be combined with those of the '571 Publication and the '190 patent entitled "Controlled Release Formulation for Poorly Soluble Basic Drugs," which describes a "controlled release solid pharmaceutical composition adapted for oral administration comprising: a therapeutically effective amount of at least one basic drug having a water solubility of less than 1 part per 30 parts water . . . wherein the basic drug is a macrolide" and as the release agent a water-soluble alginate salt. The

'190 patent names the macrolides erythromycin, clarithromycin, dirithromycin, azithromycin, roxithromycin, and ABT-229 for use with the alginate salt release agent. Sandoz argued that the subject matter of the '718 patent would have been obvious in view of the '571 Publication showing extended release formulations of erythromycin derivatives, in combination with the controlled release formulations and pharmacokinetic properties of azithromycin in the PCT Application, and the modified release alginate salt formulation of clarithromycin in the '190 patent. Sandoz argued that a person of ordinary skill in this field would have desired to improve the administration of clarithromycin by finding an extended release formulation having optimum release and biological properties, and would have selected and tested the HPMC from the '571 Publication, in view of the formulation of azithromycin with HPMC in the PCT Application and the '190 patent's use of an alginate salt to modify the release of clarithromycin. Sandoz stressed that the PCT Application states the known principle of using controlled release formulations to reduce the dosing frequency for short half-life compounds. Sandoz argued that no more than routine experimentation was needed to find a controlled release formulation that would meet the pharmacokinetic requirements stated in the '718 claims.

Sandoz applied similar arguments to the claims of the '616 patent, stating that the PCT Application teaches that control of azithromycin release reduces gastrointestinal side effects, and that the '190 patent shows the interchangeability of azithromycin and clarithromycin in the formulation using an alginate salt. Sandoz argued that this combination of references renders obvious a clarithromycin formulation with reduced gastrointestinal side effects as claimed in the '616 patent. In its supplemental argument based on KSR, Sandoz argued that Abbott merely "pursue[d] known options" for both the

'718 and '616 patents, based on the Court's exposition that: "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." KSR, 127 S. Ct. at 1742.

In the district court Abbott disputed the premises presented by Sandoz, challenged the analysis of the content and significance of the references, and argued that KSR did not hold, as Sandoz proposed, that the recognition of a problem of itself renders the solution obvious. Abbott argued that more is needed than recognizing the problem, as this court discussed in Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc., 381 F.3d 1371, 1377 (Fed. Cir. 2004) ("Recognition of a need does not render obvious the achievement that meets that need. . . . Recognition of an unsolved problem does not render the solution obvious.") Abbott pointed out that the Court qualified its discussion by explaining that the "problem" should have "a finite number of identified, predictable solutions," KSR, 127 S. Ct. at 1742, to expose its eventual solution to unpatentability as "obvious to try." Id. Abbott stressed the difference between new biological compositions whose performance and effectiveness in combination cannot be confidently predicted but must be made and evaluated, and new mechanical combinations of known elements each of which predictably performs its known function in the combination.

Abbott stressed that its choice of extended release components is not shown or suggested by the prior art to produce the pharmacokinetic properties of Abbott's claims. The Court recognized in Dennison Mfg. Co. v. Panduit Corp., 475 U.S. 809 (1986) that the district court is not to rely on hindsight, and that "in addressing the question of obviousness a judge must not pick and choose isolated elements from the prior art and combine them so

as to yield the invention in question if such a combination would not have been obvious at the time of the invention.” 475 U.S. at 810. In Graham v. John Deere Co., 383 U.S. 1 (1966) the Court recognized that the obviousness inquiry must “guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue.” Id. at 36.

Abbott agreed that the basic principles of pharmacokinetics were known, but argued that the limitations in the '718 claims, whereby the bioavailability of the product was characterized, were not shown as achieved in any reference or any combination of references. Abbott pointed out that the PCT Application is directed specifically to azithromycin and shows “scores” of possible formulations, all using in vitro data, and does not contemplate metabolite activity in vivo as is manifested for chlorithromycin. Abbott stated that “the ‘422 publication discloses more than a dozen possible classes of delivery devices,” Abbott Brief at 42, that “the ‘422 publication merely provides in vitro dissolution data for a subset of its disclosed compositions,” and that the formulation in the PCT Application “did not even have equivalent bioavailability as IR [immediate release] azithromycin.” Id. at 41.

Abbott described in the '718 and '616 specifications that the '190 patent reference presents "C<sub>max</sub> values [that] are not statistically significantly different from those of the IR formulation." '718 patent, col. 2, lines 11-12; '616 patent, col. 2, lines 13-14 (referring to Ser. No. 08/574,877, the '190 patent). Abbott stated that Sandoz concedes that the '190 patent does not describe pharmacokinetic limitations based on clarithromycin plasma concentrations, and that neither the PCT Application nor the '190 patent discloses the pharmacokinetic limitations and properties set forth in the '718 and '616 claims, and that

neither the PCT Application nor any other reference provides guidance as to which formulation would provide the pharmacokinetic characteristics required by the '718 claims.

Thus Abbott argued in the district court that a skilled artisan would not have known the effect of substituting clarithromycin for azithromycin in any specific formulation that might be selected from the PCT Application, for it is undisputed that there are significant differences among erythromycin derivatives. Abbott presented evidence to the district court that azithromycin and clarithromycin exhibit different properties in four biological processes of relevance to oral drug administration: absorption, distribution, metabolism, and excretion.

These differences were tabulated by Abbott's expert, Professor Stanley S. Davis, as follows:

	Azithromycin	Clarithromycin
Absolute Bioavailability	About 34% from 600 mg dose	About 50% from 250 mg dose
Pharmacokinetics	Linear	Non-linear
Active Metabolite	None reported in the Physicians Desk Reference	14-hydroxy clarithromycin
Metabolism	Metabolites possess little or no activity	Extensively metabolized to an active metabolite
Elimination Half Life	About 70 hours	3-4 hours for 250 mg IR dose (14-OH metabolite, 5-6 hours)
First Pass Effect	Not significant	Extensive
Volume of Distribution	Large-2200 litre	250 litre

Supplemental Declaration of Dr. Davis, February 7, 2007. The parties do not dispute that the PCT Application describes only in vitro data, and that in vitro data are not predictably transferable to in vivo conditions. Dr. Davis testified that "it simply isn't the case that in vitro controlled release data will automatically correlate with the pharmacokinetic parameters in vivo, and in fact, for many of the formulations of the '422 application, they affirmatively do not so correlate." Id.

The district court concluded that a person of ordinary skill in this field would not have predicted which formulation, that might be selected from the prior art, would provide the required pharmacokinetics. The district court referred to the dissimilarities in the pharmacokinetic properties for azithromycin as shown in the PCT Application, considered the content of the '190 patent, and concluded that the bioavailability of the formulations claimed in the '718 patent were not predictable from these references. The court referred to the testimony of another Abbott expert, Dr. Daniel Weiner, that "the '190 patent does not disclose any clarithromycin-specific PK [pharmacokinetic] data" or "any DFL [degree of fluctuation]<sup>2</sup> values at all." Declaration of Daniel Weiner, Ph.D., January 9, 2007. Dr. Weiner explained that the pK values reported in the '190 patent are based on total antibiotic activity, which consists of the combined concentrations of clarithromycin and its active metabolite, while the pharmacokinetic elements of the '718 patent relate specifically to clarithromycin plasma concentrations. Dr. Weiner concluded, and the district court agreed, that a skilled artisan would not have had a reasonable expectation of producing effective

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<sup>2</sup> The variation between maximum and minimum concentration is measured by the degree of fluctuation, called "DFL", calculated as  $(C_{\max} - C_{\min})/C_{\text{avg}}$ , with  $C_{\text{avg}}$  the average concentration over a dosing interval. Appx. 463 ¶28.

compositions based on the mention of clarithromycin along with azithromycin in the '190 patent, because of their different mechanisms of antibiotic activity and the effect of this activity on pharmacokinetic behavior.

The district court observed that the in vivo azithromycin controlled release formulations in the PCT Application have less total bioavailability than their immediate release counterparts, supporting Abbott's argument that the behavior of differing biological systems, even when structurally similar, is not predictable. See Alza Corp. v. Mylan Laboratories, 464 F.3d 1286, 1297 (Fed. Cir. 2006) ("Alza's evidence of in vitro dissolution rates is irrelevant absent evidence demonstrating that the in vitro system is a good model of actual in vivo behavior."). The district court concluded that the in vivo extended release properties claimed in the '718 patent are sufficiently dissimilar to or unpredictable from the in vitro controlled release data for azithromycin in the PCT Application that a person of ordinary skill in the field of the invention would not have had the degree of confidence of success in transferring the PCT Application's azithromycin formulation to the different metabolic and solubility systems of clarithromycin as would render the '718 claimed invention unpatentable on the ground of obviousness.

In reaching these conclusions, the district court relied on the Federal Circuit's decision on the same patents in Abbott Laboratories v. Andrx Pharmaceuticals, Inc., 473 F.3d 1196 (Fed. Cir. 2007) (herein "Andrx"). This court, sustaining the district court's grant of a preliminary injunction, had concluded that obviousness was not likely to be established, reversing this court's prior ruling reversing the grant of a preliminary injunction in Abbott Laboratories v. Andrx Pharmaceuticals, Inc., 452 F.3d 1331 (Fed. Cir. 2006) (herein

"Teva"). Sandoz argued to the district court that the Federal Circuit's ruling in Andrx is incorrect, and on this appeal Sandoz urges us to reject Andrx and reinstate Teva.

In Teva a panel of this court held that the claims of the '718 patent were likely to be held not infringed. This court also stated that there was a substantial likelihood that claim 4 of the '718 patent would be held invalid for obviousness based on the PCT Application together with the '190 patent. This court held that the preliminary injunction should be denied, although the panel cautioned that its ruling "in no way resolves the ultimate question of invalidity." Teva, 452 F.3d at 1347. In Andrx a later panel of this court, on an enlarged record, rejected the invalidity ruling in Teva and held that the '718 claims were likely to withstand the attack on validity. Andrx, 473 F.3d at 1203-07.

Reviewing this history as applied to Sandoz' arguments herein, the district court explained that this court in Teva had not been made aware of the differences between the pharmacokinetic criteria described in the '190 patent and those of the '718 patent. The district court explained that the pharmacokinetic data in the '190 patent were based on measurements of total antibiotic activity in the body, which includes both clarithromycin and its active metabolite formed after ingestion, whereas the data in the '718 patent are specific to clarithromycin alone. The court found that "Abbott has shown . . . 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," Abbott, 500 F. Supp.2d at 841.

Sandoz argued, in its supplemental briefing in the district court after the KSR decision, that this court's decision in Andrx does not survive scrutiny under the principles set forth in KSR, and stressed that application of KSR renders it "obvious to try" the various

release agents in the PCT Application, such that any successful composition would be unpatentable, whether or not the results were predictable. Sandoz argued that the '190 patent shows that clarithromycin and azithromycin have similarities as well as differences, and that it would be obvious to experiment to determine which formulations were effective in view of these differences and similarities. Sandoz stressed that the Abbott scientists had knowledge of the prior art including the PCT Application, and that they developed the Abbott formulation in only one month of research effort. Sandoz quoted the Court's admonition in KSR that a court "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ," 127 S. Ct. at 1741, and that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." Id. at 1739.

The district court, applying KSR, reconsidered its prior determination and framed the question as "whether an ordinary person skilled in the art would have seen a benefit to combining an erythromycin derivative with a polymer with the same PK [pharmacokinetic] limitations as embodied in claims 1 and 4 of the '718 patent given the state of the pharmaceutical industry at the time." Abbott, 500 F. Supp.2d at 851. The court concluded: "Based upon what evidence and argument Sandoz offered, the answer was and remains no." Id. The district court explained that "this Court's preliminary factual findings . . . found that Sandoz had not produced evidence indicating that the PK limitations were disclosed in the prior art or were inherent to the structural limitations of the prior art compositions." Id. at 852. The district court observed that "[t]he KSR opinion only focused on the Federal Circuit's strict use of the TSM [teaching, suggestion, motivation] test in performing the obviousness analysis; it did not mention or affect the requirement that each and every claim

limitation be found present in the combination of the prior art references before the analysis proceeds." Id. at 852.

