IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICAL COMPANY, LTD., and TAP PHARMACEUTICAL PRODUCTS INC.,	)	
Plaintiffs and Counterclaim-Defendants,	)	
v.	)	C.A. No. 06-033 (SLR)
TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES LTD.,	)	
Defendants and Counterclaim-Plaintiffs.	)	

PLAINTIFFS TAKEDA'S AND TAP'S OPENING POST-TRIAL BRIEF CONCERNING INFRINGEMENT OF THE '321 PATENT

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NATURE AND STAGE OF THE PROCEEDINGS

Patent owner Takeda and exclusive licensee TAP (collectively, "Plaintiffs") bring this lawsuit under the Hatch-Waxman Act, alleging that Teva's Abbreviated New Drug Application ("ANDA") No. 77-255 for two generic versions of PREVACID® (15 and 30 milligrams, referred to as "Teva's Product"), infringes U.S. Patent Nos. 4,628,098 (PTX 1, "the '098 Patent") and 5,045,321 (PTX 3, the "'321 Patent"). Teva concedes infringement of the '098 Patent. *See* Final Pre-Trial Order, Statement of Admitted Facts ¶ 31 (D.I. 146). This case was tried to the Court from October 29 through November 6, 2007 on the issues of infringement of the '321 Patent, and Teva's obviousness (as to the '098 and '321 Patents) and inequitable conduct (as to the '098 Patent) challenges. As set forth below, the record evidence demonstrates that Teva's Product infringes claim 2 of the '321 Patent as properly construed.

SUMMARY OF ARGUMENT

After extensive research and development efforts, Takeda scientists discovered lansoprazole, a proton pump inhibitor ("PPI"). The discovery of this novel compound was a breakthrough. It provided a new and powerful treatment for ulcers and other debilitating conditions. However, like many compounds in the field, lansoprazole was extremely unstable, especially in the presence of acids (including stomach acid). Without an effective means for stabilizing it, lansoprazole would degrade on the shelf or before it reached its intended destination -- the small intestine, where it is absorbed into the bloodstream. Takeda scientists solved this problem with the invention claimed in the '321 Patent -- in particular claim 2, which teaches how to stabilize lansoprazole by placing it "in contact . . . evenly" with the basic inorganic salt magnesium carbonate.

There is no dispute that Teva's Product contains magnesium carbonate, which functions as a stabilizer. The key dispute is whether the magnesium carbonate in Teva's Product performs this function by "contacting evenly" with lansoprazole as claimed in the '321 Patent. Teva attempted to design around the '321 Patent by purportedly physically separating lansoprazole and magnesium carbonate in its product. Teva's non-infringement argument literally rests on less than a hair's breadth. Testing presented at trial has shown that the thin 2-micron talc "impenetrable layer" (1/50th the width of a human hair) that Teva claims to have employed does not prevent lansoprazole and magnesium carbonate from being in contact evenly with each other. Teva's own development documents confirm this failure.

The end result is a product in which, as described in claim 2 of the '321 Patent, the lansoprazole and magnesium carbonate are in contact evenly with one another, thereby stabilizing the lansoprazole sufficiently for commercial use.

THE ASSERTED CLAIM

Claim 2 of the '321 Patent, written in independent form, recites:

> 2. A pharmaceutical composition, wherein the composition is made up into tablets or granules and then coated by a coating agent, which comprises an effective amount of the anti-ulcer compound 2-[[3-methyl-4-(2,2,2-trifluoroethoxy-2-pyridyl]methylsulfinyl]benzimidazole [*i.e.*, lansoprazole], and magnesium carbonate; the amount of magnesium carbonate relative to parts by weight of the benzimidazole compound [lansoprazole] being about 0.3-20 parts by weight; the benzimidazole compound [lansoprazole] being in contact with the basic inorganic salt evenly.

(PTX 3 (Col. 17, l. 63-Col. 18, l. 31)). To establish infringement of claim 2, Plaintiffs must prove by a preponderance of the evidence that the following elements are present in Teva's Product: (1) a "pharmaceutical composition"; (2) "wherein the composition is made up into tablets or granules, and then coated by a coating agent"; (3) "which comprises an effective

amount of [lansoprazole]"; (4) "magnesium carbonate"; (5) "the amount of the magnesium carbonate relative to parts by weight of the [lansoprazole] being about 0.3-20 parts by weight"; and (6) the [lansoprazole] being in contact with the [magnesium carbonate] evenly. (PTX 3, ('321 Patent, Col. 17, ll. 62 – Col. 18, ll. 34)). The evidence presented at trial established the presence of each of these elements in Teva's Product.

