UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

WARNER-LAMBERT COMPANY	:	
	:	
Plaintiff,	:	Civ. Action No. 99-922(DRD)
	:	
v.	:	
	:	**OPINION**
TEVA PHARMACEUTICALS USA, INC.	:	
	:	
Defendant.	:	
	:	
SCHWARZ PHARMA, INC.	:	
	:	
and	:	
	:	
SCHWARZ PHARMA AG	:	
	:	
Third Party Interveners	:	
	:	

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Debevoise, Senior District Judge

Plaintiff, Warner-Lambert Company ("Warner-Lambert"), the owner of U.S. Patent No. 4,743,450 ("the '450 patent"), instituted this patent infringement suit against Teva Pharmaceuticals, USA, Inc. ("Teva"), claiming that a Teva generic drug formulation containing the active ingredient quinapril hydrochloride infringed the '450 patent. Teva, using the Federal

Drug Administration ("FDA") procedure known as an Abbreviated New Drug Application ("ANDA"), had sought approval from the FDA to engage in the commercial manufacture, use and sale of its formulation. In connection with its ANDA submission Teva filed a so-called "Paragraph IV Certification" with respect to the '450 patent, asserting that the '450 patent is invalid under 35 U.S.C. §§ 102 and 103. This patent infringement action ensued.

I. Background

U.S. Patent No. 4,743,450 ("the '450 patent") issued on May 10, 1988, and named the following individuals as inventors: Michael Harris, Gerard Hokanson, Kuchi Murthy, Robert Reisch, and Frank Waldman. The '450 patent lists Warner-Lambert Company as its assignee. The '450 patent issued from Application No. 17,962 that was filed on February 24, 1987. Warner-Lambert's drug product, Accupril is covered by the '450 patent. It has enjoyed great commercial success, its sales reaching more than one half billion dollars a year.

The '450 patent is directed to stabilized compositions of a class of non-sulfhydryl Angiotension Converting Enzyme ("ACE") inhibitors. It states that ACE inhibitors can undergo three types of degradation - - cyclization, hydrolysis and oxidative discoloration. It further states that certain additives have a stabilizing effect on the composition. It mentions the following ACE inhibitors that can be used in the invention: "enalapril, quinapril, or indolapril, their corresponding free acids or pharmaceutically acceptable acid addition or base salts thereof."

Cyclization takes place when one part of an ACE inhibitor compound reacts with a different part of the same compound to form an altered, inactive "cyclized" compound. Hydrolysis is the reaction with water to form an hydrolysis degradation product. Oxidation forms products having unwanted coloration.

The '450 patent sets forth seventeen claims, two of which (claims 1 and 16) are independent claims. Claims 16, and 17 are presently at issue.

Claim 1 reads:

> 1. A pharmaceutical composition which contains:
>
> (a) a drug component which comprises a suitable amount of an ACE inhibitor which is susceptible to cyclization, hydrolysis, and discoloration,
>
> (b) a suitable amount of an alkali or alkaline earth metal carbonate to inhibit cyclization and discoloration, and
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> (c) a suitable amount of a saccharide to inhibit hydrolysis.

Claims 16 and 17 are process claims that read:

> 16. A process for stabilizing an ACE inhibitor drug against cyclization which comprises the step of contacting the drug with:
>
> (a) a suitable amount of an alkali or alkaline earth metal carbonate and,
>
> (b) one or more saccharides
>
> 17. The process of claim 16 wherein the drug is selected from the group consisting of quinapril, enalapril, and indolapril, or a pharmaceutically acceptable acid addition salt thereof.

After holding a hearing in accordance with Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996), aff'g 52 F.3d 967 (Fed. Cir. 1995) (en banc), the court construed the phrase "an alkali or alkaline earth metal carbonate" as used in claims 1 and 16 of the '450 patent to include only a carbonate and as not including a bicarbonate. In a related case, Schwarz Pharma, Inc., Schwarz Pharma AG and Warner Lambert Company v. Teva Pharmaceuticals USA, Civil No.

01-4995 (the "Schwarz Pharma Action") the court granted Teva's motion for summary judgment based on the same construction of "carbonate." The Court of Appeals reversed, Schwarz Pharma, Inc. v. Teva Pharmaceuticals, USA, Inc., 2004 WL 193228 (Fed. Cir. Jan. 29, 2004), construing "the term ["carbonate"] to include both the carbonate and bicarbonate ions."[1]

After discovery in the instant case had been completed (but before the decision of the Federal Circuit Court of Appeals in the Schwarz Pharma Action) Warner-Lambert and Teva filed motions for summary judgment. The court set forth its findings of fact and conclusions of law in an opinion dated October 2, 2003 (the "October 2, 2003 Opinion"). Finding that there are no genuine issues of material fact with respect to infringement, the court denied Teva's motion for summary judgment of non-infringement of claims 1, 4-10 and 12 of the '450 patent and granted Warner-Lambert's motion for summary judgment of infringement of claims 1, 4-10, 12, 16 and 17 of the '450 patent.

Finding that there are no genuine issues of material fact with respect to the validity of claims 1, 4-10 and 12 of the '450 patent the court granted Warner-Lambert's motion for summary judgment of validity as to those claims. Finding that there are genuine issues of fact concerning whether claims 16 and 17 were obvious to a person skilled in the art, the court denied Warner-Lambert's motion for summary judgment of validity of claims 16 and 17.

The court found that Merck's pre-existing Vasotec tablet, which Warner-Lambert did not disclose to the Patent and Trademark Office ("PTO") was highly material in that a reasonable examiner would have considered the Vasotec product important in deciding whether to allow the

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[1] The Schwarz Pharma plaintiffs were permitted to intervene in the instant action just prior to trial.

application to issue as a patent. However, the court concluded that whether Warner-Lambert's inventors intended to deceive the PTO by withholding information concerning Vasotec raised questions of material fact. Therefore, the court denied Teva's motion for summary judgment that the '450 patent is unenforceable due to Warner-Lambert's inequitable conduct and denied Warner-Lambert's motion for summary judgment of no inequitable conduct.

The subsequent decision of the Federal Circuit Court of Appeals in the Schwarz Pharma Action did not affect these rulings. There remained for trial the issues of anticipation and obviousness of claims 16 and 17 of the '450 patent and the issue whether the '450 patent is unenforceable because Warner-Lambert withheld from the PTO the existence of Vasotec with an intent to deceive the PTO. A trial was held on May 3-6, 2004. The evidence establishes that the '450 patent was neither obvious nor anticipated in the prior art nor did Warner-Lambert's inventors act with an intent to deceive the PTO by failing to call to the patent examiner's attention the Merck Vasotec product.

II. Development of Vasotec and Accupril

ACE inhibitors are a class of drugs used for treatment of hypertension. Squibb introduced captopril, the first ACE inhibitor tablet marketed in the United States, by the early 1980s. Captopril was both expensive and had adverse side effects. Various pharmaceutical companies, including Warner-Lambert and Merck, sought to formulate another ACE inhibitor which would not have these side effects.

Merck developed the next ACE inhibitor, enalapril, which it sold under the trade name Vasotec in the United States beginning in January 1986. Warner-Lambert's ACE inhibitor, quinapril hydrochloride, an acid salt of quinapril, received FDA approval in November, 1991 and

was marketed under the name Accupril. Quinapril itself is the subject of U.S. Patent No. 4,344,949 ("the '949 patent") that issued to Warner-Lambert on August 17, 1982 and expired on April 3, 2003. Warner-Lambert listed the '450 patent and the '949 patent with respect to Accupril in the FDA publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book").

