United States District Court,
S.D. Florida.

BRISTOL-MYERS SQUIBB COMPANY and E.R. Squibb & Sons, L.L.C,
Plaintiffs.
v.
ANDRX PHARMACEUTICALS, INC. and Andrx Pharmaceuticals, L.L.C,
Defendants.

No. 03-60703-CIV

June 4, 2004.

Background: Brand name manufacturer filed claim against generic drug manufacturer for infringement of one of its pharmaceutical patents under the Hatch-Waxman Act.

Holdings: The District Court, Huck, J., held that:
(1) generic drug manufacturer did not literally infringe patent for blood pressure tablet, and
(2) there was no infringement of patent under the doctrine of equivalents.

Judgment denying liability entered.

5,006,344. Not Infringed.

Laura Besvinick, Luca Roberto Bronzi, Hogan & Hartson, Miami, FL, Pasquale A. Razzano, Henry Park, David F. Ryan, Fitzpatrick Cella Harper & Scinto, New York City, for Plaintiffs.

James Costigan, Alan B. Clement, Katharine G. Loving, Hedman & Costigan, New York City, Teresa Ragatz, Eric David Isicoff, Michael Darren Bon, Isicoff Ragatz & Koenigsberg, Miami, FL, for Defendants.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

HUCK**, District Judge.**

THIS MATTER is before the Court for a ruling on the issues presented during a bench trial held from April 26 to 30, 2004. In this patent infringement action, the crux of the Plaintiffs' case relies on their suggestion that one of the ingredients, microcrystalline cellulose, in the Defendants' proposed medicinal tablet formulations can be divided into two portions, one portion of which functions actively as a binder and disintegrant and a second portion of which acts passively as a filler. The Court finds, largely on the ground that this is an artificial division of a single ingredient into two components that is neither based on

scientifically sound principles nor satisfies the Court's construction of the patent claims, that the Defendants' products do not infringe Plaintiffs' patent.

Background and Procedural History

On April 10, 2003, Plaintiffs Bristol-Myers Squibb and its wholly owned subsidiary E.R. Squibb & Sons, L.L.C. (collectively referred to as "Bristol"), Delaware corporations located in New York, New York, filed this claim for infringement of one of its pharmaceutical patents against Andrx Pharmaceuticals, Inc., and its wholly owned subsidiary, Andrx Pharmaceuticals, L.L.C. (collectively referred to as "Andrx"), Florida corporations located in Davie, Florida, under the Hatch-Waxman Act, 35 U.S.C. s. 271(e)(2). FN1 The Hatch-Waxman Act establishes rules for patent infringement in pharmaceutical product cases which create a statutory act of infringement before a potentially infringing company actually brings its product to the market. *See* Glaxo Wellcome Inc. v. Andrx Pharm., Inc., 344 F.3d 1226, 1228 (Fed.Cir.2003); Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1347 (Fed.Cir.2000). Under the Hatch-Waxman Act, the producer of a generic pharmaceutical product does not have to provide the extensive safety and efficacy data required in a New Drug Application ("NDA") that must be submitted to the Food and Drug Administration ("FDA") before a new brand name drug can be put on the market. Rather, the generic company may submit an Abbreviated New Drug Application ("ANDA") which must merely provide sufficient technical data to demonstrate that the generic drug is bioequivalent to the brand name drug, meaning that it provides equivalent blood plasma levels of the active ingredient over time as the brand name product. The names of all new drugs for which patents have been issued are recorded in an FDA publication called "Approved Drug Products with Therapeutic Equivalence Evaluations," which is more commonly referred to as the "Orange Book."

FN1. Because both the Plaintiffs and Defendants include a parent and wholly owned subsidiary, and because the distinctions between the related companies are unimportant to any issue in this case, the Court will refer to both parties in the singular as "Bristol" and "Andrx."

[1] The generic drug manufacturer must also explain to the FDA why its product does not infringe any patent listed in the Orange Book by certifying that (1) the brand name manufacturer has not filed a patent with the FDA, (2) the patent has expired (a "Paragraph II certification"), (3) the patent will expire before the generic product enters the market, or (4) the patent for the brand name drug is invalid or will not be infringed by production, use, or sale of the generic product (a "Paragraph IV certification"). 21 U.S.C. s. 355(j)(2)(A)(viii). If an ANDA applicant completes a Paragraph IV certification, the applicant must also submit a detailed notice to the patent owner explaining the factual and legal basis for the opinion that the patent is invalid or that the generic product will not infringe the patent. Id. at s. 355(j)(2)(B). Upon receipt of a Paragraph IV notification letter, the patent owner may file a suit for patent infringement within forty-five days of receipt of that letter, in which case the FDA may not approve the ANDA for thirty months or until a United States court finds for the defendant based on non-infringement, patent invalidity, or patent unenforceability. 21 U.S.C. s. 355(j)(5)(B)(iii). The patent holder can thus establish infringement by showing that the generic company's certification "is in error as to whether commercial manufacture, use, or sale of the new drug (none of which, of course, has actually occurred) violates the relevant patent." Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 678, 110 S.Ct. 2683, 110 L.Ed.2d 605 (1990).

On December 27 and 30, 2002, Andrx filed two ANDAs, Nos. 76-608 and 76-620, with the FDA seeking approval to sell different dosage levels of generic versions of Bristol's antihypertensive drug products

containing fosinopril sodium which are sold under the brand name Monopril(R) and Monopril(R) HCT (a fosinopril product that also contains a second active ingredient, the diuretic hydrochlorothiazide ("HCT")). Although the Orange Book lists two patents for Monopril(R) and Monopril(R) HCT, the parties agree that the issues in this case all relate only to whether Andrx infringed United States Patent No. 5,006,344 (" the '344 patent"), issued April 9, 1991, and owned by Bristol's subsidiary, E.R. Squibb & Sons, Inc. FN2 The '344 patent, which does not expire until July 10, 2009, describes a stable tablet containing fosinopril sodium or fosinopril sodium and HCT in combination with other inert pharmaceutical ingredients, known in the field as excipients. With respect to the '344 patent, on December 23, 2002, Andrx representative Ted Whitlock signed Paragraph IV certifications as to each fosinopril product Andrx intends to manufacture and sell, and, on February 21 and 24, 2003, signed two Notices of Certification of Invalidity or Noninfringement of a Patent, which were sent to Bristol Meyers Squibb Company. FN3 On April 10, 2003, within forty-five days of receipt of the Paragraph IV notice letters, Bristol timely filed identical complaints in both the United States District Court for the Southern District of Florida and the United States District Court for the Southern District of New York. Andrx filed an answer in this case on May 13, 2003. After some initial discovery and motions directed to determining the proper venue for this action, the New York case was transferredto the Southern District of Florida, and this case proceeded on the merits.FN4

FN2. Although the active ingredient in both drugs, fosinopril sodium, was covered by its own United States Patent No. 4,337,201, that patent expired on December 4, 2002.

FN3. Andrx sent two new certifications to the proper patent owner on May 20, 2003, because it had misidentified the owner as Bristol-Myers Squibb Company, when, in fact, the '344 patent was owned by Bristol's wholly owned subsidiary, E.R. Squibb & Sons, Inc. No other changes were made to the notification.

FN4. The New York case was transferred to this Court on December 4, 2003, and was assigned the case number 03-62283-CIV. It was transferred to the undersigned on April 2, 2004, and was dismissed without prejudice as duplicative on April 16, 2004.

On December 15, 2003, Andrx moved this Court to conduct a separate claim construction hearing under Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed.Cir.1995), *aff'd,* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). After full briefing and oral argument, the Court concluded that a separate *Markman* hearing was not necessary because the case was being tried only to the Court and because there was a significant overlap between the evidence of infringement and evidence that would be presented in a claim construction hearing. Therefore, the Court held that conducting two separate proceedings would be inefficient and more costly and, on January 15, 2004, denied Andrx's motion for a separate *Markman* hearing. On January 5, 2004, Bristol moved to amend its complaint to include a claim for willful infringement. The Court granted that motion on January 15, 2004. However, on February 6, 2004, the Court also granted Andrx's cross-motion to bifurcate the trial on willfulness, deciding that, if necessary, an additional trial on willfulness related primarily to Andrx's reliance on opinion of counsel, if Andrx chose to use such evidence, would be convened shortly after the first trial, allowing a brief period for additional discovery on that issue.

On February 6, 2004, the Court also denied as premature Andrx's motion in limine to exclude evidence

regarding an experiment conducted by UPM Pharmaceuticals, a company utilized by Bristol. The Court noted that, because that motion relied heavily on concerns over the scientific validity and relevance of the experiment which would need to be resolved in a *Daubert* hearing, the Court would allow the parties, at trial, to present evidence and argument regarding that experiment and would decide at that time whether that evidence should be excluded. On March 9, 2004, with the consent of both parties, the Court specially set the trial on infringement for April 26, 2004. Prior to trial, Bristol filed a motion in limine to exclude evidence of patent invalidity on the ground that Andrx had not provided an expert opinion on invalidity due to indefiniteness, arguing that Andrx would not be able to prove indefiniteness due to double inclusion without expert testimony. The Court denied that motion on April 15, 2004.

The Court commenced a five day non-jury trial on April 26, 2004. Bristol presented evidence in the form of lay testimony from Dr. Nemichand Jain, one of the inventor's named in Bristol's '344 patent, from Stephen Davis, the patent lawyer who prepared the '344 patent application for Bristol, and from Ted Whitlock, Andrx's in-house legal counsel who prepared the Paragraph IV certifications and notice letters. Bristol also presented expert testimony, both in its case-in-chief and in its rebuttal case, from Dr. Alexander Klibanov, a Professor of Chemistry and Bioengineering at the Massachusetts Institute of Technology. Andrx presented lay testimony from Dr. Guohua Zhang, the Andrx formulator responsible for overseeing the development of Andrx's generic fosinopril products, and expert testimony from Dr. Reza Fassihi, a Professor of Biopharmaceutics and Industrial Pharmacy at the Temple University School of Pharmacy. The Court considers both experts to be well-qualified to testify both as to the scientific principles of tablet formulation as well as to how one of ordinary skill in the art of pharmaceutical formulation would read the '344 patent. In addition to this live testimony, the parties submitted deposition testimony from Jain, Whitlock, Zhang, and the following eight other witnesses: Dr. Ajit B. Thakur, Dr. Robert L. Jerzewski, Mr. Lewis Gryziewicz, and Dr. Thomas M. Wong, who were all Bristol employees who were involved in the development of the patented tablet formulations; Dr. DaCheng Tian and Dr. Xiu Xiu Cheng, Andrx employees who were involved in the formulation of the Andrx generic fosinopril products; Dr. Tony Yu, an employee of UPM Pharmaceuticals who conducted a model study for Bristol in connection with this litigation; and Larry Rosenthal, Executive Vice President of Sales and Marketing at Andrx. The parties also entered in evidence seventy-three Joint Trial Exhibits, thirty Plaintiffs' Trial Exhibits, and twenty Defendants' Trial Exhibits.FN5 During trial, the parties made or renewed several motions, on which the Court deferred ruling and will consider herein. The parties filed post-trial proposed findings of fact and conclusions of law on May 10, 2004. After careful consideration of the pleadings, motions, trial and deposition testimony, exhibits, and other submissions, the Court finds as follows.

FN5. When referring to exhibits filed by the parties, the Court will identify the Joint Trial Exhibits as JTX, Plaintiffs' Trial Exhibits as PTX, and Defendants' Trial Exhibits as DTX. The page number cited for exhibits that contain excerpts from treatises will refer to the page number of the treatise.

Pending Motions

Both sides raised or renewed motions during and at the close of trial. Andrx moved under Rule 52 for judgment as a matter of law both on Bristol's entire case and specifically on the claim for willful infringement. The motion as to the entire case is denied on the ground that this Court's decision on both the claim interpretation and infringement is based on factual and legal findings as to disputes of material fact, particularly with respect to how one of ordinary skill in the art of pharmaceutical formulation would interpret the patent claims. Therefore, judgment solely as a matter of law is inappropriate. As to Andrx's

motion for judgment as a matter of law on willful infringement, that motion is denied as moot given the Court's finding of non-infringement.

Bristol moved during the trial to convert its previously denied in limine motion regarding excluding evidence of patent invalidity due to double inclusion to a motion to dismiss that claim on the ground that no expert opinion was provided on this theory and that, without such an opinion, Andrx had not met its burden of proving by clear and convincing evidence that the patent is invalid for indefiniteness. In closing arguments, Defendant conceded that its double inclusion argument would only be relevant if the Court agreed with Bristol's claim interpretation by finding that an excipient can function as both a single agent that is binder and disintegrant and as a filler, despite the separate listings in Claim 1 for these ingredients. Due to the Court's claim interpretation, there is no risk of double inclusion, and the patent cannot be held invalid on that ground. Therefore, the Plaintiff's motion is denied as moot.

Finally, Andrx renewed its motion in limine to exclude testimony and related evidence concerning a model study conducted by an outside laboratory, UPM Pharmaceuticals, on three batches of tablets containing different amounts of extragranular microcrystalline cellulose ("MCC"). Andrx argues that the study should not be admitted because it does not meet the federal standard for scientific admissibility. *See* Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 113 S.Ct. 2786, 125 L.Ed.2d 469 (1993). Determinations of admissibility must be based on a finding that the evidence is sufficiently reliable to be admitted and that it is relevant to the issues in the case. *See* id. at 589, 113 S.Ct. 2786; *see also* Kumho Tire Co. v. Carmichael, 526 U.S. 137, 147, 119 S.Ct. 1167, 143 L.Ed.2d 238 (1999); Allison v. McGhan Med. Corp., 184 F.3d 1300, 1310 (11th Cir.1999). The cases make clear that a primary rational for the exclusion of evidence that does not meet the *Daubert* standard is its "inability to assist in factual determinations, its potential to create confusion, and its lack of probative value." Allison, 184 F.3d at 1311-12. Judges are to act as gatekeepers to assure that only evidence that will assist the factfinder is admitted. Daubert, 509 U.S. at 592, 113 S.Ct. 2786.

