United States District Court,
D. New Jersey.

ZENITH LABORATORIES, INC,
Plaintiff.
v.
BRISTOL-MYERS SQUIBB CO,
Defendant.

July 21, 1992.

William L. Mentlik, Arnold H. Krumholz, Lerner, David, Littenberg, Krumholz & Mentlik, Westfield, N.J., Mark C. Ellenberg, Peter D. Dodson, Cadwalader, Wickersham & Taft, Washington, D.C., for plaintiff.

Frederick B. Lacey, LeBoeuf, Lamb, Leiby & MacRae, Newark, N.J., S. Leslie Misrock, Pennie & Edmonds, New York City, David G. Keyko, Winthrop, Stimson, Putnam & Roberts, New York City, for defendant.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

WOLIN**, District Judge.**

Bristol-Myers Squibb Company ("Bristol"), a Delaware corporation, is the owner of United States Patent No. 4,504,657 ("the '657 patent"), issued on March 12, 1985. The '657 patent includes a single claim for a specific crystalline form of cefadroxil monohydrate (hereinafter "Bouzard monohydrate"). FN1 Cefadroxil is a cephalosporin antibiotic compound that has a number of medical uses. Bristol previously owned the now-expired United States Patent No. 3,489,752 which issued on January 13, 1970 and claimed all forms of cefadroxil.

This action was filed by Zenith Laboratories, Inc. ("Zenith"), a New Jersey corporation, against Bristol on August 5, 1991. Among other claims for relief, Zenith seeks a declaration that "cefadroxil DC", a hemihydrate form of cefadroxil for which Zenith has obtained Food and Drug Administration ("FDA") approval to market in finished dosage form as a generic equivalent to cefadroxil monohydrate, does not infringe the '657 patent.FN2 Although Bristol does not contend that cefadroxil DC infringes the '657 patent in its manufactured, pre-ingested state, it does contend that after ingestion, the drug "converts" to the Bouzard monohydrate inside the body, or " *in vivo*," and that such conversion renders cefadroxil DC an infringing compound under the doctrine of equivalents, or, alternatively, that sales of cefadroxil DC by Zenith would constitute inducement of infringement of the '657 patent.

In an Opinion dated February 21, 1992, the Court granted summary judgment in Zenith's favor on the issue of *in vivo* conversion, and found that Zenith was entitled to a declaration that cefadroxil DC does not infringe the '657 patent. An Order reflecting this ruling was filed on March 4, 1992. On motion for reconsideration in an Opinion and Order dated April 13, 1992, the Court vacated its March 4, 1992 Order,

motivated in substantial part by the uncommon manner and speed by which the record was created for the motion, and by how early in the proceedings the motion was brought. Recognizing the immediacy of the rights at stake, the Court set down the issue of infringement for trial on an accelerated basis following expedited discovery.

The issue of infringement was tried to the Court between May 26, 1992 and June 5, 1992, during which six days of evidence was received. The primary factual issue at trial was whether cefadroxil DC converted *in vivo* to the Bouzard monohydrate. Set forth below is a summary of the testimony at trial, and the Court's findings of fact and conclusions of law as required by Federal Rule of Civil Procedure 52(a). Based on these findings and conclusions, a judgment will be entered in Bristol's favor.

I. *THE EVIDENCE AT TRIAL*

The evidence at trial consisted for the most part of expert testimony presented by both parties. Both parties' experts conducted a number of experiments to investigate whether cefadroxil DC converts *in vivo* to the Bouzard monohydrate. These experts were presented an witnesses to explain their theories of conversion, experimental methodologies, test results, and conclusions based on those results. Additional experts were presented to provide foundations for assumptions made by some of the experts who conducted experimental studies, or to rebut the assumptions, methodologies, theories, or conclusions of other expert witnesses. The Court will summarize each party's case in the order presented at trial.

A. *Zenith's Direct Case*

C. David Smith

Zenith's first witness was C. David Smith, its vice president of quality assurance. Mr. Smith testified as to the status of Zenith's FDA application, and as to the formulation for Zenith's cefadroxil DC capsules. He testified that the capsules contain, in addition to the cefadroxil material, lactose, sodium starch glycolate and magnesium stearate. (Tr. 17) FN3 These nonactive ingredients, known as "excipients", are included in the capsules for different purposes. Lactose is used as a filler. Sodium starch glycolate swells greatly when exposed to water, and is included as a disintergrate to break apart the capsule. (Tr. 18) Magnesium stearate is a lubricant useful in machining the capsules. (Id.)

Edwin C. Rothotein-

Zenith next presented the testimony of Edwin C. Rothstein, president of Leberco Testing, Inc. ("Leberco"), an independent testing laboratory located in New Jersey. Leberco was retained by Zenith to perform dissolution and solubility tests on cefadroxil DC and the Bouzard monohydrate, both in their formulated and bulk forms.

1. *Dissolution Tests*

Rothstein testified that Leberco technicians conducted dissolution tests in which they recorded the rates at which 500 milligram capsules of cefadroxil DC and Bouzard monohydrate dissolved into simulated gastric juice. (Tr. 39) The tests were performed by placing 500 milligram capsules in a dissolution basket rotated at 100 revolutions per minute ("rpm") in 900 milligrams of simulated gastric juice without enzymes. (PX 21) FN4 The percentage of material dissolved into the dissolution media was measured and recorded at intervals of 3, 5, 7.5, 10 and 20 minutes. (Id.) Six runs were performed and averaged on each substance. From the

results of this experiment, Rothstein concluded that between three and five minutes, cefadroxil DC had a higher dissolution rate than the Bouzard monohydrate. (Tr. 40) He also concluded that cefadroxil DC had a higher total solubility than Bouzard monohydrate. (Id.) The same tests were run using 1000 milligram tablets. (Id.) Rothstein concluded that the results of this experiment were essentially the same as with the first test. (Tr. 40-41; PX 22)

Rothstein testified that Leberco performed an additional experiment designed to determine whether the dissolution rates observed were affected in any way by any difference between the Zenith gelatin capsule and the Bristol gelatin capsule. The experiment consisted of comparing the dissolution rate of 350 milligrams of cefadroxil DC in a Zenith capsule with the dissolution rate of 350 milligrams of cefadroxii DC in a Bristol capsule. (PX 23) From the measured results of this test, Rothstein concluded that the gelatin capsule shell had no effect on the dissolution rates of the two cefadroxil materials. (Tr. 41)

One further dissolution experiment was conducted by Leberco. A comparison was made of the dissolution of capsules of cefadroxil DC and Bouzard monohydrate in 30 milliliters of simulated gastric juice at 37 (deg.)C in a dissolution basket rotated at three rpm. (PX 24) Rothstein testified that the dissolution test could not be performed due to the small quantity of fluid used. (Tr.-42) Therefore, only visual observations could be made. (Id.) Rothstein testified that after three minutes, the Zenith capsule had released most of its contents, but that the Bristol capsule still contained most of its contents. (Id.)

2. ***Solubility and Bulk Density Tests***

Rothstein testified that Leberco technicians performed solubility tests on cefadroxil DC and Bolizard monohydrate. Solubility is a measure of the quantity of a given material that can be dissolved in a given solvent at a given temperature and pressure in a given volume. (Tr. 46) Rothstein testified that five grams of a material was placed in 100 milliliters of deionized water that was maintained at a specific temperature and intermittently agitated for ten hours. Undissolved materials were then filtered, and the clear filtrate was then spectrophotometrically analyzed to determine its cefadroxil content. (Id.) This was done for each cefadroxil material at three temperatures: 4 (deg.)C, room temperature (between 23 (deg.)C and 25 (deg.)C) and 50 (deg.)C. (Id.) From the test results obtained (see PX 25, 26), Rothstein concluded cefadroxil DC is "clearly more soluble" than the Bouzard monohydrate under the conditions utilized. (Tr. 43)

Leberco also measured the bulk densities of cefadroxil DC and Bouzard monohydrate. (PX 25) From the tests, Rothstein concluded that cefadroxil DC has a bulk density considerably lower than that of Bouzard monohydrate.

Dr. Martha Greenblatt

The testimony of Dr. Martha Greenblatt was offered into evidence on Zenith's direct case through deposition transcript. Greenblatt was deposed by Zenith *de bene esse* on May 21, 1992. The transcript was accepted into evidence without objection. On Zenith's rebuttal case, Greenblatt testified in court.

Greenblatt is a professor at Rutgers University in New Jersey who teaches solid state chemistry, and is an expert in xray crystallography. (Deposition Tr. 5) She was asked to perform an experiment that was intended to determine whether, at the time a capsule of cefadroxil DC bursts in simulated gastric acid, cefadroxil DC has already converted to Bouzard monohydrate. This was accomplished by Greenblatt placing a Zenith capsule in simulated gastric acid until the capsule breached, and at the moment that cefadroxil began to pour out of the capsule, she froze the material in liquid nitrogen. (Dep. 11) This experiment was repeated. She

then freeze-dried the frozen samples, and recorded the x-ray powder diffraction patterns of two samples. (Dep. 15-16; PX 31)

In the first experiment, Greenblatt placed a Zenith capsule in a dissolution basket that was then immersed in 100 milliliters of simulated gastric acid maintained at 37 (deg.)C and rotated at six rpm. At one minute, 54 seconds, Greenblatt observed that the capsule had burst, and removed the basket from the beaker and placed it into the liquid nitrogen within five seconds. A second experiment was performed in which Greenblatt observed a burst in the capsule at approximately two minutes. Both frozen-samples were placed in a freeze-drier overnight.

The next day, 20 hours after the samples were frozen (Tr. 894), x-ray diffraction patterns of the samples were recorded and designated Z1 and Z2. (PX 31) These patterns were compared to "standard" patterns made from samples of cefadroxil DC and Bristol's Bouzard monohydrate.FN5 According to Greenblatt, the patterns for Z1 and Z2 were "identical" to the standard cefadroxil DC pattern. (Dep. 17) From the comparison, Greenblatt concluded that the cefadroxil DC samples she placed in acid and freeze-dried had not undergone any structural change in their crystal form. (Dep. 22)

Dr. Ralph R. Pfeiffer

Dr. Pfeiffer is a consultant at Purdue School of Pharmacy in the solid state drug chemistry group. (Tr. 65) He also does consulting and teaches seminars on polymorph formation and solvate formation, most recently for the F.D.A. (Tr. 66) He has extensive experience, including 30 years at Eli Lilly company, in x-ray powder diffraction analysis, in the identification of polymorphs and solvates of drugs, and in other areas related to crystal formation and behavior. (Tr. 66) Pfeiffer was offered as an expert in x-ray powder diffraction analysis, crystal theory and the behavior of oral drug dosages in the human body.