The process for formulating Merck's Vasotec and the process for formulating Warner-Lambert's Accupril have several common features. Each involves a process for stabilizing an ACE inhibitor against cyclization; each involves contacting the ACE inhibitor with a carbonate which includes the carbonate or bicarbonate ion; each involves contacting the ACE inhibitor with a saacharide. Critical to the issues addressed at trial is the extent of the knowledge Warner-Lambert's scientists had at the time of filing the application for the '450 patent about the stability or instability of Merck's enalapril product and about how Merck solved any instability problems. Also critical to the issues addressed at trial is the extent to which information about the Merck solution of instability problems was in the public domain and available to persons of ordinary skill in the art. These questions can best be answered by examining the step-by-step development work of Merck and of Warner-Lambert as they sought to formulate a stable ACE inhibitor product.

1. Development of Vasotec: The testimony of Gerald S. Brenner, PhD, and various trial exhibits describe the steps that led to the manufacture and sale of Merck's Vasotec product. Dr. Brenner received his doctorate in organic chemistry in 1961 and shortly afterwards entered Merck's employment. After ten years work in various research capacities he was assigned the task of starting and directing a preformulation group in the Department of Research and

Development. The preformulation group is charged with developing active ingredients so that they can be manufactured for commercial use. This includes the study of stability and degradation when a drug is combined with incipients required to manufacture it in usable form.

In the early 1980's Dr. Brenner's preformulation group became responsible for the development by a target date of a commercial formulation of enalapril maleate. It soon became apparent during compatibility studies that when mixed with frequently used formulation excipients the enalapril maleate suffered from two forms of degradation, cyclization to form diketopiperazine ("DKP") and hydrolysis. It did not degrade by oxidation or discoloration. Cyclization was a phenomenon which neither Dr. Brenner nor any members of the team working with him had ever observed before nor were they aware of any information about it in the pertinent literature.

As a preliminary step towards eliminating cyclization members of the preformulation group studied the effect of pH on enalapril. When enalapril was tested in solution at a low pH, cyclization product was the principal degradate. At a higher pH, cyclization was reduced and diacid, the product of hydrolysis was the major degradate. When the scientists added buffers to solid dosages in order to achieve pH levels that had appeared promising to reduce cyclization during the solution studies stability was not obtained. In other words, successful efforts at achieving stability in solution could not be translated to the solid state product.

Having determined that enalapril maleate was itself stable but that it was unstable with most common excipients, and having tried and failed to achieve stability through the use of various buffering substances in solid dosage form, the Merck scientists undertook the complex and time consuming effort to ascertain what they could do chemically to block the destabilizing

reaction. They developed a working hypothesis. Dr. Brenner described the hypothesis and its validation in considerable detail (Tr. pp 606-607). He summarized the hypothesis as follows:

> Our feeling was that we could inhibit the cyclization by converting OH, which is a fairly good leading group to a much poorer leading group, and that poor leading group would be ONA. In other words, converting enalapril, which is an acid, to its sodium salt. So that was our working hypothesis that we could inhibit cyclization by converting the acid group to an ONA group, a sodium salt.

(Tr. p. 608)

Implementing this process was complicated and time consuming. A dry blend could not be used, because the process required enough water to dissolve some of the enalapril and some of the sodium bicarbonate. The chemical background had to be determined and countless experiments had to be conducted to test the hypothesis. Further, stability was affected by the type of mixing equipment, the duration of the mixing, the temperature of the mixing, holding time in the mixer before the wet granulation was dried and the particle size of the sodium bicarbonate used in the process. As Dr. Brenner put it, "[t]he . . . concept that eventually worked for us was the neutralization of enalapril and the conversion of enalapril to enalapril sodium." (Tr. p. 633).

It required three to four years from the time when the preformulation group commenced its work until a stable product was developed. Merck received FDA approval in December 1985 and introduced Vasotec in the market in January 1986.

During the 1985-'86 period Dr. Brenner and other Merck product development managers discussed the question whether Merck should seek to patent its process for stabilizing enalapril or whether it should maintain the process as a trade secret. They had no desire to assist Merck's competitors to solve the stability problems that affected ACE inhibitors. There was publicly

available information which disclosed some information about Vasotec and its European counterpart, Renitec. The tablet itself was available. The Vasotec package insert listed the drug's starting ingredients other than sodium bicarbonate. The 1985 edition of the European Dictionnaire Vidal and the Dutch publication Pharmaceutisch Weekblad listed Renitec's ingredients, including sodium bicarbonate and lactose. There appeared in a 1986 issue of the journal Drug Development and Industrial Pharmacy an article by N.R. Bohidar, J.L. Bavitz and P.K. Shiromani[2] entitled "Formula Optimization for a Multiple Potency System with Uniform Tablet Weight." ("Bohidar"). This article did not disclose that enalapril was the drug being studied. One paragraph read:

EXPERIMENTAL

> In the system studied, it was known that the drug could undergo cyclization at a low pH while at higher pH's it could hydrolyze. Cyclization can be prevented through 'in-situ' deprotonation of the drug during wet granulation. A salt is obtained through equimolar reaction between the drug and sodium bicarbonate.

Merck's officials were aware of the publicly available information but concluded "that knowing the ingredients themselves, the typical work in the field could not discern the process by which Merk made Enalapril tablets" (Dr. Brenner, Tr. p. 157). Referring to Bohidar, Dr. Brenner testified that "[i]t was felt that there wasn't enough detail in that article to allow one to develop the stable article." (Dr. Brenner, Tr. p. 163). As to the totality of the available public information, i.e., the tablets, the package insert, the Dictionnaire Vidal reference and Bohidar, "[i]t was the feeling within Merck having access to only that data, that was insufficient to teach somebody the role of sodium bicarbonate in the stabilization of the formulation." (Dr. Brenner,

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[2] Both Bohidar and Shiromani were employed in Merck's research department and devoted some of their time to the development of the enalapril formulation.

Tr. p. 164). Consequently, Merck decided to maintain its enalapril formulation as a trade secret.

2. Development of Accupril: In the early 1980's Warner-Lambert sought to formulate its ACE inhibitor quinapril in commercial form in order to compete with Captopril. Two of the inventors named in the '450 patent testified, Dr. Michael Ray Harris and Dr. Kuchi S. Murthy. Dr. Harris had a Ph.D. in physical pharmacy and was the lead inventor on the quinapril project after he became involved with it in 1984 or 1985. Dr. Murthy possessed a Ph.D. with a pharmaceutics major and a physical chemistry minor. During the 1969-93 period he was a Scientist/Senior Scientist and Research Associate in Product Development at Warner-Lambert or an affiliate of Warner-Lambert. He was assigned to the quinapril project in the early 1980's.

Warner-Lambert monitored its competitors which were seeking to introduce an ACE inhibitor drug into the market and learned in 1983 or '84 that Merck had filed an NDA for an enalapril product. It learned, of course, that Merck introduced into the market its Vasotec product in January 1986.