We agree that the obviousness of selection of components, when there is no prediction in the prior art as to the results obtainable from a selected component, differs from the issue in KSR, where the Court provided guidance that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." 127 S. Ct. at 1740. The Court explained the conditions in which "obvious to try" may negate patentability, depending on the relation of the prior art teaching to the later-developed technology. The Court explained that when the problem is known, the possible approaches to solving the problem are known and finite, and the solution is predictable through use of a known option, then the pursuit of the known option may be obvious even absent a "teaching, suggestion, or motivation" concerning that option. Then, "if this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." 127 S. Ct. at 1742.

Abbott argued that the "known options" in the prior art were not "finite, identified, and predictable," the words of KSR, and are identified only with hindsight knowledge of Abbott's new formulation and its pharmacokinetic properties. Abbott pointed to the discussion in the PCT Application of over a dozen possible drug delivery modes, including matrix systems, membrane-moderated or reservoir systems, osmotic pumps, coated hydrogel tablets and multiparticulates, sustained release compositions with delayed-release layers, pH-dependent coated tablets, bursting osmotic core devices, bursting coated swelling core devices, pH-triggered bursting osmotic core devices, pH-triggered bursting coated swelling core devices, enzyme-triggered supported liquid membrane devices, bacterially degradable

coating devices, and swelling plug devices, all classes of controlled release for drug delivery systems, each containing sub-classes and variations. PCT App. at 8-38. The expert witnesses pointed out the difficulties in predicting the behavior of any composition in any specific biological system.

The evaluation of the choices made by a skilled scientist, when such choices lead to the desired result, is a challenge to judicial understanding of how technical advance is achieved in the particular field of science or technology. Such understanding is critical to judicial implementation of the national policy embodied in the patent statute. In Publication of Tomlinson, 363 F.2d 928 (CCPA 1966) our predecessor court discussed the role of "obvious to try" in scientific and technologic research and in patentability:

Slight reflection suggests, we think, that there is usually an element of "obviousness to try" in any research endeavor, that is not undertaken with complete blindness but rather with some semblance of a chance of success, and that patentability determinations based on that as the test would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of "research."

Id. at 931. The Court in KSR did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is "obvious to try," without considering the nature of the science or technology. The methodology of science and the advance of technology are founded on the investigator's educated application of what is known, to intelligent exploration of what is not known. Each case must be decided in its particular context, including the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality of the prior art, and the predictability of results in the area of interest.

The district court discussed the differences between the pharmacokinetic properties shown in the '190 patent reference and the properties in the '718 patent claims, the differences in the chemical and biological properties of azithromycin and clarithromycin, the differences between in vitro and in vivo data, and the differences between azithromycin and clarithromycin. For example, Abbott's expert Dr. Davis stated that "the absorption of clarithromycin is affected by a phenomenon known as the 'first pass effect' which does not occur for azithromycin," and that azithromycin's "metabolism occurs only post-absorption." Dr. Davis also stated that "the half-life for azithromycin is about 70 hours, whereas that for clarithromycin is about 3-4 hours at low IR doses." First-pass metabolism was explained as meaning that a significant amount of the drug is metabolized and converted into another compound before it enters the circulation; Dr. Davis stated that a person of skill in this field, having this knowledge, would not have assumed that the two drugs would exhibit similar behavior if placed in the same formulation. The district court concluded that it was not predictable, from the in vitro behavior of azithromycin, how any specific clarithromycin extended release formulation would perform in vivo.

Sandoz presented other arguments, for example, that the FDA regulations state the requirements for approval of extended release formulations, thereby rendering obvious a formulation that meets these requirements. However, knowledge of the goal does not render its achievement obvious. The district court appropriately applied the KSR standard of whether the patents in suit represented an "identified, predictable solution" and "anticipated success," the words of KSR, to the problem of producing extended release formulations having the pharmacokinetic properties in the claims.

On the record of the preliminary injunction proceedings, and considering this court's

ruling in Andrx and the guidance of the Court in KSR, we do not discern reversible error in the district court's ruling that Abbott is likely to prevail on the issues of patent validity based on anticipation and obviousness.

II

INEQUITABLE CONDUCT

Sandoz also argued that the '718 and '616 patents are unenforceable due to Abbott's "inequitable conduct" in the Patent and Trademark Office. Sandoz stated that Abbott submitted a false declaration to the PTO, and also that Abbott withheld from the examiner the results of certain tests after the patent applications were filed and that were inconsistent with information in the patent applications. The district court found that there was no intent to deceive the examiner, and that the criticized activity did not constitute inequitable conduct.

The evidentiary standard for determining whether there was inequitable conduct in obtaining a patent that is otherwise valid was set forth by this court, sitting en banc for the purpose, in Kingsdown Medical Consultants, Ltd. v. Hollister Inc., 863 F.2d 867 (Fed. Cir. 1988). The court explained that "[t]o be guilty of inequitable conduct, one must have intended to act inequitably," and held: "Inequitable conduct resides in failure to disclose material information, or submission of false material information, with an intent to deceive, and those two elements, materiality and intent, must be proven by clear and convincing evidence." Id. at 872. Mistake or negligence, even gross negligence, does not support a ruling of inequitable conduct. The court held:

We adopt the view that a finding that particular conduct amounts to "gross negligence" does not of itself justify an inference of intent to deceive; the involved conduct, viewed in light of all the evidence, including evidence

indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive.

Id. at 876. When both materiality and deceptive intent have been established the district court determines, in the court's discretion, whether inequitable conduct has occurred; appellate review is on this basis. See id. at 876 ("As an equitable issue, inequitable conduct is committed to the discretion of the trial court and is reviewed by this court under an abuse of discretion standard. We, accordingly, will not simply substitute our judgment for that of the trial court in relation to inequitable conduct.").

### ***The '718 patent***

Sandoz first challenges the district court's findings with respect to a declaration by an inventor, Dr. Linda Gustavson, comparing the products of the pending '718 application with the products in a prior art Abbott patent, U.S. Patent No. 4,808,411, directed to a pediatric clarithromycin suspension that is administered twice daily. Dr. Gustavson submitted data to the PTO comparing the '718 and the '411 formulations, and stated that "the ER [extended release] formulation as claimed, is supported by the above results, namely,  $C_{max}$  of clarithromycin in plasma is statistically significantly lower than that for IR [immediate release] formulation given twice daily." The declaration also stated that "AUC is maintained over 24 hours; and  $C_{min}$  is substantially equivalent to that of the IR suspension".<sup>3</sup> However, in this litigation Dr. Gustavson testified that she had not analyzed statistical significance, and that "it could not definitively be concluded from the data that the difference between the ER  $C_{max}$  and the  $C_{max}$  for a twice-a-day dosed suspension would

have been statistically significantly different." Based on this admission, Sandoz argued that the Gustavson submission to the PTO was a material misrepresentation, that intent to deceive is presumed, and that inequitable conduct was thereby established.

Abbott did not dispute that Dr. Gustavson did not analyze statistical significance, but argued that it was not material to patentability and that a reasonable examiner would not have found otherwise. Abbott pointed out that the actual data were before the PTO, and that the results did show a numerically lower  $C_{max}$  value. Sandoz pointed out to the district court that Abbott's patent attorney argued nonobviousness to the PTO based on the Gustavson declaration, and Abbott responded that the declaration correctly stated that the pharmacokinetic properties of the product in the '411 patent are markedly different from those of the product of the '718 patent. We have been directed to no evidence of deceptive intent, or "bad faith or intentional misconduct", in the words of PTO Rule 56; on this appeal Sandoz repeats that deceptive intent should be inferred from the misstatement.

The district court cited Impax Labs., Inc. v. Aventis Pharm., Inc., 468 F.3d 1366, 1374 (Fed. Cir. 2006) for its summary that a ruling of inequitable conduct requires clear and convincing evidence that the applicant while prosecuting the patent "(1) made an affirmative misrepresentation of material fact, failed to disclose material information, or submitted false material information, and (2) intended to deceive the [PTO]." In determining materiality, the district court applied the standard that "[u]ndisclosed information is material if it satisfies 37 C.F.R. §1.56 and if there is a substantial likelihood that a reasonable examiner would have

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<sup>3</sup> The AUC is a calculation of the "area under a curve" when drug concentration is plotted over time, and is a measure of bioavailability of the drug.  $C_{min}$  is the minimum rug concentration over a dosing interval.

considered the undisclosed information important in deciding whether to allow the patent to issue." Although the Federal Circuit has not always been consistent in defining "materiality" in accordance with the PTO Rules, the principles are consistently directed to deceptive actions by patent applicants. In Digital Control, Inc. v. Charles Machine Works, 437 F.3d 1309 (Fed. Cir. 2006) the court observed that four separate tests have been applied for materiality.

The district court, applying the tests of materiality to the Gustavson statement about statistical significance, stated that it was "obviously troublesome that Gustavson made her assertion without having actually performed the statistical test." The district court concluded that the Gustavson statement was not material to patentability, "despite the fact that it satisfies the definition of 'material' provided by 37 C.F.R. §1.56(b)." The court stated that:

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.

500 F.Supp.2d at 822. Relevant is the ruling in Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1570 (Fed. Cir. 1997) (that "Information is material if a reasonable examiner would have considered it important to the patentability of a claim").

The district court also found that there was no evidence of intent to deceive the examiner. The court rejected Sandoz's argument that deceptive intent is inferred from materiality alone, for precedent requires independent proof of deceptive intent. See

Kingsdown, 863 F.2d at 872 (intent to deceive the examiner into granting the patent is a separate and essential element of inequitable conduct in the PTO); Baker Oil Tools, Inc. v. Geo Vann, Inc., 828 F.2d 1558, 1565 (Fed. Cir. 1987) ("The material facts upon which a holding of inequitable conduct rests relate to both the intent of the actor and the materiality of the information."). Weighing the materiality of the statement and the absence of evidence of intent to deceive, we do not discern an abuse of discretion in the district court's conclusion that inequitable conduct was not established by the statement concerning statistical significance.

Sandoz next challenged the fact that Abbott did not provide to the patent examiner the results of some clinical tests conducted after the '718 patent application was filed, that were reported to the FDA and included on the Biaxin® XL product label. The test results relate to taste perversion<sup>4</sup> results in a later clinical trial, and a study comparing clarithromycin with azithromycin. Sandoz stated that Abbott should have provided the patent examiners with these results and the product label, which report tests wherein the immediate release formulation has a lower incidence of taste perversion than the extended release formulation, contrary to the information in the '718 patent. Sandoz argued that the inventors knew or should have known of this discrepancy, and thus that intent to deceive is established. Abbott responded that the challenged taste tests were from dosages that were not directly comparable, and that they did not change the correctness of the data in the patent application. Abbott presented the expert testimony of Dr. Davis that "the

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<sup>4</sup> "Taste perversion" is defined in the '718 patent as "the perception of a bitter metallic taste normally associated with erythromycin derivatives, particularly, with clarithromycin." Col 3, lines 53-55.

comparison between the taste perversion incidence rate for Biaxin® IR and Biaxin® XL in the label does not relate to the invention disclosed and claimed in the '407 patent, which is for a reduction in taste perversion for the same total dose." Supplemental Declaration of Professor Stanley S. Davis, February 7, 2007(emphases in original).

The district court concluded that the taste results met the materiality criteria of Rule 56 but that a reasonable examiner would not consider the information important in deciding whether to grant the patent. The court explained that a reasonable examiner would compare data at comparable dosages, and that the data were not comparable. Although Abbott and Sandoz argued about whether the inventors knew or should have known of this discrepancy between this taste data from the Phase III clinical trial, and the taste data in the patent application, the district court observed that there was no evidence of deliberate withholding of this information in order to deceive the patent examiner. "Intent to deceive can not be inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent." Hebert v. Lisle Corp., 99 F.3d 1109, 1115, 1116 (Fed. Cir. 1996) ("To establish inequitable conduct the information that is known to the applicant and not provided to the PTO must be both material to patentability, and withheld in order to deceive or mislead the examiner."); Molins PLC v. Textron, Inc., 48 F.3d 1172, 1181 (Fed. Cir. 1995) ("While intent to deceive the PTO may be found as a matter of inference from circumstantial evidence, circumstantial evidence cannot indicate merely gross negligence.").