STATEMENT OF FACTS

A. The '321 Patent Addresses Complex Problems Arising From Lansoprazole's Natural Instability

Lansoprazole acts as a PPI. PPIs prevent parietal cells in the stomach from pumping acid into the gastrointestinal tract. (PTX 453, at p. 4, Byrn0285). PPIs represent a groundbreaking treatment for patients suffering from such common debilitating diseases as duodenal ulcers, gastric ulcers, Gastroesophageal Reflux Disease (GERD), Zollinger-Ellison syndrome and erosive esophagitis. (*Id.*, at pp. 19-20, Byrn0300-301). Takeda's discovery of lansoprazole, and the method of stabilizing it, was the culmination of a lengthy drug discovery and development program. (*See* PTX 1 ('098 Patent), PTX 3 ('321 Patent), Tr. 1128:14-1129:2 (Kubo Direct)).

Despite lansoprazole's potential as an anti-ulcer agent, there was a significant barrier to its development as a pharmaceutical product. Lansoprazole was unstable under a variety of conditions, and tends to degrade when exposed to acid,[1] to other ingredients commonly used in pharmaceutical compositions, or to heat, moisture or light. (PTX 3 ('321 Patent, at col. 1, ll. 33-41)). Degradation can impact drug potency and produce toxicity risks. (Tr. 82:4-21 (Byrn Direct)).

[1] An acid is a substance with a pH in water less than 7. (Tr. 83:17-20 (Byrn Direct)).

Like many drugs, lansoprazole needs to reach the small intestine to produce a therapeutic benefit. (Tr. 462:24-463:1 (Chambliss Direct)). To reach the small intestine, lansoprazole needs to pass through the stomach. Because the stomach is a naturally acidic environment, lansoprazole will, if taken orally, degrade in the stomach before it can be absorbed into the bloodstream through the small intestine. (Tr. 84:3-11 (Byrn Direct)). A variety of methods are available for delivering acid-sensitive drugs to patients. (Tr. 87:3-88:10 (Byrn Direct)). One way is to use an enteric coat to surround the drug in the formulation, so that it does not dissolve in the stomach. (Tr. 84:17-24 (Byrn Direct)). But the use of an enteric coat, by itself, creates its own problems. The '321 Patent explicitly teaches that enteric-coating polymers -- which are acidic themselves -- will cause lansoprazole to degrade. (PTX 3, ('321 Patent, at Col. 1, ll. 49-60), Tr. 84:25-85:9 (Byrn Direct)).

What the '321 inventors discovered is that by placing lansoprazole in contact with magnesium carbonate evenly, the stability problems associated with lansoprazole can be overcome. (Tr. 88:24-89:9 (Byrn Direct)). This creates a basic environment having a pH of about 9 surrounding lansoprazole that neutralizes any acids before they can reach the lansoprazole and cause it to degrade. (*Id.*; *see also* Tr. 96:9-19, 97:3-9) (Byrn Direct)).

B. The '321 Patent Teaches A Variety Of Ways To Place Lansoprazole In Contact With Magnesium Carbonate Evenly

The '321 Patent recognizes that "in contact . . . evenly" can be achieved in a variety of ways, including physically blending together lansoprazole and magnesium carbonate and placing them in contact mediated through moisture, which creates a basic environment that stabilizes the lansoprazole. (PTX 3 ('321 Patent, at Col. 9, ll.21-24, ll. 54-56)).

One way of achieving contact evenly is by *homogeneously* admixing lansoprazole and magnesium carbonate. (PTX 3, ('321 Patent, at Col. 9, ll. 45-48)). The specification, however,

teaches that this is not the only way of achieving the goal of "contact . . . evenly." The '321 Patent expressly states that "[t]he method of admixing is ***optional*** if the benzimidazole compound can finally be in contact with the basic inorganic salt of magnesium and/or of calcium evenly." (*Id.*, at Col. 9, ll. 45-48, and ll. 56-59 (emphasis added)). In fact, the '321 Patent details other methods of achieving "contact . . . evenly": ". . .the basic inorganic salt of magnesium and/or of calcium . . . may be added to a mixture of the benzimidazole compound and the additives as prepared by preliminary admixing." (*Id.* (Col. 9, ll. 60-66)).