The initial Warner-Lambert quinapril formulation used in clinical trials had serious stability problems. In particular the formulations were subject to cyclization. Neither Dr. Harris nor Dr. Murthy, nor any other members of the Warner-Lambert quinapril team had any knowledge about cyclization degradation; they had seen nothing in the literature regarding degradation pathways of ACE inhibitors and had had no prior experience with a drug that exhibited this form of degradation.

Like the Merck scientists, the Warner-Lambert scientists first hypothesized that cyclization could be minimized by controlling the pH. They formulated quinapril in solution to determine the extent of degradation at each pH level. A May 7, 1986 memorandum (PTX 55)

detailed the studies to be carried out. The experiments involved bringing quinapril, which has a pH between 2 and 3 to pH levels between 4.0 and 8.0 by adding alkaline excipients. The memorandum noted that Vasotec had a pH level of 6.5, obtained through inclusion of sodium bicarbonate, a fact that had been ascertained by dissolving a Vasotec tablet in water and measuring the pH level. It was observed that in solution quinapril degradation through cyclization was minimized at the higher pH level. Dissolving the Vasotec tablet and testing the solution provided no information that enalapril was subject to cyclization degradation or about the role of sodium bicarbonate or whether it was used as a stabilizer.

A July 18, 1986 memorandum (PX 42) discussed the results of the May experiments during which alkaline compounds with high pH were placed in solution with quinapril. The compounds used were four alkaline excipients: sodium bicarbonate, potassium phosphate, N-Methyl-D-Glucamine, and Tris (hydroxmethyl amino methane). The tests, like similar tests which Merck scientists had conducted, resulted in failure. Notwithstanding encouraging results in reducing cyclization when quinapril's pH was increased in solution, both dry blending and conventional wet granulation procedures failed to suppress cyclization of the drug. The results in solution were not transferable to the solid state and, in the words of Dr. Harris, "and we therefore abandoned this process . . . Based on the data we generated, this theory failed, so we didn't believe that pH was involved at this point. Solid state." (Tr. p. 56). As a consequence of the failure of the experiments attempting to reduce cyclization by using sodium bicarbonate to adjust pH, the Warner-Lambert scientists lost interest in Vasotec. As Dr. Murthy stated, "Well, the thing is, Merck's Vasotec was of great interest to us in the beginning of our program, but when - once we tried the bicarbonate experiment, and it did not - and we were not successful, our

interest waned considerably about Vasotec." (Tr. pp. 497-98). Neither Dr. Harris nor Dr. Murthy could recall any discussions about Vasotec among the Warner-Lambert scientists after digesting the results obtained from the pH experiments called for in the May 7, 1986 memorandum.

Like the Merck scientists, Warner-Lambert scientists turned to a new approach after their experiments adjusting the pH failed. Merck, as recited above, turned to an in-depth study of the chemical reactions leading to cyclization and the chemical means of avoiding cyclization. Warner-Lambert started one-on-one excipient compatibility studies. This involved mixing quinapril with different excipients, storing them and then studying the stability of the mixture.

After experimenting with a member of excipients Warner-Lambert's scientists found that a carbonate and ascorbic acid were compatible with quinapril and generated a stable quinapril tablet. An August 4, 1986 memorandum (PTX 31) reflected that they believed that they were close to developing a final tablet from two schemes - one using ascorbic acid as a stabilizer and the other using magnesium carbonate and lactose as stabilizers.

An August 20, 1986 memorandum (PTX 132) referred to both stabilization approaches and with respect to the use of magnesium carbonate stated, "[t]he results after 5 days storage at 60° look promising . . ." A September 4, 1986 memorandum (PTX 133), after describing favorable results with tablets containing ascorbic acid as the stabilizer, described the success obtained through the use of magnesium carbonate and lactose:

> Because of the impressive results that have been observed thus far with the backup formulation (5mg) which utilizes magnesium carbonate as the stabilizer, this formulation is now being optimized with respect to disintegration and preparing higher dosage strengths. A suitable 5mg tablet has been developed. The addition of polyplasdone XL provides for excellent disintegration without

> significantly affecting stability (5 days 60°). Thus, emphasis will now be focused on preparing a stable 40mg tablet. It is felt that the 10mg tablet could be made by doubling the 5mg formulation and the 20mg tablet could be made by halving the 40mg formulation. The formulations under investigation vary the amounts of magnesium carbonate and lactose and include: [There followed a table setting forth the various combinations of incipients that were tested].

Dr. Brenner contrasted the Merck approach to stabilization of enalapril with the Warner-Lambert stabilization of quinapril after each had failed to achieve stabilization by adjusting the drug's pH:

> The . . . the original concept in . . . that eventually worked for us was the neutralization of Enalapril and the conversion of enalapril to enalapril sodium.

(Tr. pp. 633-34).

> Warner-Lambert went off and developed an alternate way of using magnesium carbonate to get a suitable tablet. We went off in another direction of converting the acids to the sodium salt. Both ultimately gave stable tablets. But both companies learned independently that stabilization by providing the micro environment alone would not be successful.

(Tr. pp. 646-47).

Warner-Lambert continued to refine the product and the process that it had developed. It continued pH studies and other studies in an attempt to learn the precise chemical reactions that took place during the stabilization process. Ph, however, does not have a role in the stabilization of either Vasotec or quinapril.

Throughout its trial and post-trial briefs Teva argues that Warner-Lambert's initial concentration on pH and its continued interest in pH in one context or another is evidence that it drew upon Vasotec in order to develop its own stabilized product. For example, in its post-trial brief Teva stated, "the inventors continued their Vasotec - and sodium bicarbonate - inspired pH

testing of quinapril through the beginning of 1987, just weeks before the filing of the '450 patent application." (p. 34) (emphasis added). The facts are otherwise. Independently of each other, both Merck and Warner-Lambert scientists began their stabilization efforts through experimentation with varying pH levels, a well-known and commonly used approach. Warner-Lambert's own studies demonstrated that in solution the pH range for maximum stability was 4.0 to 8.0. They knew through simple testing that Vasotec's pH level was 6.5. Using four alkaline excipients, phosphate, N-Methyl-D-Glucamine, Tris (hydroxmethyl amino methane) and sodium bicarbonate, the Warner-Lambert scientists tested pH of 5.0 and 6.5.

Attempts to stabilize the compound by adjusting pH failed both for Merck and Warner-Lambert, and each of them pursued its own separate path to achieve stabilization. The chemical reaction that results in a stabilized Vasotec is not controlled by pH. The Warner-Lambert scientists knew that Vasotec contained sodium bicarbonate; they may have speculated that it played a stabilization role, but they could not have known whether or how sodium bicarbonate contributed to stabilization of Vasotec. Teva's contention that Warner-Lambert's continued exploration of pH reactions demonstrates that it was inspired by Vasotec and its use of sodium bicarbonate is wide of the mark. Warner-Lambert conducted pH studies at the outset on its own initiative, not because Vasotec contained sodium bicarbonate. From time to time it conducted pH studies, not to imitate Vasotec or its stabilization process, because Warner-Lambert had already achieved stabilization of quinapril by means of its own formulation. It simply sought additional data that might prove useful.

On February 24, 1987 Warner-Lambert filed Patent Application No. 17,962 on its stabilized product and stabilization process. On May 10, 1988 the '450 patent issued.