Materiality is not evidence of intent, which must be established as a separate factual element of a discretionary ruling of inequitable conduct. The district court finding that the

factual premises of both materiality and intent to deceive were not established in connection with the taste data, did not abuse its discretion in declining to find inequitable conduct on this ground.

Finally, Sandoz criticized Abbott's failure to provide the PTO with a study designated W98-268, done after the patent application was filed, which compared the pharmacokinetic values of clarithromycin upon administration under various conditions. The district court described the issue as: "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" but "[t]he 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." 500 F. Supp.2d at 823. Sandoz stated that Abbott committed inequitable conduct by failing to disclose these results to the PTO.

Dr. Weiner stated in his January 9 Declaration that "the '190 patent does not disclose any clarithromycin-specific PK data," and "the '190 patent does not disclose any DFL values at all," and explained that "subsequent studies conducted by Abbott indicate that the commercial embodiment of the invention of the '190 patent does not have a statistically significantly lower DFL than the IR formulation. . . . Before the present litigation, Abbott had conducted five crossover studies in which the pharmacokinetic parameters for clarithromycin (i.e., clarithromycin specifically, not clarithromycin combined with its metabolite) were measured for both the MR [modified release] and IR formulations: W95-914, W95-195, W95-197, W98-268 [the study that Sandoz accuses Abbott of withholding], and TAI-99-001." The mean DFL values in Table VII in the '718 patent are

based on Study W95-195. See Supplemental Declaration of Dr. Ronald Sawchuk, February 7, 2007 ("Table VII reflects data from a multiple dose study involving MR formulation and an IR formulation that was conducted in Germany in 1995. See Ex. 12, Study W95-195."). The studies conducted before the '718 patent application was filed showed the data reported in the specification.

Many details were explained to the district court, as to all the studies, their context, and their relationship. The district court found that "contrary to Sandoz's assertion, Study W98-268 does not demonstrate that the prior art MR formulation has the same PK properties as that claimed for the ER formulation. Therefore, Study W98-268 is not material to the patentability of the '718 patent." Abbott, 500 F. Supp.2d at 824. The district court found that the '718 patent "speaks of the PK relationship of extended release and immediate release formulations, not of modified release and immediate release formulations. . . . [and] 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."

Id. The district court found that the W98-268 study was not material under either Rule 56 or the reasonable examiner standard. Clear error has not been shown in this finding.

On the preliminary injunction record, the district court did not abuse its discretion in ruling that Sandoz was not likely to succeed in establishing inequitable conduct in Abbott's prosecution of the '718 patent application. We agree with the district court that the scales do not "tilt towards finding inequitable conduct." Id. at 829.

### ***The '616 patent***

Sandoz argued that inequitable conduct as to the taste perversion claim in the '718 patent taints the '616 patent because a taste perversion claim was included in the '616 application when it was filed, although that claim was cancelled before any PTO examination on the merits. The district court declined to hold the '616 patent unenforceable based on a withdrawn claim, citing 37 C.F.R. §1.56(a):

Rule 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.

The district court deemed it "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." Abbott, 500 F. Supp.2d at 829. This court held in Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1583 (Fed. Cir. 1991) that "[a] reference that is material only to withdrawn claims can not be the basis of a holding of inequitable conduct."

Rule 56 is in accord.

Sandoz also argued as to the '616 patent that Abbott did not report to the PTO the results of clinical trials conducted before the continuation in-part '616 application was filed. Sandoz' expert Dr. Marcello Pagano, in his Declaration dated January 25, 2007, stated: "I have reviewed the bronchitis and sinusitis studies [and] the claims of the '616 patent for a method of reducing gastrointestinal adverse side effects are not supported by the data from those two clinical studies." The results of these studies were provided to the FDA, but not to the PTO. Dr. Pagano stated: "Since neither the sinusitis nor the bronchitis studies produced favorable results to support a claimed reduction in gastrointestinal adverse side

effects, Abbott had to manipulate its data and report the number of discontinuations due to gastrointestinal adverse side effects to the PTO . . ." The district court found that the information from these clinical trials was not material to patentability, stating that: "it is clear from both Table VI and Table VIII [of the '616 patent] 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." Abbott, 500 F. Supp.2d at 828. These findings have not been shown to be clearly erroneous.

There was no evidence of intent to deceive with respect to the results of these clinical trials. Materiality, even if found, does not establish intent. This is not a case of new information that affects the fundamental invention; this is a case of challenging every action or inaction of the "conduct" of patent solicitation, although patentability is unaffected. The purpose of Kingsdown was to bring patent practice into the mainstream of the law and administrative practice. The law severely punishes fraudulent practices, and the patent practice includes recognition that the inventor usually knows more about the field than does the "expert" patent examiner. However, routine actions that do not affect patentability and that are devoid of fraudulent intent are not subject to a different standard than other inquiries into fraudulent procurement. The Administrative Procedure Act governs patent examination, see Dickinson v. Zurko, 527 US 150 (1999), and actions of patent examiners are reviewed with recognition of examiner expertise so well as recognition of the occasionally imperfect examination process. "It was to mitigate the 'plague' whereby every patentee's imperfections were promoted to 'inequitable conduct' that this court reaffirmed that both materiality and culpable intent must be established." Allied Colloids, Inc. v. American Cyanamid Co., 64 F.3d 1570, 1578 (Fed. Cir. 1995).

We conclude that the district court did not abuse its discretion in holding that the '718 and '616 patents were not likely to be held unenforceable based on inequitable conduct in obtaining the patents.

### III

#### INFRINGEMENT

The first step in most infringement suits is the procedure called 'claim construction,' where the scope of the claim is defined by the court. At the preliminary injunction stage the district court's claim construction is reviewed, as for other legal issues, for the likelihood of correctness of the ruling. This likelihood is based on the underlying facts as found at this stage of the proceedings, recognizing that "the burdens at the preliminary injunction stage track the burdens at trial." Gonzales v. O Centro Espírito Beneficente União do Vegetal, 546 U.S. 418, 429 (2006).

For the patents here in suit, the issue of infringement was resolved, at this preliminary injunction stage, as a matter of claim construction. The dispositive question was whether the term "pharmaceutically acceptable polymer" is limited to the polymers named in the specification, or can include other pharmaceutically acceptable polymers. If so limited, it is likely that there would not be literal infringement; if not so limited, then literal infringement would be possible. (Infringement under the doctrine of equivalents was not addressed by the district court, although Sandoz argues the issue "in an abundance of caution.").

The meaning and scope of "pharmaceutically acceptable polymer" as used in these patents has been litigated in other cases, none of which had been finally decided, but some of which had been appealed to the Federal Circuit based on the grant of a preliminary injunction. The district court now construed "pharmaceutically acceptable polymer" in

accordance with the construction by the Federal Circuit in Andrx, supra. Sandoz argues on this appeal that the correct construction is that of the Federal Circuit's earlier decision in Teva, supra. Sandoz argues that because Teva was the earlier ruling, it could not be overturned by the later Andrx panel, citing Newell Cos., Inc. v. Kenney Mfg. Co., 864 F.2d 757, 765 (Fed. Cir. 1988) ("Where there is a direct conflict [between Federal Circuit panels], the precedential decision is the first.").

Abbott responds that the decision in Andrx was properly followed by this district court, for in Teva the "construction" of "pharmaceutically acceptable polymer" was not at issue, and this court's comment thereon was dictum. The court in Andrx recognized the non-binding nature of that comment in Teva. Indeed, the district court in Teva had stated that "[a]t this early stage of the proceedings, the parties have raised no issue as to claim construction". Abbott Laboratories v. Andrx Pharmaceuticals, Inc., No. 05 C 1490, 2005 WL 1323435, at \*3, \*4 (N.D. Ill. June 03, 2005) (Teva conceding literal infringement but challenging validity).

The panel in Andrx decided the questions now raised by Sandoz concerning the "construction" of "pharmaceutically acceptable polymer" and the pharmacokinetic requirements in the claims. The Andrx panel also explained its departure from the panel decision in Teva. The district court herein, applying Andrx, held that a person of ordinary skill in this field would interpret "pharmaceutically acceptable polymer" in terms of the following description in the '718 specification:

"Pharmaceutically acceptable" as used herein, means 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 lines 40-47. The district court referred to the '718 specification's listing of pharmaceutically acceptable polymers, but applied the Andrx ruling that the polymers are not limited to those that are named in the following paragraph:

The pharmaceutically acceptable polymer is a water-soluble hydrophilic polymer selected from the group consisting of polyvinylpyrrolidine, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, vinyl acetate/crotonic acid copolymers, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures thereof.

'718 patent, col. 3 line 65 to col. 4 line 4. The district court construed "pharmaceutically acceptable polymer" as:

[A]ny 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.

Abbott, 500 F. Supp.2d at 834. The district court, following Andrx, held that the usage "from the group consisting of" in the specification is not exclusive, as it would be in a Markush-form claim, and did not negate the broader description that is also contained in the specification, as quoted above.

This aspect was debated in the district court, and again on this appeal. Sandoz argues that since "pharmaceutically acceptable polymer" is limited by the specification to water-soluble hydrophilic polymers, and that since the listed methacrylic acid copolymers are known to include water-insoluble as well as water-soluble polymers, the term

"pharmaceutically acceptable polymer" must be construed to mean that the formulation cannot include any water-insoluble methacrylic acid or other polymer. The district court, receiving this argument, reasoned 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." Abbott, 500 F. Supp.2d at 834. Sandoz argues that this reasoning is flawed, and that this court in Andrx erred in rejecting this argument. However, we are not persuaded that the Andrx panel's ruling warrants rejection on this argument, for we agree with the district court that the fact that some methacrylic acid copolymers are water-insoluble does not require limiting "pharmaceutically acceptable polymer" to the named polymers.

We conclude that the district court's claim construction, which is that of Andrx, is correct, and that the district court properly declined to follow Teva. Sandoz' argument that Teva was the correct construction and should be revived by the Federal Circuit is hard to square with Sandoz' statement to the district court that "a very important point to make here is Sandoz does not rely on the Federal Circuit opinion in the Teva case. . . . Sandoz agrees with Abbott." Statement at the February 12, 2007 preliminary injunction hearing, transcript at A11085.

Sandoz further argues that the district court erred by using the word "matrix" in its definition of "pharmaceutically acceptable polymer," quoted above, pointing out that this word does not appear in the claims or specification. However, claim construction often calls upon words other than those of the patent, lest the claim simply define itself. "Claim construction" is for the purpose of explaining and defining terms in the claims, and usually

requires use of words other than the words that are being defined. See Multiform Desiccants, Inc. v. Medzam, Ltd., 133 F.3d 1473, 1477 (Fed. Cir. 1998) (claims are construed as an aid to the decision-maker, by restating the claims in non-technical terms).

Abbott's expert Dr. Davis had used the word "matrix" in his explanation of the technology of extended release. He explained that a "pharmaceutically acceptable polymer. . . alone or in combination with other polymers, is capable of forming a matrix when mixed with the drug to control and extend drug release into the GI tract and thence to the bloodstream." Declaration of Professor Davis, January 10, 2007. Sandoz does not dispute that this explanation comports with the description in the specification. Also, Abbott cites several scientific publications that use the word "matrix" in this context, and Sandoz does not argue that the word has a different meaning from that with which it was used by the district court. There is no ground for discarding the district court's claim construction based on the word "matrix."

Sandoz also argued that the claims must be construed so that the "pharmaceutically acceptable polymer" is the only release agent in the composition, argued that the presence of any other agent that affects release of the drug removes the composition from the scope of the '718 claims. Abbott pointed out that the claims use the conventional signal "comprising," which means that other ingredients may be present in the composition, in addition to those explicitly set forth. See CIAS, Inc. v. Alliance Gaming Corp., 504 F.3d 1356, 1360 (Fed. Cir. 2007) ("In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to'."); Georgia-Pacific Corp. v. United States Gypsum Co., 195 F.3d 1322, 1327-28 (Fed. Cir. 1999) ("'comprising' . . . is inclusive or open-ended and does not exclude additional unrecited elements or method steps").