Andrx claims that evidence related to the UPM study should not be admitted because the test was not conducted in such a way as to render it reliable and that the test is not relevant because the tablets that were tested are not sufficiently similar to the Andrx formulations that the Court can draw any inferences related to the Andrx products from the results of those tests. Bristol contends that all of the concerns that Andrx raises regarding the UPM study, even if accepted, would only affect the weight this Court should afford the evidence, not its admissibility.

Having read the parties' memoranda on the issue and having heard testimony from both experts, the Court agrees with Bristol that Andrx has not shown that the evidence is sufficiently unreliable and irrelevant that this Court should not consider it at all. Dr. Klibanov testified that the experiment was a model study that was conducted in accordance with a standard and accepted disintegration test procedure. He acknowledged that model studies are not as reliable as would be studies that use product formulations that more closely mimic the behavior of the actual accused infringing product. However, he testified that model studies are used quite commonly in science and noted that even Andrx's expert had conducted a model study in this case. The Court agrees that the question of reliability and relevance in this case is merely one of degree, and cannot agree with Andrx that the evidence is not useful or probative in deciding the issues in this case. This is especially true since this is a bench trial, where the Court must evaluate the evidence regardless of whether it ultimately decides to exclude it. *See* Seaboard Lumber Co. v. United States, 308 F.3d 1283, 1302 (Fed.Cir.2002) (holding that, while issues of prejudice are "of lesser import in bench trials, where no screening of the factfinder can take place, the *Daubert* standards of relevance and reliability must still be met"); *see also* Multi-Medical Convalescent & Nursing Center, 550 F.2d 974, 977 (4th Cir.1977) ("In a non-

jury trial ... little harm can result from the reception of evidence that could perhaps be excluded .... because the judge ... is presumably competent to disregard what he thinks he should not have heard, or to discount it for practical and sensible reasons."). Thus, some courts have held that, in cases where the judge is the factfinder, the criteria for finding evidence admissible can be applied less strictly. *See* SmithKline Beecham Corp. v. Apotex Corp., 247 F.Supp.2d 1011, 1042 (N.D.Ill.2003) (holding that, while *Seaboard Lumber* held that *Daubert* must be applied even in bench trials, "it did not say it must be followed *rigidly*," and, therefore, "[i]n a bench trial, it is an acceptable alternative to admit evidence of borderline admissibility and give it the (slight) weight to which it is entitled"), *aff'd,* 365 F.3d 1306 (7th Cir.2004); *see also* Goodman v. Highlands Ins. Co., 607 F.2d 665, 668 (5th Cir.1977) (after noting that an evidentiary ruling should not be disturbed on appeal absent a showing of manifest error, holding that "a trial judge sitting without a jury is entitled to even greater latitude concerning the admission of evidence"). Therefore, the Court will consider Andrx's substantive objections to the UPM study when addressing the merits of the case, but denies Andrx's motion to wholly exclude the evidence.FN6

FN6. Additionally, Bristol's Trial Exhibits 30 to 34 (PTX 30-34), which were conditionally offered by Bristol subject to the ruling on Andrx's motion to exclude, are admitted in evidence.

Legal Standards

A. *Claim Construction*

To prevail on a claim of infringement, the plaintiff must establish by a preponderance of the evidence that the accused product infringes the properly construed claims of the patent, either literally or under the doctrine of equivalents. Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc., 261 F.3d 1329, 1336 (Fed.Cir.2001). A determination of infringement involves a two-step analysis. First, the court must properly construe the asserted claims. Second, the court must determine whether the accused product infringes the properly construed claim. Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed.Cir.1995), *aff'd,* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). The function and purpose of a patent claim is to define the scope of the invention and the extent of the patentee's rights. Markman, 517 U.S. at 373-74, 116 S.Ct. 1384. It has been said that patent claims define the metes and bounds of the invention. Markman, 52 F.3d at 1000. In this respect, the patent, similar to a deed, serves an important public notice function, informing the public as to what is claimed and what is not claimed. *See* PSC Computer Prods., Inc. v. Foxconn Int'l Inc., 355 F.3d 1353, 1358-59 (Fed.Cir.2004).

[2] [3] [4] Claim construction is a matter of law exclusively for the court, and entails determining the meaning and scope of the patent claims asserted to be infringed. Markman, 52 F.3d at 976-978. It begins with the language of the claim itself. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996). A court need only construe the claim terms actually in controversy, and only to the extent necessary to resolve that controversy. Vivid Tech., Inc. v. Am. Sci. & Eng'g, Inc., 200 F.3d 795, 803 (Fed.Cir.1999). A patent is written for and directed to persons of ordinary skill in the art to which the subject matter of the patent pertains. Id. at 804; In re Hayes Microcomputer Prods., Inc. Patent Litig., 982 F.2d 1527, 1533-34 (Fed.Cir.1992). Thus, claim terms must be construed as they would be understood by a person of ordinary skill in the art at the time the invention was made. Vivid Tech., 200 F.3d at 804; Interactive Gift Express, Inc. v. Compuserve, Inc., 256 F.3d 1323, 1332 (Fed.Cir.2001) ("It is important to bear in mind that the viewing glass through which the claims are construed is that of a person skilled in the art.").FN7 Such persons are presumed, as a matter of law, to be aware of all pertinent prior art published or known in the United States prior to that date. Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc., 807

F.2d 955, 962 (Fed.Cir.1986).

FN7. The parties have agreed that, in the context of this case, the claim terms must be construed as of about 1989 or 1990. Although Bristol asserts that the specific date from before which the claims should be construed is either June 10, 1989, or June 26, 1990, the trial testimony and stipulations mostly identified the more general period of 1989 or 1990, and it appears that someone of ordinary skill in the art of pharmaceutical formulation would have understood the disputed terms in the same manner at any point within that general time frame.

In construing a claim, the first step is to analyze the claim language itself. Markman, 52 F.3d at 979. The second step is to examine the specification. It is well established that, because "[t]he specification contains a written description of the invention that must enable one skilled in the art to make and use the invention," claims must be read in view of the specification of which they are a part. Markman, 52 F.3d at 979. While claim terms generally are to be given their plain and ordinary meaning, that is not the case where the patent specification clearly indicates that the inventor intended a different meaning. National Recovery Techs., Inc. v. Magnetic Separation Sys., 166 F.3d 1190, 1195 (Fed.Cir.1999). Thus, the specification may, and often does, limit the claimed invention. *SciMed,* 242 F.3d at 1340-41; *see also* Watts v. XL Sys., Inc., 232 F.3d 877, 882 (Fed.Cir.2000). Finally, the third step is to examine the patent prosecution history. The prosecution history constitutes an undisputed public record of proceedings in the United States Patent and Trademark Office and is of primary significance in understanding the claims. Markman, 52 F.3d at 980.

In addition to the intrinsic evidence, in interpreting the claims, the court also may consider extrinsic evidence, including expert and inventor testimony, prior art, dictionaries and treatises, where necessary. *See, e.g.,* Tanabe Seiyaku Co. v. United States Int'l Tr. Comm'n, 109 F.3d 726, 732 (Fed.Cir.1997); Vitronics, 90 F.3d at 1582; Interactive Gift, 256 F.3d at 1332 ("Consultation of extrinsic evidence is particularly appropriate to ensure that [a judge's] understanding of the technical aspects of the patent is not entirely at variance with the understanding of one skilled in the art.") (internal citation omitted). Extrinsic evidence is also permissible to explain general scientific principles and the meaning of technical terms of art that appear in the intrinsic evidence when, after consulting the intrinsic evidence, the disputed claim terms are still unclear. Markman, 52 F.3d at 980-81; Vitronics, 90 F.3d at 1583. Extrinsic evidence, however, cannot contradict the interpretation of the claims based on the intrinsic evidence. *See* Aqua-Aerobic Sys., Inc. v. Aerators Inc., 211 F.3d 1241, 1245 (Fed.Cir.2000); Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys., 132 F.3d 701, 706 (Fed.Cir.1997). Rather, extrinsic evidence, including expert testimony, may be received, at the court's discretion, to assist the court in arriving at the correct conclusion as to the true meaning of the language employed in the patent. Markman, 52 F.3d at 980-81.

B. *Infringement*

[5] [6] [7] [8] In order to infringe a patent, the accused product must meet each and every claim limitation, either literally or under the doctrine of equivalents. Cortland Line Co. v. Orvis Co., 203 F.3d 1351, 1356 (Fed.Cir.2000). In accordance with the public notice function of patent claims, the infringement inquiry requires attention to each claim element rather than the invention as a whole. *See* Pennwalt Corp. v. Durand-Wayland, Inc., 833 F.2d 931, 934 (Fed.Cir.1987).FN8 In order for a product to literally infringe a patent claim, the patentee must prove by a preponderance of the evidence that the accused product includes elements that are literally identical to each and every limitation of the patent claim. *See* Biovail Corp. Int'l v. Andrx Pharms., Inc., 239 F.3d 1297, 1302 (Fed.Cir.2001); Abbey v. Bill Ussery Motors, Inc., 74 F.Supp.2d

1217, 1221 (S.D.Fla.), *aff'd sub nom.* Abbey v. Robert Bosch GMBH, 217 F.3d 853 (Fed.Cir.1999). If an express claim limitation is absent from an accused product, there can be no literal infringement as a matter of law. Wolverine World Wide, Inc. v. Nike, Inc., 38 F.3d 1192, 1199 (Fed.Cir.1994).

FN8. There is no legally recognizable or protected "gist" or "heart" of the invention, and it is error for the trial court to restrict a multicomponent claim to one component to find infringement by one who uses only that component or does not use all of the components required in the claim. W.L. Gore & Assoc. v. Garlock, Inc., 721 F.2d 1540, 1548 (Fed.Cir.1983); Everpure, Inc. v. Cuno, Inc., 875 F.2d 300, 303 (Fed.Cir.1989); Porter v. Farmers Supply Serv., Inc., 790 F.2d 882, 885 n. 4 (Fed.Cir.1986).

[9] [10] [11] Where no literal infringement is found, doctrine of equivalents infringement may sometimes be found where the accused product is insubstantially different from the claimed element, that is, where it performs substantially the same function in substantially the same way to obtain substantially the same result. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 23-25, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997). Like literal infringement, infringement under the doctrine of equivalents cannot be established unless every limitation of a claim is satisfied, either exactly or by a substantial equivalent. Carroll Touch, Inc. v. Electro Mech. Sys., Inc., 15 F.3d 1573, 1576 (Fed.Cir.1993). Any infringement analysis under the doctrine of equivalents must deal with each claimed element, rather than a less focused consideration of the invention as a whole. *See* Pennwalt, 833 F.2d at 935. Proof of equivalency can be made "through testimony of experts or others versed in the technology; by documents, including texts and treatises; and, of course, by the disclosures of the prior art." Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 609, 70 S.Ct. 854, 94 L.Ed. 1097 (1950). The Federal Circuit, however, gives little weight to conclusory statements on equivalence offered by expert witnesses; factual evidence of equivalence is required. *See* Lemelson v. United States, 752 F.2d 1538, 1551 (Fed.Cir.1985); Tronzo v. Biomet, Inc., 156 F.3d 1154, 1160 (Fed.Cir.1998).

Findings of Fact and Conclusions of Law

I. Claim Construction

A. *Factual Background*

Fosinopril sodium is an angiotensin-converting enzyme inhibitor that is used for the treatment of essential hypertension. It functions by inhibiting the ability of the enzyme that catalyzes conversion of angiotensin I, a protein found naturally in the body, to angiotensin II. The drug is primarily prescribed for lowering blood pressure. It is undisputed that Bristol, which developed fosinopril as an active pharmaceutical ingredient, held a patent on that active substance which expired near the end of 2002. However, in the process of conducting long-term shelf stability studies of their first formulation of the commercial tablet products, Bristol's scientists discovered that one of the non-active ingredients, or excipients,FN9 specifically the lubricant magnesium stearate, interacted poorly with the fosinopril, leading to reduced shelf stability.FN10 In response to this problem, Bristol's researchers began searching for alternative formulations that would meet the FDA's requirements for long-term shelf stability. FN11 They discovered that use of the alternative lubricants sodium stearyl fumarate ("SSF") or hydrogenated vegetable oil ("HVO") alleviated the shelf-life stability problem that resulted from the interaction of fosinopril and magnesium stearate, and found that SSF was preferable. That discovery was clearly identified as the point of novelty that justified Bristol's

application for a patent on their tablet formulation.

FN9. According to one treatise from 1990, *Pharmaceutical Dosage Forms,* excipients are "inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch-all term which includes various subgroups comprising diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants or flow promoters, colors, flavors, fragrances, and sweeteners." (PTX 39 at 151).

FN10. Without getting into unnecessary detail on tablet production processing, it is noted that lubricants are used in tablet formulations primarily for two purposes related to the manufacturing of these tablets. First, the lubricant helps prevent the final blend from sticking to machine parts during processing. Second, the actual tablets are formed when they are compressed into tablets in a tablet press, and the lubricant assists with ejection of the tablet from the press after compression.

FN11. The FDA requires that tablet formulations retain the various indicia of their "stability profiles" over their approved shelf life periods, including potency or assay value, degradation products limitations, dissolution profile, appearance, moisture content, hardness, and friability.

Nonetheless, the '344 patent claims a specific formulation that includes ingredients in addition to the active ingredient and the lubricant, which results in additional claim limitations. The parties are in agreement that the Andrx products must satisfy each of those claim limitations in order to be infringing.FN12 Bristol has asserted against the Andrx product only infringement of Claim 1 of the patent, which describes:

FN12. Although Andrx claims that Bristol could have broadly claimed the invention by designating ranges for only the fosinopril and preferred lubricant of SSF or HVO, the attorney who prepared the patent application for Bristol, Stephen Davis, testified that the more specific formulation was necessary in order to minimize the risk that the patent would subsequently be found invalid for inoperative terms or indefiniteness. Moreover, while Bristol appears to discount the care with which the Andrx formulators attempted to "design around" the '344 patent, Andrx points out that it is entirely lawful to deliberately design around a patent. *See* Kimberly-Clark Corp. v. Johnson & Johnson, 745 F.2d 1437, 1457-58 (Fed.Cir.1984).