A trial at which evidence is produced and witnesses are examined and cross-examined is a better vehicle for determining the facts of a case than a motion for summary judgment where documents and deposition testimony form the basis for a court's factual findings. The present case illustrates the soundness of this observation. The evidence presented at the trial of this case requires changes or modifications of certain of the subsidiary factual determinations set forth in the court's October 2, 2003 Opinion deciding the parties' summary judgment motions. These changes or modifications do not require revision of the rulings on the motions for summary judgment; they are, however, significant insofar as they relate to resolution of the remaining issues in the case.

III. Discussion

A. Date of Conception: Teva relies heavily upon the testimony and expert opinion of Joseph Schwartz, Ph.D., to establish that for purposes of novelty and anticipation the date of invention is presumed to be the filing date of the patent application - in this case, February 24, 1987. Dr. Schwartz has a doctorate in pharmaceutical chemistry and is Professor of Pharmaceutics and Director of Industrial Pharmacy at the University of the Sciences in Philadelphia. He is highly respected in his profession, and a number of pharmaceutical companies, including Merck, have retained his services as an expert witness.

The purpose of Dr. Schwartz's testimony concerning the date of conception was to establish that conception did not occur any time prior to the '450 patent application filing date, a matter of some significance when determining what constituted prior art. Dr. Schwartz referred to two aspects of claim 16 of the '450 patent: i) the use of a suitable amount of an alkali or alkaline earth-metal carbonate to stabilize an ACE inhibitor drug against cyclization and ii) the

construction of "to inhibit cyclization" to mean reducing cyclization to a point that the resulting drug product is stable in accordance with generally understood guidelines in existence in 1987 which would meet the requirements for FDA approval.

Having reviewed the testimony and documentation that Warner-Lambert produced, Dr. Schwartz found in pre-February 24, 1987 material that Warner-Lambert scientists had discovered that an alkaline carbonate stabilized on ACE inhibitor against cyclization. He could not find, however, sufficient stability data suitable to present to the FDA for product approval. Under his theory conception would not occur until such data was obtained. In other words, because the FDA required NDA batch stability tests as a condition of approval, Warner-Lambert would have had to have run such stability tests, an operation which it did not in fact complete until after issuance of the '450 patent.

Dr. Schwartz admits that he has no legal training as to what constitutes conception under the patent law and had to rely on the advice of Teva's attorneys with respect to the criteria for conception.

Teva correctly notes that the date of invention for purposes of novelty and anticipation is presumed to be the filing date of the patent application. Mahurkar v. C.R. Bard, Inc., 79 F.3d 1572, 1576-77 (Fed. Cir. 1996). A patentee has an initial burden of coming forward with evidence of conception, Id. at 1578, and the court must consider all of the evidence so that an evaluation can be made of the inventor's claim of conception. Id. at 1577.

An invention is conceived when the inventor forms in his mind a definite and permanent idea of the complete and operative invention as it is thereafter to be applied in practice. Conception is complete when one of ordinary skill in the art could carry out the conceived idea

without unduly extensive research or experimentation which would undermine the specificity of the conception. Burroughs Wellcome Co. v. Barr Labs., Inc., 40 F.3d 1223, 1228 (Fed. Cir. 1994).

Dr. Schwartz's understanding of the legal concept of conception was flawed. There was no requirement that conception could occur only after the inventors had produced sufficient stability data to convince the FDA that Warner-Lambert was entitled to approval of its Accupril product. "[A]n inventor need not know that his invention will work for conception to be complete. He need only show that he had the idea; the discovery that an invention actually works is part of its reduction to practice." Id. at 1228.

As recited above, after completion of the studies called for in the May 7, 1986 memo (PTX 55) to test the hypothesis that quinapril could be stabilized against cyclization by means of pH adjustment, the Warner-Lambert scientists recognized the failure of that approach and experimented with many excipients.

In July 1986 the formulation team noted promise in formulations containing magnesium carbonate as a potential stabilizer against cyclization. An August 4, 1986 memo (PTX 31) noted that the scientists were close to a final tablet bared upon two "schemes" - one using ascorbic acid as a stabilizer and the other using magnesium carbonate and lactose as stabilizers. An August 20, 1986 memo from Dr. Harris (PTX 132) stated that results of the carbonate lactose formulations looked promising and that Dr. Harris believed he had solved the cyclization problem as of that date.

A September 4, 1986 memo of Dr. Harris (PTX 133) set forth the details of the successful studies of the stabilizing effects of magnesium carbonate and lactose. Dr. Harris testified that

"[a]t this point we're just tweaking. No major changes. Just tweaking to finalize." (Tr. p 69). The studies to which the September 4 memo referred had to have taken place no later than August, 1986. Conception had taken place at that time and was reflected in the August 20, memo. The conception date of the invention described in the '450 patent was no later than September 4, 1986.

B. Inequitable Conduct: Teva claims that the '450 patent is unenforceable due to Warner-Lambert's inequitable conduct before the PTO, specifically, its failure to disclose the existence of Vasotec as prior art. As stated in Teva's pretrial brief (p. 10):

> Matters came to a head with the preparation of the '450 patent, which was filed on February 24, 1987. DTX 1. As the application was being prepared, Dr. Murthy (and the other named inventors) faced an important choice - whether or not to disclose the existence of Vasotec and risk delay or outright rejection of the application. Although he was aware of his duty of candor to the PTO, Dr. Murthy opted for nondisclosure. This choice to suppress highly material prior art renders the patent unenforceable.
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> "Applicants for patents are required to prosecute patent applications in the PTO with candor, good faith, and honesty." Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995) (citing Precision Instrument Mfg. v. Auto. Maint. Mach., 324 U.S. 806, 818 (1945)). "A breach of this duty constitutes inequitable conduct." Id. This duty is not limited to claims that are ultimately allowed. Breach of the duty of candor at any point in the prosecution of the application may constitute inequitable conduct and may render all claims that finally issue from that application unenforceable. Fox Indus. v. Structural Preservation Sys., 922 F.2d 801, 803-04 (Fed. Cir. 1990).
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> Inequitable conduct is an issue of law based on two factual findings: (1) materiality, i.e., an affirmative misrepresentation of material fact, a failure to disclose material information, or a submission of false material information; and (2) an intent to deceive. Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1256 (Fed. Cir. 1997). Materiality and intent must be established by clear and convincing evidence, id.

The court's summary judgment opinion found that Vasotec was material, that is, "there is

a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent." Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1575 (Fed. Cir. 1996). Whether Vasotec was as "highly material" as stated in that opinion is subject to question in view of the facts developed at the trial. Nevertheless, the existence of Vasotec was material to some degree in that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent. Information concealed from the PTO may be material even though it would not invalidate the patent. Gardco Mfg., Inc. v. Herst Lighting Co., 820 F.2d 1209, 1213 (Fed. Cir. 1987).

Intent to deceive is another matter. "To be guilty of inequitable conduct, one must have intended to act inequitably." FMC Corp. v. Manitowoc Co., Inc., 835 F.2d 1411, 1415 (Fed. Cir. 1987). To prove that a party acted inequitably in failing to disclose information or a reference, "there must be clear and convincing evidence that the applicant made a deliberate decision to withhold a known material reference." Baxter Int'l, Inc. v. McGaw, Inc., 149 F.3d 1321, 1329 (Fed. Cir. 1998).