Moreover, the '321 Patent distinguishes between the physical condition of being "in contact with the basic inorganic salt evenly" and the methods of preparing the compositions -- such as by admixing. Claim 2 of the '321 Patent relates to a product having even contact, but does not require any specific process for achieving even contact.

Thus, the '321 Patent inventors understood and taught that homogenous admixing was merely one way to accomplish the objective of placing lansoprazole "in contact evenly" with the magnesium carbonate. One of the inventors, Dr. Hirai, confirmed this: "As stated in the claim of this patent, it is necessary to have sufficient contact between benzimidazole [lansoprazole] and then -- and stabilizer [magnesium carbonate] for stabilization. I think that there are many method[s] to do that." (Tr. 1531:2-6 (Hirai Dep.)).

C. The '321 Patent Teaches The General Principle of Creating A Uniform Basic Environment To Stabilize Lansoprazole

While teaching multiple methods for achieving contact evenly, the '321 Patent teaches a single objective: to create an alkaline (*i.e.*, basic) environment that stabilizes lansoprazole. Specifically, the '321 Patent explicitly teaches that there should be significant amounts of moisture or residual water in the formulation: "the moisture amount in the composition is preferably about 6 to 60 percent and more preferably about 20 to 40 percent." (PTX 3, ('321

Patent, at col. 9, ll. 54-56)). The '321 Patent also teaches that the basic inorganic salts (such as magnesium carbonate) used in the invention must "show basicity (pH of not less than 7) when they are in the form of a 1% aqueous solution or suspension. (*Id.*, at Col. 9, ll. 21-24). These express descriptions of water, residual moisture and suspensions inform one of skill in the art that the water/moisture serves a stabilizing purpose. (Tr. 90:6-16 (Byrn Direct)). A person of skill in the art would understand that the moisture or residual water would combine with magnesium carbonate to create a basic environment that would surround and stabilize the lansoprazole. (Tr. 90:17-91:10, 91:23-92:14 (Byrn Direct)). Because the residual water surrounding the lansoprazole is connected together, it would all have the same basic pH of about 9. (Tr. 90:17-91:10, 96:9-18; 97:3-9 (Byrn Direct)).

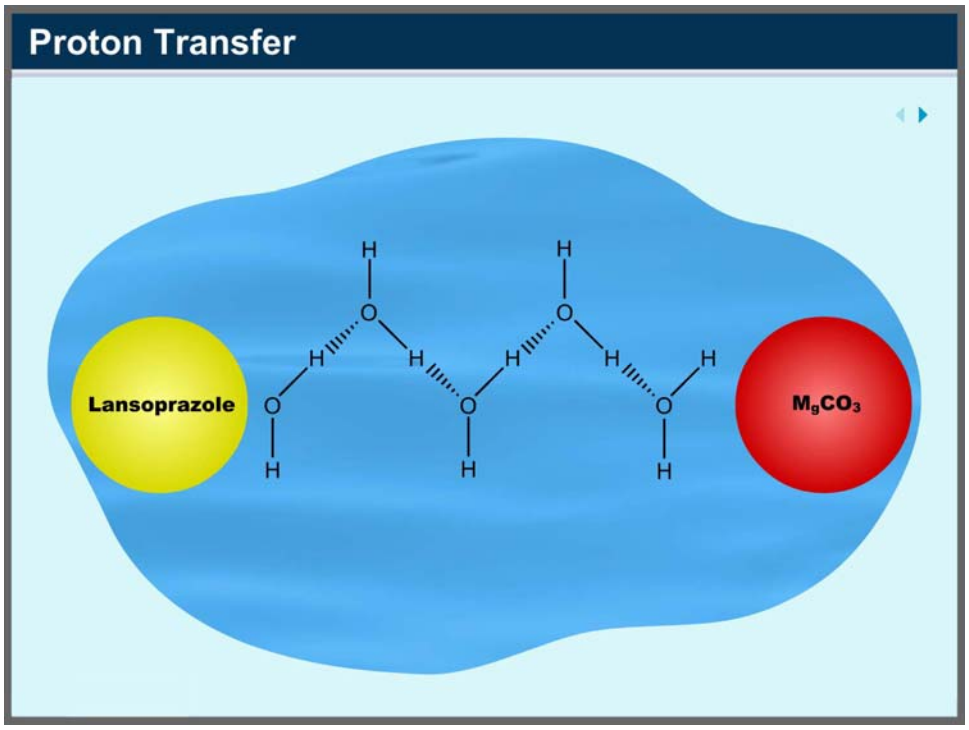
The inventors described their invention -- combining lansoprazole and magnesium carbonate in a uniformly basic environment -- by referring to "the benzimidazole compound being in contact with the basic inorganic salt evenly." (Tr. 1532:17-22 (Hirai Dep.)) ("What we call evenly contacted has a broad range and that means that contact -- sufficient contact between the active ingredient [*i.e.*, lansoprazole] and the stabilizer [*i.e.*, magnesium carbonate] for the purpose of stabilization. And uniformly contacted is, in my understanding one way for that purpose."). The inventors understood that the "contact … evenly" between lansoprazole and magnesium carbonate could include physical touching, but that physical touching is not required -- mechanochemical processes (*e.g.*, contact mediated through water) as well as physical touching could be used to place the benzimidazole compound "in contact with the basic inorganic salt evenly":