Pfeiffer testified as to his comparison of x-ray diffraction patterns of cefadroxil DC and a prior art form of cefadroxil known as "Gottstein" cefadroxil. (Tr. 71-2) For the Gottstein pattern, Pfeiffer relied on the pattern attached to the declaration of Timothy Marr, which was filed with the United States Patent and Trademark Office in 1982. (Tr. 71; PX 33) Zenith also offered the declaration of David Whitehaad, which was also filed with the United States Patent and Trademark Office, in which Whitehead declared that the Gottstein material utilized by Marr had not changed in the eleven years since it was first prepared. (PX 37) Pfeiffer used one of Dr. Greenblatt's patterns as representative of cefadroxil DC. (Tr. 71) He concluded, after comparing the patterns, that cefadioxil DC and Gottstein cefadroxil "are of the same crystal structure." (Tr. 72) Based on this conclusion, Pfeiffer also concluded that the structure-dependent properties of both materials-including equilibrium solubility, melting point and density-would be the same. (Tr. 82-83) Pfeiffer further opined that if one material converted to the Bouzard monohydrate when exposed to an aqueous environment, so would the other. (Tr. 83)

Dr. Pfeiffer testified that in his opinion, it was unlikely that cefadroxil DC could convert *in vivo* to the Bouzard monohydrate. (Tr. 83-84) He believed that a number of conditions existed in the stomach that would preclude the dissolution and recrystallization processes that would be required for conversion. (Tr. 84) Specifically, he believed that cefadroxil DC would dissolve very quickly in the stomach and prevent the creation of a super-saturated environment needed for recrystallization. (Tr. 88-89) In addition, Pfeiffer believed that the mixing action of the stomach would tend to disperse any super-saturated region that might otherwise form. (Tr. 89)

Dr. Pfeiffer testified further as to the conditions that he believed were necessary for conversion to occur. In addition to the super-saturated solution, he testified that nucleation must occur. (Tr. 89) Conditions that could produce nucleation include evaporation, cooling of the solution, and inducement of mechanical stress. (Tr. 90) Recrystallization could also occur if nuclei were already present. (Tr. 90) Pfeiffer opined that none of these conditions are present in the stomach. (Tr. 91)

Pfeiffer testified as to the conclusions that he drew from the tests performed by Leberco, introduced through Dr. Rothstein. He concluded from the results of the equilibrium solubility tests performed by Leberco that cefadroxil DC did not convert to Bouzard monohydrate because at the end of ten hours in simulated gastric acid, different amounts of the two-material dissolved into identical volumes of the fluid. To Pfeiffer, this indicated that no conversion occurred because if it had, equal amounts of material would have dissolved. (Tr. 92) This is true even though, in their dissolved states, cefadroxil DC and Bouzard monohydrate are identical-they are simply the compound cefadroxil. (Tr. 92)

On one last topic, Pfeiffer opined that Dr. Greenblatt's experiments minimized the chance that changes would occur in cefadroxil DC after it had been removed from the dissolution medium. (Tr. 93) He further agreed with her conclusion that no conversion had occurred. (Tr. 93)

B. *Bristol's Case*

Dr. Howard Goldin

Bristol's first witness, Dr. Goldin, is a Boardcertified doctor of internal medicine and gastroenterology. (Tr. 246) He was offered as an expert on the conditions that exist inside the human stomach. Goldin was asked to provide a protocol for simulating stomach conditions, which could be used in *in vitro* experiments intended to determine whether cefadroxil DC converted *in vivo* to the Bouzard monohydrate. (Tr. 253) According to Goldin, ethical constraints precluded actual *in vivo* experiments from being conducted for this purpose. (Tr. 253)

The protocol provided by Goldin consisted of the use of 30 milliliters of actual gastric juice maintained at body temperature (370C) and gently agitated at three rpm., (Tr. 254, 264) Goldin also recommended that simulated gastric juice (a 0.1 solution of hydrochloric acid) could be used. (Tr. 255) The stirring rate was chosen as an approximation of the agitation that occurs in the stomach. Goldin testified that for the most part, the stomach is in a flaccid state, with only intermittent gentle waves that "barely agitate the contents of the stomach." (Tr. 265) For only approximately five out of every 90 to 120 minutes are there vigorous contractions in the stomach. (Tr. 265) An *in vitro* stirring rate of 100 rpm, in Dr. Goldin's opinion "far exceed[s] the physiologic spectrum of the human stomach." (Tr. 270)

Samples of actual gastric juice provided to Bristol for experimentation uses by Dr. Goldin were obtained from Goldin's patients during a routine suction of the contents in preparation for an endoscopic examination. (Tr. 265-66) The patients had all fasted prior to the examination. (Tr. 265) Most of the gastric acid obtained had a pH of between one and two. (Tr. 266) The average volume of acid suctioned from the patients was 30 milliliters. (Tr. 267) Essentially all of a stomach's contents are removed by the suctioning. (Tr. 267) The pH of gastric acid in a non-fasting patient is generally higher (less acidic) due to neutralization by the ingested solids or liquids. (Tr. 266)

Goldin opined that experiments utilizing his specified conditions would simulate *in vivo* conditions. (Tr. 270) He further opined that he did not believe that much of a difference would be observed if gastric acid

from non-fasting patients were used, even if it consisted of a greater volume of fluid. (Tr. 274-75) Goldin opined that a volume of gastric acid between 30 and 240 milliliters was within the physiologic range of the human stomach. (Tr. 278) He also opined that a stirring rate between three and ten rpm would also be within that range, but that 25 rpm would fall outside of the range. (Tr. 281-82)

Goldin ultimately concluded that he would expect conversion to occur *in vivo* if it occurred *in vitro* under the conditions that he specified. (Tr. 284-85)

Dr. Robert J. Levine

The testimony of Dr. Levine was offered into evidence by Bristol through deposition transcript. Levine was deposed by Bristol *de bene esse* on May 11, 1992. The transcript was accepted into evidence without objection as defendant's exhibit 20. (Tr. 317-18)

Levine is a professor of medicine at Yale University School of Medicine in Connecticut, specializing in medical ethics. (Dep. 5) His previous experience included serving as chief of the clinical pharmacology section at Yale University School of Medicine. (Dep. 11) He has reviewed more than 5,600 proposals to do medical research on human subjects. (Dep. 13) In Levine's opinion, no institutional review board would approve research on human subjects solely to defend a patent. (Dep. 1415) He further opined that he did not believe that an *in vivo* experiment could be designed to test whether cefadroxil DC converts to Bouzard monohydrate that would not be subject to the same criticisms to which the *in vitro* experiments have been subjected. (Dep. 15)

Dr. Gerond V. Lake-Bakaar

Dr. Lake-Bakaar is a physician who, like Dr. Goldin, specializes in internal medicine and gastroenterolocjy. (Tr. 31819) He teaches medicine at the State University of New York at Stony Brook. (Tr. 319) Bristol offered Lake-Bakaar as an expert in gastroenterology. (Tr. 320)

Lake-Bakaar testified that he conducts research in gastroenterology and has on a number of occasions designed *in vitro* studies that were intended to simulate *in vivo* conditions, (Tr. 320, 326), and that such tests are frequently relied on by gastroenterologists to predict *in vivo* results, (Tr. 327). In his opinion, the *in vitro* conditions employed by Dr. Harry Brittain, a witness for Bristol discussed infra, of 30 milliliters of 0.1 N HCl maintained at 37 (deg.)>>>C with gentle agitation, closely simulates conditions in the human stomach. (Tr. 332-33) In his experience, Dr. Lake-Bakaar, has encountered varying volumes of gastric acid in patients, ranging between 20 and 80 milliliters. (Tr. 333) He also opined that mixing rates between three rpm and 100 rpm covered a range that exceeded the range of agitation that he believes occurs in the human stomach. (Tr. 336) In his opinion, 10 rpm is the average rate of mixing in the human stomach, to the extent it can be quantified in those terms. (Tr. 336, 369-70) Lake-Bakaar further opined that little difference exists between the gastric juice of fasted and nonfasted patients. (Tr. 337)

Dr. Lake-Bakaar testified that, in his opinion, Dr. Brittain's failure to account for emptying and replenishment of stomach juices does not affect the validity of his simulations, because the emptying rate of the human stomach is sufficiently slow such that it would be minimal over the short time interval that elapsed before Brittain observed conversion in his experiments. (Tr. 334-35) Lake-Bakaar estimated that in five minutes, the human stomach replaces approximately five percent of its gastric acid. (Tr. 334) This rate remains constant without regard to whether additional fluid has been ingested. (Tr. 35859)

He further opined that Brittain's failure to take into account absorption of materials through the stomach wall did not affect the validity of his simulation, because, with the exception of extremely acidic compounds, such absorption is minimal. (Tr. 335) He also testified that he did not believe "sink" conditions existed in the human stomach. (Tr. 337) In his understanding, "sink" conditions exist when the concentration of a solvent is altered by, for example, emptying and replacement. (Tr. 337-38)

For his final conclusion, Lake-Bakaar opined that, if conversion actually occurs under the range of conditions observed by Dr. Brittain in his *in vitro* experiments, he believes that conversion would also occur *in vivo*. (Tr. 339-40)

Dr. Harry G. Brittain

Dr. Brittain has a doctorate in chemistry, has done extensive post-doctoral fellowship work, taught chemistry at several colleges, and has, since 1985, worked for Bristol or one its predecessor corporations. Brittain was offered as an expert in physical-chemistry, x-ray powder diffraction analysis and optical microscopy. (Tr. 384) As part of his job responsibilities at Bristol, Dr. Brittain examines, compares and analyzes x-ray powder diffraction patterns on a regular basis. (Tr. 630-31) Relying on the conditions specified by Drs. Goldin and Lake-Bakaar, Dr. Brittain-conducted numerous experiments that were designed to determine whether cefadroxil DC converts to Bouzurd monohydrate *in vivo* after ingestion. He designed all of his own experiments. (Tr. 495) The conditions and results of these experiments are summarized in tables received into evidence as defendant's exhibits 42a-d.

1. *Brittain's Theory of the Conversion Mechanism*

Dr. Brittain testified that he believes conversion occurs because cefadroxil DC, when wetted, partially dissolves and forms a saturated layer around the undissolved material, and then recrystallizes as the Bouzard monohydrate. (Tr. 510) He opined that when liquid enters a cefadroxil DC capsule, a microenvironment of saturation is created that allows partial dissolution of cefadroxil DC crystals that act as nuclei for the formation of Bouzard monohydrate-crystals. (Tr. 629, 806) He does not believe that the beaker in which he conducted his experiments had any effect on the conversion because he believes that conversion occurs inside of the capsule. (Tr. 510)

2. *Initial Experiments*

The first experiments undertaken by Brittain to investigate conversion are summarized in defendant's exhibit 17. By placing a range of weights of cefadroxil DC in a series of test tubes with one milliliter of water and observing in which tubes all of the drug dissolved, Brittain determined that the equilibrium solubility of cefadroxil DC was approximately between 10.1 and 16.3 milligrams per milliliter. (Tr. 390; DX 17) This was considered consistent by,Brittain with his understanding that cefadroxil DC has an equilibrium solubility of 12 milligrams per milliliter. (DX 17)

Brittain also observed that the fine cefadroxil DC powder that he placed in the test tubes turned granular in appearance after being in contact with the water for one minute. (Tr. 390; DX 17) Upon examination by optical microscope at 400 magnification, Brittain observed that the granular solids in the solution had a significantly different appearance from the unwetted cefadroxil DC. The initial cefadroxil DC consisted of small needle-shaped crystals, but the wetted cefadroxil consisted of much larger rhombic crystals. (Tr. 396-97; DX 17) The larger rhombic crystals are characteristic, in Brittain's opinion, of crystals of Bouzard monohydrate. (Tr. 400)

A significant difference was also observed between the birefringence of both samples. The wetted sample was significantly birefringent, but the unwetted sample was only slightly birefringent. (DX 17) The phenomenon of birefringence is the degree to which the indices of refraction in a given material scatters light passed through the material. By passing polarized light through a substance and then observing the substance through a second polarizer rotated 90, from the initial polarizer, the relative degree to which light is scattered as it passes through different substances can be observed as varying intensities of brightness. (Tr. 383) Birefringence can be a useful test for identifying crystals, or comparing whether two substances are the same crystal. (Tr. 383) If the same crystals are present, they will have the same birefringent characteristics. According to Brittain, the birefringence of cefadroxil DC is "extremely weak". (Tr. 401)

3. *Second Series of Experiments*

The next series of experiments performed by Dr. Brittain is summarized in defendant's exhibits 14 and 18, but is described in greater detail in Brittain's laboratory notebook, offered into evidence as defendant's exhibit 16. In that experiment, he initially photomicrographed dry cefadroxil DC to reconfirm its particle size and shape as small needles, and verified that it exhibited weak birefringence. (Tr. 405) He also ran an x-ray powder diffraction analysis of a sample of dry cefadroxil DC that he possessed, to obtain a diffraction pattern for use as a reference in his future experimentation-. (Tr. 40607) He also obtained an x-ray diffraction pattern for Bouzard monohydrate. (Tr. 410)