A stable tablet comprising on a weight percentage basis from about 1% to about 25% fosinopril sodium, up to about 25% of a diuretic, [1] from about 30% to 90% of a filler, [2] from about 2% to 10% of a disintegrant, [3] from about 1% to about 5% of a binder, or [4] from about 5% to about 15% of a single agent which is both binder and disintegrant, and from about 1.3% to about 4% of a lubricant selected from the group consisting of sodium stearyl fumarate and hydrogenated vegetable oil.
The parties have stipulated that the Andrx formulations meet each of the claim limitations of Claim 1 except for [1] and [4], and that the alternative claim limitations [2] and [3] are not being asserted by Bristol against the proposed tablet formulations. The dispute as to claim limitations [1] and [4] relates to the inclusion of about 30% of total tablet weight of MCC in the Andrx products. Andrx claims that the 30% MCC was included in its formulations as a filler, and that its tablets do not contain a disintegrant, a binder, or a single agent that acts as a binder and disintegrant, and, therefore, do not infringe Bristol's patent. Bristol, on the other hand, claims that a portion of the MCC in the Andrx formulation functions as a "single agent which is both binder and disintegrant," and the remainder of the MCC acts as a filler in combination with lactose.

The only disputed claim terms are thus "filler," "disintegrant," "binder," and "single agent which is both binder and disintegrant."
The '344 patent was issued pursuant to an application filed with the patent office with the Serial No. 543,639 (" '639 application"). That application was a continuation-in-part ("c-i-p") application of a prior parent application assigned the Serial No. 377,683 (" '683 application"), which was abandoned. A c-i-p application is an application that can rely on the earlier filed parent application for priority as to subject matter that is common to both applications, but cannot rely on the earlier filing date as to subject matter that is newly added in the c-i-p application. The testimony at trial established that the additional material disclosed in the c-i-p application included a new alternate claim limitation of "from about 5% to about 15% of a single agent which is both binder and disintegrant," raised the upper limit of the lubricant in the formulation from 3% to 4%, and provided some new examples and identified preferred ingredients for certain claim terms.

B. ***Proposed Claim Constructions***

At the close of the trial, the Court asked both parties to submit their proposed claim constructions. The essential point of difference is that Andrx argues that a person of ordinary skill in the art of pharmaceutical formulation would have read the claim as requiring a filler which is separate from the excipient or excipients which act as binder and disintegrant or as a single agent that is both binder and disintegrant. Specifically, Andrx proposes the following claim construction as to the relevant portion of Claim 1:

... [1] from about 30 to about 90% of a **first excipient which is a** filler, *including but not limited to, lactose or a combination of lactose and microcrystalline cellulose;* and [2] from about 2% to 10% of a **second excipient which is a** disintegrant, *including but not limited to, sodium carboxymethyl starch, cross linked sodium carboxymethyl starch, crospovidone, cross linked sodium* carboxymethylcellulose*, sodium starch glycolate, and mixtures thereof;* and [3] from about 1% to about 5% of a **third excipient which is a** binder, *including but not limited to, povidone,* hydroxypropyl cellulose*, and mixtures thereof,* or [4] from about 5% to 15% of **a second excipient that is a** single agent which is both binder and disintegrant, *including but not limited to pregelatinized starch;* and ...

Andrx would also read the "is" in the clause "which is both binder and disintegrant" as connoting "equality" or "consists of," such that the single agent would be limited to those two functionalities. Andrx further argues that, based on dependent patent claims, the patent specification, and the prosecution history, a person of ordinary skill in the art would understand the patent to define MCC as a filler in the '344 patent and not as a single agent that is both binder and disintegrant. Finally, Andrx argues that, if the Court finds it necessary to resort to extrinsic evidence, then the expert testimony shows that a person of ordinary skill would classify an excipient based on its primary function in a formulation and that, in the Bristol patent and Andrx formulations, such a person would classify MCC as a filler and not additionally as a single agent that is both binder and disintegrant.

Bristol's claim construction would read the claim simply as stated in the patent without any modifiers being inserted, adding only parenthetical notations containing Bristol's understanding of the ordinary and customary meanings of the terms "filler," "disintegrant," "binder," and "single agent which is both binder and disintegrant."FN13 Nonetheless, Bristol represented at trial they would not object to Andrx's claim construction with regard to the "including, but not limited to" clauses in italics above, but do object to the clauses in bold which modify the binder, disintegrant, and single agent limitation to require a "second" or "third" excipient that is separate from the filler. Bristol contends that importing such a requirement into the

claim language is not warranted because the claim language does not use any terms which would require different or separate excipients for the filler and single agent which is both binder and disintegrant and that the intrinsic evidence does not show any intent by the inventors to require different and separate excipients. Moreover, Bristol would not read "is" in the "single agent" clause as limiting the functionality that the single agent can serve to only binder and disintegrant. Bristol also rejects Andrx's claim that the patent "defines" MCC as filler, arguing that it merely designates MCC as a preferred filler without limiting it to performing only that function in other, conceivable formulations. Finally, Bristol submits that the extrinsic evidence supports that a person of ordinary skill in the art of pharmaceutical formulation would have understood that multifunctional excipients such as MCC can serve more than one role in a pharmaceutical formulation and that such a person would not have understood the patent to preclude a formulation that would have utilized a single agent that serves as filler, binder, and disintegrant. Because both Bristol and Andrx employ a wet granulation process, Bristol states that the Court need not consider how the claim terms of the '344 patent might be interpreted in contexts other than the wet granulation process.

FN13. Bristol's description of the ordinary and customary meanings of the disputed claim terms are as follows: (1) Filler-an excipient used to bulk up a tablet to sufficient mass to make it easier to handle and consume; (2) Disintegrant-an excipient which, after a tablet is consumed, functions extragranularly to break up (cause rupture of) the tablet matrix and intragranularly to break up the granules, thus exposing greater surface area to the liquids in the digestive tract, thereby accelerating dissolution of the drug; (3) Binder-an excipient which imparts cohesive qualities to powdered materials to assist in creation of granules; and (4) "Single agent which is both binder and disintegrant"-an excipient which can exhibit the functionalities of both a disintegrant and a binder as explained in (2) and (3), above. The treatise *Pharmaceutical Dosage Forms* notes that the purpose of a binder is "to add cohesiveness to powders, thereby providing the necessary bonding to form granules, which under compaction form a cohesive mass or compact referred to as a tablet," and the purpose of a disintegrant is "to facilitate breakup of a tablet after administration." (JTX 43 at 83, 86).

C. *Analysis*

Both parties submitted various learned treatises and testimony of experts who can be regarded as possessing at least "ordinary skill in the art of pharmaceutical formulation," as well as testimony from the inventor of the Bristol product, the formulator of the Andrx product, and patent lawyers from each company. Consistent with the *Markman* directive, the Court will start with the plain language of the patent claim, and then evaluate the other intrinsic evidence. Although not necessary to complete the claim construction, the Court will then discuss the relevant extrinsic evidence.

1. *The Single Agent Limitation*

[12] Looking at the plain language of Claim 1 of the '344 patent, it appears that a person skilled in the art would see a list of ingredients, each of which describes a separate agent. There is an active ingredient, a diuretic, a lubricant, a filler, a disintegrant, and a binder, or, in lieu of the final two items, a single agent that is both. There is no express limitation in the patent for a single agent that is both a filler and a binder, nor an express limitation for a single agent that is both a filler and a disintegrant. This is true even though the 1990 edition of the *United States Pharmacopeia /National Formulary* (" *USP/NF* "), which is one of the primary reference materials relied on by skilled pharmaceutical formulators (and which is relied on by both Bristol and Andrx in this case), demonstrates that there were fillers that were known in 1990 to also act as a binder (starch) or as a disintegrant (dextrin). (JTX 40 at 1858). Most importantly, there is no express

limitation in the patent claim for a single agent that is binder, filler, and disintegrant, even though there are two excipients that are listed in the *USP/NF* under all three functionalities, MCC and pregelatinized starch. Bristol's argument that there is no requirement of separateness would be better supported if the single agent limitation for the binder and disintegrant had never been added to the patent claim, because Bristol's argument in the presence of that single agent limitation would, as Andrx has asserted, render that single agent limitation superfluous.FN14 Since a term is included in Claim 1 for a single agent that is both binder and disintegrant, it does suggest that the claim is designating the filler as a different product from the binder, the disintegrant, or the single agent that is both. Otherwise, the patent claim should have designated additional alternatives of single agents that are both filler and binder, filler and disintegrant, or filler, binder, and disintegrant. Bristol does not dispute that at least a portion of the MCC is acting as a filler in the Andrx formulations.

FN14. Andrx has cited cases where the Federal Circuit has interpreted dependent patent claims in a manner so as to prevent those dependent claims from being rendered superfluous. *See* Xerox Corp. v. 3Com Corp., 267 F.3d 1361, 1366-67 (Fed.Cir.2001); Comark Comms., Inc. v. Harris Corp., 156 F.3d 1182, 1187 (Fed.Cir.1998). While those cases are not directly on point in determining whether a single claim limitation within a claim should be read so as to not make it superfluous, that idea does accord with general concepts of legal interpretation, and the cases do lend some support to the Court's interpretation of the claim limitations of Claim 1 of the '344 patent.

Bristol argues, however, that adding the term "separate" or "first" and "second" excipient into the patent claim constitutes importing language unsupported by the plain meaning of the claim, in violation of the concept that a patent claim should be interpreted in the broadest manner supported by the intrinsic evidence. *See* CCS Fitness, Inc. v. Brunswick Corp., 288 F.3d 1359, 1366 (Fed.Cir.2002) (holding that, where a claim term is expressed in a general manner, it is error to narrow the term without clear and unambiguous support from the intrinsic evidence); Teleflex Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1325 (Fed.Cir.2002) (imparting a "heavy presumption" that a claim term carries its broadest ordinary and customary meaning); Texas Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193, 1203 (Fed.Cir.2002) (where more than one definition is consistent with the intrinsic evidence, "the claim terms may be construed to encompass all such consistent meanings"), *cert. denied,* 538 U.S. 1058, 123 S.Ct. 2230, 155 L.Ed.2d 1108 (2003).FN15 Nonetheless, while the Court uses the term "separate" to explain its construction, there is no need to import any additional words into the claim. Rather, the Court finds that the use of the alternative "single agent" limitation merely shows that the language was defining single excipients, each one of which must be different, unless one of them is both a binder and a disintegrant. The language of the claim need not be altered at all to understand that the patent provides an alternative, and that the use of the alternative term would alert a skilled practitioner to the fact that every other term describes an ingredient that is separate from the others.

FN15. While Bristol contends the Court should look first at dictionaries to determine the ordinary meaning of the terms of the patent, the Court's claim construction does not turn on the actual definitions or ordinary meanings of the words as much as it does on the structure of the overall wording of the claim limitations. Thus, the Court finds that little use would be served by consulting dictionaries for specific definitions of the disputed claim terms.

As to the meaning of the word "is" in the single agent limitation, Andrx claims the term should mean "equal

and limited to," whereas Bristol submits it should mean "equal but not limited to." Both parties have cited examples of more open-ended ("comprising") or more closed ("consisting of") terms that have been given specific meanings in patent claims, but none of which would make sense grammatically in place of "is" in the phrase "a single agent which is both binder and disintegrant." Thus, there is no reason to believe that, in that claim limitation, any word more precise than "is" could or should have been used, and the meaning of "is" must be viewed in the context of the phrase and the claim. *See* Brookhill-Wilk 1, LLC v. Intuitive Surgical, Inc., 334 F.3d 1294, 1300 (Fed.Cir.2003) (holding that "the correct meaning of a word or phrase is informed only by considering the surrounding text .... [R]esort must always be made to the surrounding text of the claims in question, the other claims, the written description and the prosecution history."). In that light, the Court agrees that the "is" in that phrase is meant to limit the single agent to an excipient that is only a binder and a disintegrant. Otherwise, again, the phrase would be redundant and superfluous, since, absent the single agent limitation, a multi-functional excipient already would have been covered by reading the binder and disintegrant limitations as allowing one excipient to satisfy both functions. Regardless of whether the inventors intended for "is" to limit the functionalities of the single agent to binder and disintegrant, the Court believes that a skilled formulator would have read this limitation as doing so.FN16

FN16. Moreover, the extrinsic evidence from the parties' experts is not that helpful on this point, since each expert merely offered opposing opinions as to how a person of ordinary skill would interpret the single agent limitation, but without being able to refer to examples of prior patents that have used such language and without any other indication that the use of the "single agent" phrase is a term of art that would have been well understood by practitioners. Rather, Dr. Fassihi merely testified that a person of ordinary skill would read "single agent which is both binder and disintegrant" as limiting the functionality of that single agent to those two purposes. Bristol presented testimony from its expert, Dr. Klibanov, that one skilled in the art would have understood that there are many multifunctional excipients and that such a person would not have understood the "single agent" patent term to limit the function that an excipient could serve in a formulation to only binder and disintegrant functionalities. Thus, this extrinsic evidence shows only that these two skilled practitioners would not interpret the claim in the same way, and the Court need only decide whether either view comports with a reasonable interpretation of the claim language based upon all of the other considerations.

Andrx argues that the prosecution history also supports its "separate" argument, claiming that the addition of the "single agent" limitation in the c-i-p application demonstrates that Bristol did not believe that its original phrasing of Claim 1 coveredmulti-functional excipients that perform more than one role. Andrx notes that the parent '683 application does not describe a single agent that is both a disintegrant and binder. Andrx claims that the addition of the limitation describing and claiming "from about 5% to about 15% of a single agent which is both binder and disintegrant" as an alternative to "from about 2% to about 10% of a disintegrant" and "from about 1% to about 5% of a binder" constituted newly added matter. Bristol, however, presented testimony from Stephen Davis, who prepared the patent application for Bristol, explaining that the "single agent which is both a binder and disintegrant" was included in the '639 application as new matter because, as Claim 1 was previously written, if one simply added up the percentages of "from about 2% to 10% of a binder" and "from about 1% to 5% of a disintegrant," the apparent operative range for a product that served both functions would be from about 3% to about 15%. Thus, Bristol suggests, one would have concluded that a single agent used in a concentration of only 3% would properly function in the formulation. However, as Davis testified, Bristol had determined that concentrations as low as 3% are insufficient to provide both disintegrant and binder functionalities when a single agent such as pregelatinized starch is used for both functions. Therefore, he felt Bristol needed to

disclose the lower range limitation as "from about 5%" so that the patent would not be found invalid due to an inoperative term if concentrations of under 5% of a single agent would not produce a stable tablet. Nevertheless, Davis and Dr. Klibanov both testified that a person of ordinary skill in the art of pharmaceutical formulation would have understood, even under the original patent application that did not include the "single agent" limitation, that the patent claims would have covered a formulation using a single agent which functioned both as a binder and a disintegrant.