> Q. So do I understand, sir, that you do not know whether this phrase ["contact . . . evenly"] requires there to be physical contact between the active ingredient [lansoprazole] and the inorganic salt [magnesium carbonate].
>
> A. Although we do not know the mechanism, but I think that physical or mechanochemical or any other conditions are included, that's the situation or the phenomenon, but we do not know the mechanism.

(Tr. 1500:21-1501:6 (Makino Dep.)).

At trial, Plaintiffs' expert, Professor Stephen R. Byrn, Ph.D., described the mechanochemical process involved with the '321 Patent through which the uniformly basic environment of the invention is created. (Tr. 91:23-92:14, 93:9-95:15 (Byrn Direct)).[2] Professor Byrn also explained how particles of magnesium carbonate and lansoprazole, even though not physically touching, may interact, or be "in contact," if they are connected by moisture or residual water. (Tr. 94:13-22 (Byrn Direct)). This contact without physical touching is through a phenomenon known as proton transfer, which was made famous in the 1960s by Dr. Manfred Eigen who won a Nobel Prize for describing and measuring the rate of proton transfer. (Tr. 91:23-92:14, 92:16-18, 92:22-93:8, 94:11-96:8 (Byrn Direct)).

[2] Dr. Byrn is head of the Department of Industrial and Physical Pharmacy at Purdue University, where he has taught for over 35 years. He is an expert in pharmaceutical formulation, pharmaceutical stability, acid-base chemistry, solid-state chemistry, and analytical chemistry techniques and the author of "Solid State Chemistry of Drugs" 1st and 2nd editions, and "Quantitative Pharmaceutical Chemistry," 7th edition. (PTX 444 (Byrn CV), Tr. 76:23-80:20 (Byrn Direct)).



In the process of proton transfer, magnesium carbonate, as a basic inorganic salt, interacts with water (H_2O) to remove a proton (H^+, an acid) from the water. This proton remains with the magnesium carbonate. The removal of the proton leaves a hydroxide (OH^-, a base) on the water adjacent to the magnesium carbonate. (Tr. 94:23-95:1 (Byrn Direct)). That hydroxyl then attracts a proton from the next adjacent water molecule. (Tr. 95:1-4 (Byrn Direct)). These acid-base reactions set into effect a series of proton transfers by which basic hydroxide ions eventually surround the lansoprazole. (Tr. 91:23-92:14; 93:9-24; 94:13-95:15 (Byrn Direct)). This congregation of hydroxides, or base, surrounding the lansoprazole stabilizes it by neutralizing any acid that approaches the lansoprazole before the acid can cause the lansoprazole to degrade. (*Id.*) Dr. Byrn provided the only explanation at trial concerning how magnesium carbonate stabilizes lansoprazole in Teva's Product. Teva admits that the use of magnesium carbonate in Teva's Product is designed to stabilize the lansoprazole and that Teva's Product is stable. See discussion below.