For this experiment, Brittain placed a dry 10 milligram sample of cefadroxil DC on a microscope slide, wetted it with water, and observed it under a microscope. (Tr. 411-12; DX 14) He observed that the cefadroxil material transformed from very small crystals to large block-like crystals. (Tr. 412) In a second experiment, Brittain placed 100 milligrams of cefadroxil DC on a slide, and wetted it with 0.1 N HClsolution. (Tr. 413) He observed the same phenomena as in the prior experiment, except that the crystal faces appeared better formed, and the birefringence was more distinctive. (Tr. 413) The transformation of the crystals occurred within 30 seconds of being wetted. (DX 14) The sample remained in the solution for five minutes before it was removed and subjected to x-ray diffraction analysis. When the x-ray powder diffraction pattern obtained from the wetted cefadroxil DC was compared to the reference patterns, Brittain observed that the pattern for the wetted cefadroxil was equivalent to the reference pattern for Bouzard monohydrate. (Tr. 415)

A third experiment in this series was performed to determine whether cefadroxil DC converted to Bouzard monohydrate within a capsule immersed in fluid. In two separate runs, handfilled capsules of cefadroxil DC were placed respectively in 250 milliliters of water and in 250 milliliters of 0.1 N HCl solution and allowed to sit for respectively four and ten minutes, and were then removed, sliced open, and examined under the microscope for crystal shape and size, and for birefringence. (Tr. 416-18, 423; DX 16) These visual tests confirmed that the material had converted to Bouzard monohydrate. (Id.) X-ray diffraction analysis further confirmed that conversion had occurred. (Tr. 418, 424, 425)

4. *Dissolution Experiments*

In a series of dissolution experiments, Dr. Brittain utilized the *in vivo* conditions specified by Dr. Goldin, in an attempt to determine with more certainty whether conversion would occur in the human stomach. Those conditions consisted of 30 milliliters of simulated gastric juice maintained at 37 (deg.)C and stirred at three rpm.

In the first experiment, approximately 300 milligrams of cefadroxil DC was placed in a clear capsule and lowered into a dissolution kettle that contained 30 milliliters of simulated gastric juice stirred at three rpm for a period of eight minutes. (Tr. 438) Optical microscopy was performed on the capsule, which revealed to Brittain, consistent with previous experiments, that the crystals had changed from small needles to large monohydrate crystals, and that the birefringence had also increased significantly. (Tr. 439) The same conditions were repeated and the same results were obtained. (Tr. 441-42) X-ray powder diffraction patterns were not run because the x-ray unit was not operating on that day. (Tr. 442)

Brittain later ran many other dissolution experiments, using varied condition of temperature, volume, dissolution medium, and stirring rate. Tests were performed on hand-filled capsules containing between 300 and 500 milligrams of cefadroxil DC, as well as on actual formulated Zenith cefadroxil DC 500 milligram capsules including excipients. Capsules were immersed in media maintained at 37 (deg.)C and at 25 (deg.)C. Dissolution media volumes were varied between 30 and 900 milliliters. Both simulated gastric juice and actual gastric acid provided by Dr. Goldin were used as dissolution media, with pHs ranging between 1 and 6.5. Stirring rates were varied between zero and 100 rpm. Brittain testified at length during trial as to the conditions of these experiments. His laboratory notebook provides a contemporaneous record of the details of these experiments. (DX 16) The results of these experiments are summarized in table form in defendant's exhibits 42a-42c. For all of these experiments, similar tests were performed to reach uniform results. Optical microscopy observation of crystal size and birefringence, together with x-ray powder diffraction analyses, uniformly indicated to Dr. Brittain that conversion of cefadroxil DC to Bouzard monohydrate occurred under all of the varied experiment conditions. Brittain concluded that the pH of the dissolution medium had little or no effect on whether conversion would occur. (Tr. 533) He also concluded that the volume of the dissolution medium and stirring rate had little or no effect on whether conversion would occur. (Tr. 540-41)

5. *Protonation Experiment*

One of the claims raised by Zenith on motion for summary judgment was that cefadroxil DC wetted with acid could not recrystallize once dissolved, because the cefadroxil would become protonated as it reacted with the acid. Protonation occurs when a compound binds with free hydrogen ions as the acid reacts with the compound. (Tr. 468) To test this assertion, Brittain ran fourier transform infrared reflectance ("FTIR") analyses of the material he believed was converted cefadroxil and of unwetted Bouzard material, to obtain FTIR spectra. (Tr. 46667) FTIR analysis is commonly used to determine whether a material has protonated. (Tr. 467) Brittain concluded from a comparison of the two spectra that the cefadroxil DC material had converted to the Bouzard monohydrate, and that it was not protonated. (Tr. 467)

6. *Light-Scattering Experiments*

Although he did not believe that removing cefadroxil from the dissolution medium had any effect on the conversion process, Dr. Brittain designed a light-scattering experiment with which he could investigate whether conversion could he observed without removing a sample from the dissolution medium. (Tr. 548)

The apparatus used to conduct the light-scattering experiments consisted of a laser light source that was passed through a square cuvette containing three milliliters of liquid. (Tr. 550-52) On an adjacent side of the cuvette was a photomultiplier tube that received the light passing through the cuvette at a right angle to the laser source, and converted it to an electrical current that varied in proportion to the intensity of the scattered light. (Tr. 552) The electrical current was then converted to a voltage output that also varied in proportion to the scattered light intensity, which was amplified and displayed on an output device. (Tr. 552)

To isolate the laser light passing through the cuvette, and to minimize the effect of changes in ambient light levels, the laser light source was pulsed at a chosen frequency. Through use of a lock-in amplifier, which amplified only the converted voltage signal with the same frequency as the pulsed laser source, the final displayed output, as recorded on a strip chart recorder, measured essentially just light that had originated from the laser light source. (Tr. 553) This apparatus was designed and built by Dr. Brittain.

To validate the system, Brittain mixed twenty milligrams of microcrystalline cellulose, a water insoluble substance, with water in a cuvette. (Tr. 554) The mixture was alternately stirred with a magnetic stirrer, then allowed to settle, while the laser source passed through the cuvette. (Tr. 554-55) The output recorded on the strip chart recorder showed changes in negative voltage that varied from a lesser negative voltage when the material was completely settled, to a maximum negative voltage when the stirring occurred. (Tr. 555) This indicated that the apparatus measured changes in the intensity of light scattered from the original laser source. (Tr. 555) When more particles are suspended in solution, more light is scattered.

Brittain then used the apparatus to determine whether changes in light could be detected as the cefadroxil DC was mixed in simulated gastric juice. To separate the possible effect on the test that dissolution, as opposed to conversion, would have on the light-scattering measurement, Brittain started with a filtered saturated solution of cefadroxil DC, because no further dissolution could occur if the saturated solution was held at a constant temperature. (Tr. 557) In the first series of runs, he added 25 milligrams of Bouzard monohydrate to the saturated solution, which was mixed vigorously while the scattered light intensity was measured by the light-scattering apparatus. (Tr. 558-59) Three strip chart traces were obtained in three separate runs, which revealed a fairly constant negative output. (Tr. 559) The materials in the cuvettes were examined by microscopy to verify that the Bouzard material was still present. (Tr. 561)

In the next series of runs of the experiment, Brittain replicated the conditions used in the first series, except that he used cefadroxil DC instead of Bouzard monohydrate. (Tr. 562) This experiment was also run and recorded three different times. (Tr. 563) The curves plotted in all three runs were essentially the same. (Tr. 568) They show a sharp arc-shaped decrease in negative voltage output through most of the first minute of the experiment, and then a gradual steady increase in negative voltage intensity through the remainder of the experiment. (DX 16, pages 148-49) Dr. Brittain believed that the initial decrease in intensity was due to dissolution of the cefadroxil DC crystals, which resulted in less scattering of the laser signal because fewer solid particles were present to scatter the light. (Tr. 565) He also believed that the later increase in the scattered light intensity was consistent with conversion, because it indicated that some physical change had occurred in the tube at the approximate time that he had observed conversion in his other experiments. (Tr. 566-67, 569)

Another experiment was conducted in which Brittain used the same conditions of solution and stirring as used in the light-scattering experiment, but instead of measuring light intensity with the light scattering apparatus, he took a series of nine photomicrographs of material extracted out of the cuvette at different time intervals during a four minute period. (DX 16, pages 150-53) Birefringence was also examined. (Tr. 573) Brittain observed very small Bouzard crystals in the first photograph taken at 14 seconds. (Tr. 573) In each successive photograph, he observed larger and more crystals up until approximately two minutes, after which the appearance did not change significantly. (Tr. 575) From this, he concluded that evaporation did not play any role in conversion, because if the material converted only due to evaporation on the slide, each photograph would look the same. (Tr. 575) Brittain related these results to the light-scattering measurements by observing that the Bouzard crystals only began to aggregate at approximately one minute, the time at

which the light scattering intensity began to increase. (Tr. 576) He opined that the aggregation of crystals at one minute was consistent with the change in light-scattering intensity that was observed beginning at that time interval. (Tr. 576)

Brittain conducted another series of light-scattering experiments in which he re-ran the first two series of experiments-except that instead of using a saturated cefadroxil solution as the dissolution medium, he used only simulated gastric juice, in which he placed a greater quantity of cefadroxil material. (Tr. 577) This was done so that he could determine whether conversion occurred in an unsaturated solution. (Tr. 579-80)

When Brittain recorded the light scattering intensities of the Bouzard material, he plotted a different tracing from that obtained in the first series of experiments. Instead of a constant light-scattering intensity, he recorded a pattern that began as a maximum negative voltage and gradually decreased to a constant intensity value. (Tr. 580) Brittain opined that the initial maximum scattered light intensity was consistent with the fact that none of the cefadroxil had yet dissolved, and that the gradual decrease in intensity represented the dissolution of the Bouzard monohydrate until it reached an equilibrium, at which point the light scattering intensity remained constant. (Tr. 580; DX 16, pages 155-56)

In the next experiment, Brittain plotted scattered light intensities over time for light passed through simulated gastric juice in which he placed cefadroxil DC. The scattered light intensity curves he obtained in these experiments were more complex than in the other light scattering experiments. The initial intensity was not as great as the initial intensity of the Bouzard material suspended in the gastric juice. Brittain believed that this was consistent with the fact that cefadroxil DC crystals-are smaller than Bouzard crystals, and hence would not refract as much light. (Tr. 581) Over the first minute, the scattered light intensity decreased, consistent with dissolution of the cefadroxil DC crystals into the gastric juice. (Tr. 581) At approximately one minute and eighteen seconds, however, the scattered light intensity increased steadily, surpassing the initial intensity, until the four and one-half minute mark, at which point the intensity remained relatively constant, decreasing only slightly. (Tr. 581) Brittain concluded from the fact that the final intensity was greater than the initial intensity that a definite change had occurred in the physical characteristics of the cefadroxil DC. (Tr. 581-82) This was consistent with his observations in other experiments that conversion to Bruzard had occurred. (Tr. 582) Brittain conducted microscopy experiments similar to those run in connection with the first set of light-scattering experiments, in which he reproduced the conditions of the light scattering experiment-this time cefadroxil DC in simulated gastric juice-and took a series of microphotographs to record visual and birefringence changes in the crystals over time. (Tr. 587-88) Brittain observed that as early as 12 seconds into the experiment, Bouzard crystals were evident. (Tr. 588) From the strength of the birefringence of the crystals, and from the depth of the crystals, Brittain opined that evaporation could not have been the cause of the formation of the crystals. (Tr. 589)

