IN THE UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

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WARNER-LAMBERT COMPANY,	)	
	)	
Plaintiff,	)	Civil Action No. 99-922 (DRD)
	)	
v.	)	Hon. Dickinson R. Debevoise
	)	
TEVA PHARMACEUTICALS USA,	)	
	)	
Defendant.	)	
	)	

PLAINTIFF WARNER-LAMBERT COMPANY'S POST-TRIAL BRIEF

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INTRODUCTION

Teva's counsel, in his opening, promised that "at least one of the inventors will testify before this Court that he ***knew*** that sodium bicarbonate was a stabilizer in Vasotec®." (Trial, Tr. 9:9-:12). Teva recognized that, unless it could make a threshold showing by clear and convincing evidence that Warner-Lambert withheld ***known*** material information, then the Court must reject its inequitable conduct defense. Teva, however, never delivered on its promise.

As is now known, Merck very carefully and deliberately concealed the information available about its Vasotec® formulation and process, such that no competitor in the 1986 time period would be able to discern the role of sodium bicarbonate in that process. Indeed, Merck was so confident that it could conceal this information from competitors like Warner-Lambert, that it made the very risky decision to forego patent protection on its process and instead, maintain it as a trade secret. And, as Teva's expert Dr. Schwartz knows from first hand conversations with Merck's attorneys, Merck still believed this information – the very information Dr. Schwartz told this Court was known in 1986 – to be secret as late as 1994.

Merck's confidence in its ability to keep the stabilizing role of sodium bicarbonate secret, a decision reached after much deliberation by the top technical management at Merck, was well-justified. From the thin threads of information that were available during their quinapril formulation

development work, the Warner-Lambert inventors had no basis for ***knowing***, and did not in fact ***know***, that sodium bicarbonate was the stabilizer in Merck's formulation. Accordingly, the Warner-Lambert inventors had no basis to know any alleged materiality of the Vasotec® formulation, Teva thus did not make good on its promised showing, and its heavy burden to prove inequitable conduct was not met.

Nor is there so much as a shred of evidence of any intent to deceive. Today, Teva no longer even contends that the Vasotec® formulation has any materiality with respect to the primary claim of the '450 patent, claim 1, or any of the fifteen dependant claims that follow it. And indeed, it is undisputed that these claims are valid over the Vasotec® formulation. To believe that the inventors intended to deceive the Patent Office, therefore, one would have to believe that they were willing to risk their concededly valid and important invention for the sake of two claims at the back end of their patent. There is no evidence of this, certainly no clear and convincing evidence of this, and the very premise is facially implausible. Because Teva did not meet its heavy burden of proving intent to deceive by clear and convincing evidence, Warner-Lambert is entitled to Judgment that the '450 patent is enforceable.

I. FACTS

A. In Early 1986, The '450 Patent Inventors Were Faced With Solving A Difficult And Unusual Stability Problem Exhibited By The Drug Quinapril

1) The instability of quinapril became the biggest roadblock to the drug's commercialization

In early 1986, expectations within Warner-Lambert were high for the commercial success of a promising drug candidate, quinapril. Quinapril was a member of the then relatively new class of non-sulfhydryl Angiotensin Converting Enzyme ("ACE") inhibitors, drugs that were known to be effective in the treatment of high blood pressure and heart failure. By early 1986, Warner-Lambert had obtained enough results from clinical trials to convince management the drug quinapril would likely prove to be safe and effective as an ACE inhibitor. (Harris, Tr. 32:3-:15).

In the clinical trials, a simple capsule formulation was employed, which included the excipients mannitol and syloid 244 in addition to quinapril. (Harris, Tr. 32:16-:25, 34:10-:14; PTX 42, WL 29055). Warner-Lambert discovered, however, that this formulation quickly degraded via cyclization, requiring remanufacture and frequent re-supply of the clinics. (Harris, Tr. 34:15-35:21; PTX 42, WL 29055).

When the clinical capsule formulations began to display this cyclization problem, Dr. Michael Harris, an experienced Warner-Lambert formulator, was asked to prepare a tablet formulation that would solve this problem. (Harris, Tr. 35:22-36:3). Dr. Harris, working with one other

Warner-Lambert formulator, Frank Waldman, attempted a "dry" tablet formulation, under the assumption that moisture in the formulation was causing the cyclization. (Harris, Tr. 36:4-37:7). Specifically, excipients with a low moisture content were combined with quinapril via "dry blending," in which no water was added. (Harris, Tr. 36:4-38:12; PTX 42, WL 29056). However, accelerated stability testing of this first tablet formulation once again displayed unacceptable levels of degradation via cyclization. (Harris, Tr. 40:6-42:7; PTX 42, WL 29071).

The failure of this first tablet formulation was completely unexpected. (Harris, Tr. 42:18-:21). Dr. Harris, based on his many years of experience in pharmaceutical formulation, had assumed that moisture was causing the degradation demonstrated by the clinical supplies, and fully expected the first attempt at the dry tablet formulation to completely solve this problem. (*Id.*) When this conventional attempt to address this problem failed, the instability of quinapril became something of a crisis. (Harris, Tr. 42:1-:7). Quinapril was well along in its successful clinical trials, but for the first time, Warner-Lambert management recognized that development of a stable formulation could be a significant roadblock to the commercialization of this promising drug. (Harris, Tr. 42:22-43:17).