D. Teva's Infringing Product

Teva's Product includes 15 mg and 30 mg lansoprazole delayed-release capsules. *See* Pre-Trial Order, Statement of Admitted Facts ¶ 26 (D.I. 146).

Teva's Product has the following composition:

TEVA *LANSOPRAZOLE D.R. CAPSULES USP 15 mg and 30 mg* *Abbreviated New Drug Application*

FORMULA COMPOSITION

LANSOPRAZOLE D.R. CAPSULES USP 15 mg & 30 mg

Ingredient	Amount (mg) / Capsule	
	15 mg strength	30 mg strength
Sugar Spheres NF (Suglets 850-1000 micron)	90.0	180.0
Drug Coating Dispersion		
Hypromellose USP (2910, Formerly Hydroxypropyl Methylcellulose NF; Pharmacoat 606)	7.5	15.0
Strong Ammonia Solution NF (Ammonia Sol. Conc.)	*	*
Talc Extra Fine USP	7.5	15.0
Lansoprazole USP	15.0	30.0
Purified Water USP	*	*
Subcoated I Coating Dispersion		
Hypromellose USP (2910, Formerly Hydroxypropyl Methylcellulose NF; Pharmacoat 606)	2.0	4.0
Talc Extra Fine USP	3.0	6.0
Purified Water USP	*	*
Subcoat II Coating Dispersion		
Hypromellose USP (2910, Formerly Hydroxypropyl Methylcellulose NF; Pharmacoat 606)	4.0	8.0
Magnesium Carbonate USP	6.0	12.0
Purified Water USP	*	*
Enteric Coating Dispersion		
Methacrylic Acid Copolymer Dispersion NF** (Eudragit L-30 D-55)	16.0	32.0
Triethyl Citrate NF	1.5	3.0
Talc Extra Fine USP	6.75	13.5
Titanium Dioxide USP	0.75	1.5
Purified Water USP	*	*
Total fill weight	**160.0**	**320.0**

PTX 445A, Byrn 0036, TVL 6617.

The manufacture of Teva's Product begins with a sugar core of about 850-1000 microns in diameter. (*Id.*, Tr. 119:18-20 (Byrn Direct)). A series of four dispersions, each of which is a mixture of solid active and inactive ingredients dispersed within liquid solvents, are then sprayed, one after another, onto the sugar core. (*Id.*, Tr. 119:20-121:19, 122:4-123:20 (Byrn Direct)). The first dispersion, which Teva calls the "Drug Coating Dispersion," is a mixture of solid lansoprazole, talc, and hypromellose dispersed in a solution of water and ammonia. PTX 445A, Byrn0036, TVL 6617, Tr. 122:5-11 (Byrn Direct). Next, a second dispersion, which Teva calls the "Subcoat 1 Coating Dispersion," containing a small amount of hypromellose and a small amount of talc dispersed in water, is sprayed on top of the first layer. (PTX 445A, Byrn 0036, TVL 6617, Tr. 120:11-121:3 (Byrn Direct)). Because the second dispersion is sprayed on with water, there is blending and intermixing of the components of the Drug Coating and Subcoat 1. (Tr. 122:5-123:10 (Byrn Direct)). Next, a third dispersion, which Teva calls the "Subcoat 2 Coating Dispersion," containing hypromellose and magnesium carbonate dispersed in water is sprayed on. (PTX 445A, Byrn 0036, TVL 6617, Tr. 123:11-19 (Byrn Direct)). Once again, because the dispersion contains water, there is blending and intermixing of the magnesium carbonate with lansoprazole and talc from the previous applications. (*Id.*) Finally, a fourth dispersion, which Teva calls the "Enteric Coating Dispersion," containing the enteric coating agent (Eudragit), talc, titanium dioxide and triethyl citrate, is applied on to the built-up the granule. (PTX 445A, Byrn 0036, TVL 6617, Tr. 123:20 (Byrn Direct)).