The Court finds this argument unpersuasive for three reasons. First, even if the subjective intent of the inventors were to add the single agent limitation only to increase the lower range limit, the objective reading of the patent claim, the specification, and the prosecution history by a person of ordinary skill in the art is the appropriate standard for deciphering claim terms that are not clearly defined in the patent itself. *See* Markman v. Westview Instruments, 52 F.3d 967, 985-86 (Fed.Cir.1996) (holding that the inventor's subjective intent is entitled to little or no probative weight except as documented in the prosecution history and that "the focus in construing disputed terms in claim language is not the subjective intent of the parties to the patent contract when they used a particular term [but] rather is on the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean"), *aff'd,* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). In this case, the prosecution history does not record that the subjective intent of disclosing the new matter was to increase the lower range limit. Based on the objective standard, the Court agrees with Andrx that the addition of the single agent limitation in the c-i-p application would be read by someone of ordinary skill as an indication that multifunctional excipients that served more than one function under the '344 patent claim were not covered by the scope of the original Claim 1. Further, the fact that additional limitations for single agents providing all three functionalities was not added to the patent at the same time would have indicated to a person of ordinary skill either that no excipient could provide all three functionalities in the formulation or that such a formulation would not infringe.

Second, Plaintiff's argument that the c-i-p disclosure of the single agent was needed to raise the lower limit of the concentration of binder and disintegrant if a single agent were used does not appear to be a necessary reason for such a disclosure. It is undisputed that the total concentrations of disintegrant and binder-reached by adding the concentrations at the lower and upper limit of each-under the original Claim 1 would have been from 3% to 15%, whereas the c-i-p disclosed that a single agent could be used in concentrations from 5% to 15%, a smaller range within the 3% to 15% range. Bristol's witnesses testified that their research found that concentrations higher than 3% had to be used when a single agent that was both binder and disintegrant was used, and that there was a danger that the binder and disintegrant terms would be found to be inoperative if a single agent was unable to function properly at the 3% level. However, from the testimony of both Bristol and Andrx's witnesses, it is clear that, when used separately, some binders and some disintegrants are more efficient than others, and thus the more efficient excipients will function at lower concentrations in a formulation than the less efficient excipients.FN17 Thus, the inclusion of a range of concentrations for the binder (1%-5%) and disintegrant (2%-10%) in the original application was partially necessary to account for the different efficiencies of various binders and disintegrants. Therefore, some of these less efficient excipients may not function at the lower end of the range for whichever function they are intended to fulfill. Yet, according to Bristol's theory, if carried a bit further, the binder range limitation would then be inoperative due to the fact that, for example, some non-preferred binders probably will not function at concentrations of as low as 1% but must be included at a higher percentage, as high as 5%, of tablet weight in order to impart their binding function. Clearly, the fact that all excipients will not function at all concentrations in a range limitation does not render that limitation inoperative, so the fact that a single agent which is both binder and disintegrant would be required in concentrations of more than 3%

would similarly not make the binder and disintegrant terms inoperative. Thus, it was not necessary to include that additional limitation in Claim 1 for the sole purpose of raising the lower range limitation to 5%. As a result, a person skilled in the art would have looked for another reason for the addition of the single agent in the c-i-p application, and would have concluded that the prior claim language meant that each of the excipients listed in the claim were to be different. That skilled person would then reasonably conclude that the claim language should be read as listing a filler that is a separate excipient from the binder, disintegrant, or single agent that is both.

FN17. For example, Dr. Klibanov testified that the different binders and disintegrants would exhibit different strengths and are not equally efficient. Dr. Jain similarly stated that a formulator could use a smaller amount of an efficient binder or an efficient disintegrant for functional effect.

Third, Bristol's suggestion that it needed to include the single agent limitation to raise the lower limit of the range suggests it should have been equally concerned about filing as new matter another single agent limitation for an excipient that provides all three functionalities in order to raise the upper range limit for a tri-functioning agent. The MCC in Andrx's formulation is included in ranges of about 30%, and is thus outside the 5% to 15% range for a single agent which is both binder and disintegrant. According to Bristol's own definition and expert trial testimony, the filler constitutes the bulk of most solid tablets. Nonetheless, no tri-functioning agent with higher range limitations was added; rather, Bristol argues that a skilled formulator would have been able to determine which percentage of a tri-functioning agent was performing the role of "single agent which is both binder and disintegrant" and which was acting as filler. If Bristol intended for an excipient to be able to perform all three functions, it should have added this as new material at this time in order to avoid the possibility that the patent would be found invalid for lack of enablement, as discussed further below.

2. *MCC as a Filler in* the '344 Patent

[13] Andrx also argues that MCC is "defined" as a filler in the '344 patent. Andrx notes that three of the dependent '344 patent claims, Claims 3, 12, and 18, contain the recitation "wherein said filler is a mixture of lactose and microcrystalline cellulose." Moreover, the '344 patent specification states in two places that "[t]he preferred filler is lactose or lactose and microcrystalline cellulose" and that the patented product includes a filler that is "preferably lactose or lactose combined with microcrystalline cellulose." Andrx further observes that MCC is described as a filler in the parent '683 application, noting that it mentions MCC ten times, but never as a single agent. While Bristol does not dispute these observations, it contends that MCC is never "defined" as a filler in Claim 1, in the patent specification, or in the prosecution history, but is merely listed as a preferred filler.

[14] [15] [16] [17] [18] The Court agrees with Bristol that the patent does not define MCC as a filler. The Court recognizes that not every conceivable and possible future embodiment of the invention must be disclosed in the patent specification. *See* SRI Int'l Inc. v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1121-22 (Fed.Cir.1985); Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1344 (Fed.Cir.2001). A court must not import limitations from the specification, including examples and preferred embodiments, or from the prosecution history, into the claims. Comark Communications, Inc. v. Harris Corp., 156 F.3d 1182, 1186-87 (Fed.Cir.1998) (stating that the Federal Circuit has repeatedly held that limitations from the specification are not to be read into the claims); Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1566 (Fed.Cir.1992) (reading a claim in light of the specification must not be confused with

reading into the claim a limitation that is in the specification but is not in the claim). The law recognizes that, because patent specifications are directed to those skilled in the relevant art, they require only a description of the inventor's known "best mode." *See* 35 U.S.C. s. 112; SRI v. Matsushita, 775 F.2d at 1121 (quoting Autogiro Co. of America v. U.S., 181 Ct.Cl. 55, 384 F.2d 391, 398 (1967)) ("Claim interpretation must not make use of 'best mode' terms."). Moreover, under the doctrine of claim differentiation, dependent claims are presumed to be narrower in scope than the independent claims on which they depend. AK Steel v. Sollac & Ugine, 344 F.3d 1234, 1242 (Fed.Cir.2003). Therefore, limitations stated in dependent claims cannot be read into independent claims. Wenger Mfg., Inc. v. Coating Mach. Sys. Inc., 239 F.3d 1225, 1234 (Fed.Cir.2001); SRI v. Matsushita, 775 F.2d at 1122 (it is error as a matter of law to read into a claim limitations from other claims). Each claim in a patent is presumed to be different in meaning and scope. Wenger, 239 F.3d at 1234. Because the absence of such a difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states that this presumption is significant. Comark, 156 F.3d at 1187; SRI v. Matsushita, 775 F.2d at 1122 (a limitation from a second claim not contained in a first claim cannot be read into the first claim for purposes of determining either validity or infringement-to do so would render the second claim superfluous). Because MCC is never identified as anything other than a "preferred filler" in the specification and is only defined as the filler in dependent claims not at issue in this case, it would be error for the Court to construe Claim 1 as "defining" MCC as the filler.

Andrx's argument that the patent defines MCC as a filler also relies on extrinsic expert testimony that an excipient's function in a patent is determined by its primary function. Although the parties have provided slightly different formulations for the disputed terms in the patent, the key difference is that Andrx states that binders and disintegrants are excipients whose *primary* function is to facilitate, respectively, cohesion of powdered materials or breakdown of a dosage form when placed in an aqueous solution, whereas Bristol would not qualify their definitions by referring to the excipient's *primary* function.FN18 The Court sees no justification for importing the qualifying term "primarily" into the ordinary meaning of the excipients defined in Claim 1 of the '344 patent. While it is conceded that the Bristol patent examples and specification do not assign a primary role of disintegrant or binder to MCC due to the presence of a strong binder and strong disintegrant in each dependent claim and example, the Court does not agree that a skilled formulator would necessarily discount the possibility that MCC in another formulation could have a different primary purpose or purposes. Therefore, the modification of the definition of the excipients with the term "primary function" is unnecessary where a listed or preferred excipient could play a different role in an alternative formulation. Thus, although Andrx refers to various extrinsic evidence suggesting that the inventors had experimented with MCC and considered it to be a filler, such extrinsic evidence cannot be used to overcome the clear language of the patent claim, specification, and prosecution history, none of which refer to MCC as anything other than a preferred filler.

FN18. Additionally, Bristol's definition of a binder expressly references that substance's role in creating granules, whereas Andrx argues that a binder can be a wet granulation, dry granulation, or direct compression binder, and does not reference the creation of granules.

Nonetheless, while the patent does not "define" MCC as a filler, the Court believes that the patent language and knowledge of a person of ordinary skill would have led such a person to the conclusion that MCC was acting only as a filler in the Andrx formulations. First, Dr. Fassihi testified that, in determining the function of a multi-functional excipient in a product, the skilled formulator would look at the total percentage by weight of that excipient in the product. Learned treatises support that products appearing in higher percentages are likely to be fillers, since fillers make up the bulk of most tablets. Moreover, the suggested

ranges for MCC when used for purposes other than filler are consistently lower: one treatise, the 1990 edition of *Modern Pharmaceutics,* suggests percentages of 0-8% if used to "improve adhesion of film coat to core" and 5-15% if used as a disintegrant, whereas the range when used as a binder/filler goes all the way from 5-95%. (PTX 8 at 363). FN19

FN19. The 2002 edition states MCC can be used in percentages of 0-8% to "improve adhesion of film coat to core," from. 2-.5% as a glidant, from 5-20% as an antiadherent, from 5-20% as a disintegrant, and from 5-95% as a binder/filler. (DTX CE at 294).

Further, the repeated references to MCC in the patent is something that a skilled formulator would take into account in determining whether Claim I precluded use of a single agent that functions as filler, binder, and disintegrant. It is undisputed that MCC is mentioned several times throughout that patent claims, the specification, and the prosecution history as a filler without ever being designated as a single agent that can act as a binder and disintegrant. Moreover, although the example of pregelatinized starch was given as an excipient that acts as a binder and disintegrant in one formulation, there are no examples and no claims that would indicate that any single agent, including pregelatinized starch, can act as binder, disintegrant, and filler. The 1990 *USP/NF* supports that pregelatinized starch and MCC are the only two excipients that were recognized at that time to have the ability to perform all three functions. However, nothing in the patent would have notified a person of ordinary skill that the MCC and pregelatinized starch could act at one time in all three capacities under the claims of this patent. As noted, the only "single agent" limitation is of a binder and disintegrant, and this limitation was added at the same time as the examples which use pregelatinized starch as such a single agent.

Nonetheless, Bristol contends that the addition as new matter in the c-i-p application that a single agent "such as pregelatinized starch" could be used should have clued a skilled pharmaceutical formulator to the fact that multi-functional excipients were available and might satisfy multiple claim limitations. Bristol argues that one skilled in the art would have known that pregelatinized starch has three functionalities, not just two, and that MCC is an excipient "such as pregelatinized starch" which also can exhibit those three functionalities. The Court finds that the teachings of this "new matter" is quite different. The Court believes that the facts that the multi-functional excipient pregelatinized starch was added to the specification and examples, that the patent claim was changed to add the single agent limitation without anywhere in the specification, examples, or prosecution history identifying the fact that pregelatinized starch can also serve as a filler in the formulation, and that no claim limitation for a single agent that is binder, disintegrant and filler was added to the patent claim would all lead a skilled formulator to reasonably conclude that the filler must be a separate excipient. Further, the fact that MCC is repeatedly referenced in the patent, yet was never identified even as a binder/filler, much less a single agent that is binder and disintegrant, would only further suggest to a skilled formulator that neither of the two products that the *USP/NF* lists as providing three functionalities can be used to satisfy both the filler and single agent limitation in this particular patent. This is particularly true since Andrx has submitted substantial extrinsic evidence in the form of learned treatises showing that a skilled pharmaceutical formulator in 1990 would have regarded MCC as a binder/filler which provides binding ability when tablets are compacted, but would not have regarded it as a wet granulation binder. Thus, the skilled formulator would have been unlikely to consider MCC to be serving three functions in the Andrx formulations which were produced through a wet granulation process.

3. *Range Limitation*

[19] [20] In its Paragraph IV notice letter to Bristol, Andrx clearly stated its argument which, at the end of the day, is the most persuasive argument that its product does not infringe:

Even if MCC were considered to have multiple functions for purposes of claim construction in the Listed Patent, the Andrx Proposed Products use at least 28% MCC. This amount greatly exceeds the maximum amount of disintegrant, binder, or single agent which functions as both a disintegrant and binder recited in the claims of the Listed Patent. Thus, MCC in the Andrx Proposed Products cannot be considered as an equivalent of any one of a disintegrant (2-10%), a binder (1-5%) or both a binder and a disintegrant (5-15%) as required by the claims of the Listed Patent.