Teva contended at trial, with complete justification on the basis of the record as it existed prior to trial, that, in effect, at the time Warner-Lambert's patent attorney was preparing the application for the '450 patent the Warner-Lambert inventors assembled, discussed Vasotec and decided not to disclose the Merck product to their patent attorney. This contention is based on Dr. Murthy's deposition testimony about which he was questioned during the trial:

> Q. All right. But you actually recall, don't you, Doctor, that you discussed specifically with your co-inventors whether or not to disclose Vasotec to your patent attorney?

A. Honestly, I cannot recall that, if they were ever discussed.

Q. You have your deposition transcript?

A. Yes.

Q. Could you turn to page 118, please. I want to read your testimony starting on line 10, on page 118. Do you see that?

A. Yes.

Q. The question was: did you tell your patent attorney about the Vasotec product, Merck's Vasotec product? And then Mr. O'Malley objects to this. The question was vague. And the answer you gave: We discussed it among the other inventors and we didn't think it was relevant because it did not deal with magnesium carbonate or lactose.

"QUESTION: When you say "we," discussed it among the other inventors, what do you mean by that?

"ANSWER: The five authors, the four.

"QUESTION: You mean, Doctor - - Doctors Harris, Hokason, Reisch and Waldman?

"ANSWER: Yes.

"QUESTION: When did these discussions take place?

"ANWER: On line 4 of page 119. "I can't recall a specific date, but around that time of filing."

And that was truthful testimony. That was your best recollection when you gave your deposition testimony, wasn't it, Doctor?

A. That was my best recollection.

(Tr. pp. 498-99).

Dr. Murthy then corrected his deposition testimony, stating that in fact the last discussions about Vasotec were at the time of the failed sodium bicarbonate studies, which

would have been in May or June 1986, before the conception date of the invention claimed in the '450 patent and long before preparation of the patent application:

> THE WITNESS: Here's what I recall today, your Honor. At the time when I testified to this was back in 2001. I was recalling - - I was trying to recall events that took place about 14 years. And it was true that we discussed about sodium bicarbonate, and we discussed it with Enalapril and Merck's product at the beginning of our program. But after we ran experiments, sodium bicarbonate at different levels and different methods or incorporation, we were not successful in stabilizing this product. Sodium bicarbonate did not help us in any way. So the whole sodium bicarbonate, and Enalapril, and Vasotec fell off the table as - - after we stabilized our product with magnesium carbonate and lactose. And so we did not - - it's true that I - - I did testify to this effect, but after reflecting on it, it just - - I was mixed up with the dates at the time. It was true, we did discuss about this, but that was the beginning of the program and not at the time of the filing. The discussions took place much earlier, at the beginning of the program.

(Tr. pp. 500-03).

Because of Dr. Murthy's deposition testimony Teva was justified in arguing that at the time of the preparation of the patent application the Warner-Lambert inventors assembled, discussed Vasotec and decided not to tell Warner-Lambert's patent attorney about Vasotec, with the consequence that Vasotec was not brought to the attention of the PTO. The trial evidence establishes that this is not what happened and that Dr. Murthy was simply mistaken in this regard when he testified at his deposition.

Dr. Murthy's trial testimony that Vasotec and enalapril were not discussed among the inventors (they "fell off the table") after the failure to stabilize quinapril by adjusting its pH through the use of sodium bicarbonate is supported by the testimony of Dr. Harris, who recalled no discussion of Vasotec after the failure of the pH studies called for in the May 7, 1986 memo (PTX 55). Neither Dr. Murthy nor Dr. Harris now work for Warner-Lambert. Both were completely credible witnesses.

The sequence of events extending from May 1996 through the filing of the patent application is consistent with Dr. Murthy's and Dr. Harris's testimony about their discussions of Vasotec. Vasotec was a subject of interest to them when they ascertained the pH of the Vasotec tablet in solution, when they entertained the hypothesis that adjusting the pH of quinapril would solve the problem of cyclization degradation and when they sought to achieve a suitable pH through the use of sodium bicarbonate. When they failed to achieve stability through adjustment of the pH of quinapril[3] they turned their efforts towards finding an excipient that would stabilize quinapril. By late June or July 1986 Vasotec and its use of sodium bicarbonate were no longer of interest to the Warner-Lambert scientists and they had no reason to discuss Vasotec.

The fact that Warner-Lambert's quest for stability took place in two stages and the fact that Vasotec was of interest to the Warner-Lambert scientists only during the first, unsuccessful stage, were not fully recognized in the October 2, 2003 Opinion deciding the parties' summary judgment motions and were only fully appreciated by the court after considering the testimony and other evidence presented at the trial. Consequently some of the factors set forth in the earlier opinion as indicative of an intent to deceive are not in fact evidence of such an intent. That Warner-Lambert scientists kept themselves informed about the 'pril competition, including Merck's efforts, is neither surprising or reprehensible. There was no reason why Warner-Lambert should not have continued its efforts to stabilize quinapril after Merck released Vasotec in January 1986. Knowledge that Vasotec contained sodium bicarbonate did not disclose the manner, if any, in which it contributed to stabilization of enalapril, and the Warner-Lambert

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[3] In solid form quinapril does not have a pH and reference to quinapril's pH refers to the pH measured when a quinapril tablet is suspended in water.

scientists simply used sodium bicarbonate to achieve various pH levels, a technique which failed to achieve stability and which (unknown to the Warner-Lambert scientists) had failed to achieve stability when the Merck scientists pursued the same route to stabilization.

The Warner-Lambert scientists knew that sodium bicarbonate was used in the Vasotec formulation but did not know its function. In fact during the course of Merck's development of a stable formulation its scientists at first used sodium bicarbonate to adjust enalapril's pH; later during their analysis of the chemistry of the cyclization degradation process they employed sodium bicarbonate in connection with the reaction that converted enalapril maleate to a stable enalapril sodium. There is no evidence that the Warner-Lambert scientists were aware of this function of sodium bicarbonate in Vasotec. The two articles that Teva claims alerted Warner-Lambert to the mechanics of stabilizing enalapril entered the public domain after Warner-Lambert had finalized its inventive concept for stabilizing quinapril. It has not been established that the Warner-Lambert inventors were aware of them prior to the February 1987 filing date. In fact those articles did not reveal the Merck process. This will be discussed at greater length in connection with Teva's contention that claims 16 and 17 are invalid on the ground of obviousness.

Teva notes that originally filed claims 18 and 19 of the '450 patent application (which ultimately became claims 16 and 17) were directed to the combination of an ACE inhibitor with an alkali or alkaline earth-metal salt and a saccharide. This was broad enough to include sodium bicarbonate, an alkaline earth metal salt. Claim 16 provides for a combination of an ACE inhibitor with an alkali or alkaline earth-metal carbonate and a saccharide. As construed the term "carbonate" includes sodium bicarbonate; a component of Vasotec. At the time he signed the

patent application Dr. Murthy was aware that it covered enalapril. Teva contends that these facts demonstrate that Dr. Murthy and the other Warner-Lambert failed to disclose the existence of Vasotec with the intent to deceive the PTO.