7. *Sealed System Experiments*

A further set of experiments was performed in an attempt to minimize the effects that evaporation could have on cefadroxil solution observed microscopically. Brittain observed cefadroxil DC in simulated gastric juice placed in the well of a thick microscope slide over which he had placed a slide cover that was sealed with nail polish. (Tr. 593) This experiment was a standard laboratory technique for creating a sealed system that can be observed by microscope. (Tr. 593) Photomicrographs were taken at approximately two, four, six and eight minutes. (Tr. 594; DX 37) In each successive photograph, distinctive large triangular crystals believed by Brittain to be Bouzard crystals can be seen in greater quantity. (DX 37; Tr. 595)

Brittain conducted a second type of sealed system experiment, in which he filled test tubes that could be sealed by screwing on a threaded cap with cefadroxil DC in approximately 23 milliliters of water or simulated gastric juice. (Tr. 600-02) The goal of this experiment was to determine whether cefadroxil DC converted in a larger quantity of fluid in a sealed environment. (Tr. 601) Samples were maintained in a bath at 370C and allowed to equilibrate for one half hour. -(Tr. 601-02) Samples were then examined by microscopy and x-ray powder diffraction. Again, Brittain concluded that Bouzard crystals had formed. (Tr. 603, 605) These results were believed consistent with the sealed slide tests, and caused Brittain to conclude that evaporation played no role in the conversion of cefadroxil DC to Bouzard monohydrate. (Tr. 605)

8. *Freeze-Drying Experiments*

Brittain simulated the freeze-drying experiments of Dr. Greenblatt, with minor variations. He placed a Zenith cefadroxil DC capsule in 30 milliliters of simulated gastric juice maintained at 370C and stirred at 10 rpm. (Tr. 606-07) At approximately two and three,quarters minutes, instead of Dr. Greenblatt's one and three quarters minutes, Brittain removed the capsule from the dissolution apparatus and, within five to ten seconds, as opposed to Dr. Greenblatt's approximately five seconds, plunged the sample into liquid nitrogen. (Tr. 607) Dr. Brittain opined that the five second difference had no scientific significance. (Tr. 618)

After five minutes in the nitrogen, Brittain removed the sample and place it in a freeze-drying ("lyophilization") apparatus that he had constructed himself. (Tr. 608) The following day, he removed the contents and conducted microscopy and x-ray powder diffraction analyses of the sample. (Tr. 613) From these tests, Brittain concluded that the samples he observed contained Bouzard monohydrate. (Tr. 613)

Brittain conducted another experiment in which he replicated the dissolution and sample removal aspects of Dr. Greenblatt's experiment, removing the sample at one and three quarters minutes. (Tr. 619) He then sliced the capsule and performed microscopy and x-ray powder diffraction analyses of the contents. Brittain first observed that the contents of the capsule did not appear sufficiently wetted, in his opinion, for conversion to occur. (Tr. 620) The results of his microscopy examination was that although some Bouzard crystals were present, the bulk of the sample was cefadroxil DC with weak birefringence. (Tr. 612) Likewise, the x-ray powder diffraction analysis yielded a pattern that signified to Brittain a mix of cefadroxil DC and Bouzard crystals. (Tr. 621-22) Brittain concluded that if a sample of cefadroxil DC is not sufficiently wetted, no conversion will occur. (Tr. 622-23)

9. *Gottstein comparison*

To rebut Dr. Pfeiffer's testimony, Dr. Brittain made an independent comparison of the Gottstein and Zenith cefadroxil DC x-ray powder diffraction patterns. (Tr. 642) He concluded that the two patterns were on the border between being considered by him "similar" or "equivalent". (Tr. 642) From this, he did not believe that he could conclude that Gottstein would convert to Bouzard monohydrate. (Tr. 644-45)

Brittain recorded an x-ray diffraction pattern of a compound represented to him by Bristol to be Gottstein cefadroxil. When he compared the pattern obtained from the Bristol sample to the Marr pattehn relied on by Dr. Pfeiffer, Brittain found that 21 of 24 peaks matched, and concluded that the patterns were equivalent. (Tr. 819-20) He then wetted 200 milligrams of the substance he believed was Gottstein cefadroxil and, after eight minutes, recorded another x-ray powder diffraction pattern. (Tr. 821) Brittain concluded from the second x-ray pattern that the Gottstein material had not changed, and that no-Bouzard monohydrate could be detected. (Tr. 822) After another fifteen minutes had elapsed, which would have allowed evaporation to have occurred, he ran another powder pattern, which again remained unchanged. (Tr. 822-23) Yet another

x-ray powder pattern was made after one hour had elapsed, with similar results. (Tr. 823) From this Brittain concluded that Gottstel.n cefadroxi.1 does not convert to Bouzard monohydrate when wetted. (Tr. 824)

C. *Zenith's Rebuttal Case*

Dr. Martha Greenblatt

Greenblatt was presented as a live witness on Zenith's rebuttal case. She testified that at the time of her initial experiments and deposition, she had not considered whether leaving the capsules in the simulated gastric acid for a longer period of time would have had any impact on the results of her tests. (Tr. 846) Since it was brought to her attention, Greenblatt had formed the opinion that leaving the capsules immersed for a longer period of time would not have changed her results, because the capsules had already opened and she believed that the capsules, contents had already been wetted. (Tr. 847) To verify this opinion, Greenblatt instructed a graduate student to conduct a further experiment in which he replicated her earlier experiments except that he increased the length of time in which the capsule remained in the gastric fluid before they were removed, from approximately two minutes to almost three minutes. (Tr. 864-65; PX 46) Greenblatt concluded that the results of this experiment were no different than the results of her earlier experiments-no conversion could be detected from the x-ray powder patterns. (Tr. 865)

Dr. Anthony P. Simonelli

Dr. Simonelli, the last witness to testify at trial, is a professor emeritus at the University of Connecticut. (Tr. 929) Dr. Simonelli performed no experiments of his own that were introduced at trial, but only gave his expert opinions based on the experiments of others. He was offered as an expert in biopharmaceutics, which is the study of how formulations of drugs interact with a biological environment/system (otherwise known as a body, be it human or other animal), and how changes in drug formulations affect their absorption by the biological system. (Tr. 929-30) Simonelli was also offered as an expert in the identification and analysis of polymorphic and solvate transformation in solid state and heterogeneous systems, and in the fields of nucleation and crystal growth, and x-ray diffraction analysis and optical microscopy. (Tr. 931-33, 935)

Simonelli testified at length about the nucleation process that must precede any recrystallization of dissolved cefadroxil DC. He differed substantially with the theories of Dr. Brittain. Simonelli opined that Dr. Brittain's experiments did not prove that conversion occurred in the dissolution beaker. (Tr. 958) He instead believed that the recrystallization occurred on the microscope slide after a sample was removed from the beaker, because the conditions for nucleation and crystal growth are "fantastically higher on the slide than they are in the beaker," due to the greater saturation on the slide, (Tr. 959), and the cooling effect of evaporation, which aids precipitation of solids from a solution, (Tr. 980-81). Simonelli testified that Brittain's slide observations would not be representative of *in vivo* conditions, because evaporation and cooling, factors present on the slide that he believed greatly enhance crystal growth, are not present in the human stomach. (Tr 981) He also believed that the stirring motion present in the stomach would diminish the possibility of nucleation and crystal growth. (Tr. 981) Simonelli further opined that other factors present in the stomach but not on a slide that might inhibit nucleation and crystal growth include the dissolved gelatin capsule, (Tr. 982-83), excipients, (Tr. 984), and the presence of macromolecules such as proteins and enzymes, (Tr. 1008, 1018).

Simonelli believed that Brittain's sealed system experiments are not conclusive because they at most eliminate only one factor as a possible explanation for the conversion: evaporation. (Tr. 986) He was at a loss to explain the difference in results between Dr. Brittain's and Dr. Greenblatt's second freeze-drying test

results. He postulated that the difference in time it took Brittain to remove the sample from the dissolution beaker and plunge it in the liquid nitrogen-at most five seconds-may account for the difference. (Tr. 987-88)

Simonelli opined that Brittain's light-scattering experiments also did not establish that conversion occurred in solution as opposed to on the slide, but were merely inconclusive. (Tr. 993, 995) He further opined that "sink" conditions present in the stomach would ale? inhibit nucleation and crystal growth. (Tr. 1012) According to Simonelli, sink conditions exist when the concentration of a compound is negligible in the bulk of a dissolution medium and is high near the surface of the compound being dissolved. (Tr. 1013-15) He believed that Dr. Lake-Bakaar was wrong in concluding that the rapidity of the conversion would counteract the sink effect, because he believes that the speed of the conversion does not affect the action of the sink conditions in preventing a localized supersaturation zone. (Tr. 1015-17) Simonelli conceded that the speed of the reaction is not unimportant, but, all else being equal, the presence of sink versus non-sink conditions would impact on the likelihood of nucleation and crystal growth. (Tr. 1017)

In general, Simonelli concluded that Brittain's experiments did not sufficiently simulate *in vivo* conditions to be indicative of nucleation and crystal growth in the human stomach. (Tr. 1008-09) He did not disagree with the conditions in the human stomach specified by Drs. Goldin and Lake-Bakaar, but disagreed that the beaker experiments of Dr. Brittain adequately accounted for other factors present in the stomach that would adversely affect the likelihood of conversion. (Tr. 1018-19)

II. *FINDINGS OF FACT*

The central fact issue that the Court must determine is whether the cefadroxil DC in,Zenith's formulated capsules converts to Bouzard monohydrate *in vivo*. This one issue was the focus of much scientific theorizing am experimentation, and has resulted in a trial record that contains a number of theories and an abundance of data. A subsidiary issue that Zenith asserts circumscribes the breadth of the claim in the '657 patent is whether "Gottstein" cefadroxil is in fact cefadroxil DC, and whether Gottstein cefadroxil converts *in vivo* to the Bouzard monohydrate. This issue accounted for a minor portion of the evidence presented at trial.

A. *In Vivo Conversion*

Zenith's position on the conversion of cefadroxil DC into Bouzard monohydrate rests on the results it obtained from several experiments, and on expert opinion testimony that attempted to refute the results obtained by Bristol from its experiments. Zenith had three sets of experiments conducted to support its position that conversion does not occur.

First, Dr. Rothstein supervised an experiment to measure and compare the dissolution rates of cefadroxil DC and Bouzard monohydrate. Second, Dr. Rothstein supervised an experiment to measure and compare the equilibrium solubility and bulk density of those two compounds. Both the dissolution rates and equilibrium solubilities, as well as initial bulk densities, were found by Rothstein to be different for both compounds. In reliance on this data, Zenith expert Dr. Pfeiffer opined that conversion did not occur. His theory was that if cefadroxil DC first converted to Bouzard monohydrate before dissolving, the equilibrium solubility for the two materials would be identical, because in essence the same material would be dissolving into the dissolution medium.

The third set of experiments offered into evidence by Zenith were the freeze-drying experiments of Dr. Greenblatt. Greenblatt conducted two sets of experiments, differing only in the time at which the dissolving

capsule was removed from the dissolution vat and frozen in liquid nitrogen. The first set of experiments, with the shorter dissolution period, was offered into evidence on Zenith's direct case through deposition transcript with exhibits. The second set of experiments was offered into evidence on Zenith's rebuttal case through Greenblatt's live testimony and exhibits. The results obtained by Greenblatt were the same for both experiments: no conversion occurred.

Bristol's position with respect to Zenith's experiments is that they were scientifically inaccurate and otherwise flawed. Bristol's position on the conversion of cefadroxil DC into Bouzard monohydrate rests on the results it obtained from a number of experiments conducted by Dr. Brittain, and on expert opinion testimony that laid a foundation for some of the assumptions made by Brittain in attempting to simulate *in vivo* conditions. Drs. Levine and Goldin were offered as experts to support Bristol's position that actual *in vivo* experiments could not be conducted due to medical ethics constraints, and that no satisfactory *in vivo* experiment could be designed to test the conversion hypothesis that would be any more probative of the issue then are the *in vitro* experiments of Dr. Brittain. Drs. Goldin and Lake-Bakaar were offered as experts in gastroenterology to lay the foundation for the conditions utilized by Dr. Brittain to simulate conditions inside the human stomach.