Sandoz argues that the district court's claim construction is incorrect because it ignores the distinction between "pharmaceutically acceptable polymers" and "pharmaceutically acceptable excipients." We discern no support for this challenge. Abbott points out that the distinction between "polymer" and "excipient" lies in its role in the composition, as the patent states: "The compositions of the invention further comprise pharmaceutically acceptable excipients and/or fillers and extenders, such as lactose . . .". '718 patent, col. 4, lines 21-23. We discern no flawed judicial understanding of the term "excipient."

Sandoz also argued that the components of its accused formulation are merely "excipients" in that they do not extend the release of the clarithromycin, while Abbott pointed out that Sandoz described its product to the FDA as "extended release." Sandoz stated that the extension of release for its product is achieved not by the polymer that is present in its composition, but by other components. The district court considered the arguments concerning the role of the maltodextrin and the silicified microcrystalline cellulose in the Sandoz product. The court discussed the evidence of release rates and amounts released, including the information in Sandoz' approved ANDA, the comparative data presented by both sides, and various technical articles provided by both sides on the physical and chemical characteristics of the components of the Sandoz formulation. The court found 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." Abbott, 500 F. Supp.2d at 837.

Sandoz argues that the district court erred in its evaluation of the evidence, stating that Abbott did not show by direct testing that any of the polymers in the Sandoz product

actually extends the release of clarithromycin. Sandoz argues that the district court erred in finding unpersuasive certain laboratory tests conducted by Sandoz to show that maltodextrin has no significant impact on the dissolution rate of clarithromycin. Abbott responds that the district court did not err, and that Sandoz must be deemed to have admitted that maltodextrin and silicified microcrystalline cellulose are polymers that, alone or in combination with other components, are capable of extending drug release. Abbott pointed out to the district court that the developer of the Sandoz formulation, Dr. Nirmal Mulye, in his patent application (US 2004/0224017 A1) entitled "Process for Preparing Sustained Release Tablets," stated that "the present inventor has found that the addition of maltodextrin in effective amounts provides the desired release profile," that "maltodextrin also tends to slow down the release of a medicament in a controlled release formulation[,]'" and that "the maltodextrin used in the present invention is to counteract the accelerated rate of release of the drug . . ." We have not been directed to clear error in the district court's findings on this question.

Sandoz raises additional arguments, some discussed by the district court, and some newly presented on this appeal. All have been considered. We conclude that the district court's findings and rulings at this stage of the proceedings have not been shown to constitute reversible error. The ruling that Abbott had shown a reasonable likelihood of proving infringement is sustained.

#### IV

#### THE EQUITABLE FACTORS

Sandoz states that the district court incorrectly resolved and weighed the equitable factors relevant to the grant of a preliminary injunction. Sandoz states that the factors of

irreparable harm, the balance of harms, and the public interest, all weigh in its favor, and outweigh any finding that Abbott is likely to prevail on the issues of validity or enforceability and infringement. The district court considered these factors, and explained its reasoning in exercising its discretion to grant the preliminary injunction.

### ***Irreparable Harm***

Sandoz argued that any harm to Abbott is not irreparable, for damages are available for infringement, if the eventual final judgment is adverse to Sandoz. Sandoz pointed out that the generic producers Teva and Ranbaxy are already in this market, by settlement with Abbott, such that any price erosion due to generic competition is already occurring. The district court considered these relationships, and concluded that they do not negate the market share and revenue loss upon Sandoz' entry while the litigation proceeds. Precedent supports this conclusion. See, e.g., Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (likelihood of price erosion and loss of market position are evidence of irreparable harm); Bio-Technology Gen. Corp. v. Genentech, Inc., 80 F.3d 1553, 1566 (Fed. Cir. 1996) (loss of revenue, goodwill, and research and development support constitute irreparable harm); Polymer Technologies, Inc. v. Bridwell, 103 F.3d 970, 975-76 (Fed. Cir. 1996) (loss of market opportunities cannot be quantified or adequately compensated, and is evidence of irreparable harm).

### ***The Balance of Hardships***

The district court discussed and weighed the hardships argued by both parties, and found that the balance of hardships tipped in favor of Abbott. The court found that preserving the status quo preserves the current market structure, recognizing that Abbott

has licensed other generic producers. The district court concluded 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." Abbott, 500 F. Supp.2d at 845.

We agree that the fact that a patentee has licensed others under its patents does not mean that unlicensed infringement must also be permitted while the patents are litigated. Precedent illustrates that when the patentee is simply interested in obtaining licenses, without itself engaging in commerce, equity may add weight to permitting infringing activity to continue during litigation, on the premise that the patentee is readily made whole if infringement is found. In this case the district court received Abbott's argument that it could not be made whole if it prevails in this litigation, for the added erosion of markets, customers, and prices, is rarely reversible. See Sanofi-Synthelabo, 470 F.3d at 1383 (rejecting hardship claim of generic challenger whose "harms were almost entirely preventable' and were the result of its own calculated risk to launch its product pre-judgment").

Clear error has not been shown in the district court's finding that the harm to Sandoz of delay in entering this market while this case is litigated, is outweighed by the harm to Abbott in view of the likelihood that Abbott will succeed in sustaining the validity and enforceability of its patents.

### ***The Public Interest***

Sandoz argues that the public interest favors the availability of less expensive forms of successful medicines. The district court considered this argument, and stated:

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.

500 F. Supp.2d at 846. The district court appreciated that the public interest includes consideration of whether, by shifting market benefits to the infringer while litigation is pending for patents that are likely to withstand the attack, the incentive for discovery and development of new products is adversely affected. The statutory period of exclusivity reflects the congressional balance of interests, and warrants weight in considering the public interest. In Sanofi-Synthelabo, 470 F.3d at 1383, this court referred to the significant "public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents." As the Court explained in Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470 (1974): "The patent laws promote this progress by offering a right of exclusion for a limited period as an incentive to inventors to risk the often enormous costs in terms of time, research, and development." Id. at 480.

Sandoz states that the Court's recent decision in eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388 (2006) negates any presumption of entitlement to an injunction upon a finding of likelihood that a patent will be sustained and found infringed. The district court did not apply such a presumption, but fully considered all of the legal and equitable factors. At the preliminary injunction stage, the legal and equitable factors may be of different weight when the patentee is itself engaged in commerce, as contrasted with a patentee that is seeking to license its patent to others. We need not resolve this aspect for all possible situations, for as between Abbott and Sandoz the district court objectively weighed the legal probabilities

and the equities, and exercised its discretionary judgment as to the entirety of the cause. We have been shown no basis for believing that the district court abused its discretion.

V

#### THE INJUNCTION BOND

Sandoz also appeals the amount of the injunction bond, which the district court set at \$40 million. Sandoz provides no substance for appellate review of the amount of the bond, simply stating in its brief that it "presented [to the district court] at least colorable evidence that its losses from the injunction and recall would be \$200 million," but not describing the evidence or arguing its merits. Sandoz simply states that its proposed number should have been accepted, in the event that the \$40 million is later shown to be inadequate.

This aspect has not been presented in reviewable substance. On this appeal, abuse of discretion has been shown in the district court's setting of the terms of the injunction. See Russell v. Farley, 105 U.S. 433, 441 (1881) (the court's discretion in setting the terms of an injunction is rooted in equity).

VI

#### THE ISSUE OF CONFLICTING PRECEDENT

The district court found the likelihood that the patentee would succeed on the merits and that the equities favored the patentee, and exercised its discretion to enjoin infringement during the litigation. The dissent states that the district court applied the incorrect standard, and that if the infringer "raises a substantial question concerning either infringement or validity," diss. op. at 2, it is an abuse of discretion to enjoin infringement pendente lite. The dissent quotes with approval a past panel statement that "In resisting a

preliminary injunction, however, one need not make out a case of actual validity. Vulnerability is the issue at the preliminary injunction stages, while validity is the issue at trial.” Id. Indeed, this court’s precedent makes this statement, in direct conflict with other, earlier statements that the standard is not vulnerability, but likelihood of success on the merits.

In response to the arguments expounded in the dissenting opinion, I summarize the law governing the grant of a preliminary injunction. The criteria relied on in the dissent are not the criteria of any other circuit, nor of the Supreme Court. The correct standard is not whether a substantial question has been raised, but whether the patentee is likely to succeed on the merits, upon application of the standards of proof that will prevail at trial. The question is not whether the patent is vulnerable; the question is who is likely to prevail in the end, considered with equitable factors that relate to whether the status quo should or should not be preserved while the trial is ongoing. The presentation of sufficient evidence to show the likelihood of prevailing on the merits is quite different from the presentation of substantial evidence to show vulnerability.

Thus the evidence that favors the patent must be considered in deciding a motion for a preliminary injunction, as well as the evidence against the patent. The trial court then decides which side is likely ultimately to prevail. The dissent presents only the case against the patent, apparently on the theory that this is all that is needed to raise a “substantial question”.

Indeed, a showing of a substantial question concerning validity or infringement can serve to avert judgment on the pleadings, or to avoid the grant of summary judgment, but it is not the same as showing likelihood of eventual success on the merits. The dissent

recognizes that it is not the same and that it “requires less proof”, but errs in stating that this is sufficient to defeat the grant of a preliminary injunction. Precedent is clear that the standard is the likelihood of success of the plaintiff at trial, with recognition of the presumptions and burdens. See, e.g., Gillette Co. v. Energizer Holdings, Inc., 405 F.3d 1367, 1370 (Fed.Cir.2005); Ranbaxy Pharmaceuticals., Inc. v. Apotex, Inc., 350 F.3d 1235, 1239 (Fed.Cir.2003); Reebok Int'l Ltd. v. J. Baker, Inc., 32 F.3d 1552, 1555 (Fed. Cir. 1994); Smith Int'l, Inc. v. Hughes Tool Co., 718 F.2d 1573, 1579 (Fed.Cir.1983).

Supreme Court precedent, every regional circuit, and controlling Federal Circuit precedent, apply to the preliminary injunction the combination of criteria that includes likelihood of success on the merits and equitable considerations. No other court has held that when the attacker has presented a “substantial question” on its side of the dispute – that is, more than a scintilla but less than a preponderance of evidence in support of its side – no injunction pendente lite is available. Further, equitable factors are of particular significance at the preliminary stage, where the question is whether to change the position of the parties during the litigation. See Camenisch, 451 U.S. at 395 (the preliminary injunction preserves the position of the parties during the litigation). The dissent does not mention the equitable factors that were considered by the district court, as required by precedent; the dissent simply states that the injunction must be denied if the attacker has raised a substantial question.

Supreme Court precedent is clear in stating that the same burdens and standards of proof apply in deciding the merits for preliminary injunction purposes, as in deciding the same questions upon full litigation. See, e.g., Gonzales, 546 U.S. at 429 (placing the burdens of proof for showing likelihood of success at the preliminary injunction stage). The

Court explained in Amoco Production Co. v. Village of Gambell, AK, 480 U.S. 531, 546 n.2 (1987) that: “The standard for a preliminary injunction is essentially the same as for a permanent injunction with the exception that the plaintiff must show a likelihood of success on the merits rather than actual success.”

There is no reason why patent cases require unique treatment. See eBay Inc. v. MercExchange, L.L.C., 547 U.S. 388, 394 (2006) (“[T]he decision whether to grant or deny injunctive relief rests within the equitable discretion of the district courts, and that such discretion must be exercised consistent with traditional principles of equity, in patent disputes no less than in other cases governed by such standards.”). The general criterion of likelihood of success on the merits, in the context of the equities of the particular case, are uniform throughout the regional circuits. All are consistent with the rulings of the Supreme Court, and, although the words vary, all refer to the likelihood of the eventual outcome, not whether a substantial question has been raised. In brief sampling, starting with the First Circuit, the court summarized the standard in Wine and Spirits Retailers, Inc. v. Rhode Island, 418 F.3d 36 (1st Cir. 2005):

The sine qua non of this four-part inquiry is likelihood of success on the merits: if the moving party cannot demonstrate that he is likely to succeed in his quest, the remaining factors become matter of idle curiosity.

Id. at 46 (citation omitted). The referenced “four-part inquiry” is “(1) the likelihood of success on the merits; (2) the potential for irreparable harm [to the movant] if the injunction is denied; (3) the balance of relevant impositions, i.e., the hardship to the nonmovant if enjoined as contrasted with the hardship to the movant if no injunction issues; and (4) the effect (if any) of the court’s ruling on the public interest.” Id. (alteration in original) (citations

omitted).