Warner-Lambert responded to this potential crisis by making the development of a stabilized composition of quinapril its highest priority. Five experienced pharmaceutical formulators (the eventual inventors of the '450 patent) were released from their other duties and assigned essentially

full time to this project; an unusual commitment of manpower at this time to a formulation project. (Harris, Tr. 43:18-44:10).

The five Warner-Lambert formulators assigned to solve the cyclization problem exhibited by quinapril, though very experienced and skilled in the field, had little or no information to draw from in the Spring of 1986 to solve this significant problem. As Teva's expert, Dr. Schwartz, conceded at trial, degradation of a drug via cyclization is rare. (Schwartz, Tr. 294:12-295:2).

Not surprisingly then, none of the five formulators assigned to this project had ever encountered cyclization of a drug prior to quinapril. (Harris, Tr. 45:5-:14). Nor had any of these scientists seen discussions of cyclization or stabilization of drugs against cyclization in the literature prior to this project.[1] (Harris, Tr. 45:19-46:2).

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[1] In fact, this degradation pathway is so rare that neither of the two testifying experts in this litigation (Dr. Schwartz for Teva and Dr. Brenner for Warner-Lambert), with over seventy years combined experience in pharmaceutical formulation, have any personal experience with this degradation pathway outside of the ACE inhibitors involved in this case. (Brenner, Tr. 601:7-:15; 602:2-:7; Schwartz, Tr. 294:17-:21). Nor did lead '450 inventor, Dr. Harris, ever encounter this rare degradation pathway ever again after the quinapril project. (Harris, Tr. 46:16-:22).

2) Dr. Murthy's failed experiment with sodium bicarbonate was merely one of dozens of experiments performed during the development work

With little or no background or experience in cyclization, the Warner-Lambert formulators tried a great many things in an effort to stabilize quinapril. In total, "over a hundred" formulations were prepared and tested during the Spring and early Summer of 1986. (Harris, Tr. 47:15-:23). In pursuit of their goal, the quinapril team would meet nearly every day to review data from the previous experiments and to discuss ideas on how next to proceed. (Harris, Tr. 46:23-47:7). Many ideas, based on a variety of different theories, were discussed and then pursued in the lab. It was also not unusual for upper management from Warner-Lambert's R & D group to sit in on these daily meetings from time-to-time, to monitor the team's progress and to contribute ideas. (Harris, Tr. 47:24-48:4). Management's constant presence created pressure and a sense of urgency to succeed in this difficult assignment. (Harris, Tr. 48:5-:8).

Early on in this development process, the Warner-Lambert formulators believed that pH might have a role in stabilizing quinapril against cyclization in a tablet formulation. Specifically, through their own experiments, the inventors determined that in a ***solution*** (as opposed to a solid tablet), quinapril is stable against cyclization in the pH range of 4.0 to 8.0. (Harris, Tr. 48:9-50:23; PTX 55). Based on this finding, the formulation team ran an experiment in May 1986 to determine whether

quinapril could be stabilized by creating a pH environment in the solid tablet formulation that approximated the middle of the stable solution pH range of 4.0 to 8.0. (PTX 55). Specifically, the formulation team attempted quinapril tablet formulation at pH's of both 5.0 and 6.5; 5.0 being close to the lower limit of stability (4.0) seen is the solution studies, and 6.5 being close to the upper limit of 8.0. (Murthy, Tr. 421:20-422:7).

To test this internal Warner-Lambert theory, the formulators needed an alkaline or basic substance to mix with the very acidic quinapril to raise the pH to the target range of 5.0 to 6.5. (Harris, Tr. 51:6-:25). The formulators chose four different alkaline excipients to combine with quinapril, including potassium phosphate, N-Methyl-D-Glucamine, Tris (hydroxymethyl) amino methane, and sodium bicarbonate. (Harris, Tr. 52:21-53:4; PTX 42, WL 29114).

Warner-Lambert's experiment based on its early pH theory was not an attempt to "mimic" the stabilization mechanism of Vasotec®, which of course, was unknown to the Warner-Lambert formulators. (Murthy, Tr. 522:1-529:20). Three out of the four alkaline excipients employed in this experiment had no connection whatsoever with Merck's Vasotec® formulation. (Murthy, Tr. 522:12-523:9). Moreover, if the formulators were attempting to use Vasotec® as a guide in this experiment, it would have made little sense to prepare some of the formulations at a pH of 5.0. That pH is between 10 and 100 times more acidic than the pH measured for the Vasotec® formulation. (Murthy, Tr. 523:20-524:5). Instead, by testing

tablet formulations at pH's as low as 5.0, the Warner-Lambert formulators were simply trying to cover the pH range (4.0 to 8.0) that their own internal solution studies indicated might be stable for quinapril (Murthy, Tr. 524:9-:18), as reflected in Dr. Murthy's May 7, 1986 memorandum:

> "The pH of the current tablet formulation (1% suspension in distilled water) will be determined.
>
> ***The amount of sodium bicarbonate required to increase the pH of the tablet suspension to 5.0 and 6.5 will be determined.***
>
> ***This is based on the presently available information on the solution kinetics of quinapril which suggests that the pH range for the maximum stability of the compound is 4.0 to 8.0.***
>
> Also Vasotec® (Merck's enalapril maleate) tablets are formulated to have a pH of 6.5 through the inclusion of sodium bicarbonate."
>
> "The calculated quantities of sodium bicarbonate needed to bring the pH of tablet suspension to 5.0 and 6.5 will be included in proposed experimental tablet formulations, which will be evaluated for short term stability through storage at 37° C and 45° C. Our current tablet formulations will serve as the controls in these experiments."