Both the circumstances and Dr. Murthy's completely credible testimony negate any such intent. By the time the application was being prepared the Warner-Lambert scientists had excluded sodium bicarbonate as an excipient that would stabilize quinapril. Thus the language of original claims 18 and 19 was too broad, as it unambiguously included sodium bicarbonate through the use of the words "alkaline earth-metal salt." Although as a result of the January 29, 2004 opinion of the Court of Appeals for the Federal Circuit in the Schwartz Pharma case the word "carbonate" as used in claim 16 includes both the carbonate and bicarbonate ions, this was not the meaning that the Warner-Lambert inventors attributed to it when they signed the patent application. Based on their success with magnesium carbonate and failure with sodium bicarbonate, they were thinking only in terms of an excipient possessed of the carbonate ion.

Referring to the phrase "[a] suitable amount of an alkali or alkaline earth metal salt," Dr. Murthy testified, "Because I took it to mean mostly carbonates because those are the ones that worked. There was no bicarbonate that has worked for us in our efforts to stabilize the product, so we did not have any bicarbonate in mind." (Tr. p. 542). Elaborating further, Dr. Murthy stated:

> We do not - - we did not have in mind sodium bicarbonate, otherwise we would have been very specific about it. Because our experiments with sodium bicarbonate did not help us in the stabilizing of quinapril. So we didn't - - at least I did not have in mind sodium bicarbonate and to prevent cyclization of quinapril.

(Tr. p. 489).

This testimony of Dr. Murthy is totally consistent with the course of Warner-Lambert's efforts to stabilize quinapril against degradation through cyclization. The experiments looking to stabilization by adjusting pH through the use of sodium bicarbonate had failed, and, in the words of Dr. Harris, "we went back to the drawing board, so to speak, and started one-on-one excipient compatibility studies again and what those are, you mix quinapril with different excipients and store them and study their stability." (Tr. p. 60).

Having achieved success with magnesium carbonate, it is natural that the failed sodium bicarbonate no longer seemed relevant to the Warner-Lambert scientists. Notwithstanding the construction that the Court of Appeals has given to the word "carbonate," it was not the intent of the '450 patent inventors to claim either the Vasotec formulation or sodium bicarbonate[4]. The evidence does not support Teva's argument that failure to disclose Vasotec, which contained sodium bicarbonate, was intended to deceive the PTO.

B. Obviousness: In the October 2, 2003 Opinion the court found that in Warner-Lambert's formulation lactose serves the function of inhibiting hydrolysis and that there is no evidence that the lactose contained in Merck's Vasotec tablets serves that function or that Warner-Lambert's scientists thought that it did. Consequently summary judgment of validity was entered with the respect to claim 1, 4-10 and 12 of the '450 patent.

There remained for trial Teva's contention that claims 16 and 17 of the '450 patent were

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[4] Original claims 1-17 of the '450 patent application all claim use of a suitable amount of a saccharide to inhibit hydrolysis. This claim limitation is absent from the Vasotec formulation. These 17 original claims are also limited to ACE inhibitors that are susceptible to discoloration. Enalapril is not susceptible to discoloration. The term "alkali or alkaline earth metal salt" in original claims 18 and 19 was broad enough to include sodium bicarbonate. For the many reasons set forth in this opinion this fact does not establish an intent to deceive the PO, by failing to disclose the existence of Vasotec.

obvious in light of Merck's Vasotec tablets. An invention is invalid if "the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." Graham v. John Deere Co., 338 U.S. 1, 14 (1966). As codified in 35 U.S.C. § 103, an invention is not patentable if it "would have been obvious at the time the invention was made to a person having ordinary skill in the art." Merck & Co. v. Biocraft Labs., 874 F.3d 804, 809 (Fed. Cir. 1989). Teva has the burden of proof of obviousness.

Resolution of the question of obviousness requires (i) a determination of the scope and content of the prior art; (ii) the level of ordinary skill in the art; and (iii) the differences between the claimed invention and the prior art. Advanced Display Systems, Inc. v. Kent State University, 212 F.3d 1271, 1284-85 (Fed. Cir. 2000). For the purposes of the summary judgment motion the court adopted Dr. Schwartz's definition that the prior art in the circumstances of this case is the stabilization of pharmaceutical compounds. The evidence at trial does not lead to a different definition. The parties did not disagree for the purposes of the summary judgment motion upon the level of ordinary skill in the art, and the same level will be assumed here:

> a pharmaceutical formulator, that is a person having a working knowledge of drug development and formulation, who has either an advanced degree in pharmaceutics, chemistry or related science with one or more years of industry experience or a bachelor's degree in pharmaceutics, chemistry or a related science and at least five or more years of industry experience or the equivalent.

In the early 1980's when Merck and Warner-Lambert commenced their efforts to stabilize an ACE inhibitor (enalapril in the case of Merck and quinapril in the case of Warner-Lambert) none of the scientists at either company had any knowledge of cyclization degradation. In contrast to hydrolysis, the most common degradation pathway, none of them had addressed cyclization degradation in any drug on which they had worked, nor had they known of any drug

which degraded via cyclization, nor had they seen anything concerning it in the literature. Likewise Teva's expert, Dr. Schwartz, in his thirty-five years of drug formulation experience had never before encountered a drug that degraded via cyclization. He testified that in 1986 it was generally believed that carbonates and sodium carbonates promoted degradation via cyclization rather than promoting stability.

The only materials and information upon which Teva relies as prior art are those which relate, or which might be inferred to relate, to Vasotec or its development. They consist of: i) the Vasotec tablet itself that appeared on the market in January, 1986; ii) the package insert that accompanied the tablets which disclosed that "in addition to the active ingredient enalapril maleate, each tablet contains the following inactive ingredients: iron oxides, lactose, magnesium stereate, starch, and other ingredients (it did not mention sodium bicarbonate); iii) the 1985 Dictionnaire Vidal monograph concerning Renitec (the European name for the Vasotec tablet) and the related Dutch publication Pharmaceutisch Weekblad that disclosed that Renitec contained enalapril maleate, lactose, sodium bicarbonate, corn starch, magnesium stereate, iron oxide red and iron oxide yellow; iv) the article by N.R. Bohidar, J.F. Bavitz and P.K. Shiromani which appeared in 1986 in the publication Drug Development and Industrial Pharmacy v) an article by P.K. Shiromani and J.F. Bantz which also appeared in 1986 in Drug Development and Industrial Pharmacy ("Shiromani"); and vi) an article by Toshihiro Kato of Nippon Merck-Banyu Co., in Japan (entitled "Flow-injection spectrophotometric Determination of Enalapril in Pharmaceuticals with Bromothymol Blue" that appeared in a 1985 edition of Analytica Chimica Acta, printed in the Netherlands. ("Kato")

While Kato would certainly lead those of skill in the art to conclude that Merck was

seeking to formulate a stable enalapril product, that would come as no surprise to Merck's competitors and the article did not disclose how Merck effectuated stabilization. The '450 patent's conception date was no later than August 20, 1986. Bohidar was not available to the public until after September 9, 1986 and Shiromani was not released to the public until after Bohidar's release. They were not, therefore, prior art.

Dr. Schwartz testified that in his opinion a person skilled in the art with minimal experimentation could have determined how to stabilize quinapril against cyclization degradation simply by reference to the Vasotec tablet itself, the package insert and Dictionnaire Vidal. According to him it would have been possible to determine the precise amounts of Vasotec's starting ingredients through reverse engineering. He believed that (as of September 1986) "[i]f a person who is skilled in the art knows the exact quantities of all of the tablet ingredients and is also led to conclude that sodium bicarbonate is performing a stabilizing role through pH adjustment [ ] it is possible to carry out the process for manufacturing Vasotec using the descriptions that [he] identified [ ] in the product insert, and also having the tablet in your hand" (Tr. p. 267).