The Second Circuit also applies the standard four factors. I cite a case that emphasized the equitable considerations; in Laureyssens v. Idea Group, Inc., 964 F.2d 131, 135-36 (2nd Cir. 1992) (emphasis in original) the court stated: “A party seeking a preliminary injunction must establish (1) irreparable injury and (2) a likelihood of success on the merits or a sufficiently serious question going to the merits and a balance of hardships tipping decidedly in the moving party's favor.”

The Third Circuit also stated that the district court must consider four factors: “[A] the likelihood that the applicant will prevail on the merits at final hearing; [B] the extent to which the plaintiffs are being irreparably harmed by the conduct complained of; [C] the extent to which the defendants will suffer irreparable harm if the preliminary injunction is issued; and [D] the public interest.” Opticians Ass'n of Am. v. Independent Opticians of Am., 920 F.2d 187, 191-92 (3rd Cir.1990) (alterations in original) (citation omitted). In Eli Lilly & Co. v. Premo Pharmaceutical Laboratories, Inc., 630 F.2d 120 (3rd Cir. 1980) the court explained that when analyzing a preliminary injunction:

the moving party must generally show (1) a reasonable probability of eventual success in the litigation and (2) that the movant will be irreparably injured pendente lite if relief is not granted. . . . Moreover, while the burden rests upon the moving party to make these two requisite showings, the district court “should take into account, when they are relevant, (3) the possibility of harm to other interested persons from the grant or denial of the injunction, and (4) the public interest.” . . . While these factors structure the inquiry, however, no one aspect will necessarily determine its outcome. Rather, proper judgment entails a ‘delicate balancing’ of all elements. On the basis of the data before it, the district court must attempt to minimize the probable harm to legally protected interests between the time that the motion for a preliminary injunction is filed and the time of the final hearing.

Id. at 136. Indeed, rulings of the Federal Circuit, along with requiring this “reasonable probability of eventual success,” have recognized the “delicate balancing’ of all elements.”

See H.H. Robertson Co. v. United Steel Deck, Inc., 820 F.2d 384, 387-88 (Fed. Cir. 1987).

Similarly in the Fourth Circuit the inquiry is: “1) Has the petitioner made a strong showing that it is likely to prevail upon the merits? 2) Has the petitioner shown that without such relief it will suffer irreparable injury? 3) Would the issuance of the injunction substantially harm other interested parties? 4) Wherein lies the public interest?”

Blackwelder Furniture Co. of Statesville, Inc. v. Seiling Mfg. Co., 550 F.2d 189, 193 (4th Cir. 1977) (when reviewing the grant of denial of interim injunctive relief “our review of the lower court’s application of the law is not limited by the same ‘clearly erroneous’ rule which restricts our review of its findings of fact under Rule 52(a)”; see First-Citizens Bank & Trust Co. v. Camp, 432 F.2d 481, 484 (4th Cir. 1970) (applying the four-factors and reversing the district court’s grant of a preliminary injunction)).

In the Fifth Circuit the four factors are recited as “(1) a substantial likelihood that plaintiff will prevail on the merits, (2) a substantial threat that plaintiff will suffer irreparable injury if the injunction is not granted, (3) that the threatened injury to plaintiff outweighs the threatened harm the injunction may do to defendant, and (4) that granting the preliminary injunction will not disserve the public interest.” Canal Authority of State of Florida v. Callaway, 489 F.2d 567, 573 (5th Cir. 1974). The “substantial likelihood of prevailing” is not the same as raising a substantial question.

Again for the Sixth Circuit, the “well-established” factors are: “(1) the likelihood that the party seeking the preliminary injunction will succeed on the merits of the claim; (2)

whether the party seeking the injunction will suffer irreparable harm without the grant of the extraordinary relief; (3) the probability that granting the injunction will cause substantial harm to others; and (4) whether the public interest is advanced by the issuance of the injunction,” Six Clinics Holding Corp. II v. Cafcomp Systems, Inc., 119 F.3d 393, 399 (6th Cir. 1997). The court recognized that “a finding that the movant has not established a strong probability of success on the merits will not preclude a court from exercising its discretion to issue a preliminary injunction if the movant has, at minimum, ‘show[n] serious questions going to the merits and irreparable harm which decidedly outweighs any potential harm to the defendant if the injunction is issued.’” Id. at 400 (alteration in original). This ruling gave weight to the court’s discretion to preserve the status quo during the litigation, when the equitable factors warrant such discretion.

In the Seventh Circuit:

As a threshold matter, a party seeking a preliminary injunction must demonstrate (1) some likelihood of succeeding on the merits, and (2) that it has “no adequate remedy at law” and will suffer “irreparable harm” if preliminary relief is denied. If the moving party cannot establish either of these prerequisites, a court’s inquiry is over and the injunction must be denied. If, however, the moving party clears both thresholds, the court must then consider: (3) the irreparable harm the non-moving party will suffer if preliminary relief is granted, balancing that harm against the irreparable harm to the moving party if relief is denied; and (4) the public interest, meaning the consequences of granting or denying the injunction to non-parties.

Abbott Laboratories v. Mead Johnson & Co., 971 F.2d 6, 11 (7th Cir. 1992). This court has observed that the standard for granting or denying a motion for a preliminary injunction is not unique to patent law, and has ruled that the standard of the regional circuit should apply, here the Seventh Circuit. See Mikohn Gaming Corp. v. Acres Gaming, Inc., 165

F.3d 891, 894 (Fed. Cir. 1998) (“The Federal Circuit has generally viewed the grant of a preliminary injunction as a matter of procedural law not unique to the exclusive jurisdiction of the Federal Circuit, and on appellate review has applied the procedural law of the regional circuit in which the case was brought.”).

In the Eighth Circuit, “The relevant factors on a motion for a preliminary injunction are: (1) the probability of success on the merits; (2) the threat of irreparable harm to the movant; (3) the balance between this harm and the injury that granting the injunction will inflict on other interested parties; and (4) whether the issuance of an injunction is in the public interest.” Entergy, Arakansa, Inc. v. Nebraska, 210 F.3d 887, 898 (8th Cir. 2000). In Shrink Missouri Government PAC v. Adams, 151 F.3d 763, 764 (8th Cir. 1998) the court stressed that “[t]he most important of the [preliminary injunction] factors is the appellants' likelihood of success on the merits.”

The Ninth Circuit stressed the importance of the equitable factors: “Preliminary injunctive relief is available to a party who demonstrates either: (1) a combination of probable success on the merits and the possibility of irreparable harm; or (2) that serious questions are raised and the balance of hardships tips in its favor. These two formulations represent two points on a sliding scale in which the required degree of irreparable harm increases as the probability of success decreases.” Perfect 10, Inc. v. Amazon.com, Inc., 487 F.3d 701, 713-14 (9th Cir. 2007).

In the Tenth Circuit, “To obtain a preliminary injunction, the moving party must establish that (1) the moving party will suffer irreparable injury unless the injunction issues; (2) the threatened injury to the moving party outweighs whatever damage the proposed injunction may cause the opposing party; (3) the injunction, if issued, would not be adverse

to the public interest; and (4) there is a substantial likelihood that the moving party will eventually prevail on the merits.” Resolution Trust Corp. v. Cruce, 972 F.2d 1195, 1199 (10th Cir. 1992) (“When a party seeking a preliminary injunction satisfies the first three requirements, the standard for meeting the fourth ‘probability of success’ prerequisite becomes more lenient. The movant need only show ‘questions going to the merits so serious, substantial, difficult and doubtful, as to make them a fair ground for litigation.’”).

In the Eleventh Circuit, “A district court may grant injunctive relief if the movant shows (1) a substantial likelihood of success on the merits; (2) that irreparable injury will be suffered unless the injunction issues; (3) that the threatened injury to the movant outweighs whatever damage the proposed injunction may cause the opposing party, and (4) that if issued the injunction would not be adverse to the public interest.” All Care Nursing Service, Inc. v. Bethesda Memorial Hosp. Inc., 887 F.2d 1535, 1537 (11th Cir. 1989).

In the District of Columbia Circuit, “In considering whether to grant preliminary injunctive relief, the court must consider whether: (1) the party seeking the injunction has a substantial likelihood of success on the merits; (2) the party seeking the injunction will be irreparably injured if relief is withheld; (3) an injunction will not substantially harm other parties; and (4) an injunction would further the public interest.” CSX Transp. Inc. v. Williams, 406 F.3d 667, 670 (D.C. Cir. 2005).

All of the circuits have placed the preliminary injunction in terms of the likelihood of success on the merits and equitable factors. No circuit has held that it suffices simply to raise a “substantial question.” Raising a substantial question achieves the threshold requirement of the well-pleaded complaint; it does not demonstrate a likelihood of prevailing. See Christianson v. Colt Industries Operating Corp., 486 U.S. 800, 808-809

(1988) (“A district court’s federal-question jurisdiction, we recently explained, extends over ‘only those cases in which a well-pleaded complaint establishes either that federal law creates the cause of action or that the plaintiff’s right to relief necessarily depends on resolution of a substantial question of federal law [.]’”) (citation omitted); Litecubes, LLC v. Northern Light Products, Inc., 523 F.3d 1353, 1360 (Fed. Cir. 2008) (“Under what is known as the ‘well-pleaded complaint rule,’ subject matter jurisdiction exists if a ‘well-pleaded complaint establishes either that federal patent law creates the cause of action or that the plaintiff’s right to relief necessarily depends on resolution of a substantial question of federal patent law, in that patent law is a necessary element of one of the well-pleaded claims.’”) (citations omitted).

Federal Circuit precedent developed to match the rest of the nation. See Hybritech Inc. v. Abbott Laboratories, 849 F.2d 1446, 1451 (Fed. Cir. 1988) (“The first factor required to be established by a party seeking a preliminary injunction is that it stands to have a reasonable likelihood of success on the merits when the trial court finally adjudicates the dispute. In seeking a preliminary injunction pursuant to section 283, a patent holder must establish a likelihood of success on the merits both with respect to validity of its patent and with respect to infringement of its patent.”); H.H. Robertson Co., 820 F.2d at 387 (observing that the preliminary injunction in the Third Circuit “is substantially the same standard enunciated by this court,” and that “[t]he standards applied to the grant of a preliminary injunction are no more nor less stringent in patent cases than in other areas of the law”); Roper Corp. v. Litton Systems Inc., 757 F.2d 1266, 1270-73 (Fed. Cir. 1985) (reviewing denial of a preliminary injunction by assessing likelihood of success and irreparable injury); Pretty Punch Shopettes, Inc. v. Hauk, 844 F.2d 782, 783 (Fed. Cir. 1988) (determining

likelihood of success on the merits); Nutrition 21 v. United States, 930 F.2d 867, 869 (Fed. Cir. 1991) (applying the four-factor test including likelihood of success on the merits); Texas Instruments Inc. v. Tessera, Inc., 231 F.3d 1325, 1329 (Fed. Cir. 2000) (in an ITC proceeding, applying the traditional four-factor test including likelihood of success on the merits); Hoop v. Hoop, 279 F.3d 1004, 1007 (Fed. Cir. 2002) (applying the traditional four factor test including likelihood of success); Ranbaxy, 350 F.3d at 1239 (applying the four factors of “(1) a reasonable likelihood of success on the merits; (2) irreparable harm if the injunction were not granted; (3) the balance of the hardships and (4) the impact of the injunction on the public interest” and holding that the showing of a reasonable likelihood of success on the merits must be “in light of the presumptions and burdens that will inhere at trial on the merits”).

### ***Summary***

To summarize my concern for the conflict that is here continued, I again point out that the dissenting opinion, despite its initial recitation of the correct four-part criteria for deciding the grant or denial of a preliminary injunction, then applies the different and incorrect criterion of whether the defendant raised a “substantial question” that may render the patent “vulnerable”. That standard conflicts with precedent of the Supreme Court and all of the regional circuits, all of which require that likelihood of success on the merits be determined and weighed along with the equitable factors. It is not the law that raising a “substantial question” will “negate the patentee’s likelihood of success.” Diss. op. at 3. Raising a substantial question may avoid dismissal on the pleadings,

but contrary to the view of the dissent, establishing that there is an issue for trial is not the same as establishing the likelihood of prevailing at trial.