(PTX 55, emphasis added).

Warner-Lambert attempted to employ both dry blends (no water added to the formulation) and wet granulations (a mixing process that does employ water) to stabilize quinapril in its pH-based experiment. (Harris, Tr. 53:11-:17; PTX 42, WL 29108). As explained below (pp. 20), had Dr.

Murthy really known or suspected how Merck stabilized its Vasotec® formulation, *i.e.*, through a chemical reaction between the enalapril and sodium bicarbonate, he would have known that a dry blend would be useless to accomplish stabilization via this mechanism. The Warner-Lambert formulators, however, were not attempting to effectuate any kind of chemical reaction. (Harris, Tr. 54:2-:15).

Both the dry blends and wet granulations failed in this experiment. (Harris, Tr. 55:13-56:13; PTX 42, WL 29108). Specifically, the four alkaline excipients, including sodium bicarbonate, failed to prevent cyclization from occurring in these formulations and accordingly, the Warner-Lambert researchers were unable to establish that the solution stability of quinapril -- and consequently pH -- had any relevance in the solid state (*i.e.*, tablet), as reflected in the Comprehensive Summary Report authored by the five Warner-Lambert inventors:

> "C. Preliminary Studies
>
> The stability of quinapril ***in solutions*** buffered to pH's between 5 and 8 supported the theory stated above. The cyclization reaction appeared to be blocked and CI-928 appeared as the main decomposition product. Therefore, efforts were made to buffer the tablet formulation employing potassium phosphate or sodium bicarbonate to control pH. The amount of potassium phosphate or sodium bicarbonate required to achieve a pH of about 6 for a 1% suspension of the tablet components was used. When wet granulated blends of these mixtures were prepared, it was

found that cyclization was still occurring and hydrolysis was not evident.

* * *

The results of these preliminary trials indicated that the stability data from solution studies was not directly transferable to solid state formulations. Therefore, the use of buffers to control the pH of tablets was abandoned."

(PTX 42, WL 29058, emphasis added; Harris, Tr. 56:2-:13; Murthy, Tr. 529:2-:24).[2]

Before May 1986, Dr. Murthy believed that sodium bicarbonate was part of the Vasotec® formulation, and knew from measuring the pH of Vasotec® tablets suspended in water that sodium bicarbonate helped create an alkaline pH of 6.5 in the Vasotec® tablets. (Harris, Tr. 57:4-:14). Beyond knowing the pH of Vasotec® tablets, and knowing that Merck's formulation included sodium bicarbonate, the formulators had very little other useful knowledge regarding Merck's formulation. Prior tests had been run on Vasotec® tablets to determine how much moisture the tablets absorbed, but these tests were not designed to determine how Merck stabilized its formulation, and provided no insight into the stabilization of that formulation. (Murthy, Tr. 515:2-516:10). A package insert for

[2] In the Court's summary judgment opinion, it seems that the Court believed PTX 42 to reflect an experiment with sodium bicarbonate separate from that discussed in Dr. Murthy's May 1986 memorandum. (PTX 55). It is not. PTX 42 simply summarizes the failed result of that same experiment. (Harris, Tr. 52:9-:17).

Vasotec® had been seen by, at least, Dr. Murthy, but this insert simply listed some inactive ingredients for Vasotec®, and disclosed no information regarding the instability of the active ingredient enalapril, or how any instability had been eliminated in the formulation. (Murthy, Tr. 516:11-518:1).

Knowing the chemical structure of enalapril, and its similarity to the structure of quinapril, it could be surmised that enalapril was potentially prone to (or "susceptible to") cyclization, but the inventors had seen nothing confirming that enalapril did in fact degrade via this pathway. (Murthy, Tr. 512:25-513:1). Nor, therefore, had the inventors seen any information disclosing the extent to which, or the conditions under which, enalapril degraded via this cyclization pathway. (Murthy, Tr. 513:11-:18).

Significantly, the inventors had absolutely no knowledge at this time that sodium bicarbonate functioned as a stabilizer in Vasotec®. (Harris, Tr. 58:11-:15; Murthy, Tr. 519:18-22). Indeed, as discussed below (pp. 27-28), Merck had been very careful to deliberately conceal the stabilization mechanism employed in Vasotec® in this timeframe, and the role of sodium bicarbonate in that stabilization process.

As Dr. Murthy freely and candidly testified, Vasotec® of course was of general interest to Warner-Lambert, since it was known that Merck was developing this competing product. (Murthy, Tr. 371:10-:17). But Vasotec® only was of interest for a brief time and then, only for the limited purpose of aiding in the selection of one of the four alkaline agents

to add to the quinapril formulations to test the formulators' ***own*** pH theory. After this pH theory failed, along with many other theories before and after this experiment, even this limited interest in Vasotec® disappeared or "fell off the table," at least from the formulators' perspective. (Murthy, Tr. 526:11-:25). Today, the Warner-Lambert inventors do not recall discussing Vasotec® -- and any relevance it might have had to the stabilization of quinapril -- after the failed experiment reflected in the May 1986 memorandum. (Murthy, Tr. 544:12-:20). Nor has Teva pointed to any Warner-Lambert documents in which the inventors discuss Vasotec® in any context after this failed experiment.

B. The Warner-Lambert Formulators Conceived Of The '450 Patented Invention By August 1986

Following the failed experiments attempting to solve the cyclization problems of quinapril by "adjusting the pH" of the tablets with alkaline excipients, the Warner-Lambert formulators returned to their process of trying other ideas and other formulations. (Harris, Tr. 60:6-:14).