Even if the Court rejected all of Andrx's other arguments, it would still find that there is no infringement in this case because, as a matter of claim interpretation, the Court finds insufficient basis for Bristol's argument that a skilled formulator would have not only known that a single excipient could have fulfilled more than one role in Claim 1 of the patent, but would also have known that such an excipient could and should be broken down by percentage to determine which portion contributes to which functionality. Rather, the Court agrees with the evidence presented by Andrx, including the testimony of Dr. Fassihi, that a skilled formulator would consider all 30% of the MCC to be contributing to any and all of the functions it is serving in the formulation, and percentage would still fall far outside of the range of from about 5% to about 15% of a single agent which is both binder and disintegrant. As discussed below, the artificial division of MCC into percentage components is not scientifically well grounded and would not be regarded as appropriate by one skilled in the art of pharmaceutical formulation. Moreover, such a division would require extensive experimentation in order to determine the percentage of excipient attributable to each function and would violate the patent concept that patent claims should be written such that a person of ordinary skill could replicate the claimed invention without undue experimentation.FN20

FN20. A patent can be found invalid for lack of enablement where "the written description fails to teach those in the art to make and use the invention as broadly as it is claimed without undue experimentation." In re Cortright, 165 F.3d 1353, 1356 (Fed.Cir.1999); *see also* Nat'l Recovery Techs, Inc. v. Magnetic Separation Sys., 166 F.3d 1190, 1196-97 (Fed.Cir.1999).

[21] [22] [23] Although the Court has determined that, under this construction of Claim 1, the patent is not invalid for indefiniteness due to double inclusion under 35 U.S.C. s. 112, the doctrine of double inclusion lends further support to the Court's construction. It is well settled that patent claims should be interpreted to preserve their validity. *See* Texas Instrs., Inc. v. United States Int'l Trade Comm'n, 846 F.2d 1369, 1372 (Fed.Cir.1988). Under the doctrine of double inclusion, a patent claim can be held invalid for indefiniteness if the inclusion of a single element to satisfy more than one claim limitation would not define the patent sufficiently clearly such that a person of ordinary skill in the art could determine the scope of the claimed invention. *See* In re Kelley, 49 C.C.P.A. 1359, 305 F.2d 909, 916 (Cust. & Pat.App.1962). Courts have held that a claimed invention cannot be automatically held indefinite due to double inclusion, but rather that double inclusion must be determined on a case-by-case basis. *Id.* (cautioning against automatic reliance on a rule against double inclusion but noting, instead, that the governing consideration is "what is a reasonable construction of the language of the claims"). However, based on patent prosecution cases, double inclusion is more likely to be found where the separate structures are not clearly identifiable. *See* Techler v. Norstrud, 475 F.2d 1192, 1195 (Cust. & Pat.App.1973); In re Kelley, 305 F.2d at 915 (noting that double inclusion of an element is objectionable when "separation of their functions ... require[s] an arbitrary structural division"); Kreidel v. Parker, 25 C.C.P.A. 1242, 97 F.2d 171, 173 (Cust. & Pat.App.1938) (holding a patent

invalid for double inclusion where "it is not possible to ... tell where the shoulder ends and the flaring mouth begins. It is thought that the count requires that the shoulder and mouth be distinct parts and not arbitrary divisions of a single element."). In this case, based on Bristol's theory, a skilled pharmaceutical formulator would have this very difficulty in determining what percentage of MCC to attribute to the single agent limitation and what percentage to assign to the filler limitation. A skilled formulator would be aware of the concept that a claim must be read to preserve its validity, and would be concerned that dividing one excipient into two components in the manner suggested by Bristol might make the patent invalid on double inclusion grounds. Thus, a skilled formulator would be unlikely to read the claim as allowing for a construction where one excipient could be broken into portions to satisfy more than one claim limitation.

D. ***No Infringement Based on Claim Interpretation***

Now that the Court has construed Claim 1, the second step of the *Markman* test is to determine whether the accused product infringes the patent under that construction of the claim. The Court finds that Andrx did not infringe Bristol's product when it submitted its ANDA to the FDA in late 2002. By Bristol's own theory, which concedes that MCC acts, in part, as a filler, Andrx cannot literally infringe the patent under the terms of the '344 patent Claim 1 as construed, because the product does not contain a filler and then one more, separate excipient that serves as a binder and disintegrant or two different excipients, one of which acts as a binder and the other as a disintegrant. Bristol submits that, nonetheless, even under this claim interpretation, Andrx still infringes Claim 1 under the doctrine of equivalents. The Court rejects this argument because, even under the doctrine of equivalents, each claim limitation must be met in the accused product in order for it to infringe. *See* Tronzo v. Biomet, Inc., 156 F.3d 1154, 1160 (Fed.Cir.1998) ("If a theory of equivalence would vitiate a claim limitation, there can be no infringement under the doctrine of equivalents as a matter of law."). Since the filler and single agent which is both binder and disintegrant would be the same excipient even under the doctrine of equivalents, the claim which, as construed, requires that these two limitations be satisfied by separate excipients would not be satisfied. Finally, the Court rejects Bristol's equivalence argument on its finding that MCC is not an equivalent to pregelatinized starch, as discussed below.

II. Scientific Evidence Regarding Infringement

Even if the Court had not construed Claim 1 as requiring that the excipient which serves as filler be in addition to the excipient or excipients which serve as binder and disintegrant, the Court would find that Andrx's fosinopril products do not infringe Bristol's '344 patent because the scientific evidence provided at trial supports Andrx's position that the "single agent" limitation of Claim 1 of the patent is not met in Andrx's formulation, or, at the very least, that Bristol has not met its burden of proving infringement by a preponderance of the evidence.

A. ***Factual Background***

[24] To provide context for consideration of the infringement questions, the parties provided testimony explaining the basic procedures for tablet manufacturing. There are three general methods for tablet manufacture: direct compression, dry granulation, and wet granulation. In the direct compression process, the ingredients are merely mixed together and pressed into tablets. In a typical dry granulation process, the active ingredient, filler, disintegrant, and binder are all blended together. The blend is then compacted by a densification process in which the binder assists in compaction of the powders into granules. The densified material is then put in a device called a "mill," which creates consistently sized granules, the lubricant is blended with the granulation, and the lubricated granulation is compressed into tablets. In a typical wet granulation process, the active ingredient, filler, disintegrant, wet granulation binder, and granulating solvent

are mixed together. The binder causes the intragranular materials to agglomerate into clumps of materials which are then dried. The dried materials are then milled. The presence of the wet granulation binder permits the creation of granules which improve the flow properties of the granulation.FN21 The balance of the filler and disintegrant is then blended extragranularly with the granules. Lastly, the lubricant is added to create the final blend, which is compressed into tablets.

FN21. Dr. Jain described flow as the ability of a powder to move through the opening of a funnel or a hopper. It is important that powders have good flow characteristics because they have to be able to flow through the hopper and then into the dies when making the tablets. Dr. Jain and Dr. Klibanov both testified that fosinopril is a fluffy, sticky material with poor flow, and, as a result, direct compression and dry granulation processes could not be used due to these properties. The difficulties in tableting fosinopril were also noted in the '344 patent.

Bristol manufactures its Monopril(R) and Monopril(R) HCT tablets using a wet granulation process, with alcohol as the solvent. Bristol's three dosages of Monopril(R) tablets consist of the various percentages of the active ingredient fosinopril, a filler which is a combination of lactose and MCC, the binder povidone, the disintegrant crospovidone, and the lubricant SSF. The two dosages of Monopril(R)-HCT tablets consist of the active ingredients fosinopril and the diuretic HCT, lactose as a filler, the binder povidone, the disintegrant croscarmellose sodium, and the lubricant SSF. Andrx also uses a wet granulation process for its fosinopril products, with water as the solvent. Andrx represented to the FDA in its ANDA that its fosinopril and fosinopril with HCT products would consist of the active ingredient fosinopril (plus HCT in the HCT product), lactose and MCC as a filler, colloidal silicon dioxide as the glidant, and SSF as the lubricant (with the addition of a coloring agent in the HCT product). Andrx did not identify any ingredient that would function as a binder or a disintegrant.

The five products described in Andrx's ANDAs are produced by first making a common wet granulate premix which is prepared by mixing lactose, fosinopril and MCC in a granulation machine. Water is sprayed onto the mixture during the granulation. Different amounts of these granules then are compressed with other ingredients to make the final tablets, depending on the fosinopril dosage strength of that particular tablet. Upon completion of the granulation, colloidal silicon dioxide is added as glidant, and the mixture is milled to form a milled granulation, which then is further blended to form the granulate premix. The granulate premix then is blended with additional lactose, additional MCC and additional colloidal silicon dioxide, and for the products containing HCT, the HCT and a pink colorant also are added at this stage. SSF then is added to form a final blend. The final blend then is compressed into tablets of different shapes and colors, depending on the strength and content of the formulation. Although Andrx has not begun mass production of these tablets due to this suit for infringement, Andrx has produced at least one batch, often referred to as the "pivotal" batch, of the formulations that they proposed to the FDA in their ANDAs.

The essence of the factual issues in this case relates to Bristol's claim that MCC can and does act as a binder and disintegrant in the Andrx formulation and that approximately 10% of that excipient acts as a binder and disintegrant, with the remaining 20% of MCC acting passively as a filler. In support of its position, Bristol points to several pieces of evidence that it believes supports that the MCC in the Andrx product functions as both a binder and disintegrant. Andrx's position is that MCC can be a dry granulation binder and compaction aid and can be a disintegrant when used in certain concentrations, but that it does not serve as either a binder or disintegrant in the Andrx formulation due to Andrx's use of a wet granulation process and due to the high concentrations of MCC used in their formulation. Andrx further argues that, even if MCC

were serving both functions, the total concentration of MCC is 30%, which is well outside the range of from "about 5% to about 15%," the range designated in the patent for the alternative single agent that is both binder and disintegrant. The parties agree that, if MCC does not provide either binder or disintegrant functionality or if the percentage of MCC that acts as a binder and disintegrant falls outside the range of "from about 5% to about 15%," then the Andrx product does not literally infringe. The Court will address each of these alternatives below.

B. ***MCC as a Binder***

As to whether MCC in the Andrx products functions as a binder, Bristol points to the stipulated fact that granules were formed during the manufacture of the common granulation of Andrx's pivotal batch. Bristol provided expert testimony from Dr. Klibanov that these were strong granules, as evidenced by the fact that Andrx used a Fitzmill, which is a high-energy, high impact mill, to granulate the common granulation. Bristol then argues that, because the evidence shows that Andrx creates good granules in its wet granulation process, its proposed formulations must contain an excipient that imparts wet binding functionality. Dr. Klibanov opined that the MCC in the Andrx formulation was acting as that wet granulation binder. Bristol also argues from the evidence presented that only the MCC could have been acting as a wet granulation binder in Andrx's formulation, as none of the other excipients that are added intragranularly, nor the active ingredient fosinopril, can impart these functionalities.

Andrx denies that any portion of the MCC acts as a wet granulation binder, providing evidence that, while MCC undeniably can act as a dry granulation binder or a compaction aid in a direct compression tablet production process, it does not impart binding functionality in a wet granulation process. Dr. Fassihi testified that a wet granulation binder is an agent having the primary function of forming a viscous solution that, upon its addition to a powder blend, causes particles to agglomerate. On the other hand, a bonding agent, sometimes referred to as filler/binder or compaction aid, is a material that has the capability of holding itself and other excipients together upon the application of force. According to Dr. Fassihi, because MCC is not water-soluble, it cannot form a viscous solution that causes particles to agglomerate in the Andrx granulation, since Andrx uses water as the granulating fluid. Andrx argues that Bristol has proffered absolutely no credible evidence to show that MCC acts as a wet granulation binder.FN22 Further, though Andrx concedes that granules were formed during the first stage of the wet granulation process, it denies that these granules were strong. Dr. Fassihi explained that one indicia of how hard granules are is the number of "fines," or fine powder particles, that result from the milling process. To determine the percentage of fines, the granulated product is passed through a number of sieves with different size openings in order to "size" the granules so that the appropriate sized granules are used in the final tablet formulation. The particles that pass through all the sieves are the fines. Dr. Klibanov testified that, with too many fines, the final blend of a formulation will likely suffer flow and compression problems. In the Andrx pivotal batch, about 31% of the product were identifiable as fines, which Dr. Fassihi testified is a large amount and a good indication that the granules were soft, stating that under normal conditions, a formulator would not want more than 10-15% of the granules to be fines.FN23 Dr. Fassihi further testified that the use of the Fitzmill in the granulation process does not, in itself, indicate that hard granules were formed, because the Fitzmill can produce milled granules of different sizes by changing the mesh size and the tolerances. Its use is, therefore, not limited to milling strong granules.

FN22. Andrx does not dispute that MCC is a filler/binder which provides mechanical binding functionality in direct compression and dry granulation processes. In fact, Andrx introduced evidence that MCC is well known in the industry as a filler/binder due to its high dilution potential, good binding index, good lubricity,

good brittle fracture index, good Young's modulus of elasticity, and yield stress value.

FN23. Dr. Fassihi stated that the approximately 30% of fines in the Andrx formulations could be used because fosinopril is a fluffy drug that sticks to everything and that the primary goal of the wet granulation process was to distribute that active ingredient into the powder so that these properties that made production difficult would be eliminated. Thus, the high percentage of fines was not an unwelcome result in the fosinopril product, since the goal of distributing the fosinopril into the powder was still accomplished.