The bulk of Bristol's evidence consists of the numerous experiments conducted by Dr. Brittain to verify that cefadroxil DC converts to Bouzard monohydrate. Brittain designed and conducted a variety of experiments to test different aspects of the conversion issue, all of which confirmed in his opinion that conversion would in fact occur *in vivo*. Zenith's position with respect to Bristol's experiments is that they at best prove that conversion occurs on a microscope slide under conditions different from those present in the human stomach. Zenith's experts opined that Bristol did not even prove that conversion occurs in a dissolution beaker, much less *in vivo*.

The Court finds that Bristol presented by far the more compelling case on the issue of conversion.

1. ***Use of in Vitro Experiments***

The opinions of Drs. Levine and Goldin that, given the nature of the experiments which would be required, *in vivo* experimentation could not be justified under medical ethics constraints merely to prove patent infringement, stands unrefuted by Zenith. Both doctors were adequately qualified to give this opinion and were credible witnesses. Therefore, the Court finds that Bristol's use of *in vitro* experiments to establish *in vivo* events is in principle a valid methodology. Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir.1985); Nelson v. Bowler, 626 F.2d 853, 856 (C.C.P.A.1980).

2. ***Validity of Brittain's Simulated In Vivo Conditions***

The conditions prescribed by Drs. Goldin and LakeBakaar to simulate conditions in the human stomach, i.e., 30 milliliters of simulated or actual gastric juice maintained at 37 (deg.)C and stirred at three to ten rpm, were also unrefuted by Zenith. Further substantially unrefuted was Dr. Lake-Bakaar's opinion that the emptying rate of the stomach and the secretion rate of additional gastric juice are sufficiently slow in comparison to the rate at which Brittain believed conversion occurred such that failure to account for those factors would not constitute a flaw in Brittain's experiments. Both doctors were adequately qualified to give these opinions and were credible witnesses. Therefore, to the extent Bristol established the occurrence of conversion under these conditions that was not attributable to some other condition present in the *in vitro* experiment that is not present *in vivo,* it has proved that *in vivo* conversion also would occur.

3. *Brittain's Experiments*

Dr. Brittain spent far more time on the witness stand during this trial than did any other witness. over the course of nearly three full days of testimony, the Court had the opportunity to observe and listen to Brittain at great length. The Court's impression of Dr. Brittain is that he is a talented research chemist, who possessed a significant ability to thoroughly understand a problem and, through his broad knowledge of laboratory instrumentation, design multiple experiments to test many aspects of that problem. He was also, for the most part, a very credible witness.

Dr. Brittain's explanation of the *reason* that conversion occurs, and the *process* by which it occurs, however, seemed to be somewhat beyond the scope of his expertise. On this point, Zenith's Dr. Simonelli seemed more knowledgeable. In fact, though, the Court does not believe that any witness presented in this case has anything more than a superficial understanding of the "mechanism" or "pathway" by which conversion occurs. At issue in this case, however, is not "why" conversion occurs, but only "whether" it occurs. Thus, although Dr. Brittain's explanation of the conversion process seemed beyond the ken of his expertise and was somewhat lacking in credibility, the Court finds that Brittain has established by a preponderance of evidence, well within his range of expertise, that cefadroxil DC in fact converts *in vivo* to Bouzard monohydrate.

The strength of Brittain's experiments and results is their totality. Piece by piece, Brittain built an impressive collection of data. The results of each series of experiments strengthen the results of each other set of experimental results. The total effect of the experiments is to prove with sufficient certainty the fact of conversion *in vivo*.

In support of its motion for summary judgment, Zenith submitted expert affidavits that concluded that the protonation of cefadroxil DC molecules dissolved in gastric acid would prevent recrystallization of dissolved cefadroxil DC. At trial, Bristol introduced testimony and test results by Brittain to refute this claim. Those experiments tested for protonation, and the results indicated that protonation did not occur. Zenith offered no evidence at trial to refute this evidence. Accordingly, the Court finds that protonation plays no role in inhibiting conversion.

The largest number of experiments conducted by Brittain were the dissolution experiments in which he placed both bulk powder or formulated capsules in varied amounts of water or simulated or actual gastric juice and later tested the samples for conversion. The dissolution medium volume and stirring rate conditions employed encompassed and exceeded the wide range of possible conditions *in vivo*. Through the use of three tests-visual observation, birefringence comparison and x-ray diffraction pattern comparison-Brittain concluded uniformly that under any of the conditions used, he detected conversion.

Brittain first established indisputably through photomicrography that cefadroxil DC crystals are much smaller than Bouzard monohydrate crystals, and are much different in shape. He also established that cefadroxil DC crystals exhibit a much weaker birefringence than do crystals of Bouzard monohydrate, which are highly birefringent. Thus, through microscopy, Brittain could determine with a high degree of certainty whether a sample of wetted cefadroxil DC had changed its crystalline form, and could conclude to a lesser extent that the form to which it had changed was Bouzard monohydrate. Although changes in the physical properties of shape, size and birefringence of the cefadroxil DC crystals could be conclusively determined through microscopy, Brittain could not determine by observation alone that the larger, more birefringent crystals were necessarily Bouzard. To determine conversion to Bouzard with great certainty,

Brittain ran x-ray powder diffraction patterns, a technique that in essence takes the "fingerprint" of a crystalline compound. Through x-ray diffraction analysis, Brittain determined with much greater confidence that all of the conversions suspected after optical examination had in fact been to Bouzard monohydrate.

Zenith contends that Brittain failed to establish that any of the x-ray diffraction patterns, including his Bouzard monohydrate reference pattern, conform to the x-ray diffraction pattern that forms the claim of the '657 patent. The Court disagrees. -With respect to the reference pattern, Bristol has put into evidence numerical tables representing both the patent pattern and Brittain's reference pattern. (DX 1; DX 16 at 19) According to Zenith's own expert,.pr. Pfeiffer, differences of 0.2 or less are insignificant in comparing x-ray diffraction patterns. (Tr. 233) According to Dr. Brittain, whose expertise on x-ray powder diffraction pattern analysis the Court accepts, patterns with at least a 954 match of peaks are "identical" compounds. (Tr. 633) Using Dr. Pfoiffer's margin of error, a simple comparison of the tables reveals that 21 out of 22 peaks in the patent pattern are matched by peaks in Brittain's reference pattern. Although Pfeiffer would find a "match" even with a variation of up to 0.2, most of the matches have differences of less than 0.05. In fact, only one match even approaches, but does not exceed 0.1. Thus, there are 21 clear matches out of 22 peaks in the patent pattern. The ratio of 21/22 exceeds the 95% peak matches Brittain would require to conclude that two compounds are identical. The Court thus concludes that Zenith's claim that Brittain's reference pattern is not of the same compound claimed in the '657 patent is without any merit.

The Court further finds credible Brittain's conclusions that the patterns obtained from wetted cefadroxil samples recovered from his experiments are equivalent to the reference pattern for Bouzard monohydrate. Dr. Brittain's expertise with the analysis and comparison of x-ray diffraction patterns was amply demonstrated, and the Court accordingly adopts Brittain's conclusions. Zenith's assertion that the comparisons are inconclusive because Brittain concluded only that the patterns were "equivalent" and not "identical" is rejected by the Court. Although under Brittain's rating system "identical" is the higher rating, the Court accepts Brittain's opinion that a finding of "equivalence" is sufficient to support his conclusion that conversion had occurred. The standard of proof in this case is not the "beyond a reasonable doubt" standard.

The Court finds that Brittain's laboratory procedures for the dissolution experiments were consistent, well-documented and highly credible. Zenith has not with any force directly refuted the results of Brittain's microscopy and x-ray diffraction tests. Zenith's criticisms of Brittain's results are based on contentions that the conversion occurred not in the dissolution beaker, but on the microscope slide, under conditions greatly differing from actual *in vivo* conditions. Alternatively, Zenith contends that even if conversion does occur in the beaker, the beaker conditions are significantly different from *in vivo* conditions. The Court finds these contentions also without merit.

A major basis for Zenith's contention that conversion occurs on a slide and not in a beaker or the stomach is that on the slide, a much more saturated solution exists, which Dr. Simonelli opined was much more conducive to nucleation and crystal growth. The Court finds that Bristol demonstrated with a high degree of certainty that conversion occurs *inside* of an ingested capsule, and that the environment inside of a capsule penetrated by gastric liquid would be of a similar or greater saturation level to that existing.on a slide. Thus, the Court finds that Zenith's distinction between beaker and slide conversion is meaningless to the extent it is based on differences in saturation levels. To the extent that the beaker/slide argument is premised on conditions present on a slide that are not also present inside of a capsule ingested *in vivo,* it has been adequately been overcome by Bristol's affirmative proofs.

Zenith, through Drs. Simonelli and Pfeiffer, posited that several material differences exist between the conditions present on a slide and those present *in vivo,* which impact greatly on the question of *in vivo* conversion. First, both Pfeiffer and Simonelli identified evaporation and cooling as two factors present on a slide but not in the stomach. They opined that evaporation is conducive of cooling, which is conducive of precipitation of crystals out of solution. As will be discussed below, Brittain conducted experiments that refuted the significance of either of these factors.

Simonelli and Pfeiffer further opined that the stirring action and replenishment of fluids in the stomach would adversely affect the occurrence of nucleation and crystal growth. Dr. Simonelli assumed that conversion occurs *after* the cefadroxil DC leaves the capsule, because the "dynamic situation" he discussed was based on the movement of the capsule contents as they poured out of the capsule. (Tr. 981) Dr. Pfeiffer's opinion was similarly flawed. Because the Court finds that conversion occurs inside of an ingested capsule, it finds that stomach agitation as an inhibitor of conversion is of minimal significance, and opinions relying on it are not entitled to much, if any, weight. Further, the Court finds that Simonelli's suggestion that the replenishment of fluids in the stomach is similarly without credibility. Dr. Lake-Bakaar's testimony as to the extremely slow rate of stomach emptying and replenishment was highly credible and stands unrefuted. The Court therefore finds Simonelli's opinion as to this factor to be lacking in credibility.

Other factors identified by Simonelli as existing in the stomach but not on a slide include the presence of gelatin, excipients and macromolecules such as food particles, proteins and enzymes. The Court finds this testimony to be worthy of no weight.

First, on cross-examination, Simonelli conceded that macromolecules such as food particles or proteins could enhance nucleation and crystal growth, as well as inhibit them. (Tr. 1026-27) Second, excipients were present on the slide as well as *in vivo* in those dissolution experiments conducted by Brittain that used Zenith capsules. Dr. Simonelli's attempted explanation of why excipients would have a lesser impact on a slide than they would in a capsule, (Tr. 984), seemed contrived and lacked credibility. Third, macromolecules of the variety identified by Simonelli were present on the slide in those dissolution experiments conducted by Brittain that used actual gastric juice. Last, Simonelli's testimony that dissolved gelatin may inhibit nucleation and crystal growth, though probably true in the abstract, does little to refute the results of Brittain's experiments. According to Simonelli, Brittain's experiments failed to account for the presence of gelatin because his samples were taken from the inside of the capsule. (Tr. 983) Because the Court finds that conversion occurs inside the capsule, it finds Simonelli's criticism to lack merit.

Yet another factor Simonelli identified as present in the stomach but not on a slide was "sink" conditions. Simonelli's opinion, however, was premised on conversion occurring outside of the capsule, in a low concentration solution. Because the Court finds that conversion occurs inside of the capsule, this factor is of little consequence. Moreover, Brittain demonstrated that conversion occurs even under conditions that Simonelli agreed would constitute sink conditions. (Tr. 1022-23) Although Dr. Simonelli impressed the Court as a scientist of distinction with vast experience, his opinion testimony in this case was not supported by any experimental data, was in good measure highly speculative in nature, and did not cast significant doubt on Bristol's experimental evidence of conversion.