Specifically, the inventors continued their formulation development with one-on-one excipient compatibility studies. In connection with these studies, the inventors used accelerated stability studies to evaluate these formulations. From these accelerated stability studies, the team could "not only get an idea of how the products perform under those conditions, but you can also get an accelerated idea of how they will perform at a longer

term at room temperature," giving a "benchmark as to final stability that these drugs or tablet formulation would display if left at room temperature for a longer period of time." (Harris, Tr. 38:24-39:13).

Based on numerous tests and experiments over the course of the project, the inventors determined that accelerated stability conditions of five-day storage at 60 degrees centigrade was a good "surrogate" for the inventors to determine whether they were going to have satisfactory long-term stability results for the formulation tested. (Harris, Tr. 73:25-74:11, 75:21-76:2). Dr. Schwartz, Teva's expert, agrees that such testing may have "utility [in] product development to give scientists confidence" (Schwartz, Tr. 195:18-:24).

As a result of their one-on-one excipient studies, it was discovered that magnesium carbonate had a stabilizing effect on quinapril. (Harris, Tr. 62:14-:18). When quinapril was wet granulated with magnesium carbonate, the cyclization reaction appeared to be blocked. Once magnesium carbonate was found to stabilize the ACE inhibitor against cyclization, the inventors varied the amount of lactose in the formulation to control remaining degradation by hydrolysis. (PTX 42, WL 29059).

More particularly, Dr. Harris testified that the inventors discovered, by August 4, 1986, that magnesium carbonate was a stabilizer. Dr. Harris testified that as of August 4, 1986, the inventors had identified what they felt were two satisfactory tablet formulations, one of which included magnesium carbonate and lactose. The inventors had determined,

therefore, by this time that the quinapril/magnesium carbonate/lactose formulation would solve their stability problem. (Harris, Tr. 61:25-64:21). Dr. Harris confirmed that, by August 20, 1986, the inventors had in fact solved the problem of degradation by cyclization with the quinapril/magnesium carbonate/lactose formulation. (Harris, Tr. 64:22-66:25).

This testimony is corroborated by contemporaneous Warner-Lambert documents. For example, an August 4, 1986 memorandum reports planned testing of a "backup" formulation which contained magnesium carbonate and lactose. (PTX 131). An August 20, 1986 memorandum reports the results of this testing. It concludes that the quinapril/magnesium carbonate/lactose formulation demonstrated the "expected trend" and "look[s] promising". The memorandum expressly confirms that the inventors, by that time, believed they had discovered a process of stabilizing quinapril against cyclization:

> "The amount of PD109,488 [cyclization degradation product] remained controlled . . . in all cases."

(PTX 132).

By September 4, 1986, the inventors reported that the commercial 5 mg formulation "had essentially been completed" and that the inventors had received "impressive results" regarding stability. At this time, the inventors were "tweaking" the final tablet properties, such as

disintegration, which were not related to stability. Such optimization, Dr. Harris testified, would only have occurred after a formulation had been proven to be stable. (Harris, Tr. 67:1-69:19, 121:13-123:1; PTX 133).

In fact, each time tests were performed using the inventors' conceived formulation including magnesium carbonate, cyclization was consistently inhibited. A September 2, 1986 data sheet specifically shows the "impressive results" of stability testing for several lots of a quinapril/magnesium carbonate/lactose formulation, each of which showed that the ACE inhibitor had been stabilized against cyclization. (PTX 243; Harris, Tr. 69:20-70:6, 72:23-74:17).

After the invention had been conceived and accelerated stability testing demonstrated it worked, batches representing the commercial product were placed on formal testing to collect data for FDA submission. Confident in earlier test results, product planning personnel at Warner-Lambert reported that "no registration problems are envisioned for this formulation." (Harris, Tr. 123:6-:25; PTX 58, WL 46311). And, in fact, no problems did occur.

C. Solving The Quinapril Stability Problems Resulted In Recognition For The Warner-Lambert Formulators, Commercial Success For The Drug Product

The Warner-Lambert formulators' arduous, but ultimately successful efforts in finally stabilizing quinapril did not go unnoticed at Warner-Lambert. Three of the formulators, Drs. Murthy, Harris and

Hokanson received a corporate Award for Meritorious Scientific Achievement, the highest award given by Warner-Lambert for outstanding accomplishments in Research & Development. (Harris, Tr. 76:13-77:16).

Moreover, with the most significant roadblock to commercialization of quinapril finally removed, the drug product was able to eventually garner FDA approval. (Harris, Tr. 77:17-78:3). As expected by Warner-Lambert management, Accupril® went on to achieve tremendous success in the marketplace, with total sales eventually reaching well over half a billion dollars a year. (Harris, Tr. 79:20-:23).

D. The '450 Inventors Never Intended To Claim Either The Vasotec® Formulation Or Sodium Bicarbonate

The '450 patent application was filed with 19 claims. (DTX 2, pp. 19-21). Original claims 1-17 all claim use of a suitable amount of a saccharide to inhibit hydrolysis. Today, it is undisputed that this claim limitation is absent from the Vasotec® formulation. (*Summary Judgment Opinion*, PTX 235, p. 23). All of these 17 original claims are also limited to ACE inhibitors that, *inter alia*, are "susceptible to discoloration." (*Id.*) Today, it is likewise known that enalapril is not susceptible to discoloration. (Brenner, Tr. 593:25-594:2).