E. Teva's Products Are Stabilized By Magnesium Carbonate, Not The Talc Sublayer

The importance of magnesium carbonate in Teva's Products is undeniable. Teva's ANDA makes it very clear that magnesium carbonate is a stabilizer. (PTX 445A, Byrn 034, TVL 6615). Teva's own product development history establishes that magnesium carbonate was

essential as a stabilizer. Teva's lansoprazole project manager and 30(b)(6) deposition witness, Ms. Simona DiCapua, testified that Teva experimented with "tens" of lansoprazole formulations with and without magnesium carbonate. (Tr. 1654:6-9 (DiCapua Dep.)[3]; *see also* PTX 446A, D). Not surprisingly, Teva found that using magnesium carbonate resulted in the "best" lansoprazole formulation. (Tr. 1654:10-13 (DiCapua Dep.)). Based on stability data Teva presented to the FDA, Teva proposed a shelf life of two years for its lansoprazole products. (PTX 445A, Byrn 181, TVL 7711).

Some of Teva's attempts to develop a stable lansoprazole formulation are shown in PTX. 446A-E. In two of these tests from PTX 446A, Teva attempted to stabilize lansoprazole without using magnesium carbonate:

K-number	Drug Layer	Subcoat 1	Subcoat 2	Enteric coat	Stability
K-29723	227 mg sugar spheres 15 mg HPMC 15 mg Talc extra fine 30 mg Lansoprazole	N/A	N/A	43 mg Eudragit L-30 D-55 4.0 mg Triethyl Citrate 18.0 mg Talc extra fine 2.0 mg Titanium Dioxide	1 month 40ºC/75%RH Total degradation products: 2.4%
K-30022	180 mg sugar spheres 10 mg HPMC 15 mg Talc extra fine 30 mg Lansoprazole	18 mg HPMC 0.5 mg TRIS 28.5 mg Talc extra fine	N/A	43 mg Eudragit L-30 D-55 4.0 mg Triethyl Citrate 18.0 mg Talc extra fine 2.0 mg Titanium Dioxide	9 days 40ºC/100% RH Total degradation products: 0.7%

For example, test formulation K-29723 consists of a lansoprazole "drug layer" surrounded by an enteric coat and without any magnesium carbonate in the formulation at all. Another formulation, K-30022, contains a drug layer surrounded by a "subcoat" and then an enteric coat. This formulation also contained no magnesium carbonate. Teva found both formulations to be unstable. As PTX 446A reports, "[w]e can see that Talc in both the drug layer and the subcoat alone is not providing a stable product."

[3] Ms. DiCapua was tasked by Teva to develop a generic version of Plaintiffs' "innovative product Prevacid." (Tr. 1645:6-10 (DiCapua Dep.).

Indeed, the very person who designed Teva's Product admitted that talc does not serve as a stabilizer in Teva's formulation, and that lansoprazole formulations with talc but no magnesium carbonate resulted in "very bad stability results." (Tr. 1659:6-18 (DiCapua Dep.)). Ms. DiCapua admits that while Teva does not "have a full understanding of the mechanism of stabilization", Teva "found that in this particular [ANDA] formulation it [magnesium carbonate] stabilized" the formulation. (Tr. 1653:13-19 (DiCapua Dep.)).

One issue Teva never addressed at trial is how this stability is achieved. Only Plaintiffs' expert, Dr. Byrn, provided that explanation -- through "even contact" between lansoprazole and magnesium carbonate in Teva's Products.

F. Teva Was Unable to Develop A Product With A Talc Layer That Could Prevent Lansoprazole And Magnesium Carbonate From Mixing

Teva's litigation position is that its Product does not practice claim 2 of the '321 Patent, because it purportedly includes a 2-micron-wide talc "layer" or "subcoat" that keeps the lansoprazole and magnesium carbonate separate and not in contact. (Tr. 492:22-493:3 (Chambliss Direct), Tr. 138:10-24 (Byrn Direct)). However, Teva's internal documents tell a different story. In fact, Teva was unable throughout the development process to create a talc "layer" or any other layer or subcoat that actually kept the lansoprazole and magnesium carbonate separate.

Teva development records establish that Teva's purported layers or subcoats consistently failed to keep lansoprazole and magnesium carbonate separate, and proved instead to be porous and penetrable. For example, in PTX 446B, Teva's scientists state that while there was supposed to be a separate drug layer and subcoat, instead, "[t]here is no clear separation between the drug layer and the subcoat," and the "drug layer and the subcoat are porous. The enteric layer is denser and has layer like morphology." (PTX 446B, Byrn 0200, TVL 52765 (emphasis added.))