The Court agrees with Andrx and finds that MCC is not a wet granulation binder. At the very least, Bristol has not carried its burden of proving by a preponderance of the evidence that MCC acts as a wet granulation binder in Andrx's formulations. The Court has reviewed the literature provided jointly and separately by the parties, and has considered the testimony of both experts. While recognizing that MCC can act as a binder in dry production processes due to its undeniable usefulness as a compaction aid, the Court concludes that it serves, at most, as an aid to the wet granulation process, but not as a true wet granulation binder. With limited exceptions, the scientific literature is consistent in referring to MCC as a dry granulation binder and compaction aid, but not as a wet granulation binder.FN24 MCC is a good compression binder because, according to *Remington's,* it is thought that the "individual crystallites are held together largely by hydrogen bonding." (JTX 49 at 1636). Nevertheless, some literature supports the proposition that MCC can serve a useful function in wet granulation, such as a filler, as an "auxiliary wet binder," or as a compaction aid in the post-granulation phase of the wet granulation production process.FN25 Although not admitted in evidence at trial, Bristol filed as Exhibit 6 to its opposition to Andrx's motion for summary judgment a product description of Avicel, the brand of MCC used in the Bristol and Andrx formulations, which was printed from the web site of FMC, the manufacturer of the product. That product information lists many uses for Avicel, including "wet granulation," but then describes it as "an *auxiliary* binder in wet granulation," further explaining its role in wet granulation processes as follows:

FN24. Excerpts from a number of treatises that would have been available in 1990 and that one or both experts testified are recognized as learned treatises in the field of pharmaceutical formulation were entered in evidence. The *USP/NF* from 1990 only identifies MCC as a "tablet binder," but does not specify that it acts as a wet granulation binder. (JTX 40 at 1858). In fact, in the section on "Tablets," the *USP/NF* merely mentions that "the most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression," without also indicating that MCC can act as a wet granulation binder. (PTX 77 at 1696-1697). Similarly, the *Merck Index* states only that MCC is a "binder-disintegrant," without identifying it as a wet granulation binder. (JTX 41 at 337; PTX at 1958). *Pharmaceutical Dosage Forms* reports that "[i]f a substance possesses the proper crystalline structure, it can be compressed directly into a tablet without further treatment," and then notes that MCC "has found wide application in the formulation of direct compaction products" due not only to its function as a diluent with good bonding properties, but also because its capillary properties can reduce disintegration times. (JTX 43 at 69, 79). Moreover, while that treatise does note that MCC "possesses the ability to function both as binder and disintegrant in some tablet formulations," it does not discuss MCC in the section on common granulation binders, nor is it listed in the table of "[b]inders commonly used in wet granulation," suggesting that MCC binds only as a compaction aid. (JTX 43 at 80, 83-85; PTX 39 at 162). *Modern Pharmaceutics* describes MCC as a binder/filler, not a wet binder, even though it does describe three other "multiple-use excipients," including povidone and starch, as "wet binders." (PTX 8 at 363). A 2002 edition of the same publication lists two multiple-use excipients as wet or dry binders and two others as wet binders, but only

lists MCC as a binder/filler. (DTX CE at 294). *Remington's* similarly supports that MCC is only a binder/filler, stating MCC is used as "a tablet diluent and disintegrant. It can be compressed into self binding tablets which disintegrate rapidly when placed in water." (JTX 42 at 1319). *Pharmaceutical Compaction Technology* describes MCC as one of the best rated and most used filler-binders in direct compression because of its "extremely good binding properties as a dry binder." (DTX CD at 429). In its table of suggested primary candidates as excipients for tablet and capsule formulations, *Pharmaceutics: The Science of Dosage Form Design* lists MCC as a diluent only, listing two other excipients, including modified starch, as both binders and disintegrants, two, including povidone, as just binders, and two as just disintegrants. (DTX CZ at 250). Dr. Klibanov admits that "compaction aids and fillers are almost interchangeable" and states that when a reference is made to a binder/filler, it could mean it is referring to a compaction aid. However, he argues that such references could also be meant to indicate that the filler can simultaneously be a binder, even a wet granulation binder.

FN25. *Remington's* states that MCC "usually is used as an excipient in direct compression formulations. However, its presence in 5% to 15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying process, in minimizing case-hardening of the tablets, and in reducing tablet mottling." (JTX 49 at 1635). *Pharmaceutical Dosage Forms and Drug Delivery Systems* describes MCC as a "pharmaceutic aid as tablet disintegrant, diluent, adsorbent, and suspending agent," without any mention of its functionality as a binder. While that source does later parenthetically suggest that MCC is one of several cellulose derivatives that can be used as a wet granulation binder, the description of how it actually functions-it "contributes to the adhesion of the granules to one another, maintaining the integrity of the tablet after compression"-suggests a binding mechanism more akin to a compaction aid in the post-granulation phase than to a wet granulation binder. (PTX 40 at 138, 170). Similarly, the *Handbook of Pharmaceutical Excipients* notes that MCC can be used in either a wet granulation or direct compression process, but its function in both is described as "tablet binder/diluent," indicating its usefulness as a compaction aid rather than a function as a wet granulation binder. (JTX 47 at 55). *Pharmaceutical Dosage Forms* merely states that MCC can act as an "auxiliary wet binder promoting hard granules with less [sic] fines," noting that MCC "added to a wet granulation improves bonding on compression and reduces capping and friability of the tablet. For drugs having a relatively small dose, microcrystalline cellulose used as a filler acts as an auxiliary binder, controls water-soluble dyes, and promotes rapid and uniform evaporation of liquid from the wet granulation." (PTX 39 at 153). Finally, *Pharmaceutical Compaction Technology* notes that, "[i]n addition to its use in direct compression formulations, microcrystalline cellulose is used as a diluent in tablets prepared by wet granulation ...." (DTX CD at 430).

Avicel PH-101 is the logical choice for intragranular incorporation as it ensures faster and more trouble-free processing. Avicel PH promotes rapid, even wetting; speeds drying; reduces screen blockage; minimizes case hardening; controls dye migration; and promotes disintegration. Post granulation addition of Avicel PH imparts all of the usual direct compression advantages.
From this quotation, it appears that even Avicel's own manufacturing description, while attributing to its product a significant role, and even an "auxiliary" binding role in the post-granulation phase of the wet granulation process, does not claim that MCC acts as a true wet granulation binder. FN26
FN26. Bristol has also filed an "FMC Problem Solver" distributed by Avicel's manufacturer. (PTX 53). While that publication notes that MCC "is the substance most often used in tableting as a filler, disintegrant, flow aid, and dry binder in directly compressed tablets" it also states that Avicel "acts as a binder" in wet granulations and states that "for APIs that are water soluble, nonhygroscopic, and difficult to agglomerate,

Avicel PH MCC functions as a wet binder." These cursory descriptions prepared on behalf of the Avicel manufacturer and which do not state the mechanism by which MCC functions as a binder in these circumstances is insufficient to overcome the literature and testimony which supports that MCC is not a wet granulation binder. Moreover, this description could be entirely consistent with the Avicel product description, which states that Avicel acts as a binder to the extent that its usual functionality as a compaction aid is available when MCC is added in the post-granulation phase of the wet granulation process.

Additionally, though Bristol and Dr. Klibanov argue that an excipient need not be soluble to act as a wet granulation binder because insoluble substances can still form a glue or paste rather than a solution in the presence of the granulation solvent or can operate through other chemical forces, such as non-covalent hydrogen bonds or Van der Waals binding forces, there is no dispute that MCC is not water soluble. Although inconclusive and not dispositive, several references in the literature support Dr. Fassihi's position that a wet granulation binder must be at least partially soluble to function in that capacity. While there is also support for Dr. Klibanov's opinion that not all wet binders must be water soluble, there are no references suggesting that MCC acts as a wet binder through the alternative mechanisms posited by Dr. Klibanov.

Thus, there is significant, credible evidence that MCC is not strictly a wet granulation binder, either in general or in Andrx's proposed tablet formulations. With respect to Andrx's actual formulation, Dr. Fassihi testified that, despite the fact that Bristol used a strong binder, povidone, in its patented formulations, no binder was actually required even in the Bristol product, and, therefore, Andrx was able to produce their tablets without a binder. Dr. Fassihi further testified that since Bristol elected to use a strong binder it needed to use a strong disintegrant, crospovidone, to facilitate disintegration and dissolution of the resulting strong granules and tablets. Dr. Fassihi concluded that, when Andrx simply eliminated the strong binder, its formulations could be produced without any wet granulation binder, and in the absence of the strong binder, there was correspondingly no need for a strong disintegrant as in Bristol's tablets.

Dr. Fassihi further opined that, although the Andrx products do not have any wet granulation binder, if anything functions as or similarly to a wet granulation binder in the Andrx product, it is the fosinopril and lactose in combination with water that act as a glue.FN27 In support of this position, Andrx cites to a learned treatise, *Remington's,* which states that:

FN27. Bristol insists that Andrx should be foreclosed from arguing that lactose is a binder or disintegrant in the Andrx tablets because Andrx stated in its Paragraph IV certification that lactose was not a binder or disintegrant. However, this appears to misapprehend Andrx's argument. Andrx still maintains that its product does not include a binder or a disintegrant, but that, to the extent this Court finds that a binder or disintegrant is present, lactose is the excipient that is most likely to serve that function. Even in that circumstance, Andrx is not necessarily trying to prove that lactose is a true binder and disintegrant, but is merely providing evidence and argument to support that Bristol has not carried its burden of proving that MCC is the only excipient that can provide those functionalities in this formulation by demonstrating that lactose or lactose when combined with fosinopril could be responsible for the binding and disintegration properties of the tablets. Therefore, the Court finds it inappropriate to foreclose Andrx from providing evidence suggesting that lactose could be serving those purposes.

Materials commonly used as binders include ... sugars [such] as ... lactose.... Other agents which may be considered binders under certain circumstances are ... water and alcohol.... Alcohol and water are not binders in the true sense of the word, but because of their solvent action on some ingredients such as lactose, starch, and celluloses, they change the powdered material to granules and the residual moisture enables the materials to adhere together when compressed. (JTX-49 at 1635-36).
Andrx notes that the model study conducted by UPM, which is discussed below in greater detail, suggests, if anything, that the lactose in the formulation provides the binding functionality, since the tablets produced for those tests merely substituted lactose for the equivalent percentage of the active ingredient fosinopril in the Andrx granules. This substitution resulted in particles that produced only 15% fines, half the amount of fines that were produced from the Andrx formulation, suggesting to Dr. Fassihi that additional lactose may have been imparting more binding functionality due to the increased concentrations in those tablets.FN28 Dr. Fassihi stated that the MCC is, nonetheless, necessary in this stage of the granulation process in order to form granules because the MCC, an insoluble substance, acts as the platform to which the "glue," formed by the addition of water to lactose and fosinopril, adheres.FN29 In light of this reasonable alternative mechanism posited by Andrx for the formulation of granules, it is even more clear that Bristol has failed to meet its burden of proving that MCC is a wet granulation binder in the Andrx formulations.
FN28. Dr. Klibanov conceded that lactose "may have some marginal binder function," but stated that MCC, as a moderate binder, has more binding ability.

FN29. If lactose were serving functions other than filler in the Andrx formulations, it is present in the formulations in concentrations of from 50-60%, and therefore does not fall within the ranges of the binder, disintegrant, or single agent limitations.

C. ***MCC as a Disintegrant***

There is no dispute that MCC can function as a disintegrant in some formulations when used in certain percentages. However, the parties disagree as to whether MCC imparts any disintegrant functionality in the Andrx formulations. MCC has a porous structure which allows it to attract water through its capillary, or "wicking," action, which facilitates the absorption of water into the tablet matrix, causing the tablet to expand and then break apart. By drawing fluids into the tablet, more surface area of the tablet is exposed to the water or other solvent, the solvent breaks the hydrogen bonds that have formed between the adjacent bundles of cellulose microcrystals, and the tablet begins to break up into smaller pieces, thus decreasing the time required for disintegration and dissolution of the tablet. (JTX 43 at 87).

While Andrx has conceded that MCC can act as a disintegrant when used as a certain percentage of tablet weight, it has provided evidence and expert testimony suggesting that, at the percentages of around 30% used in its proposed formulation, MCC has, if anything, the opposite effect on disintegration by increasing disintegration time. Bristol, however, submits that a portion of the MCC is a disintegrant in the Andrx formulation and points to three experimental tests which it claims proves this. First, Dr. Klibanov testified to a simple experiment that he did wherein he observed Andrx tablets placed in water and determined that the pills disintegrated, or broke apart, rather than simply eroding or dissolving. He testified that the fact that the tablets disintegrated, despite the majority of the materials being water soluble, demonstrates that the tablets must contain a disintegrant. Dr. Klibanov claims that MCC is the only ingredient that could cause disintegration. Second, he points to the UPM test to show that increasing the concentrations of MCC from 4% to 12% resulted in decreased disintegration time. Third, Dr. Klibanov claims that a simple experiment

conducted by Dr. Fassihi also supports that MCC acts as a disintegrant in the Andrx formulations.

Yet, although there is some evidence that MCC acts as a disintegrant in the Andrx formulations, the Court concludes that Bristol has failed to prove by a preponderance of the evidence that the MCC is a disintegrant there. The experimental evidence relied on by Bristol is not as clear as Bristol maintains, and there are limitations in the application of the lessons from those experiments to the Andrx tablets. In addition, Andrx has pointed to some additional evidence which suggests that MCC does not act as a disintegrant in its tablets. Moreover, even if MCC were acting as a disintegrant, as discussed further in the next section, the entire 30% of MCC would be acting in that capacity, and would thus still exceed the range limitations of the '344 patent for either a disintegrant or a single agent which is both binder and disintegrant.

The UPM study, the most significant evidence upon which Bristol relies regarding its contention that MCC acts as a disintegrant in the Andrx tablets, had some flaws or limitations that must be taken into account in determining how much weight to give its results. The UPM study purported to evaluate the disintegration time of tablets containing the ingredients of the 20 milligram formulation of the Andrx fosinopril product. However, the test batches did not contain the active ingredient fosinopril, but rather substituted lactose for the percentage that would have constituted the fosinopril in the Andrx tablets. Dr. Fassihi testified that the lack of fosinopril makes this experiment unreliable because the interaction between the fosinopril and the lactose was thus not taken into account by the experiment. FN30 The test tablets were formed in a wet granulation process, with 4% of the MCC added intragranularly in each test tablet and an additional portion of MCC of 0%, 4%, and 8% added extragranularly respectively to the three batches. Disintegration times were measured for six tablets of each formulation using the standard *USP/NF* disintegration apparatus and procedure. The average disintegration times at each concentration of MCC were 13.1 minutes for the tablet with 4% MCC, 11.2 minutes for the tablet containing 8% MCC, and 10.3 minutes for the tablet containing 12% MCC. Bristol asserts that this shows that, as the MCC concentration increases, total disintegration times decrease, thus supporting that MCC acts as a disintegrant.