Original claims 18 and 19 are set forth below:

> 18. 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 salt and,

(b) one or more saccharides.

19. The process of claim 18 wherein the drug is selected from the group consisting of quinapril, enalapril, and indolapril, or a pharmaceutically acceptable acid addition salt thereof.

(DTX 2, p. 21, emphasis added).

It is of course true that the term "alkali or alkaline earth metal salt" could include sodium bicarbonate. But claims 18 and 19 do not claim ***every*** "alkali or alkaline earth metal salt." Instead, these claims, by their very terms, are limited to only those "alkali or alkaline earth metal salts" that, through a process of contacting the salt with the ACE inhibitor, stabilize "an ACE inhibitor drug against cyclization."

As discussed above, the '450 patent inventors had no knowledge when they filed their patent application that sodium bicarbonate was a stabilizer in the Vasotec® formulation. And, with respect to quinapril, which was of course was the focus of the inventors' work, sodium bicarbonate had failed as a stabilizer. (Murthy, Tr. 441:2-:23; 450:5-:11). Accordingly, because the inventors had no reason to believe that sodium bicarbonate was among those salts that could stabilize an ACE inhibitor against cyclization, the inventors quite reasonably did not believe that their original claims covered this salt. (Murthy, Tr. 542:1-:25).

E. No Information Was Available Prior To The August 1986 Conception Of The '450 Patent Regarding The Stabilization Of Enalapril

At trial, Dr. Brenner, former Senior Director of Pharmaceutical Research and Development at Merck, testified as to the stability of enalapril, and how Merck solved the cyclization problems in its Vasotec® formulation. Dr. Brenner is likely the most knowledgeable scientist in the world on the Vasotec® formulation. He was involved with Merck's efforts on Vasotec® from "day one" through commercialization of the product. (Brenner, Tr. 585:8-:18). He was Chairman of the Merck team given the mandate of developing a stable formulation of Vasotec®. (Brenner, Tr. 587:2-:24). Indeed, even after commercialization, when stability problems arose during manufacturing, Merck turned to Dr. Brenner to solve those problems. (Brenner, Tr. 590:11-:20). Dr. Brenner is also co-author of a comprehensive monograph on enalapril maleate. (Brenner, Tr. 591:21-598:23; PTX 238). At trial, Dr. Brenner testified about the stability of enalapril, and how Merck deliberately concealed the manner by which it solved the stability problems exhibited by enalapril.

Specifically, enalapril maleate, the drug employed as an ingredient in the Vasotec® formulation, is a very stable solid. When stored at room temperature for four years, no detectable degradation is observed. (Brenner, Tr. 594:13-595:6; PTX 238, p. 236). In fact, even when stored under the relatively harsh accelerated stability conditions of 40°C and 75%

relative humidity ("RH") in open vials for 16 weeks, relatively insignificant quantities of impurities are observed. (PTX 238, p. 236).

Merck only observed degradation via cyclization in enalapril, surprisingly, when it was combined in a tablet with common excipients, including pH neutral tablet excipients like microcrystalline cellulose. (Brenner, Tr. 596:5-:22). To solve this unexpected instability, Merck, like Warner-Lambert did with quinapril, initially studied the solution stability profile of enalapril to gain insight into the relationship between pH and stability. (Brenner, Tr. 590:19-598:9). Those studies indicated that enalapril should exhibit maximum stability at a pH of around 3. (Brenner, Tr. 597:14-18; PTX 238, p. 236). Unfortunately, as was the case with Warner-Lambert, the pH stability of this drug in solution did not translate to the solid state; tablets formulated to have a pH of about 3 would still degrade via cyclization. (Brenner, Tr. 597:23-598:23).

Like most pharmaceutical formulators in this time period, the scientists at Merck confronted with this unusual degradation pathway had no background or experience in cyclization to draw from to solve this problem. None of the Merck scientists assigned to solve the stability problem of enalapril tablets had previously worked with a drug that cyclizes. (Brenner, Tr. 601:10-602:7). Indeed, after his involvement with Merck's ACE inhibitors ended, Dr. Brenner never again worked with a drug that degrades via cyclization. (*Id.*)

To solve this difficult and puzzling stability problem, Merck committed considerable manpower to the project; two to three times the manpower that was usually devoted to the development of a drug formulation. (Brenner, Tr. 614:25-615:16). After months of effort, this Merck team finally developed a "working hypothesis" that it could stabilize enalapril maleate in a tablet by reacting it with sodium bicarbonate in the limited water that exists during wet granulation, the mixing process by which these excipients are combined during manufacture. (Brenner, Tr. 604:7-610:5).

To accomplish this *in-situ* chemical reaction, water must be present in the mixture of excipients. (Brenner, Tr. 604:7-610:5). The reactants, enalapril maleate and sodium bicarbonate, can only react if dissolved into solution in water. (*Id.*) Dry blends of the ingredients, therefore, would not facilitate the necessary reaction, and in fact did not stabilize enalapril. (*Id.*)

Unfortunately for Merck, the discovery that enalapril tablets could be chemically stabilized through a unique *in-situ* reaction process did not end its stability issues. (Brenner, Tr. 610:7-:25). Major experimentation over a 2 to 3 year period was still required to complete the development of a process capable of consistently stabilizing enalapril. (Brenner, Tr. 610:7-616:17).