One of several series of experiments conducted by Brittain to verify the occurrence of conversion in the dissolution beaker instead of on a slide, free from the effect of evaporation and cooling, was Brittain's series of lightscattering experiments. Those experiments cast great doubt on Zenith's contention that conversion occurs only as a result of the greater saturation levels, cooling and evaporation present on a slide.

Although Zenith contends that the light-scattering experiments do not prove beaker conversion because the saturation levels in the cuvettes used in those experiments were closer to slide saturation conditions than to beaker saturation conditions, this argument is not supported by the record. The lightscattering experiments used 25 milligrams of cefadroxil DC placed in a cuvette holding three milliliters of simulated gastric juice. This represents a ratio of solvate to solvent only one half that of the ratio of solvate to solvent that existed in Brittain's dissolution experiments that used 500 milligrams of cefadroxil DC in capsule form placed in 30 milliliters of simulated gastric juice. If, as Zenith contends, conversion does not occur inside the capsule because its contents leave too rapidly, then the resulting solution would be adequately proxied by the cuvette in the light-scattering experiments. Accordingly, to the extent that the light-scattering experiments prove conversion inside the cuvette, they also prove beaker conversion.

The scattered light traces recorded by Brittain are also highly corroborative of Brittain's opinion that conversion occurs free from the effects of evaporation and temperature cooling. Through several runs of the light-scattering experiment, Brittain established that undissolved Bouzard monohydrate crystals floating in a dissolution medium maintained at a constant temperature scatter more light than do undissolved cefadroxil DC crystals. This is consistent with the greater size and birefringence of Bouzard monohydrate crystals.

The Court finds that the trace at page 157 of Britain's laboratory notebook (DX 16) establishes that conversion occurred in the cuvette, as opposed to on the slide. There, the undissolved cefadroxil DC initially placed in simulated gastric juice reflected a certain intensity of light, before it diminished and then, at approximately one minute, gradually increased in intensity, reaching a level in excess of the initial level of scattered light. This trace proves without question that some physical change occurred inside the cuvette. Dr. Brittain opined that this curve is consistent with an initial dissolution phase in which the scattered light intensity declined as the cefadroxil DC dissolved, and then increased as conversion occurred and Bouzard crystals precipitated out of solution, resulting in a scattered light intensity exceeding the initial intensity reflected by cefadroxil DC crystals. The Court finds this explanation highly credible and corroborative of Brittain's other experiments.

Further corroborative of the occurrence of conversion before a sample was placed on a slide, and perhaps more revealing, are the series of photomicrographs recorded by Dr. Brittain over time under the conditions used in the light scattering experiments. Over time, Dr. Brittain observed greater numbers in larger sizes of Bouzard-shaped crystals. The appearance of these crystals in the photographs is identical to crystals observed in other experiments in which they were identified by x-ray diffraction analysis as Bouzard crystals. Accordingly, the Court finds credible Brittain's conclusion that these crystals were also Bouzard crystals. The increase and size and quantity of Bouzard crystals over time in the photographs would not be possible if, as Zenith contends, conversion occurred on the slide. Instead, each slide would have an equal amount of Bouzard crystals of equal size. Therefore, the Court finds that this experiment further buttresses the conclusion that conversion occurs even under conditions free from the effects of evaporation and cooling.

The Court finds that Dr. Brittain's light-scattering experiments were highly probative of the issue of conversion in solution versus on the slide. Zenith's only witness who addressed the results of this experiment, Dr. Simonelli, had no adequate explanation for these results. His conjecture that an aggregation and dispersion of cefadroxil DC particles, or the presence of excipients in the solution may have been the cause of changes in light-scattering intensity was speculative, and unsupported by any experimental data or literature, and is accorded little weight.

The Court also finds that Brittain's sealed system experiments prove that evaporation played little, if any, role in the microscopy observation made by Brittain. By sealing slides and test tubes, and then recording conversion over time, Brittain has refuted Zenith's claim. If evaporation played a significant role in the observed conversion, a sealed slide or test tube system should contain only those converted crystals that had already precipitated out of solution before the slide was sealed. Instead, Brittain observed continuing precipitation of Bouzard crystals long after the slide was sealed. Thus, the Court finds that evaporation, a condition that both parties agree does not exist in the stomach, was not a substantial cause, if it was a cause at all, of conversion on the microscope slide.

Last, Brittain's freeze-drying experiments also corroborate his other findings that conversion occurs inside of a capsule cefadroxil DC capsule if enough time is allowed to elapse. His findings will be compared to those of Dr. Greenblatt below.

4. *Greenblatt's Freeze-Drying Experiments*

Differences between Dr. Greenblatt's first series of freeze-drying experiments and Dr. Brittain's freeze-drying experiments could be accounted for by differences in the length of time that capsules were left in the dissolution beakers before being removed and frozen. The results of Greenblatt's second series of experiments, however, appear to directly conflict with the results of Brittain's experiments. The Court finds unlikely, and unsupported by credible evidence, Zenith's suggestion that a difference of at most five seconds between the length of time it took Greenblatt to remove a capsule from the beaker and place it in liquid nitrogen and the length of time it took Brittain to do the same could account for the difference in results. Zenith's own witness, Dr. Pfeiffer, opined that a difference of two or three seconds would be insignificant. (Tr. 188-89) The Court also finds unlikely Bristol's suggestion that grinding and desiccation of the recovered sample could cause converted Bouzard to revert to cefadroxil DC, a more unstable form of cefadroxil. Thus, the Court can only resolve this conflict by resort to an evaluation of credibility. On this count, the Court must conclude, on the basis of its observations of both witnesses and scrutiny of their testimony, that Brittain's results are significantly more credible. Brittain demonstrated repeatedly during trial his consistency in laboratory method, his understanding of the problem he was investigating, his knowledge of laboratory equipment and the ability to design and verify experiments. By contrast, although she may have significant expertise in fields of inquiry unrelated to the issues in this case, Greenblatt demonstrated little understanding of the problem at issue in this case or the reason for her procedures and thus played no role in the design of her experiments, lacked any prior experience in freeze-drying techniques, was lax in her methodology, particularly in the recording of her procedures and observations, and in fact did not even participate in the second series of experiments. The Court finds that Brittain's freezedrying results are simply better supported and vastly more credible. Accordingly, those findings are adopted by the Court.

5. *Rothstain's Dissolution Rate and Equilibrium Solubility Experiments*

Zenith contends that Dr. Rothstein's experiments prove that conversion does not occur. Specifically, Zenith contends that the observed differences in dissolution rates between cefadroxil DC and Bouzard monohydrate are inconsistent with conversion, because if conversion occurred within the capsule, similar equilibrium solubility results would be observed after the contents of the capsule were released and dissolved into solution. For this conclusion, Zenith relies on the testimony of Dr. Pfeiffer, and an article from a medical journal annexed as Exhibit B to Defendant's Exhibit 13. (Tr. 92)

Though the Rothstein results may support Zenith's position that conversion does not occur, the Court does

not find that those results overcome the extensive proofs contained in Brittain's experiments. The Court is hard-pressed to reconcile the conflict between Rothstein's experimental results and Brittain's. An explanation proffered by Bristol is that the Rothstein results are inconclusive because of the possibility of a significant degree of experimental error. The margins of error recorded by Rothstein with respect to the dissolution rate experiments support Bristol's contention. (See Tr. 54; PX 21) The absence of any effort by Rothstein to account for margin of error as to the equilibrium solubility experiments leaves the issue unresolvable. on the basis of the trial record, the Court can neither conclude that the experiment results are tainted by error, nor exclude experimental error as an explanation for the discrepancy. Thus, at bottom, the Court can only find that the powerful proofs by Bristol of the occurrence of conversion are simply much more persuasive,,and greatly outweigh the Rothstein results, from which the nonoccurrence of conversion is merely a possible inference.

B. ***Gottstein Findings***

A subsidiary fact issue raised by Zenith is whether cefadroxil DC is in fact a form of cefadroxil prior in the art to Bouzard monohydrate. Zenith contends that this issue bears on the interpretation of the claim in the '657 patent, and on the ultimate issue of infringement. Based on its review of the evidence, the Court finds that Zenith has adequately demonstrated that Gottstein cefadroxil and cefadroxil DC are similar crystalline forms of cefadroxil. The Court finds, however, that although the x-ray diffraction pattern of Gottstein cefadroxil is similar to the x-ray diffraction-pattern for cefadroxil DC, Bristol has proved that cefadroxil DC converts to Bouzard monohydrate when wet, and that Gottstein cefadroxil does not.

The only evidence Zenith relies on to support its position that the two materials are the same is Dr. Pfeiffer's comparison of the two respective compounds' x-ray diffraction patterns, and his opinion that, based solely on this comparison, if one material converted, the other would also. This opinion is completely refuted by the results of an experiment in which Brittain attempted without success, under conditions stated by Zenith's experts to be highly conducive of conversion, to make Gottstein convert to Bouzard monohydrate. Given this result, in contrast to Brittain's proof that cefadroxil DC converts to Bouzard monohydrate, the Court finds that Gottstein cefadroxil is distinctly different from cefadroxil DC. Zenith's further contention that Bristol has not proved that the material it claims is in fact Gottstein material is also without merit. Brittain relied on a comparison of an x-ray diffraction pattern that he obtained from his Gottstein sample with the same pattern Zenith relied on as representative of Gottstein, and concluded credibly that his Gottstein sample matched the Gottstein pattern relied on by Zenith. The Court finds that Bristol has proved that the material it used to test for conversion was in fact Gottstein cefadroxil.

III. *CONCLUSIONS OF LAW*

A. ***Jurisdiction and Burden of Proof***

Count I of Zenith's complaint arises under the patent laws of the United States, 35 U.S.C. s.s. 1 et seq. For reasons stated by the Court on previous occasions, a justiciable controversy has existed and continues to exist between the parties. Therefore, the Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. s. 1338(a).

As a declaratory judgment plaintiff, Zenith had the burden to prove the existence of an actual controversy, which in this case required proof that Bristol posed a threat that it would sue Zenith for infringement based on acts in which Zenith had a present intention and capacity to engage. Indium Corp. of America v. Semi-Alloys, Inc., 781 F.2d 879, 883 (Fed. Cir.1985), *cert. denied,* 479 U.S. 820, 107 S.Ct. 84 (1986). This burden

was met. As a patent owner who has been proved in a declaratory judgment action to have posed a threat to sue for infringement, Bristol bears the burden to prove infringement. Advance Transformer Co. v. Levinson, 837 F.2d 1081, 1084 (Fed. Cir.1988) (trial court did not err in finding that patent owner-defendant in declaratory judgment action had not met his burden to prove infringement); *United Sweetener USA, Inc. v. Nutrasweet Co.,* 76.0 F.Supp. 400, 417 (D. Del.1991); Deere & Co. v. Sperry Rand Corp., 322 F.Supp. 397, 398 (E.D. Cal.1970), *aff'd,* 513 F.2d 1131 (9th Cir.), *cert. denied,* 423 U.S. 914, 96 S.Ct. 218 (1975); *see also* E. Borchard, Declaratory Judgments 404-09 (2nd ed.1941); Under Sea Industries, Inc. v. Dacor Corp., 833 F.2d 1551, 1557 (Fed. Cir.1987) ("The burden is always on the patentee to show infringement"). Infringement must be proved by a preponderance of evidence. Envirotech Corp. v. Al George, Inc., 730 F.2d 753, 758 (Fed. Cir.1984).