The district court analyzed the positions of both sides as well as the equitable factors, decided that Abbott was likely to prevail on the merits and that the equitable factors weighed in favor of Abbott, and exercised its discretion to grant the preliminary injunction. The dissent states that a showing of “vulnerability” shows that the defendant is likely to prevail on the merits; that is facially incorrect. The dissent also relies on some recent (2008) Federal Circuit decisions; these decisions are not “clearly established precedent,” for they cannot overcome earlier rulings of this court. Further, until today no opinion has equated the raising of a “substantial question” with a showing of likelihood of success on the merits. The following additional cases of the Federal Circuit are cited to show the established law: Jeneric/Pentron, Inc. v. Dillon Co., Inc., 205 F.3d 1377, 1380 (Fed. Cir. 2000) (“A preliminary injunction requires the movant to show four factors . . . [and] ‘[c]entral to the movant’s burden are the likelihood of success and irreparable harm factors.’”); Intergraph Corp. v. Intel Corp., 195 F.3d 1346, 1352 (Fed. Cir. 1999) (applying 11th Circuit law for a preliminary injunction, the criteria are “(1) the party seeking the injunction has shown a substantial likelihood of success on the merits, (2) there is a substantial threat of irreparable injury in absence of the injunction, (3) the balance of harms favors the party seeking the injunction, and (4) entry of the injunction does not disserve the public interest.”); Mentor Graphics Corp. v. Quickturn Design Systems, Inc., 150 F.3d 1374, 1377 (Fed. Cir. 1998) (“A preliminary injunction requires the assessment of four factors: the likelihood of movant’s success on the merits, the irreparability of harm to the movant without an injunction, the balance of

hardships between the parties, and the demands of the public interest."); Polymer Technologies, Inc. v. Bridwell, 103 F.3d 970, 973 (Fed. Cir. 1996) ("As the moving party, Polymer had to establish its right to a preliminary injunction in light of four factors: (1) a reasonable likelihood of success on the merits; (2) irreparable harm if the injunction were not granted; (3) the balance of the hardships and (4) the impact of the injunction on the public interest."); Bio-Technology Gen. Corp. v. Genentech, Inc., 80 F.3d 1553, 1558 (Fed. Cir. 1996) ("As the moving party, Genentech had to establish a right to a preliminary injunction in light of four factors: (1) a reasonable likelihood of success on the merits; (2) irreparable harm if the injunction were not granted; (3) the balance of hardships tipping in its favor; and (4) the impact of the injunction on the public interest."); Rosemount, Inc. v. Int'l Trade Comm'n, 910 F.2d 819, 821 (Fed. Cir. 1990) ("To grant the equitable relief of an injunction prior to trial, a district court traditionally considers and balances the factors of: (1) the movant's likelihood of success on the merits; (2) whether or not the movant will suffer irreparable injury during the pendency of the litigation if the preliminary injunction is not granted; (3) whether or not that injury outweighs the harm to other parties if the preliminary injunction is issued; and (4) whether the grant or denial of the preliminary injunction is in the public interest."); Katz v. Lear Siegler, Inc., 909 F.2d 1459, 1462-63 (Fed. Cir. 1990) (applying 1st Circuit law for a preliminary injunction, the criteria are "(1) that plaintiff will suffer irreparable injury if the injunction is not granted; (2) that such injury outweighs any harm which granting injunctive<sup>1463</sup> relief would inflict on the defendant; (3) that plaintiff has exhibited a likelihood of success on the merits; and (4) that the public interest will not be adversely affected by the granting of the injunction."); Cicena Ltd. v. Columbia

Telecommunications Group, 900 F.2d 1546, 1548 (Fed. Cir. 1990) (applying 2nd Circuit law for a preliminary injunction which requires that the movant must establish “both possible irreparable injury and either (1) a likelihood of success on the merits or (2) sufficiently serious questions going to the merits to make them a fair ground for litigation and a balance of hardships tipping decidedly in the movant's favor.”); Xeta, Inc. v. Atex, Inc., 852 F.2d 1280, 1282 (Fed. Cir. 1988) (applying 1st Circuit law for a preliminary injunction, the criteria are that “as in other causes of action, the plaintiff must show that there is no adequate remedy at law, that the plaintiff will suffer irreparable injury absent the requested injunction, that such irreparable injury outweighs the harm an injunction would inflict on the defendant, that the plaintiff has shown a likelihood of success on the merits, and that the public interest will not be adversely affected by the grant of the requested injunction.”); Matsushita Electric Industrial Co. v. United State, 823 F.2d 505, (Fed. Cir. 1987) (“The preliminary injunction issued by the Court of International Trade must be upheld if that court properly found that [the movant] had shown (1) that it will be immediately and irreparably injured; (2) that there is a likelihood of success on the merits; (3) that the public interest would be better served by the relief requested; and (4) that the balance of hardship on all the parties favors [the movant].”); T.J. Smith and Nephew Ltd. v. Consol. Medical Equipment, Inc., 821 F.2d 646, 647 (Fed. Cir. 1987) (“To obtain a preliminary injunction in a patent infringement action pursuant to 35 U.S.C. § 283, a party must establish a right thereto in light of four factors: (a) reasonable likelihood of success on the merits; (b) irreparable harm; (c) a balance of hardships tipping in its favor; and (d) that the issuance of the injunction is in the public interest.”); S. J. Stile Associates Ltd. v. Snyder, 646 F.2d 522, 525 (CCPA 1981) (“The trial court

must be upheld if it examined the appropriate factors and properly concluded that any one of these requisites for a preliminary injunction had not been established by the [movant]: (1) a threat of immediate irreparable harm; (2) that the public interest would be better served by issuing than by denying the injunction; (3) a likelihood of success on the merits; and (4) that the balance of hardship on the parties favored [the movant]."); Jacobsen v. Katzer, 535 F.3d 1373, 1378 (Fed. Cir. 2008) (applying 9th circuit law for preliminary injunction in a copyright infringement claim which requires the showing of "(1) a combination of probability of success on the merits and the possibility of irreparable harm or (2) serious questions going to the merits where the balance of hardships tips sharply in the moving party's favor.").

These rulings of the Federal Circuit accord with the principles of eBay, 547 U.S. at 394, that "the decision whether to grant or deny injunctive relief rests within the equitable discretion of the district courts, and that such discretion must be exercised consistent with traditional principles of equity, in patent disputes no less than in other cases governed by such standards." This court's contrary opinions stand alone. If in fact this court believes that there should be a different rule in patent cases, this court nonetheless has the rule that in the event of conflict between panels the earlier holding prevails until overturned *en banc*.

Newell Companies v. Kenney Mfg. Corp., 864 F.2d 757, 765 (Fed. Cir. 1988) ("This court has adopted the rule that prior decisions of a panel of the court are binding precedent on subsequent panels unless and until overturned *in banc*. . . . Where there is a direct conflict, the precedential decision is the first."). If there is to be a change from this court's prior rulings, it must be done *en banc*.

As it stands, neither district courts, nor litigants, nor panels of this court, are provided

with clear guidance, or any reason to reject the stricture of eBay, 547 U.S. at 393, that “[n]othing in the patent Act indicates that Congress intended such a departure” from “the long tradition of equity practice”.

## CONCLUSION

Abuse of discretion has not been shown in the district court’s grant of the preliminary injunction, adhered to after additional consideration in view of the Court’s decision of KSR. The district court’s findings of fact underlying the legal and equitable considerations are supported, and the judicial balancing of these considerations shows no abuse of discretion. The grant of the injunction is affirmed. The case is remanded for further proceedings.<sup>5</sup>

AFFIRMED

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<sup>5</sup> Sandoz requests that we instruct that on remand this case should be assigned to a different judge, in order to “further the interests of judicial economy”. We discern no basis for this request; it is denied.

**UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT**

2007-1300

ABBOTT LABORATORIES,

Plaintiff-Appellee,

v.

SANDOZ, INC.,

Defendant-Appellant.

Appeal from the United States District Court for the Northern District of Illinois in case no. 05-CV-5373, Judge David H. Coar.

GAJARSA, Circuit Judge, dissenting.

I respectfully dissent from the court's opinion. There is no legal basis for the granting of a preliminary injunction, and its issuance is an abuse of discretion. Although generally the denial or issuance of a preliminary injunction is within the broad discretion of the district court, the decision of the district court must be reversed when it abuses its discretion. See Cybor Corp. v. FAS Technologies, Inc., 138 F.3d 1448, 1460 (Fed. Cir. 1998) (en banc) ("A district court abuses its discretion when its decision is based on clearly erroneous findings of fact, is based on erroneous interpretations of the law, or is clearly unreasonable, arbitrary or fanciful.").

"A preliminary injunction requires the movant to show four factors: (1) a reasonable likelihood of success on the merits, (2) the prospect of irreparable harm, (3) a balance of the parties' hardships in favor of injunction, and (4) no potential injury to an

important public interest.” See Jeneric/Pentron, Inc. v. Dillon Co., 205 F.3d 1377, 1380 (Fed. Cir. 2000). When the district court considers the four factors, “the likelihood of success factor plays a key role,” id., and that is the factor I will focus on in my dissent. Because of “the extraordinary nature of the relief, the patentee carries the burden of showing likelihood of success on the merits,” in light of the presumptions and burdens that will inhere at trial, with respect to the patent’s validity, enforceability, and infringement. Nutrition 21 v. United States, 930 F.2d 867, 869 (Fed. Cir. 1991) (emphasis in original); see also Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343, 1350 (Fed. Cir. 2001). If the defendant “raises a substantial question concerning either infringement or validity, i.e., asserts an infringement or invalidity defense that the patentee cannot prove ‘lacks substantial merit,’ the preliminary injunction should not issue.” Amazon.com, 239 F.3d at 1350-51. This court has explained that:

In resisting a preliminary injunction, however, one need not make out a case of actual invalidity. Vulnerability is the issue at the preliminary injunction stages, while validity is the issue at trial. The showing of a substantial question as to invalidity thus requires less proof than the clear and convincing showing necessary to establish invalidity itself.

Abbott Labs. v. Andrx Pharms., Inc., 452 F.3d 1331, 1335 (Fed. Cir. 2006) (herein “Andrx”) (quoting Amazon.com, 239 F.3d at 1359).

The majority opinion postulates that the findings of the district court are correct. It is error to so conclude because the district court failed to properly consider and weigh the ample evidence produced by Sandoz that clearly established a substantial question of invalidity and rendered the patent vulnerable to an invalidity challenge at trial. Instead, the district court erroneously required proof of clear and convincing evidence of

invalidity at the preliminary stages of the proceedings. As I explain below, this conflicts with our clearly established precedent.

Under our precedent, the likelihood of success factor is properly analyzed by considering whether the alleged infringer raises a substantial question as to validity. See, e.g., E.I. du Pont de Nemours & Co. v. MacDermid Printing Solutions, L.L.C., 525 F.3d 1353, 1358 (Fed. Cir. 2008) (“[I]f the accused infringer raises a substantial question regarding validity, the district court should find that the patentee has not shown a likelihood of success on the merits.” (internal quotation marks omitted)). Indeed, this court has consistently held that an alleged infringer can negate the patentee’s likelihood of success on the merits—and thus defeat a preliminary injunction—by raising a substantial question as to validity. For example, in Genentech, this court explained:

In order to demonstrate that it has a likelihood of success, [the patentee] must show that, in light of the presumptions and burdens that will inhere at trial on the merits, (1) it will likely prove that [the alleged infringer] infringes the [] patent and (2) its infringement claim will likely withstand [the alleged infringer’s] challenges to the validity and enforceability of the [] patent. In other words, if [the alleged infringer] raises a “substantial question” concerning validity, enforceability, or infringement (i.e., asserts a defense that [the patentee] cannot show “lacks substantial merit”) the preliminary injunction should not issue. More specifically, with regard to [the alleged infringer’s] validity defenses, the question on appeal is whether there is substantial merit to [the alleged infringer’s] assertion that the [] patent claim [is invalid].

Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1364 (Fed. Cir. 1997). Our subsequent cases consistently applied the law as it was explained in Genentech. See, e.g., Tate Access Floors v. Interface Architectural Res., 279 F.3d 1357, 1365 (Fed. Cir. 2002) (“In order to demonstrate likely success on the merits, [the patentee] must show that, in light of the presumptions and burdens applicable at trial, it will likely prove that

[the alleged infringer] infringes the asserted claims of the [] patent and that the patent will likely withstand [the alleged infringer's] challenges to its validity. If [the alleged infringer] raises a substantial question concerning infringement or validity, meaning that it asserts a defense that [the patentee] cannot prove 'lacks substantial merit,' the preliminary injunction issued improperly." (internal citations omitted; citing Genentech, 108 F.3d at 1364 and Amazon.com, 239 F.3d at 1350-51)).

Our most recent cases continue to adhere to the law as it was explained in Genentech. See, e.g., Erico Int'l Corp. v. Vutec Corp., 516 F.3d 1350, 1352, 1354 (Fed. Cir. 2008) (stating that "[the alleged infringer] must show a substantial question of invalidity to avoid a showing of likelihood of success" and vacating the preliminary injunction "[b]ecause this court finds that [the alleged infringer] has raised a substantial question as to the validity of the patent at issue"); PHG Techs., LLC v. St. John Cos., 469 F.3d 1361, 1365, 1369 (Fed. Cir. 2006) (explaining that "in order to defeat the injunction on grounds of potential invalidity, [the alleged infringer], as the party bearing the burden of proof on the issue at trial, must establish a substantial question of invalidity" and holding the district court clearly erred in finding the patentee was likely to succeed "because [the alleged infringer] has satisfied its burden of raising a substantial question of invalidity"). Thus, under our clearly established precedent, when the alleged infringer raises a substantial question regarding validity, a preliminary injunction cannot issue because the patentee has failed to demonstrate a likelihood of success on the merits.

While Section VI of the opinion contains a superfluity of citations, it does not state the law relevant to this case. It is a pleasant, ambulatory, and meandering discussion;

but it is not required to decide this case, is not part of the majority opinion, and is clearly dicta. Although Section VI discusses the relevant four-factor test and properly emphasizes the likelihood of success factor, it ignores the way this court has consistently analyzed whether or not a patentee has demonstrated it will likely succeed at trial. The real question before us in this case, as our precedent clearly explains, is whether the district court erred in finding that Sandoz had not established a substantial question as to the obviousness of the '718 patent. See, e.g., Genentech, 108 F.3d at 1364 ("[T]he question on appeal is whether there is substantial merit to [the alleged infringer's] assertion that the [] patent claim [is invalid]."). Sandoz has, in fact, raised and substantially established that the validity of the '718 patent is vulnerable, and on the record before us, Abbott failed to prove the invalidity defense "lacks substantial merit." See Amazon.com, 239 F.3d at 1350-51 ("If [the alleged infringer] raises a substantial question concerning either infringement or validity, i.e., asserts an infringement or invalidity defense that the patentee cannot prove 'lacks substantial merit,' the preliminary injunction should not issue."). Thus, the district court committed reversible error when it analyzed the likelihood of success factor and determined that Abbott had established it would likely succeed on the merits. In light of that error, I would vacate the preliminary injunction and remand for reconsideration and reweighing of the injunctive factors. Moreover, various additional legal errors taint the district court's decision.

I.

The district court's grant of a preliminary injunction rested on only two claims, claims 1 and 4 of the '718 patent. Claim 1 reads:

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<sup>[1]</sup>, so that when ingested orally, the composition induces statistically significantly lower mean fluctuation index [DFL] 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.

'718 Patent, col.11 ll.28-38. Claim 4 similarly claims an erythromycin derivative and "from about 5[%] to about 50% by weight of a pharmaceutically acceptable polymer" but has different PK parameters. Id. col.11 ll.48-58. Claim 2 and claim 3 are dependant claims of claim 1. Claim 2 claims "the pharmaceutical composition of claim 1, wherein the polymer is a hydrophilic water-soluble polymer." Id. col.11 ll.39-40. Claim 3 claims "the pharmaceutical composition of claim 2, wherein the polymer is selected from the group consisting of polyvinylpyrrolidine, 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.41-47.

Claims 1 and 4 of the '718 patent have three basic limitations: (a) an erythromycin derivative; (b) 5% to 50% by weight of a pharmaceutically acceptable

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<sup>1</sup> The specification of the '718 patent states, in a list of definitions, that "pharmaceutically acceptable" as used herein, means 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." In my judgment the district court's claim construction is ambiguous as to whether the pharmaceutically acceptable polymer must extend release or whether it can be part of a matrix in which other components extend the release. Sandoz is correct that there needs to be some showing that the polymer acts to extend release.

polymer; and (c) various PK parameters. In the preferred embodiment, the erythromycin derivative is clarithromycin and the pharmaceutically acceptable polymer is HPMC at 10% to 30% by weight of the composition. Claim 4 requires PK parameters be such 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.” Id. col.11 II.52-58. Claim 1 achieves similar results with slightly different parameters. For claim 1, the composition must have a “statistically significantly lower mean fluctuation index,” DFL, which is defined in the specification as  $DFL = (C_{max} - C_{min})/C_{Av}$ , id. col.3 II.29-30, and substantially equivalent bioavailability, which the district court found meant that the “[ER] AUC values must be between 80% to 125% within a 90% confidence level as compared to the immediate release composition AUC values.”<sup>2</sup> Abbott Labs. v. Sandoz, Inc., 500 F. Supp. 2d 807, 831 (N.D. Ill. 2007) (herein “Sandoz I”).

## II.

Sandoz based its obviousness arguments primarily on three prior art references, which it argues combined with common sense and the ordinary skill of the art at the time make the ’718 patent anticipated or obvious. First, Sandoz argues that the PCT Application WO 95/30422 (“the ’422 publication”) filed by Pfizer, discloses a controlled release dosage form of azithromycin, which like clarithromycin is an erythromycin derivative.<sup>3</sup> According to the disclosure, these controlled released compositions

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<sup>2</sup> These figures are based on FDA definitions.

<sup>3</sup> Abbott specifically carved out azithromycin from its definition of an erythromycin derivative in the ’718 patent. See Andrx, 452 F.3d at 1337.

operate to release the drug substantially slower than the immediate release versions to reduce GI side effects. And, as Sandoz points out, the controlled release compositions disclosed in the '422 publication include a hydrophilic polymer composition of azithromycin, with a preferred embodiment being a matrix tablet containing 15% to 35% HPMC. Second, Sandoz noted that the '190 patent owned by Abbott discloses and claims controlled release compositions of clarithromycin in an (non-polymer) alginate matrix which are administered once a day and have slowed absorption such that they are bioequivalent with the current immediate release twice-a-day compositions and maintain therapeutic levels at 24 hours after ingestion. Claim 14 of the '190 patent also claims other macrolides including azithromycin.<sup>4</sup> Third, Sandoz argues that the '571

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<sup>4</sup> In *Andrx*, this court relied primarily on the '190 patent, as combined with the '422 publication to find that there was a substantial question as to the obviousness of the '718 patent claims. 452 F.3d at 1340-41. First, we concluded that "Teva makes substantial arguments that the '190 patent discloses a clarithromycin composition . . . that arguably has the pharmacokinetic parameters required in claim 4 of the '718 patent." *Id.* at 1340. And we explained:

Because the '190 patent explicitly discloses only clarithromycin controlled release compositions, yet claims azithromycin compositions, . . . Abbott has represented to the [PTO] that the differences between clarithromycin and azithromycin were such that azithromycin could be substituted into a controlled release clarithromycin composition by a person of ordinary skill in the art without undue experimentation . . . As a result, based on Abbott's own '190 patent, there exists a substantial argument that a person of ordinary skill in the art would be motivated to combine the '422 publication, namely the use of HPMC in extended release macrolide compositions, with the '190 patent with a reasonable expectation of success.

*Id.* at 1341. In this case, Abbott presented evidence at trial suggesting that this court was scientifically incorrect to find that the '190 patent disclosed compounds that arguably had the same PK values as the asserted claims. Sandoz, based on this new evidence, disclaimed any reliance on the scientific evidence of the '190 patent disclosing compounds with the same PK values as the '718 patent. However, contrary to the majority opinion, Sandoz can rely on *Andrx*'s conclusion that it would have been obvious for a person skilled in the art to substitute clarithromycin for azithromycin in an

publication, filed by Eli Lilly, discloses sustained release formulations for antimicrobial agents including clarithromycin, which contain an active agent, namely a hydrophilic polymer such as HPMC, and an acrylic polymer. According to the specification, these formulations differ from the prior art that uses just hydrophilic polymers in that they are designed to allow a constant rate of release throughout the GI tract. In particular, the '571 publication disclosed using from about 5% to about 29% by weight hydrophilic polymer, and about 0.5% to about 25% by weight acrylic polymer, with the total weight of the two polymers not exceeding 30% by weight.

In addition to challenging the validity of the '718 patent based on the '190 patent, the '422 publication and the '571 publication, Sandoz also relies on various evidence that the PK parameters specified in the '718 patent were well known in the art and would have been sought by anyone designing a controlled release formulation. Most strikingly, the testimony of one of the inventors named on the '718 patent, Linda Gustavson, an Abbott employee, supports the Sandoz position. In particular, Gustavson testified as follows:

Q: Did you tell [the formulations department] what pharmacokinetic parameters there should be?

A: I mean, not specific numbers, but relative to the IR, yes. I told at least Sue that what we needed was a lower  $C_{max}$ , an AUC that met FDA requirements for bioequivalence and a  $C_{min}$  that was at least comparable to the IR.

Q: And where did you get these parameters?

...

A: A few years of experience, I guess. They're the—I mean certainly the  $C_{max}$  and AUC are very basic PK parameters determined in virtually every study that has pharmacokinetics.  $C_{min}$  [] might or might not be important depending upon the drug you were talking

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extended release formula with the anticipation of success without undue experimentation.

about and what part of the pharmacokinetics you thought might be associated with efficacy or safety. For clarithromycin, there was some thought that keeping the concentrations above some minimum level might be at least in part important to maintaining effectiveness efficacy.

Q: Would you say that these PK parameters were pretty much known in the art?

A: Absolutely, yes.

Furthermore, Sandoz submitted references from 1983 (over a decade before the '718 application was submitted), which explained, *inter alia*, that the “objectives and possible advantages of controlled release dosage” forms included “maintain[ing] therapeutic drug levels,” “reduc[ing] dosing frequency,” “reduc[ing] fluctuations in drug levels,” and “reduc[ing] side effects.” And the reference explained that the “essence of controlled drug release” was to “obtain prolonged circulating drug levels with less fluctuation compared to conventional dosage forms, and to achieve these with less frequent drug administration.” They also submitted references showing that HPMC was considered the “controlled release agent of choice” in the field.

The district court, writing prior to KSR, found that, despite this Court’s decision in Andrx to the contrary, claims 1 and 4 of the '718 patent were not obvious (at least based on the preliminary record). The trial court’s finding rested on the fact that, contrary to this court’s conclusion in Andrx, new evidence established that the '190 patent, the '571 publication, and the WO '422 publication did not disclose the specific PK limitations of the '718 patent. The court recognized that “[g]enerally, 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.” Sandoz I, 500 F. Supp. 2d at 840. See In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*) (“[S]tructural

similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness."). Still, the court concluded that Abbott had preliminarily rebutted this showing by showing the specific PK properties embodied in the claims were unobvious. The trial court found that "[t]o succeed on its obvious[ness] 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." Sandoz I, 500 F. Supp. 2d at 840. Sandoz, the court found, had not done so. Id. Moreover, the trial court found that "because the '190 prior art does not disclose the [specific] 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." Id. at 841.

Subsequently, the district court denied Sandoz's motion for a stay of the preliminary injunction pending appellate review in light of the just issued KSR opinion. The court held that under KSR it was still necessary to "demonstrate the presence of all claim limitations in the prior art" and that Sandoz had not produced evidence indicating that the PK limitations were disclosed in the prior art or inherent to the structural limitations of the prior art compositions. Abbott Labs. v. Sandoz, 500 F. Supp. 2d 846, 851-53 (N.D. Ill. 2007). According to the district court, it thus had not and did not need to reach the TSM test (or any change in the application of this test brought on by KSR). Id. at 853.