Dr. Schwartz conceded that he does not deal with degradation pathways of drug compounds on a regular basis and that outside the courtroom context he had had no experience with ACE inhibitors. He had never been involved in the formulation of an ACE inhibitor compound and had never performed accelerated stability tests on an ACE inhibitor. In thirty-five years of drug formulation experience he had never encountered drug compounds that degrade via cyclization.

Dr. Schwartz testified that if a formulator were to use the well-known method of dry

blending (contacting sodium bicarbonate with enalapril) there would be no reasonable expectation that the process would result in a stabilized enalapril. Prior to December 31, 1986 he was not aware of any publicly available information disclosing the use of a carbonate or a bicarbonate to inhibit cyclization, nor was he aware of any drugs that employed any form of pH to inhibit cyclization. He was not aware of any tablet formulation in the prior art that, prior to 1986, used sodium bicarbonate to stabilize any degradation pathway, although there were several other well-known functions of sodium bicarbonate in tablet formulations.

Despite his confidence that a person skilled in the art could perform reverse engineering on a Vasotec tablet and ascertain the starting ingredients and their amounts, Dr. Schwartz conceded that he did not know of any way to differentiate between enalapril sodium and enalapril maleate in the final product, or to take a Vasotec tablet and distinguish between the reactive and stable form and unreacted and unstable form.

In 1994 Dr. Schwartz had received from Merck confidential information concerning the formulation of the stable Vasotec tablet, including the fact that sodium bicarbonate served a stabilizing function. He was not able to conclude from the information that he was given that an acid-base reaction took place between sodium bicarbonate and enalapril, i.e., that stabilization was achieved via an acid-base reaction. In 1994 during the course of the Canadian litigation he learned that Merck did not want to discuss the reaction or how the reaction stabilized Vasotec.

In spite of Dr. Schwartz's extensive experience in the field of pharmacology, the totality of the evidence weighs heavily against acceptance of his opinion that in August 1986 a person skilled the art could have carried out the process for manufacturing Vasotec using the description of Vasotec in the package insert and in Dictionnaire Vidal and having a Vasotec in hand.

Knowledge of the information contained in Kato which was in circulation in 1985, and in Bohidar and Shiromani which entered the public domain after September 9, 1986, would not have altered the situation.

At the time in question next to nothing was known about cyclization. It took both the Merck and Warner-Lambert scientists years of trial and error before they could develop means to stabilize enalapril in the case of Merck and quinapril in the case of Warner-Lambert. Even after Merck developed its basic process of neutralizing enalapril and converting enalapril to enalapril sodium, it was necessary to refine the process through adjustment of the duration of mixing, temperature, holding time in the mixer and particle size. When giving his opinion Dr. Schwartz had the benefit of confidential information Merck provided to him in 1994 about Merck's development of Vasotec and its use of sodium bicarbonate. One cannot help but conclude that his opinion benefits from hindsight and does not reflect the position of a person skilled in the art in 1986.

Merck's decision to treat Vasotec and the process for manufacturing it as a trade secret rather than seeking a patent is strong evidence that a person skilled in the art could not have replicated the drug or the process using publicly available information. This was a decision made at the highest level of Merck's research management and was given careful thought. The Kato, Bohidar and Shiromani articles were written by Merck scientists and must have been cleared by Merck in advance of their publication to ensure that the valuable trade secret of Vasotec's stabilization process was not disclosed. Merck sought to preserve this trade secret at least through the 1994 Canadian litigation, during which the Vasotec manufacturing process was treated as confidential and sealed.

The Merck scientists were fully aware of the Dictionnaire Vidal description of the contents of Renitec, but, as Dr. Brenner testified, "[t]he consensus within Merck was that knowing the ingredients themselves, the typical work in the field could not discern the process by which Merck made enalapril tablets," specifically, "the role of sodium bicarbonate in that process." (Tr. p. 157). The Merck scientists also knew of Bohidar, but "[i]t was felt that there wasn't enough detail in the article to allow one to develop the stable product." (Tr. p.163).

Dr. Brenner, unlike Dr. Schwartz, had engaged in formulating drug products extensively during his career. This included stabilizing drug compounds against degradation. His opinions relating to obviousness are entitled to and have been accorded great weight. For example:

> Q. Dr. Brenner was there any belief or consensus of Merck in the mid 1980s whether the process to stabilize Vasotec and the role of sodium bicarbonate in that process could be discerned in the - - by anyone in the field from the combination of the Vasotec tablets, the package insert, the Dictionnaire Vidal [and] Bohidar?
>
> A. It was the feeling within Merck having access to only that data, that was insufficient to teach somebody the role of sodium bicarbonate in the stabilization of the formulation.
>
> Q. Can you explain why Merck felt that way? Why didn't Merck feel that the various threats (sic) of information you've identified now, Bohidar, the tablets, the package insert, in the Dictionnaire Vidal would not tell one in the field the role of sodium bicarbonate in the Vasotec process, and how to use that to stabilize Vasotec?
>
> A. Well, basically, you know, at that point in time when Merck decided to keep this as a trade secret, all of those individuals, mostly myself and two other individuals in the department were aware of perhaps around five years of work that had been done on enalapril, the magnitude of the work, and the difficulty of stabilizing the tablet. And with that realization in hand, the three of us were essentially, were the primary movers in making that decision, felt that with the experience and the knowledge of the difficulty in developing the process, the ingredients, themselves, wouldn't be sufficient to develop the process without the kind of experimentation that we had to do over a long period of time.

Q. Now, Dr. Brenner, not only was Merck confident that the combination of these pieces of information would not allow one of ordinary skill in the mid eighties to discern how to stabilize Vasotec. You know that Merck was also confident that that same knowledge would not teach anyone developing their own ace inhibitors in that period how to stabilize those ace inhibitors also; is that correct?

A. That in reality was more the driving force for keeping the process as a trade secret than maybe protecting enalapril.

Q. Could you explain that a little bit, please?

A. Well, in this timeframe the ace inhibitor area was a real hot area, I would say. There may have been up to maybe 10 of them that may have been developed in the industry. Looking at them structurally, we felt that most of them would be susceptible to the same mode of cyclization. And it wasn't in the Merck's commercial interest to help people in other firms solve stability problem. In fact, [if] it took them longer to solve it and longer to get on the market it would be commercially beneficial to Merck.

(Tr. p. 164-66).

The European prosecution history of the '450 patent confirms the conclusion that a person of ordinary skill in the art would not be able to discern a stability role for sodium bicarbonate in the Vasotec formulation. Original filed claim 18 of the '450 patent application read:

18. A process for stabilizing an ACE inhibitor against cyclization which comprises the step of contacting the drug with:

(a) a suitable amount of an alkali or alkaline earth-metal salt and,

(b) one or more saccharides.

Issued claim 12 of Warner-Lambert's European Patent 280999 read:

12. A process for stabilizing an ACE inhibitor drug as defined in claim 1 against cyclization which comprises the step of contacting the drug with:

(a) a suitable amount of an alkali or alkaline earth metal salt, and

(b) one or more saccharides.