B. ***Direct Infringement***

There are two forms of infringement, literal infringement and infringement under the doctrine of equivalents. "Literal infringement requires that every limitation of the patent claim must be found in the accused device." Uniroyal, Inc. v. Rudkin-Wiley Corp. 837 F.2d 1044, 1054 (Fed. Cir.), *cert. denied.,* 488 U.S. 825, 109 S.Ct. 75 (1988). Infringement under the equitable doctrine of equivalents comes into play when, although there is no literal infringement, the accused device performs substantially the same function, in substantially the same way, to achieve substantially the same result. Graver Tank & Mfg. Co. v. Linde Air Products Co., 339 U.S. 605, 608, 70 S.Ct. 854, 856-57 (1950); Uniroyal, 837 F.2d at 1057.

Because it is undisputed that the cefadroxil DC product Zenith intends to manufacture and sell would not, in its manufactured form, literally infringe the '657 patent, Bristol relies on the doctrine of equivalents to support its allegations of direct infringement by Zenith. Specifically, Bristol relies on a line of cases in which non-infringing materials that convert *in situ* to claimed materials or materials used in a claimed process have been held to infringe under the doctrine of equivalents. *See* Atlas Powder Co. v. E. I. Du Pont-de Nemours & Co., 750 F.2d 1569 (Fed. Cir.1984) (affirming finding that oilin-water emulsifying agent that converted to water-in-oil emulsifying agent *in situ constituted infringement of claimed water-in-oil emulsion);* Chemical Cleaning Corp. v. Dow Chemical Co., 379 F.2d 294 (5th Cir.1967) (affirming finding that monomethylthiourea, which disassociated during process to form thiourea, was equivalent of thiourea), *cert. denied,* 389 U.S. 1040, 88 S.Ct. 777 (1968); Broadview Chemical Corp. v. Loctite Corp., 159 U.S.P.Q. 80 (D.Conn.1968) (finding formation of quinone as result of chemical reaction during use of sealant made sealant equivalent of patented quinone-containing sealant), *aff'd in relevant part,* 406 F.2d 538 (2d Cir.), *cert. denied,* 394 U.S. 976, 89 S.Ct. 1472 (1969); Studiengesellschaft Kohle, M.B.H. v. Dart Industries, Inc., 549 F.Supp. 716 (D. Del.1982) (finding use of catalyst formed during process infringed claims directed to use of pre-formed catalysts under doctrine of equivalents), *aff'd,* 726 F.2d 724 (Fed. Cir.1984). More closely on point, Bristol has directed the Court's attention to two cases that involved "pro-drugs", which are drugs that convert *in vivo* to a patented form of drug. *See* Ortho Pharmaceutical Corp. v. Smith, 18 U.S.P.Q.2d 1977 (E.D.Pa.1990), *aff'd,* 959 F.2d 936 (Fed. Cir.1992); *Beecham Group Ltd. v. Bristol Laboratories Ltd.,* (1978) R.P.C. 153 (House of Lords 1977) (finding infringement of patent under English doctrine of "pith and marrow"). The findings of infringement in these cases were based on the doctrine of equivalents and its English counterpart. These cases support Bristol's position.

Zenith makes three arguments against the Court finding infringement under the doctrine of equivalents. It claims first that Bristol has not proved that cefadroxil DC performs the same function in substantially the same way to achieve substantially the same results. In connection with this argument, it claims that the "heart" or "essence" of the '657 patent resides in the manufacturing advances allowed by the greater bulk

density and stability of Bouzard monohydrate.

The Federal Circuit Court of Appeals has observed that although the "heart of the invention" doctrine, which it characterized as "dicta," may be useful in determining infringement under the doctrine of equivalents, it should not be used to ignore limitations in a patent claim. Perkin-Elmer Corp. v. Westinghouse Electric Corp.,822 F.2d 1528, 1533 n. 8 (Fed. Cir.1987). Analogously, the Court finds that the "heart of the invention" dicta should also not be used to improperly read additional limitations into a claim.

Zenith would have the Court apply the "heart of the invention" doctrine to read limitations into claim 1 of the 1657 patent constricting the scope of uses, purposes or functions of Bouzard monohydrate protected by the patent. The claim contains no such limitations, express or implicit; it claims the Bouzard monohydrate *per se*. A patent holder's rights are defined by the claims in its patent. Corning Glass Works v. Sumitomo Electric U.S.A., Inc., 868 F.2d 1251, 1257 (Fed. Cir.1989). The sole function of a claim is "to point out distinctly the process, machine or composition of matter which is patented, not its advantages." Preemption Devices, Inc. v. Minnesota Mining and Manufacturing Co., 732 F.2d 903, 907 (Fed. Cir.1984). Bristol has the right to exclude others from *all* uses of the Bouzard monohydrate. *See* Roberts v. Ryer, 91 U.S. 150, 157 (1875) ("The inventor of a machine is entitled to the benefit of all the uses to which it can be put"); American Standard, Inc. v. Pfizer, Inc., 722 F.Supp. 86, 103 (D. Del.1989) ("an inventor is entitled to all applications to which his invention can be put to use, including those not mentioned in the specification"); 4 *Chisum on Patents* s. 16.02[4],at 16-27 to -28 (1991) ("One does not escape infringement by using a patented invention for a purpose not contemplated or disclosed by the patentee"). The use of Bouzard monohydrate as an antibiotic is expressly stated in the patent specification. Because the Court has found that cefadroxil DC converts *in vivo* to Bouzard monohydrate before it is absorbed into the bloodstream to act as an antibiotic, the Court finds that it necessarily performs the same function in substantially the same way to achieve substantially the same result.

Second, Zenith contends that the range of equivalents to Bouzard monohydrate may not be extended to cefadroxil DC because to do so would Ilensnarell prior art. *See* Wilson Sporting Goods Co. v. David Geoffrey & Assoc., 904 F.2d 677, 684 (Fed. Cir.), *cert. denied,* 111 S.Ct. 537 (1990). This argument is predicated on a finding of fact that cefadroxil DC is the same compound as Gottstein cefadroxil. Because the Court has found otherwise, this argument fails.

Last, Zenith contends that prosecution history estoppel precludes a finding that cefadroxil DC is an equivalent of Bouzard monohydrate. *See Pennwalt Corp. v. Durand-Wayland. Inc.,* 833 F.2d 93-1, 934 n.1 (Fed. Cir.1987) (en banc) ("patentee may not recapture through equivalence certain coverage given up during prosecution"), *cert. denied,* 485 U.S. 961, 1009 (1988). The Court agrees.

Prosecution history estoppel is an affirmative defense to patent infringement. Insta-Foam Products, Inc. v. Universal Foam Systems, Inc., 906 F.2d 698, 703 (Fed. Cir.1990). Zenith contends that, because Dr. Bouzard relied on the superior manufacturing advantages of Bouzard monohydrate to distinguish it from the prior art, and the patent was granted only because of those characteristics, those manufacturing advantages limit the range of equivalents of the claimed invention by estoppel. Accordingly, it claims that because none of the manufacturing advances on which Bouzard predicated patentability of Bouzard monohydrate would be utilized by Zenith in its production of cefadroxil DC capsules, Bristol is estopped from contending that cefadroxil DC is an equivalent compound.

Prosecution history estoppel "prevents a finding of infringement even though the substituted structure is in

fact equivalent." Read Corp. v. Portec, Inc., 970 F.2d ----, Slip Op. at 7, 1992 WL 158788 (Fed. Cir. July 10, 1992). Under the doctrine of prosecution history estoppel:

a patentee cannot "recapture through equivalence certain coverage given up [by argument or amendment] during prosecution." That is not to say, however, that, whenever a limiting amendment or argument is made during prosecution, the patentee loses all coverage between what the claims literally cover and what they would have covered prior to the amendment or argument. Instead, "[d]epending on the nature and purpose of an amendmen't, it may have a limiting effect within a spectrum ranging from great to small to zero.

Hormone Research Foundation v. Genentech, Inc., 904 F.2d 1558, 1564 (Fed. Cir.1990). Reliance on superior utility over the prior art to establish nonobviousness thus would not necessarily limit the scope of the invention to its use for those purposes. In re Chupp, 816 F.2d 643, 647 (Fed. Cir.1987) (patentee need not demonstrate superiority of all uses of claimed invention over prior art to obtain patent covering those uses). "Every statement made by a patentee during prosecution to distinguish a prior art reference does not create a separate estoppel. Arguments must be viewed in context." *Read Corp.,* Slip Op. at 7.

It is undisputed that Bouzard expressly distinguished Bouzard monohydrate from the prior art solely on the basis of its superior manufacturing characteristics. Although during prosecution of the patent, Bouzard submitted a declaration to the Patent and Trademark Office that concluded that Bouzard monohydrate had a greater therapeutic value than was found in the prior art forms of cefadroxil, see Declaration of Edel Berman dated July 9, 1979, this conclusion was subsequently withdrawn through the Declaration of Edel Berman dated December 17, 1984, submitted as part of an amendment to the application on December 30, 1984, after it was discovered that the conclusion was inadequately supported by scientific evidence. The patent examiner entered the amendment "as directed to matter of form not affecting the scope of the invention" because he concluded that the therapeutic value of Bouzard monohydrate "was never a factor in determining patentability." Report of Patent Examiner Mark Berch dated February 13, 1985.

The Court finds that, through argument to the Patent Office, Bouzard narrowed the range of equivalents of Bouzard monohydrate. Because patentability was predicated solely on the manufacturing properties of the Bouzard monohydrate, the Court finds that the range of equivalents that may be found to infringe the '657 patent is limited to compounds that are equivalent in the manufacturing characteristics on which patentability was solely predicated. Thus, unlike in *Read Corp.,* where the court found that a certain feature "in itself was never asserted to be the basis for patentability over [prior art]", Slip Op. at 7, here, the only "feature" of Bouzard monohydrate-its superior manufacturing characteristics-was asserted as the basis for patentability. The range of equivalents that can infringe is therefore accordingly limited.

This case is easily distinguishable from the two "prodrug" cases relied by Bristol. In both cases, the patent in issue covered a compound in any and all forms, not just one form of the compound as does the '657 patent. The range of equivalents covered by the patents were therefore, unlike in this case, appropriately broad enough to cover equivalent structures created *in vivo*. Moreover, the issue of prosecution history estoppel was neither raised nor addressed in those two cases.

Because Zenith has established by a preponderance of evidence that the range of equivalents covered by the '657 patent is limited to equivalent structures that infringe on the manufacturing characteristics on which patentability of the '657 patent was based, the Court finds that cefadroxil DC as manufactured does not directly infringe the '657 patent under the doctrine of equivalents.

C. *Induced Infringement*

Alternatively, Bristol contends that Zenith's proposed sales of cefadroxil DC would constitute inducement of infringement under 35 U.S.C. s. 271(b). FN6 "A person induces infringement by actively and knowingly aiding and abetting another's direct infringement." C.R. Bard, Inc. v. Advanced Cardiovascular Systems, Inc., 911 F.2d 670, 675 (Fed. Cir.1990); H.B. Fuller Co. v. Nat'l Starch and Chemical Corp., 689 F.Supp. 923, 943 (D. Minn.1988). Given the Court's finding that cefadroxil DC converts *in vivo* to Bouzard monohydrate, if absorption of the converted drug into the bloodstream by a person constitutes a "use" within the meaning of 35 U.S.C. s. 271(a), then the person ingesting cefadroxii DC would literally infringe the '657 patent. Consequently, any sale of cefadroxil DC by Zenith for human consumption, in light of the findings in this opinion, would constitute a direct and knowing inducement of that infringement. Thus, the critical issue, disputed by the parties, is whether absorption of converted Bouzard monohydrate by a person who ingests cefadroxil DC constitutes a "use" within the meaning of the infringement statute.