On appeal, there is no real dispute that the '571 publication expressly discloses a "sustained release matrix formulation in tablet form comprising . . . erythromycin" and

containing from about 5% by weight to about 29% by weight of a hydrophilic polymer, thus meeting all of the structural limitations of the '718 claims. Moreover, the prior art clearly disclosed sustained release versions of clarithromycin and creating extended release formulations of erythromycin derivatives using polymers, preferably HPMC. And evidence shows that the desirability of the PK parameters claimed were well known in the art.

In light of this evidence, Sandoz raised a substantial question as to the obviousness of the '718 patent. The district court's decision to the contrary constituted an abuse of discretion. First, it was clearly error to find, as a matter of law, that since none of the prior art references cited by Sandoz explicitly disclosed a composition that had the PK limitations of the '718 patent, it had failed to demonstrate "the presence of all claim limitations in the prior art," and therefore that the '718 invention could not be obvious. Contrary to the majority, this holding relies on an improperly limited view of what types of references can be combined to show obviousness and an impermissibly cramped view of the Supreme Court's holding in KSR. There is no absolute requirement that each claim limitation be disclosed in a prior art reference. See, e.g., Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007) ("We have held that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." (emphasis added)); Tegal Corp. v. Tokyo Electron Am., Inc., 257 F.3d 1331, 1349 (Fed. Cir. 2001) (acknowledging that a claim could be obvious over a single prior art reference that does not disclose one of the limitations in the claim). Rather, in

all cases, the touchstone of the analysis is whether 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.” 35 U.S.C. § 103; KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007); see also Takeda, 492 F.3d at 1357 (explaining that “in cases involving new chemical compounds” to show a prima facie case of obviousness one must “identify some reason that would have led a chemist to modify a known compound in a particular manner” (emphasis added)). Thus, a given claim limitation may be obvious over the prior art even if no single reference had specifically disclosed that limitation. Moreover, even assuming an absolute rule that to be obvious a claim must be a combination of elements disclosed in the prior art, that standard was met here. As the Supreme Court reiterated in KSR, “inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” 127 S. Ct. at 1741. In other words, it is the rare invention that is not a combination of prior art elements.<sup>5</sup> And this is not one of such rare cases. Whether or not the prior art disclosed compounds displaying the particular PK parameters in the

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<sup>5</sup> Given KSR's broad understanding of nearly all or perhaps all inventions being combinations of elements in the prior art, the parties' dispute about whether KSR should be limited to such inventions becomes largely irrelevant. In any event, while KSR's holding is directed particularly at the TSM test, it certainly appears that the Court intended to expound principles of obviousness jurisprudence that were generally applicable. And particularly relevant to the case at bar, this court has already applied KSR's teachings to the question of whether new chemical compositions are obvious in light of the fact that chemists of ordinary skill would attempt to modify known substances in certain ways to “obtain compounds with improved properties.” Takeda, 492 F.3d at 1356. Accordingly, I think the district court clearly erred in concluding that KSR was not relevant to the question of obviousness here.

'718 patent, Sandoz did provide evidence suggesting that the PK parameters disclosed in the '718 patent were absolutely known in the art and that the prior art established that they were desirable in an extended release formula (and indeed, that at least the AUC equivalence and lower  $C_{max}$  were most likely essential to an extended release formula, at least one that would be approved by the FDA). This is sufficient to show that the claims might be a combination of elements previously known in the art. The prior art on record disclosing the PK limitations is of course further removed from the invention than, for example, a patent that disclosed a related drug formulation with the same PK limitations as the '718 patent. But while this may well make the former less likely than the latter to make the '718 patent claims obvious, there is nothing as a matter of law that prevents the invention from being considered an obvious combination of the prior art teachings contained in the current preliminary record. Cf. Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007) (explaining that while it is necessary for there to be “some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness . . . such reasoning need not seek out precise teachings directed to the specific subject matter of the challenged claim” (internal quotation marks omitted)).<sup>6</sup>

Second, it is not dispositive that Abbott was not absolutely certain that using the formulations disclosed in the '422 patent would create a formulation with the desired PK

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<sup>6</sup> See also Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1362 (Fed. Cir. 2007) (“[It] is irrelevant [to the question of obviousness] that none of the anions specifically listed in the '909 patent have a cyclic structure, because the motivation to make amlodipine besylate here is gleaned not only from the prior art as a whole rather than the '909 patent alone, but also from the nature of the problems encountered with the amlodipine maleate tablet formulations sought to be solved by the inventors of the '303 patent.”).

parameters. Even before KSR, this court’s “case law [was] clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” Pfizer, 480 F.3d at 1364. And as the Supreme Court stated in KSR, “[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.” 127 S. Ct. at 1742 (“One of the ways in which a patent’s subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent claims.”).

Third, the long standing precedent of this court and our predecessor, recently highlighted and relied upon in Pfizer is that “discovery of an optimum value of a variable” in a known process or composition is “usually obvious.” 480 F.3d at 1368 (citing In re Peterson, 315 F.3d 1325, 1330 (Fed. Cir. 2003); In re Boesch, 617 F.2d 272, 276 (CCPA 1980); In re Aller, 220 F.2d 454, 456 (CCPA 1955)). Accordingly, in Pfizer, for example, the court found that the optimization of a pharmaceutical compound to determine which acid salt was best was obvious, where “the prior art heavily suggests the particular anion used to form the salt.” Id. Similarly, here, if the PK parameters claimed were well known, and only routine experimentation by someone skilled in the art would have been necessary, in light of the HPMC formulations disclosed by the '422 publication and '571 publication, to create an ER clarithromycin-

HPMC formulation with the claimed PK parameters, this would be sufficient to create a *prima facie* case of obviousness.

Accordingly, the district court erred in concluding that the fact that the '422 publication and '190 patent did not disclose the PK limitations of the asserted claims precluded a finding of obviousness. This legal error constitutes an abuse of discretion. And contrary to the holding of the district court, Sandoz has raised a “substantial question concerning” the obviousness of the asserted claims. On this basis, I would reverse the decision of the district court.

### III.

Sandoz also argues that several acts by Abbott during the prosecution of its patent application constitute inequitable conduct and, thus, show that the district court abused its discretion in not rejecting the motion for a preliminary injunction based on the likelihood that the patents would be declared unenforceable.

The Patent Examiner initially rejected the claims of the '718 application and requested that Abbott show that one of its prior art compositions of clarithromycin, which was described as an immediate release pediatric suspension formula, did not have the same extended release properties as Abbott's claimed invention. In response, Abbott submitted a declaration by Linda Gustavson stating that the  $C_{max}$  of the ER clarithromycin “is statistically significantly lower than that for IR formulation given twice daily.” J.A. 10015. Abbott now admits that this statement was incorrect—that the data Gustavson relied on did not show a statistically significant lowering of the  $C_{max}$ —but only a non-statistically significant apparent lowering, and Gustavson herself admits that

she never performed any statistical analysis of the data and would not have known how to do it.

The district court found that the concededly false statement was immaterial since all the Examiner asked was whether the two products have the same PK properties. According to the district court, “[g]iven 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’  $C_{max}$  is immaterial despite the fact that it satisfies the definition of ‘material’ provided by 37 C.F.R. § 1.56(b).” Sandoz I, 500 F. Supp. 2d at 822. The district court reasoned that despite meeting the standard for materiality of § 1.56(b) a reasonable examiner would not have considered the statement important. Moreover, the district court emphasized that no claim of the ’718 patent requires the extended release formulation to have a statistically significant lower  $C_{max}$  than the immediate release formulation.

The Gustavson statement was material, or more to the point, there is substantial likelihood that Sandoz would be able to so establish at the merits stage. First, contrary to the erroneous conclusion of the district court, we have held that “all misstatements or admissions that satisfy [37 C.F.R. § 1.56(b)] are considered material.” Monsanto Co. v. Bayer Bioscience N.V., 514 F.3d 1229, 1237 n.11 (Fed. Cir. 2008). In addition, while no claim element in the ’718 patent specifically states that the  $C_{max}$  value must be statistically significantly lower, it does require  $C_{max}$  values that are “lower” than in the immediate release formulation. Despite the fact that in other claim elements Abbott uses the term “statistically significantly lower,” it is far from clear that one can establish that the  $C_{max}$  value is lower if the data does not show a statistically significant difference,

which by definition, as ordinarily understood, means that the data cannot conclusively establish that there is a real difference. This court previously recognized that “there is little in the [’718] patent itself that establishes the differences (if any) between parameters that are simply ‘lower’ rather than ‘statistically significantly lower.’” Andrx, 452 F.3d at 1339 n.4. Moreover, regardless of the claim construction, it would be important (if not dispositive) to a reasonable examiner to know that Abbott did not have data which showed a lower  $C_{max}$  to any statistical significance over the structurally similar prior art suspension formulas in deciding whether to allow the claim over this prior art.

On this basis alone, the district court abused its discretion because it created such a high bar for materiality that in essence no statement or withholding of information would be material if it would not change the ultimate outcome of allowing the patent. This is inconsistent with our precedent. See, e.g., Hoffmann-La Roche, Inc. v. Promega Corp., 323 F.3d 1354, 1368 (Fed. Cir. 2003) (“The fact that the examiner did not have to rely on the purity representations in issuing the patent is not inconsistent with a finding of materiality. Although the inventors’ statements regarding purity were not the principal focus of the office action response, they were clearly an important aspect of it. Under the circumstances, a reasonable examiner would have wanted to know that the patentability argument based on purity was unsupported by the experimental results cited by the inventors.” (internal citation omitted)); Merck & Co. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1421 (Fed. Cir. 1989) (rejecting a “but for” standard of materiality).

In addition, while the district court did not reach the issue of intent, the fact that Gustavson submitted a declaration to the PTO in which she claimed to have found a

statistically significant lowering of  $C_{max}$  despite now admitting to never having done any statistical analysis is sufficient circumstantial evidence of intent to raise a substantial question of inequitable conduct, if not necessarily to prove inequitable conduct on the merits.

The district court also found that the failure by Abbott to disclose a new study<sup>7</sup> was immaterial because Abbott simply “chose to rely on the results of several other studies that showed differing mean DFL values” and the totality of the evidence demonstrates that the prior art formulation did not have the “same broad PK properties as those claimed for the ER formulation.” Sandoz I, 500 F. Supp. 2d at 824. The test is not whether the Examiner would have refused to allow the patent to issue without the information, but just whether it would have been “important” to her consideration. Here the extent the PK parameters of the ER formulation differed from the clarithromycin formulations in the prior art was the primary focus of the examiner’s concerns regarding patentability, and Abbott’s ability to establish sufficient differences was the basis for allowing the claims. It was not for Abbott to decide unilaterally that it preferred the results of one set of studies that supported patentability and therefore could ignore studies reaching the opposite result. Cf. Paragon Podiatry Lab. v. KLM Labs., 984 F.2d

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<sup>7</sup> The written description of the ’718 patent states that “The mean DFL values for the controlled release formulation [another Abbott prior art reference disclosing a clarithromycin formulation] and for the IR are substantially equal in value. . . .” ’718 Patent, col.11 ll.18-19. And it explains that lower DFL values for the ER formulation of the ’718 patent show that it provides “less variable clarithromycin concentrations throughout the day than the IR and the sustained release compositions.” ’718 Patent, col.11 ll.25-26. These statements were correct based on three studies that had been done prior to filing the application. However, a new study W98-268, which Gustavson had knowledge of, and which issued while the application was pending, found that there was a statistically significant lower DFL value for the sustained release formulas than the IR formulas. Gustavson, however, failed to disclose the results of this new study.

1182, 1193 (Fed. Cir. 1993) (finding inequitable conduct for failure to disclose sales data and noting that “where the decision of whether or not to disclose sales before the critical date is close, the case should be resolved by disclosure, not by the applicant's unilateral decision.”).

Accordingly, I would also vacate the preliminary injunction based on the allegations of inequitable conduct. The evidence raises a substantial question of unenforceability that makes the patents vulnerable to being found unenforceable at trial. Thus, the district court erred when it concluded that Abbott had shown it would likely succeed on the merits.

Because of the reasons stated above, I would reverse the district court on the basis that there are substantial questions of both validity and enforceability of the '718 patent preventing a finding of likelihood of success on the merits.