Both original claim 18 of the '450 patent application and issued claim 12 of the European patent are broad enough to include sodium bicarbonate (an alkaline earth metal salt). The Vasotec formulation was before the European Examiner in the form of Dictionnaire Vidal. He did not cite Vasotec as relevant against claim 12 and, in fact, stated in a different context that "[t]he examining division agrees with the Applicant that there is no teaching in the prior art to use the combination of an alkali or alkaline earth metal carbonate and the saccharide to stabilize and ACE inhibitor as claimed in claim 1."

Thus the European Examiner, aware of Vasotec and aware that it contained sodium bicarbonate, allowed the issuance of claim 12 which includes a suitable amount of sodium bicarbonate as did original filed claim 18 of the '450 patent application and as does claim 16 of the issued '450 patent as construed by the Court of Appeals for the Federal Circuit[5]. Knowing that Vasotec contains sodium bicarbonate, the European Examiner found no basis to find that sodium bicarbonate stabilizes against cyclization in that formulation. If he had, he would not have allowed European claim 12.

Claims 16 and 17 of the '450 patent would not have been obvious at the time the invention was made to a person having ordinary skill in the art and consequently are not invalid under 35 U.S.C. §103.

D. Anticipation: Teva contends that claims 16 and 17 of the '450 patent are invalid under

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[5] Upon the cross-motions for summary judgment Teva argued that the words "as defined in claim 1" appearing in claim 12 of the European patent had the effect of disclaiming enalapril, and thus narrowing the reach of claim 12. This argument has no merit.

35 U.S.C. § 102(g)(2)[6]. Anticipation under this section requires that a single prior art reference disclose each element of the claimed invention. In re Cruciferous Sprout Litigation, 301 F.3d 1343, 1349 (Fed. Cir. 2002). If a prior art reference fails to disclose even one element of the claimed invention, then the claim is not anticipated. Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1574 (Fed. Cir. 1986). A patent as a whole is entitled to the presumption of validity, 35 U.S.C. § 282, and Teva bears the burden of proving anticipation by clear and convincing evidence. Hybritech Inc., v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1375 (Fed. Cir. 1986).

Teva argues that Merck's prior art Vasotec process meets all limitations of claims 16 and 17 of the '450 patent. As to claim 16, i) a process for stabilizing an ACE inhibitor drug, ii) against cyclization, iii) which comprises the step of contacting the drug with: (a) a suitable amount of an alkali or alkaline earth-metal carbonate, and (b) one or more saccharides. As to claim 17, the process of claim 16 wherein the drug is selected from the group consisting of quinapril, enalapril, and indolopril, or a pharmaceutically acceptable acid addition salt thereof. Teva notes that Vasotec was manufactured and sold in the United States in January 1986, well before Warner-Lambert's conception and filing date and that commercial manufacture of the Vasotec tablet could not have occurred without using Merck's Vasotec process.

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[6] "A person shall be entitled to a patent unless -

...

(g)(2) before such person's invention thereof, the invention was made in this county by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates, of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

At trial, Teva argued that "[w]ith respect to § 102(g), all you have to show is a process was actually done in the prior art. It doesn't matter if the process was secret or not." (Tr. p. 239). This is clearly not a correct statement of the law. For § 102(g) to apply, Teva must prove that, before Warner-Lambert's invention of the '450 patent, Merck had not suppressed or concealed its Vasotec process. Palmer v. Dudzik, 481 F.2d 1377, 1385 (C.C.P.A. 1973); Paulek v. Rizkalla, 760 F.2d 1270, 1273-75 (Fed. Cir. 1985). The case upon which Teva relies, Dow Chem. Co. v. Astro-Valcour, Inc., 267 F.3d 1334 (Fed. Cir. 2001), is not to the contrary.

Anticipation and obviousness are different concepts. However, many of the findings in the previous section of this opinion dealing with obviousness bear upon the issue of anticipation. Claims 16 and 17 are process claims. Vasotec itself is a product. As the Court stated in Torpharm, Inc. v. Ranbaxy Pharmaceuticals, Inc., 336 F.3d 1322, 1327 (Fed. Cir. 2003) "if the product [Vasotec] were sold by one other than the patentee [Merck] and the process of making remained unkown, then sale of the product would not pose a statutory bar to a claim on the process [claims 16 and 17]".

"To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate," Elan Pharmaceuticals v. Mayo Foundation, 346 F.3d 1051, 1054 (Fed. Cir. 2003). "Enablement requires that 'the prior art reference must teach one of ordinary skill in the art to make or carry out the claimed invention without undue experimentation." "Id. at 1054. As recounted in the previous section of this opinion the alleged prior art in this case did not disclose the function of sodium bicarbonate in Vasotec nor did it disclose the process by which Merck stabilized enalapril against cyclization degradation. That stabilization process depended on the extent to which an in-situ deprotonation reaction between enalapril and sodium bicarbonate went

to completion in the limited water of wet granulation. Numerous factors had to be controlled. Merck had developed its own proprietary test to determine the extent of the reaction.

The conception date of Warner-Lambert's invention was in August 1986, and by the end of August the Warner-Lambert scientists had demonstrated that it worked for its intended purpose. At that time the availability of a Vasotec tablet and knowledge of the tablet's starting components would not have enabled one skilled in the art to ascertain the complex process by which the Merck scientists formulated a stable enalapril tablet.

By its terms § 102(g) bars a patent if a prior invention was made by an inventor who had not suppressed or concealed it. Before Warner-Lambert's invention in August 1986, Merck had made a deliberate decision to forego patent protection and instead to conceal from the public as a trade secret its process for stabilizing Vasotec using sodium bicarbonate. In a previous section of this opinion there is described the success which Merck achieved in maintaining the process as a trade secret to the late 1980's or early 1990's and the continuing efforts on Merck's part during the 1994 Canadian litigation to withhold the role of sodium bicarbonate in that process.

At the time the invention disclosed in the '450 patent was conceived there were available to the public only the Vasotec tablet, the package insert, Dictionnaire Vidal, Pharmaceutisch Weekblad and Kato. In their totality they disclosed most of the starting components of Vasotec and that enalapril was susceptible to cyclization. As previously noted, Dr. Brenner's testimony that this information would not have enabled a person skilled in the art to determine or practice Merck's complex process for stabilizing enalapril is totally convincing. Dr. Schwartz's opinion that the process could be discovered by reverse engineering of the Vasotec tablet and a minimal number of experiments is totally unconvincing. The publication of Bohidar and Shiromani after

the date of conception did not change the situation. Merck's Vasotec process remained a trade secret secure from the public.

Thus, before (and for a considerable time after) the conception of the invention disclosed in the '450 patent, Merck's Vasotec process had been deliberately suppressed and concealed. The available information concerning Vasotec did not enable one of skill in the art to practice claims 16 and 17 of the '450 patent nor did it enable such a person to practice a process of stabilizing an ACE inhibitor against cyclization. Teva has failed to prove that claims 16 and 17 were anticipated by the Merck Vasotec process.

IV. Conclusion

The '450 patent is not invalid by reason of the failure of the Warner-Lambert inventors to call the Merck Vasotec product to the examiner's attention. Nor is the '450 patent invalid by reason of anticipation or obviousness. Judgment as sought in the complaint will be entered in favor of Warner-Lambert.

Dated: June 29, 2004

DICKINSON R. DEBEVOISE
U.S.S.D.J.