Zenith has raised several arguments against finding absorption of converted Bouzard monohydrate to constitute an infringing "use." Zenith first contends that such "uses" are not covered by the literal terms of the claim in the '657 patent. Its places great reliance to support this argument on the claim language, which states that the patent covers crystalline monohydrate " *exhibiting* essentially the following x-ray diffraction properties." (Emphasis added), *see* supra at note 1. It contends that the word "exhibiting" requires that the patent be construed to apply only to pre-ingested forms of Bouzard cefadroxil, because x-ray diffraction properties can only be "exhibited" through x-ray diffractometry, which cannot be performed on ingested cefadroxil. The Court rejects this tortured reading of the claim language. The logic of this argument, if followed, would constrict the patent claim to apply to nothing other than bulk unformulated powder. Based on the evidence received at trial, it appears that x-ray diffraction analysis cannot be performed on cefadroxil contained inside of a capsule. To read the claim as Zenith does would thus render Bouzard monohydrate placed inside of a capsule outside the scope of the patent, an absurd result.

Zenith also asserts that the claim should be construed narrowly not to extend to ingested forms of Bouzard cefadroxil, so that it does not read on prior art. *See* Whittaker Corp. v. UNR Industries, Inc., 911 F.2d 709, 712 (Fed. Cir.1990) (claim should be construed to uphold its validity). This argument, as with a similar argument raised in connection with the doctrine of equivalents, is predicated an a finding that cefadroxil DC is the same as Gottstein cefadroxil and is thus prior art. Because the Court has found that the factual predicate for this argument is invalid, this argument is also without merit.

The second argument made by Zenith why absorption of converted cefadroxil does not constitute an infringing "use" is that such "use" of Bouzard monohydrate is too insignificant and removed from the purpose for which the patent was allowed to fall within the statutory meaning of the term. Zenith relies on Kaz. Mfg. Co. v. Chesebrough-Ponds, Inc., 317 F.2d 679 (2d Cir.1963), and asserts that the case holds that a use does not infringe unless the user gains the benefits of the teachings of the patent. Id. at 680 and n.3. The Court disagrees with this reading of *Kaz*.FN7

Kaz involved the use by defendant in a television advertisement of a steam vaporizer constructed by combining parts from two different models of steam vaporizers manufactured by plaintiff. *Id*. at 680. Defendant had purchased the two vaporizers from a retailer. *Id*.- In this Court's view, the opinion in *Kaz* rests on a ground that does not support Zenith's argument. Although not stated expressly in the opinion, this Court reads *Kaz* to rest on a finding that the "use" made by defendant of the vaporizers was permissible under an implied license granted to defendant with the purchase of the vaporizers. *See* United States v.

Univis Lens Co., 316 U.S. 241, 250-52, 62 S.Ct. 1088, 1093-94 (1942) (first sale by a patentee of an article embodying his invention exhausts his patent rights in that article); Met-Coil Systems Corp. v. Korners Unlimited, Inc., 803 F.2d 684, 687 (Fed. Cir.1986). This reading of *Kaz* is supported by the court's statements that the vaporizers "were sold by plaintiff without restrictions", Kaz, 317 F.2d at 680, and that "the only right retained by the plaintiff, once it sold the patented vaporizers, was the right to be free from competition 'in the practice of the invention' ", id. at 681 (citation omitted). Zenith cannot contend that it has any license rights, implied or otherwise, under the '657 patent. Therefore, the Court concludes that *Kaz* is inapposite to the issue of "use".

The Federal Circuit Court of Appeals has not considered in any depth the breadth of "use" that is covered by 35 U.S.C. s. 271(a). Its most detailed exposition on the subject is its statement in Roche Products, Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858 (Fed. Cir.), *cert. denied,* 469 U.S. 856 (1984) (superseded by statute), that:

Because Congress has never defined use, its meaning has become a matter of judicial interpretation. Although few cases discuss the question of whether a particular use' constitutes an infringing use of a patented invention, they nevertheless convincingly lead to the conclusion that the word "use" in section 271(a) has never been taken to its utmost possible scope.

Id, at 861. In support of this statement, the Federal Circuit cited to cases recognizing an."experimental use" exception and the notion of implied license to use or sell a purchased patented article. As neither of these recognized constraints on the scope of the term "use" is in issue in this case, the Court concludes that it is bound to apply the Supreme Court's holding in *Roberts* that an inventor "is entitled to the benefit of all the uses to which" a patented invention can be put. Roberts, 91 U.S. at 157; *see also* American Standard, 722 F.Supp. at 103; 4 *Chisum,* s. 16.02[4] at 16-27 to -28.

Zenith's argument that the *in vivo* use of converted cefadroxil DC should not be found infringing under a *de minimis* exception to the bar against infringing uses codified in s. 271(a) has facial appeal. This case presents circumstances under which it might be appropriate to adopt such an exception. The only courts to address the issue, however, are of limited authority. The trial court in *Roche Products* held that a drug used in connection with an FDA application did not infringe under a *de minimis* exception; that judgment was reversed by the Federal Circuit. Roche Products, Inc. v. Bolar Pharmaceutical Co., 572 F.Supp. 255, 258 (E.D.N.Y.1983), *rev'd,* 733 F.2d 858 (Fed Cir.), *cert. denied,* 469 U.S. 856 (1984). The case relied on by the trial court in *Roche Products* for the existence of a *de minimis* exception was a Seventh Circuit opinion in which the exception was discussed in *dicta,* and in any event was factually much different from this case in that it involved a remote sale of one arguably infringing article where there was no threat of future infringement. *See* Maxon Premix Burner Co., Inc. v. Eclipse Fuel Enqlg Co., 471 F.2d 308, 317 (7th Cir.1972). In the absence of more guidance from the Federal Circuit on the meaning of the term "use" in s. 271(a), as indicated above, the Court believes it is bound by the United States Supreme Court's statement in *Roberts*.

Zenith further argues that no "use" literally occurs because the converted Bouzard crystals dissolve into solution before they are absorbed into the bloodstream to act as an antibiotic. Though true, the same is also true of cefadroxil that exists as Bouzard monohydrate before it is dissolved. Many drugs taken orally work by dissolving *in vivo* to be absorbed into the bloodstream. Zenith's argument, if adopted, would essentially bar all claims of "infringing use" involving any drug defined in the patent by its crystalline structure.

Zenith also contends that literal infringement by a user of converted Bouzard monohydrate is precluded by the reverse doctrine of equivalents. That doctrine derives from the Supreme Court's decision in Graver Tank & Manufacturing Co. v. Linde Air Products Co., 339 U.S. 605, 70 s. Ct. 854 (1950), in which the Court stated

where a device is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way, but nevertheless falls within the literal words of the claim, the doctrine of equivalents may be used [in reverse] to restrict the claim and defeat the patentee's action for infringement.

Id. at 608-09, 70 S.Ct. at 856-57. It thus allows a court to find noninfringement when an alleged infringer has proved that "even if the claims literally read on the accused device it has been so changed that it is no longer the same invention." Del Mar Avionics, Inc. v. Ouinton Instrument Co., 836 F.2d 1320, 1325 (Fed. Cir.1987). In essence, the doctrine operates to restrict a claim in a patent by limiting the "range of products" that fall within its literal language. SRI Int'l v. Matsushita Electric Corp. of America, 775 F.2d 1107, 1125 & n.22 (Fed. Cir.1985) (en banc). An accused infringer has the burden to establish noninfringement under the doctrine. Id. at 1123-24.

According to the Federal Circuit Court of Appeals, "a defense based on the reverse doctrine of equivalents is rarely offered", because products that fall within the literal terms of a patent claim are often in fact the same in substance as is described by the claim. Id. at 1123 n.19. To sustain a defense under the reverse doctrine of equivalents requires proof that the accused product "is in fact a different product." Phillips Petroleum Co. v. United States Steel Corp., 673 F.Supp. 1278, 1357 (D. Del.1987), *aff'd,* 865 F.2d 1247 (Fed. Cir.1989).

The Federal Circuit has noted the conceptual difficulties inherent in applying the reverse doctrine of equivalents to a patent claim for a chemical compound, such as is involved in this case. United States Steel Corp. v. Phillips Petroleum Co., 865 F.2d 1247, 1253 n.9 (Fed. Cir.1989). That court questioned how one can even conceptualize, under the language of the doctrine, a way to determine whether a chemical compound that falls *literally* within the claim of a patent can perform the same "function" in a substantially different "way" as that disclosed in the claim. *Id*. For such products, there is very little leeway to determine that a product *literally* reads on the claim but is so far changed in principle from the claimed compound that it does not infringe.

When a patent claims only a very specific chemical molecular structure-as does the '657 patent, which claims one specific crystalline form of cefadroxil monohydrate-an accused compound that literally infringes is not easily susceptible to the reverse doctrine of equivalents. The '657 patent claims the specific crystalline form of the compound *per se*. As the accused converted compound has been found to consist of the identical molecular structure specifically claimed in the patent, there is no escaping literal infringement. Bristol has proved that the converted cefadroxil DC both falls within the literal language of the claim, and in fact *is* the claimed compound.

Zenith's "reverse equivalents" argument is based on its contention that Bristol predicated patentability solely on certain manufacturing advantages achieved by the newly-discovered and claimed Bouzard monohydrate crystal form. Thus, it argues, because none of the manufacturing advantages of the Bouzard monohydrate are realized by cefadroxil DC when it allegedly converts to the Bouzard monohydrate *in vivo,* cefadroxil DC is not the same invention as the Bouzard monohydrate. Although the Court has found that prosecution history estoppel limits the range of equivalents that may be found to infringe, it declines to find that the

reverse doctrine of equivalents limits the scope of literal infringement. Because the converted compound is indistinguishable in any way from the patented compound, the doctrine simply has no applicability.

Accordingly, the Court concludes that use of converted Bouzard monohydrate by a patient will ingests cefadroxil DC is an infringing use. Therefore, the sale of cefadroxil DC by Zenith. would constitute inducement of infringement under 35 U.S.C. s. 271(b).

D. *Remedy*

Bristol asserts that because it has sustained its burden of proof to establish infringement of cefadroxil DC, for which Zenith has obtained FDA approval, it is entitled to the remedy prescribed in 35 U.S.C. s.s. 271(e)(2)(A):

The court shall order the effective date of any approval of the drug ... involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed....

The Court agrees. Zenith's contention that such relief should not be granted because Bristol did not assert a counterclaim seeking such relief is without merit. The statute provides that such relief "shall" be ordered when an act of infringement is established. As Bristol has sustained its burden of proof on judgement of infringement, indirect infringement has been established. Accordingly, the Court is without discretion to deny the requested relief and will therefore grant it.

CONCLUSION

For the reasons stated above, the Court finds that the sale of cefadroxil DC would would constitute inducement of infringement of the claim in the '657 patent. The attorneys for Bristol are requested to submit an appropriate form of order.

FN1. The patent claim reads:
We claim:

1. Crystalline 7-[D- *a*-amino- *a*-(phydroxyphenyl-)acetamido)-3-methyl-3-cephem4-carboxylic acid monohydrate exhibiting essentially the following x-ray diffraction properties: [followed by a table of numbers corresponding to the x-ray diffraction characteristics of the Bouzard monohydrate]

(United States Patent No. 4,504,657 at page 18, lines 65-69).
FN2. A hemihydrate is a crystal form containing two molecules of water for each molecule of a chemical compound. A monohydrate contains one water molecule for each molecule of the chemical compound.

FN3. "Tr. ----" refers to the trial transcript at the page indicated.

FN4. "PX ----" refers to plaintiff's exhibit numbered as indicated. Likewise, "DX ----" refers to the indicated defendant's exhibit.

FN5. Greenblatt verified that the patterns obtained from bulk cefadroxil DC and formulated DC with excipients were identical.

FN6. That section provides: "Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. s. 271(b).

FN7. Accordingly, the Court disagrees with the interpretation of *Kaz* in Roche Products, Inc. v. Bolar Pharmaceutical Co., 572 F.Supp. 255, 258 (E.D.N.Y.1983), *rev'd,* 733 F.2d 858 (Fed Cir.), *cert. denied,* 469 U.S. 856 (1984).

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