Through this experimentation, which resulted in some failed lots of Vasotec® over time, Merck came to realize that many factors had to

be controlled to successfully stabilize enalapril against cyclization using sodium bicarbonate. (Brenner, Tr. 616:18-617:7). For example, through these failures, Merck learned that the type of mixing equipment, the duration and temperature for mixing, the holding time in the mixing equipment after mixing and the particle size of the sodium bicarbonate, all played a critical role in the stabilization process. (Brenner, Tr. 617:18-618:14). In fact, Merck found that simply changing from one type of mixer to another, all other things staying the same, could affect the stability of Vasotec®. (*Id.*)

The need to develop the correct limits for all of these process variables was ***not*** a normal part of formulation development. (Brenner, Tr. 619:22-620:10). For example, for a typical drug product, the formulator never needed to worry about the temperature of mixing. (*Id.*) However, with respect to Vasotec®, Merck, through considerable experimentation, discovered that it needed to mix its formulation at 80°C, almost 60°C above room temperature. (*Id.*) This is a very high and unusual temperature at which to mix a pharmaceutical formulation. (*Id.*)[3] Indeed, because of the sensitivity of the stability of the Vasotec® process to these process variables or factors, major experimentation was still required to determine the proper limits for these factors even after the chemical reaction underlying the stabilization was discovered, as Dr. Brenner testified:

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[3] For example, in Warner-Lambert's experience, 80°C was disregarded as a temperature even to test formulations because the formulation "cooked at this high temperature." (Harris, Tr. 74:18-75:8).

> Q: And now the development of these factors, the time that was required, would you characterize the experimentation involved in that effort as minor experimentation?
>
> A: You know, I can only smile. Because I was involved in the whole process over the four-year period. It took an enormous amount of effort on everyone in the department.

(Brenner, Tr. 620:15-:22).

As a result of the long, difficult process of stabilizing Vasotec®, Merck came to realize that "pH adjustment" in the tablet was not the mechanism underlying the stabilization. (Brenner, Tr. 599:13-600:23). Instead, Merck came to realize that the key factor in the stabilization of enalapril in the tablet formulation is the extent to which the chemical reaction goes to completion, *i.e.*, the extent to which the sodium bicarbonate and enalapril completely react during manufacture to form the more stable salt form, enalapril sodium. (Brenner, Tr. 620:23-622:6). This factor is not controlled by pH.[4] In other words, enalapril tablets having the exact same amount of sodium bicarbonate in the formulation (all other things being equal) should display the same pH, within tolerances, in solution. However, Merck observed that such tablets could display widely differing stability

[4] To be sure, enough sodium bicarbonate has to be present in the formulation to ensure a sufficiently complete reaction, and this amount of the alkaline sodium bicarbonate raises the pH of the Vasotec® tablets, relative to tablets without this same amount of sodium bicarbonate. (Brenner, Tr. 623:19-625:1). However, Merck learned that pH is not a predictor for product stability. (*Id.*)

against cyclization, depending entirely on the extent to which the enalapril maleate and sodium bicarbonate reacted in the wet granulation. (Brenner, Tr. 621:4-623:14). Indeed, because pH was an inadequate predictor of stability – and more specifically because pH could not permit an analysis of the extent of reaction between enalapril and sodium bicarbonate – Merck developed a proprietary test or assay to determine the extent of the reaction. (Brenner, Tr. 620:15-625:12; PTX 141).

F. Merck Deliberately Concealed Its Stabilization Mechanism Until Well After the '450 Patent Conception Date

Contrary to the uninformed and/or misleading opinion of Teva's expert Dr. Schwartz (*see* pp. 46-47), the real experts in ACE inhibitor formulations at Merck knew that there was no way for one of ordinary skill in 1986 to discern the process by which it stabilized its Vasotec® formulation, from either the tablets themselves or any other publicly available information. Indeed, in a very real sense, Merck "bet the ranch" on this conclusion; a conclusion reached only after much deliberation by management at the highest levels of Merck Pharmaceutical R & D.

Specifically, there is simply no way to discern the process by which Merck stabilized its Vasotec® formulation by "reverse engineering" the tablets. (Brenner, Tr. 669:3-:12, 679:1-:19). Below is a side-by-side comparison of the Vasotec® "formulation" as it was disclosed publicly, for

example, in the Dictionnaire Vidal (DTX256), and the real composition of the tablets following the chemical reaction that stabilizes the formulation:

Dictionnaire Vidal **Disclosure of Formulation**	**Real Composition of Merck's Vasotec® Tablets**[5]
Enalapril Maleate	Maleic Acid
Lactose	Monosodium Maleate
Sodium Bicarbonate	Enalapril Sodium
Corn Starch	Disodium Maleate
Magnesium Stearate	Enalapril Maleate
	Sodium Bicarbonate
	Lactose
	Corn Starch
	Magnesium Stearate

Merck never publicly disclosed the true composition of its Vasotec® tablets.

In order to "reverse engineer the tablet" to determine the stabilization mechanism, *i.e.*, that enalapril maleate reacts with sodium bicarbonate to form the more stable salt, enalapril sodium, obviously one needs some test that can identify enalapril sodium in the tablet and distinguish it form the unstabilized starting ingredient, enalapril maleate.

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[5] Dr. Schwartz, who has no background in chemistry, represented that he could analyze the Vasotec® tablets to determine the details of the stabilization mechanism. (Schwartz, Tr. 230:7-232:19). It became dramatically clear, however, that his analysis was uninformed, when he was forced to concede that he had no clue that the above list represented the actual composition of those tablets. (Schwartz, Tr. 316:14-317:10). On redirect, however, Dr. Schwartz conceded that the above listed constituents "are present in the tablet." (Schwartz, Tr. 345:7-:13).