FN30. This failure to include that active ingredient could be particularly harmful to Bristol's claims that these results reflect the behavior of the Andrx tablets if Dr. Fassihi is correct that the fosinopril contributes some binding function to the Andrx products when it is combined with lactose and water.

The experiment is of limited use because it only tested tablets in the limited range where MCC was present from 4% to 12% of total tablet weight, and thus does not reveal anything about how a tablet prepared in a similar manner would disintegrate if it contained about 30% MCC, the percentage of MCC present in the Andrx formulations. Moreover, the experiment did not control for compression force, which is one variable that Dr. Fassihi testified can affect disintegration times. As such, the actual reason for the differences in disintegration time could be influenced by the differences in some variable related to the different compression forces used, rather than to the variation in concentrations of MCC. Dr. Fassihi also noted that the tablets prepared in this experiment produced fewer fines than the Andrx production process did, suggesting that the granules in this experiment were harder than the Andrx granules and thus may not act the same way. In addition, Dr. Fassihi had independently tested actual Andrx tablets and recorded the disintegration time for the 20 milligram Andrx tablet at 60 seconds (JTX 73), whereas the UPM test tablets did not disintegrate for 10 to 14 minutes. Thus, for whatever reason, the disintegration time for the actual Andrx product is much shorter than the disintegration time for the UPM tablets, suggesting that the UPM test may not accurately reflect the behavior of the actual tablets.

Dr. Klibanov also claims that a second test conducted by Dr. Fassihi provides further proof that MCC acts as a disintegrant in the Andrx formulation. Dr. Fassihi's experiment tested tablets produced by direct compression which consisted only of lactose and MCC in varying percentages. Three tablets of each composition were disintegrated in accordance with the standard *USP/NF* disintegration technique and the disintegration times were measured by Dr. Fassihi. The results showed that the tablets of 100% lactose fully disintegratedin 20 seconds, the tablets of 10% MCC and 90% lactose disintegrated in 15 seconds, the tablets of 30% MCC and 70% lactose also disintegrated in 15 seconds, the ones that contained 50% of each disintegrated in 32 seconds, the tablets of 70% MCC and 30% lactose disintegrated in 105 seconds, and the tablets of 100% MCC never disintegrated. Bristol focuses just on the first three tablet formulations, claiming that the five second difference between disintegration times in the 0% and 10% and 30% MCC formulations shows that MCC was having a disintegration effect on these tablets.

This test is also insufficient to prove that MCC acts as a disintegrant in the Andrx pills. Dr. Fassihi testified that the difference between 15 and 20 seconds is statistically insignificant and should not be taken as proof that the 10% and 30% MCC tablets actually disintegrated faster than the 100% lactose tablet. Moreover, these tablets were not prepared in the same manner as the Andrx products, but rather contained only the two ingredients, lactose and MCC, which were pressed into tablets through direct compression rather than through wet granulation. Thus, unlike in the Andrx product, no granules were formed. Further, although Bristol claims the Court can ignore the tablets that contain 50% or higher MCC content because none of the Andrx tablets contain more than 30% MCC, the disintegration times at those levels clearly show that increasing the concentration of MCC can have the negative effect of increasing disintegration times, which is consistent with Andrx's position that MCC only acts as a disintegrant in lower concentrations of between approximately 5% to 15% of tablet weight.

In further support of its position, Andrx points to a compatibility study conducted by Bristol during the testing of its original tablet formulation, as reported in a memorandum dated September 29, 1986.FN31 In that report on the six-month stability testing, which tested the original Bristol products, Dr. Jain, one of the inventors, reported that "[i]ncreasing the level of Avicel [MCC] in the experimental range of 5-35% w[eight on]/w[eight] has a an intermediate negative effect on tablet dissolution and distintegration. In addition, the higher levels of Avicel have a strong positive effect on tablet hardness and friability, with optimum responses in the 20-30% range." (DTX C at 1). Dr. Fassihi opined that the finding of a positive effect on tablet hardness is significant because harder tablets tend to take longer to disintegrate, and the finding of a negative effect on dissolution and disintegration demonstrates that high concentrations of MCC, as used in the Andrx formula, actually have a negative effect on disintegration. Bristol points out, however, that the underlying data from which Dr. Jain's report was generated reflects only "an intermediate negative effect on tablet dissolution" and a "weak positive effect on disintegration time" (meaning that disintegration time increases with increased concentrations of MCC), and that the data does not describe this effect as statistically significant. (DTX D at 4). Moreover, while Andrx claims this data shows MCC to be an "anti-disintegrant," Bristol says these results cannot even be applied to the Andrx product because its tablets do not contain the strong binder and strong disintegrant that were included in the Bristol tablets being tested in that optimization study. Thus, Andrx's and Bristol's tablets cannot be expected to act in the same way. Regardless, Bristol argues this test shows, at best, only a statistically insignificant weak effect on disintegration even on the Bristol tablets. The Court agrees with Bristol that this test is of limited value due to the fact that the Bristol and Andrx tablets do not contain the same ingredients and Bristol's tablets, which do contain a strong binder and strong disintegrant, cannot be expected to act in exactly the same manner as the Andrx product. These results, therefore, fail to prove that MCC does not act as a disintegrant or has a negative disintegrant effect in Andrx's formulation.

FN31. These tests evaluate the interaction between the active drug and the excipients that are to be used in the formulation.

Nonetheless, the inventors' compatibility study does provide additional evidence that MCC may have an adverse effect on disintegration in concentrations of around 30%, making it more apparent that Bristol has not met its burden of proving that MCC acts as a disintegrant in the Andrx formulation. This is especially true given that there is some evidence in the literature to support the conclusion that, as the amount of MCC increases, the tablet hardness and friability will improve due to the bonding ability of MCC and that disintegration times will increase accordingly. For example, *Modern Pharmaceutics* notes that forms of MCC, including Avicel, "have been shown to be highly porous, with strong 'wicking' tendencies, and they therefore make good disintegrants," but states that, due to its strength as a dry binder, "[o]ne disadvantage with [MCC] is that dissolution performance may be adversely affected at higher compressional forces." (DTX CU at 373). *Pharmaceutical Dosage Forms* similarly notes that the capillarity of Avicel allows it to act as an effective disintegrant, but notes that "[t]he hardness of the compressed tablet affects the disintegration time by breaking down the structure of the intermolecular spaces and destroying the capillary properties." (JTX 46 at 79). Dr. Fassihi testified that MCC begins adversely affecting disintegration times as MCC concentration increases because, as more MCC is added, it becomes more compressed in the tablet and the pores become smaller, thus decreasing the extent to which the capillary action can draw water into the tablet. Dr. Fassihi analogized this process to compressing a sponge. He stated that if a sponge is completely compressed, all of the spaces and pores will be eliminated or substantially eliminated through that compaction and the mechanism by which water is drawn in to the sponge will be correspondingly diminished. Dr. Fassihi stated MCC acts in much the same way, and, therefore, as compression forces increase, the decrease in the size of the pores causes disintegration time to increase.FN32

FN32. In response, Dr. Klibanov responded that, even if the pores do become smaller with increased compression forces, the addition of more MCC in the tablets is the equivalent of adding another sponge. Thus, even though the pores may be more compressed, there would then be twice as many of them, and the sponge would still be able to effectively draw water into its interior. Dr. Klibanov suggests that this increase in number of pores would compensate for the decrease in size of the pores with respect to the sponges ability to draw water.

Andrx also submits, through Dr. Fassihi, that a disintegrant was not necessary in its tablet formulations because they contained no strong binder and also because of the high solubility of lactose and fosinopril, which makes dissolution a relatively rapid process.FN33 However, Dr. Fassihi opined that, if there were any agent acting as a disintegrant in the Andrx product, it would be the lactose, noting that *Modern Pharmaceutics* shows that the disintegration rating for lactose is three and the solubility rating is a four, whereas MCC is rated as a two for disintegration and zero for solubility. FN34 Based on all of this evidence, the Court is unable to conclude whether MCC does or does not act as a disintegrant in Andrx's product. Because the plaintiff bears the burden of proof in a patent case, the Court finds that Bristol has failed to carry its burden of proving, by a preponderance of the evidence, that MCC is a disintegrant in the Andrx products.

FN33. The Court notes the distinction between disintegration and dissolution. Disintegration is the tablets breaking into smaller pieces over time when placed in a solvent, whereas a tablet that simply dissolves will

merely erode in solution until it disappears. Dr. Klibanov contends that his observation of an actual Andrx tablet in water demonstrates that Andrx's tablets disintegrate, and he argues that Dr. Fassihi also recognizes that the tablets disintegrate since he refers to disintegration throughout the results of his tests measuring the disintegration time of the actual Andrx tablets and of the compressed tablets of MCC and lactose.

FN34. There is a dispute over whether this table measures just self-disintegration ability or an excipient's ability to act as a disintegrant in a tablet formulation. The Court finds it likely that Dr. Klibanov is correct in identifying these ratings as self-disintegration characteristics, since the literature does not regularly identify lactose as a tablet disintegrant. However, the solubility ratings and the high concentration of lactose in the Andrx formulations do suggest that a disintegrant may not be necessary in the Andrx tablets, especially since that formulation does not include a strong wet granulation binder.

D. ***MCC as 10% Binder/Disintegrant and 20% Filler***

Even if the Court had found that the MCC in the Andrx formulation were acting as a disintegrant and a binder in the Andrx formulation, the essential failing of Bristol's case is its contention that only about 10% to 12% of the MCC functions in those two capacities. Bristol's theory in this regard is necessary in order for it to satisfy the range limitation of from about 5% to about 15% of a single agent which is both binder and disintegrant. Bristol has three primary grounds for its proposition that the MCC can be so divided. First, it points out that Andrx adds MCC in both stages of the granulation process, adding from 2% to 8% in the first, or intragranular, stage, and then adding the remaining MCC extragranularly after the granules have been formed, dried, and milled. Dr. Klibanov correctly noted that the portion added in the intragranular phase is the only portion that could act as a wet granulation binder.

Second, Bristol claims that the portion of MCC that acts as a disintegrant cannot be more than about 10% of the total MCC based on the experimental evidence from the UPM study and Dr. Fassihi's experiment, arguing that only a portion of the intragranular MCC acts as a granular disintegrant and only a portion of the extragranular MCC acts as a tablet disintegrant. Dr. Klibanov testified that, based on a statistical evaluation of the experimental data, the tablets' disintegration times plateau at about the 10% MCC level, such that the addition of any more MCC will not change the disintegration time but will only be acting passively as a filler. Dr. Klibanov also testified that the experiment conducted by Dr. Fassihi supports that only 10% of the MCC is acting as a disintegrant in the Andrx formulation because there was no difference in disintegration time between the tablets containing 10% and the ones containing 30% MCC. Third, Bristol claims that the patent itself shows that only 20% MCC is filler, and that a skilled formulator would have known from the patent that, in the absence of a strong binder and disintegrant, amounts of MCC in excess of 20% must be performing a role other than filler.FN35

FN35. Bristol contends that, based on this and other evidence, a skilled formulator would have known that MCC could have been fulfilling the single agent limitation in a formulation that did not include a strong binder and disintegrant, and argues that Andrx should have conducted empirical titration tests to determine if MCC was acting as a disintegrant and binder in its formulation. It is conceded that Andrx did not conduct any such tests. Bristol thus argues that it is entitled to an adverse inference that, if Andrx had conducted such tests, those tests would have revealed that MCC acts as a binder and disintegrant in the Andrx tablets. For the reasons stated in this order, the Court finds that Andrx had reasonable grounds, both based on their claim interpretation argument and on scientific principle, including the fact that the MCC used in their

product fell far outside the range of "from about 5% to about 15%," to believe that the MCC was not acting as a binder and disintegrant within the limitations of Claim 1 of the '344 patent. Therefore, no adverse inference is warranted based on Andrx's failure to conduct any tests.

However, the Court is persuaded that Bristol's proposition of separating MCC into two components, one actively serving as the binder and disintegrant and a second passively serving solely as a filler, is not scientifically supported. FN36 As Dr. Fassihi explained, the MCC in the tablets is mixed and spread uniformly throughout the tablet such that it is not possible that only a portion could be functioning as a binder and disintegrant. As to its binding functionality, Bristol's theory for limiting the active portion of MCC requires separating out the portion of MCC that is added in the first stage of the wet granulation process as the only portion that acts as a binder. However, even if the Court had found that this portion acts as a wet granulation binder, Bristol has failed to adequately explain why the remaining portion of MCC that is added in the post-granulation phase would be inactive, rather than be an extragranular binder acting as a compaction aid. The literature and testimony of Dr. Fassihi makes clear that MCC is one of the better filler/binders available and that it can perform this function in the post-granulation phase of the wet granulation process.FN37 Moreover, Bristol has not shown that only a portion of the MCC would be acting as a binder/filler if used in such a manner. One treatise notes that MCC has been used as a dry binder in concentrations "as high as 65% to bind active ingredients with extremely poor compressibility characteristics." (DTX BW at 215).

FN36. As discussed above, the Court also found that a skilled pharmaceutical formulator would not have read the patent to allow for a single ingredient to be pared into two different portions, each of which contributes a different functionality to the formulation. Thus, even if it were scientifically warranted to assign percentages of product to each function, the Court would still reject this argument on claim construction grounds.

FN37. Dr. Klibanov agreed that the MCC in the extragranular portion of the Andrx tablet could function as a compaction aid. However, he argued that the binder being referred to in Claim 1 of the patent is a wet granulation binder, and therefore the extragranular portion of MCC would not qualify as a binder under the '344 patent even if it were aiding in compaction.