(Brenner, Tr. 679:1-:19). As any PhD chemist like Dr. Brenner knows, however, no such test exists. (Brenner, Tr. 679:1-680:12).

Moreover, as explained by Dr. Brenner, the key factor in the stabilization of Vasotec® is the extent to which the stabilization reaction takes place during wet granulation of the formulation. This conclusion was not disclosed publicly. (Brenner, Tr. 621:7-623:14). Nor was there any known test available to determine the extent of the reaction from analysis of the tablets. In fact, Merck had to develop a proprietary (and therefore confidential) test over some period of time to determine extent of reaction. (Brenner, Tr. 680:5-681:3). Accordingly, extent of reaction could not be ascertained by an analysis of the tablets by anyone outside of Merck in the 1986 timeframe. Finally, as Dr. Brenner explained, Merck never publicly disclosed the role of the critical process variables (pp. 20-24, above) in the stabilization of Vasotec®, and these process conditions likewise could not be ascertained from any analysis of the tablets. (Brenner, Tr. 681:5-:24).

There can be little doubt that the unique process developed by Merck to stabilize its Vasotec® formulation would have warranted a United States patent. But patenting a process requires disclosure of that process to the public, with the risk that a clever competitor will borrow the teachings of the patent, and figure out a way to design around your claims. On the other hand, one can elect to maintain one's process as a trade secret. This avoids public disclosure of the process and the risk that a competitor will design around the claims. But the trade secret route comes with great risk. If a

competitor can, in fact, determine your process from analysis of your product, or other publicly available information, then one has, in effect, given away the process for free, since by electing the trade secret route, one necessarily surrenders the legal monopoly guaranteed by a United States patent.

The highest levels of Merck technical management weighed, in a very deliberate fashion, the difficult patent versus trade secret choice for the Vasotec® process. (Brenner, Tr. 155:8-169:23). Specifically, Dr. Brenner met several times over the course of a year[6] with Dr. Heimlich, who was then in charge of Pharmaceutical Research and Development, worldwide, for Merck, and Dr. Allegretti, who like Dr. Brenner, was one of the Directors of Merck's Pharmaceutical Research and Development. (Brenner, Tr. 657:8-658:8). As Dr. Schwartz conceded, each one of these gentlemen ***separately*** has "a great deal more" experience than him with the stabilization of ACE inhibitors. (Schwartz, Tr. 329:20-330:3).

These three "wise men" decided that there was simply no way that their competitors would be able to determine the stabilization process of Vasotec®, and the role of sodium bicarbonate in that process, from the information publicly available in the mid 1980's, including the tablets themselves, references like Dictionnaire Vidal, the package insert and the

[6] (Brenner, Tr. 168:13-169:12).

later *Bohidar et al.* paper.[7] (Brenner, Tr. 155:8-169:23). Over the course of their several meetings over a year, during which they carefully deliberated their choice, these members of Merck technical management decided that they could be confident enough of the inability of the competitors to figure out their process, that it was worth foregoing patent protection for the process despite the considerable risk. (Brenner, Tr. 166:22-169:23). Merck, therefore, maintained its process as a trade secret until the late 1980's or early 1990's, well after the conception of the '450 patent. (Brenner, Tr. 155:8-156:14). Indeed, as late as 1994, when Dr. Brenner left Merck, Merck had still not publicly disclosed its stabilization process, and the role of sodium bicarbonate in that process. (Brenner, Tr. 681:21-:24). Nor, to Dr. Brenner's knowledge, had any competitors reversed engineered the process by 1994. (Brenner, Tr. 681:25-682:3).

Indeed, despite his testimony at trial to the contrary, Dr. Schwartz knew that the Vasotec® stabilization process was still being concealed by Merck as late as 1994. In court filings in the Canadian litigation *Merck v. Apotex* in 1994, Dr. Schwartz's affidavit, which identified sodium bicarbonate as a stabilizer (based on confidential information received from Merck), was maintained on an outside counsel's eyes only basis. (Schwartz, Tr. 313:14-:21, 322:24-323:1). When Dr. Schwartz

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[7] The *Bohidar, et al.* paper refers to N.R. Bohidar, et al., *Formula Optimization for a Multiple Potency System with Uniform Tablet Weight*, 12 Drug Development and Industrial Pharmacy 10, 1503 (1986) (DTX 259).

testified at trial in Canada about Merck's Vasotec® formulation, Merck insisted on clearing the courtroom. (Schwartz, Tr. 327:22-328:10). And, indeed, Dr. Schwartz knew that Merck still considered the stabilization mechanism of Vasotec® to be secret in 1994, because Merck's in-house counsel expressly told him that. (Schwartz, Tr. 328:3-:17). It was a little disingenuous for Dr. Schwartz to represent to this Court that the Vasotec® stabilization mechanism would have been known in 1986, without even mentioning that he knew that Merck, a company with considerable sophistication, technical knowledge and experience with ACE inhibitors, was still going to great pains to conceal this information eight years later, in 1994.

II. ARGUMENT

A. The Inventors Conceived Their Invention By August 1986 And Teva Failed To Prove A Different Date Of Conception

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. *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). Conception is complete when one of ordinary skill in the art could carry out the invention, without unduly extensive research or experimentation which would undermine the specificity of the conception. *Id.*; *Sewall v. Walters*, 21 F.3d 411, 415 (Fed.