Likewise, as to its disintegrant functionality, Bristol's theory that 20% of the MCC acts passively while only about 10% actually acts as a disintegrant is not scientifically supported. Even if the addition of MCC beyond 10% would not further decrease disintegration times, the Court concludes that the entire 30% of MCC would nonetheless participate in its disintegrant functionality. Using Dr. Klibanov's analogy comparing adding additional MCC to compressing two sponges rather than just one (discussed in a footnote above), if one were to compress two sponges together, all of both sponges would act to draw water inside the combined, compressed sponge. As Dr. Klibanov noted, in his hypothetical combined sponge, there would be more pores, but they would be smaller than the pores of only one sponge that is compressed to the same size. Thus, it is theoretically possible that the one sponge and two sponge compactions would draw water at about the same rate, one because it has more pores and the other because it has larger pores. However, under Bristol's theory, in such a circumstance, only the first sponge would get credit for being "active" in drawing water, since the addition of the second sponge had no effect on absorption time. Nonetheless, it is clear that in the two sponge combination, both sponges, not just the first one, would be

involved in absorbing water. Similarly, even if Bristol were correct that the addition of MCC beyond 10% does not increase disintegration time, it is scientifically unsupported to suggest that any such additional MCC would not actively participate in the disintegration process.

Further, in addition to the limitations of the experimental evidence discussed above, Bristol's UPM test does not conclusively show that MCC in concentrations of more than about 10% to 12% does not further reduce disintegration times. The UPM study did not test any tablets with concentrations of more than 12%, which is about 18% less than the concentration of MCC in the Andrx formulation. Dr. Klibanov's conclusion that MCC in concentrations of more than 12% does not contribute further to disintegration ability is speculative and based only on a projection from three data points that are significantly lower than the concentration of MCC in the Andrx products. Dr. Klibanov suggests that there was no need to test all the way up to 30%, since the curve leveled off at about 10% to 12%, even though there is evidence that recommended concentrations of MCC when used as a disintegrant fall in the 5% to 15% range and that, at certain concentrations and compaction strengths above those levels, MCC can actually increase disintegration times. Thus, the UPM study does not show that MCC concentrations in excess of 10% do not contribute to disintegration, since such a conclusion would be based on unsupported speculation as to how tablets with more than 12% MCC would act. Nonetheless, Dr. Klibanov claims that, at the least, Dr. Fassihi's test shows that the disintegration ability of MCC does not change when increased from 10% to 30%, since tablets of both concentrations disintegrated in 15 seconds. However, this test is also of limited use since the method of production was direct compression rather than wet granulation, since the tablets contained only lactose and MCC, and since this experiment also tested only a limited number of concentrations of MCC and found no significant difference in disintegration times among the tablets containing 0%, 10%, and 30% concentrations of MCC. At any rate, even if this study did confirm Dr. Klibanov's conclusion that adding more than 10% MCC does not decrease disintegration time, it still does not show that the amounts in excess of 10% are passive. Thus, the Court is persuaded that, if MCC acts as a disintegrant, the entire 30% of MCC in the tablet performs such a function. Therefore, regardless of whether or not the MCC provides binder or disintegrant functionalities in the Andrx products, it does not literally infringe the Bristol '344 patent because the 30% MCC does not fall within the binder, disintegrant, or single agent range limitations.

Finally, the Court does not agree with Bristol's argument that the patent itself teaches that 20% is the optimal amount of MCC when that excipient is being used as a filler and that, therefore, any amount of MCC in excess of 20% must be serving an active role in a tablet formulation. Bristol points out that examples 8 through 15 of the patent all use 20% MCC, irrespective of the facts that some examples include two active ingredients, that some use strong binders and disintegrants and others use a single agent that is both, and that some are made by wet and others by dry granulation. In addition, Bristol notes that its commercial Monopril(R) products use 20% MCC in combination with lactose as the filler. Bristol then argues that these patent examples would teach that 20% MCC is the optimal filler concentration in any formulation, and, therefore, any amount that is above 20% must be serving another purpose. Bristol claims a skilled pharmaceutical formulator would then have expected that these extra percentages of MCC would be acting as a binder and disintegrant in any formulation that does not include a strong binder and disintegrant. Bristol also claims that the a person skilled in the art would have concluded that the amount of MCC in excess of 20%, which ranges from 8 to 12% in the five Andrx formulations, corresponds to the 8% pregelatinized starch which was used in Examples 10 and 11 in lieu of a strong binder and strong disintegrant.

The Court finds this argument unpersuasive and that the examples that use 20% MCC do not establish that percentage as the optimal amount of MCC in any formulation. To begin with, the literature on MCC shows

that one reason MCC is not generally used alone as a filler is cost. As *Remington's* notes, "Avicel is a relatively expensive diluent when compared with lactose USP or starch USP. Usually it is not used in tablets alone as the primary diluent unless the formulation has a specific need for the bonding properties of Avicel." (JTX 43 at 79).FN38 Another reason for using MCC is that, in direct compression formulations, "[s]pray-dried lactose has very good flow properties, but its compression characteristics require the addition of a binder such as MCC." (DTX CE at 295). Thus, MCC's superiority as a dry binder/filler in compaction processes makes it useful in mixtures with lower cost lactose to provide the compaction aid functionality that lactose lacks. However, the fact that 20% is used in the Bristol formulations and patent examples does not show that this is the "optimal" formulation; it could merely demonstrate that it is an amount that, when mixed with lactose, is sufficient for the combination to act as an efficient, cost effective filler. This would not discount the possibility that more MCC may be necessary in formulations with different ingredients or that more could be substituted for some of the lactose in these formulations if cost did not make it more efficient to use a higher percentage of lactose. Moreover, the fact that exactly 20% is used in every patent example and in Bristol's commercial product, regardless of what other excipients are used or what method of production is employed, does not suggest an "optimal" amount, but rather suggests that Bristol chose a nice, round number, and just added that amount of MCC to every formulation, making up for the balance of the filler by adding however much lactose was required to create the right tablet size. Further, the Court credits Dr. Fassihi's testimony that the percentage of usage of an excipient can be a clue to its function in the tablet, and that Andrx's use of MCC in concentrations of around 30% would suggest to a skilled formulator that its function in the Andrx tablets was solely as a filler. The Court thus disagrees that the evidence, and inferences from it, would lead a skilled formulator to conclude that any amount of MCC in excess of 20% would be functioning as a binder and disintegrant, rather than as filler.

FN38. Dr. Klibanov agreed that, while MCC is a "good filler," it is "[n]ot particularly cheap. In fact, it's somewhat expensive, especially compared to something like lactose."

F. ***Doctrine of Equivalents***

[25] Bristol argues that the Andrx products, even if they do not literally infringe the '344 patent, can still be found infringing under the doctrine of equivalents because Andrx merely substituted MCC for pregelatinized starch, which is identified in Claim 1 and Examples 10 and 11 of the '344 patent as a single agent which is both binder and disintegrant, thus using the teaching of the patent by making an insubstantial change to those examples.

[26] [27] The doctrine of equivalents was created to prevent pirating of the patentee's invention in situations where literal infringement does not exist. It prevents an accused infringer from avoiding liability for infringement by changing only minor or insubstantial details of a claimed invention, while retaining the invention's essential identity. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 234 F.3d 558, 564 (Fed.Cir.2000), *vacated on other grounds by* 535 U.S. 722, 122 S.Ct. 1831, 152 L.Ed.2d 944 (2002). It is used "to temper unsparing logic and prevent an infringer from stealing the benefit of the invention." *Id.* (internal citations omitted). To determine whether a change is so insubstantial that the accused product must be deemed to include the equivalent of a claim limitation, the court can apply either the "known interchangeability" test or the "function-way-result" test. Toro Co. v. White Consol. Indus., 266 F.3d 1367, 1370 (Fed.Cir.2001); Interactive Pictures Corp. v. Infinite Pictures, Inc., 274 F.3d 1371, 1383 (Fed.Cir.2001). The "known interchangeability" test looks to the knowledge of one skilled in the art at the time of infringement to see whether the artisan would consider the substitution as a reasonable alternative

design choice. Interactive Pictures, 274 F.3d at 1383; Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 609, 70 S.Ct. 854, 94 L.Ed. 1097 (Fed.Cir.1950) ("An important factor is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was."); Warner Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 37, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997) ("[T]he proper time for evaluating equivalency-and thus knowledge of interchangeability between elements-is at the time of infringement, not at the time the patent was issued."). The "function-way-result" test examines whether the element in the accused product performs substantially the same function in substantially the same way to achieve substantially the same result as the claimed product. Miles Labs., Inc. v. Shandon Inc., 997 F.2d 870, 876 (Fed.Cir.1993); Toro, 266 F.3d at 1370.

During production of its Monopril(R) HCT tablets, due to an adverse reaction between HCT and crospovidone, Bristol had experimented with other disintegrants in the HCT product, including using pregelatinized starch as both binder and disintegrant. Dr. Jain testified that he was confident that MCC also could have been used as a replacement for povidone and crospovidone in the fosinopril-HCT experimental formulations, but stated that Bristol chose to work with pregelatinized starch rather than MCC only because pregelatinized starch was considered more potent than MCC, and Bristol was interested in the more robust formulations that pregelatinized starch would be expected to yield. Patent Examples 10 and 11 use 8% pregelatinized starch as a single agent that is both binder and disintegrant, in addition to MCC as a filler in an amount of 20%. Bristol argues that Andrx used the teaching of these examples by merely substituting additional MCC in amounts of about 10% for the 8% pregelatinized starch.

However, the evidence presented demonstrates that pregelatinized starch and MCC do not act in the same manner and that a person of ordinary skill would not consider MCC and pregelatinized starch to be interchangeable. Pregelatinized starch is an excipient that is processed to have a pregelatinized portion that acts as a binder, while the remaining portion acts as a disintegrant. This method of operation is dissimilar from that of MCC. According to the *Handbook of Pharmaceutical Excipients,* pregelatinized starch "has been chemically or mechanically processed to rupture all or part of the granules in the presence of water and then subsequently dried." (PTX 49 at 293). Another treatise notes that, in operation, the free amylopectin in pregelatinized starch aids in binding, while the free amylose and unmodified starch are responsible for the disintegration function (PTX 93 at 443). Pregelatinized starch is listed in *Pharmaceutical Dosage Form's* table of "[b]inders commonly used in wet granulation" and is described as "starch that has been cooked and dried. It can be used in place of starch paste and offers the advantage of being soluble in warm water, without boiling. It can also be used as a binder by adding it dry to powder mix and wetting with water to granulate ...." (PTX 39 at 161). *Pharmaceutical Powder Compaction Technology* states that "[a]lthough pregelatinized starch is primarily a binder in wet granulation, it can be modified to make it compressible and flowable in character." (PTX 93 at 443).FN39 Thus, it is clear that most pregelatinized starch is used primarily for its wet granulation binding functionality, unlike MCC which even this publication describes only as a "filler/binder." (PTX 93 at 445).FN40 Because Bristol submits that the pregelatinized starch in the patent Examples 10 and 11 is a wet granulation binder and this Court has found that MCC is not a wet granulation binder in the Andrx product, MCC cannot be said to perform substantially the same function in substantially the same way to achieve substantially the same result as the claimed product. Further, Bristol did not present any experimental evidence showing that tablets made with only MCC rather than pregelatinized starch acted similarly with respect to binding characteristics or disintegration and dissolution times.

FN39. Starch 1500 is one such modified pregelatinized starch that can be both compressible and a wet granulation binder. Starch 1500 is noted to be "a versatile, multipurpose starch that is used as a dry binder, a

wet binder, and a disintegrant. It contains a 20% maximum cold water-soluble fraction which makes it useful for wet granulation." (PTX 39 at 161). When using Starch 1500 for two functions, "the water-soluble fraction acts as an efficient binder, while the remaining fraction aids in the disintegration of the tablet." (PTX 39 at 163).

FN40. Dr. Fassihi also testified that pregelatinized starch and MCC do not function in the same manner, but erroneously testified on the first day of his testimony that pregelatinized starch is a co-processed product made up of gelatin, a protein, and starch, a carbohydrate. On cross-examination, he admitted his mistake, but stated that he had correctly testified as to the differences in mechanism of action of pregelatinized starch and MCC. While Dr. Fassihi's mistake in identification of the chemical make-up of pregelatinized starch was not insubstantial, the Court does not agree that it is fatal to his testimony. As noted, the scientific literature fully supports that pregelatinized starch and MCC are different in the way they function and in their chemical and mechanical properties, such that one cannot be considered the equivalent of the other.

Moreover, because of the differences in product characteristics, the Court does not agree that a person of ordinary skill would have considered adding additional MCC to be a reasonable design alternative for the examples that included pregelatinized starch. First, based on the Court's claim construction, a skilled pharmaceutical formulator would have believed that the patent required a single agent excipient that was separate from the filler, and thus would have concluded that increasing the percentage of the very filler, MCC, used in Examples 10 and 11 would not qualify the additional MCC as a substitute for the separate single agent excipient. Further, the same skilled person would not consider the addition of more MCC to be a substitute for the same reason that the Court has rejected Bristol's theory throughout this opinion: a skilled formulator would neither try to nor be able to separate the total MCC in the Andrx product into percentage portions, some of which serves one function and some of which serves another. Instead, any substitution in this case would be 30% MCC for 20% MCC, not 10% MCC for 8% pregelatinized starch. Finally, MCC and pregelatinized starch, though they both are made up of the same glucose molecule, have different physical structures which allows MCC to crystalize, giving it much different mechanical and physical properties than pregelatinized starch. *Modern Pharmaceutics* and other treatises show that these differences in physical characteristics give the two compounds different characteristics with respect to properties that are important in determining use and function of excipients, including compactibility, flowability, solubility, disintegration, hydroscopcity, lubricity, and stability. (DTX CE at 295). A skilled formulator would thus not likely have deemed these products interchangeable. Accordingly, the Court finds that the Andrx products do not infringe under the doctrine of equivalents.

Conclusion

For all of the reasons stated above, the Court finds that, both based on the claim construction and on the scientific evidence, the Andrx fosinopril and fosinopril-HCT products represented in its ANDAs do not infringe Bristol's '344 patent.FN41 Simply, Bristol has not carried its burden of proving that the Andrx products contain a binder, a disintegrant, or a single agent that is both binder and disintegrant. As such, the Andrx products do not meet every limitation of the '344 patent. The Court will enter a final judgment denying liability for patent infringement this same day.

FN41. Bristol has alleged that Andrx willfully infringed its patent. Because the Court finds that Andrx has not infringed, the willful infringement argument need not be addressed.

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