Cir. 1994) (inventor Walters conceived an electronic back projecting apparatus at the time of his idea, without having yet written any software or designed any hardware to carry out function); *Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 1386-87 (C.C.P.A. 1974) (inventor conceived idea of using certain compound as an antidepressant simply at time request was made to perform testing of compound for such use).[8]

An inventor need not demonstrate that his invention will work for its intended purpose 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." *Burroughs*, 40 F.3d at 1228 (Burroughs scientists conceived idea of use of AZT to treat AIDS at the time they had the idea, and before they received key experimental test results showing such use worked) (internal citation omitted); *In re Jolley*, 308 F.3d 1317, 1321, 1325 (Fed. Cir. 2002) (conception of refrigerant compound occurred at time inventor sent e-mail simply suggesting that various compounds including claimed compound be further evaluated).

Corroboration of conception is evaluated based on all the evidence at trial under a "rule of reason" to determine if the inventors' testimony relating to conception is reasonable and thus credible. "[A]n

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[8] Decisions of the Federal Circuit's predecessor court, the Court of Customs and Patent Appeals, constitute binding precedent of the Federal Circuit. *South Corp. v. United States*, 690 F.2d 1368, 1370 (Fed. Cir. 1982) (*en banc*).

evaluation of all pertinent evidence must be made so that a sound determination of the credibility of the inventor's story may be reached." *Mahurkar v. C.R. Bard, Inc.* 79 F.3d 1572, 1577 (Fed. Cir. 1996).

Claim 16 of the '450 patent requires 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." (PTX 1, col. 6, lines 54-59). As discussed above (pp. 12-15), Dr. Harris's testimony and contemporaneous Warner-Lambert documents clearly establish that, by August 20, 1986, the inventors had thought of the idea of a process of stabilizing quinapril (*i.e.*, an ACE inhibitor) against cyclization by contacting the drug with a suitable amount of magnesium carbonate (*i.e.*, an alkali or alkaline earth metal carbonate) and lactose (*i.e.*, one or more saccharides). In fact, the evidence establishes that, by August 20, 1986, the inventors had not only conceived of the idea, but further had made quinapril/magnesium carbonate/lactose formulations and shown through accelerated stability testing of these formulations that quinapril had in fact been stabilized against cyclization:

> "The amount of PD 109,488 [cyclization degradation product] remains controlled . . . in all cases." (PTX 132).

Dr. Harris's testimony on conception is coherent, reasonable and consistent with contemporaneous internal Warner-Lambert documentation, including PTX 42, 131, 132, 133 and 243.[9]

At trial, Teva was unable to challenge Dr. Harris's testimony that the ***idea*** for the invention occurred by August 20, 1986. Instead, Teva offered its expert, Dr. Schwartz, who illogically testified that the invention was not conceived until ***after*** the '450 patent was filed.

More specifically, Dr. Schwartz admitted he had no knowledge about what constituted conception other than what Teva's counsel told him. (Schwartz, Tr. 279:25-280:7). Teva's counsel, not surprisingly, erroneously told him that for conception to exist, there must be a single document that contains a set of data sufficient for submission to the FDA to gain product approval. (Schwartz, Tr. 187:7-:24). In essence, Dr. Schwartz was told to testify that no conception can be found unless and until the invention has been proven to work for its intended purpose. (Schwartz, Tr. 284:15-285:3).

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[9] Teva had challenged PTX 42 before trial on the ground that it is dated March 1987, after the August 1986 conception of the '450 patented invention. This challenge is not well founded. PTX 42 is a comprehensive summary of the prior development of the quinapril formulation. (Harris, Tr. 33:10-34:3). Since it discusses events occurring in the past, and is fully consistent with Dr. Harris' testimony and the other documents of record concerning earlier events, it may be considered in connection with that evidence under the "rule of reason." *See, e.g., Blicharz v. Hays*, 496 F.2d 603, 606 (C.C.P.A. 1974) (February 1963 "Record of Invention" was "significant corroborative evidence" supporting other evidence showing a reduction to practice in December 1962).

That standard, of course, is wrong. Dr. Schwartz incorrectly confused conception with reduction to practice. As the cases cited above make clear, conception does not require that the inventor has tested the product at all, let alone sufficiently to obtain data to show it works for its intended purpose. Conception simply requires the idea for the invention. *See Burroughs*, 40 F.3d at 1228; *Sewall*, 21 F.3d at 415; *Rey-Bellet*, 493 F.2d at 1386; *In re Jolley*, 308 F.3d at 1321, 1325.

Dr. Schwartz also failed to apply the rule of reason to analyze the statements in the various documents based on their context in relation to the other documents and the testimony of the inventor. Tellingly, Dr. Schwartz conceded that the "idea" to formulate compositions containing magnesium carbonate and lactose preceded the September 4, 1986 memorandum (PTX 133), and that such formulations actually had been made as of that time. (Schwartz, Tr. 280:8-:25, 282:21-283:2). Conception requires no more.

Dr. Schwartz also in effect admitted that his standard for conception led to illogical results, and was inconsistent with his understanding of conception in prior litigation. Under Dr. Schwartz's erroneous standard, conception did not occur until after the inventors received batch stability test data sufficient to qualify for submission to the FDA. Consistent with this mistaken standard, he testified that the data in Warner-Lambert's possession as of March 1987 -- a month after the '450 patent was filed -- was still insufficient for submission to the FDA and