The record evidence at trial was that Teva's internal tests on its development products consistently indicated that the purported subcoats in Teva's formulations either could "not be measured" or were "layer like, porous." (PTX 446B, at Byrn 00199-00200, TVL 52764-52765) (emphasis added.).

Moreover, while Teva claims that its layers or subcoats create an impenetrable wall of separation between lansoprazole and magnesium carbonate, the record evidence reflects numerous instances where lansoprazole or other substances penetrated Teva's subcoats. For example, Teva's Ms. DiCapua explained in a September 7, 2002 e-mail:

> The last SEM [scanning electron microscope] sequence you checked shed light on **very important information**, the penetration of Lansoprazole into the subcoat or even entericoat in case where the subcoat was thin. . . . We are now trying to find subcoats which do not favor this penetration process. (PTX 446C, emphasis added).

Reports of such penetration were not isolated. Ms. DiCapua testified that, although Teva only performed SEM testing from time to time, there were in fact "several reports" where a substance penetrated through the "layers" or "subcoats" that were supposed to be keeping them separate from other substances. (Tr. 1661:1-12 (DiCapua Dep.)).

Teva cannot identify a single lansoprazole product created by its scientists with a layer or subcoat that did not permit penetration into other regions. (Tr. 1662:21-1663:2 (DiCapua Dep.)). Despite numerous memos and communications regarding defects in Teva's layers or subcoats (PTX 446A-C) and Teva's descriptions of its own tests as yielding "very important information" (PTX 446C) about penetration by lansoprazole, Teva purportedly deemed the tests "inconclusive" and abandoned further testing on the subject. *Id.*

Teva never tested the ANDA formulation at issue in this case, to see if it effectively kept lansoprazole and magnesium carbonate separate, as Teva claims:

Q. Do you continue to believe today that lansoprazole is capable of penetrating outwards in a pellet formulation?

A. We are not aware of such a penetration in the ANDA information.

Q. Have you done any test to determine whether lansoprazole penetrates outward in your ANDA formulation?

A. No.

(Tr. 1663:3-11 (DiCapua Dep.)). Thus, prior to filing its Paragraph IV Certification for its ANDA, Teva did not know whether the lansoprazole and magnesium carbonate in its Product mixed together, and made no effort to test the question scientifically.

Thus, there is no support for Teva's assertion in its opening statement that "Teva very carefully designed and crafted a multiple layer product that separated the lansoprazole from the magnesium carbonate so there would be no mixing, so there is no in contact evenly." (Tr. 74:17-19 (Teva's Opening Statement)). Teva did not test its Product prior to litigation. Teva's tests during product development show "porous" layers and subcoats and penetration by lansoprazole into other regions of the granule. At trial, Teva presented no evidence that it had ever "carefully designed and crafted" a product that did not have porous subcoats or penetration problems. As noted above, the record shows that at some point, Teva just stopped looking for problems.

As will be discussed later in this brief, Plaintiffs' tests of Teva's Product reveal that defects in the subcoats and penetration by lansoprazole and magnesium carbonate still exist, resulting in contact evenly between lansoprazole and magnesium carbonate.

ARGUMENT

I. TEVA'S PRODUCT INFRINGES THE '321 PATENT

A. Claim 2 of the '321 Patent

As noted above, there are six elements of claim 2 that must be satisfied to establish infringement: (1) a "pharmaceutical composition"; (2) "wherein the composition is made up into tablets or granules, and then coated by a coating agent"; (3) "which comprises an effective amount of [lansoprazole]"; (4) "magnesium carbonate"; (5) "the amount of the magnesium carbonate relative to parts by weight of the [lansoprazole] being about 0.3-20 parts by weight"; and (6) the [lansoprazole] being in contact with the [magnesium carbonate] evenly. (PTX 3, ('321 Patent, Col. 17, l. 62 - Col. 18, l. 34)). Each of these elements is present in Teva's Product.

Teva does not dispute the third and fourth claim elements. All parties agree that Teva's Product contains both lansoprazole and magnesium carbonate. Teva's Product contains lansoprazole -- either 15 mg or 30 mg. (PTX 445A, Byrn 0036; TVL 6617, Tr. 114:18-115:22 (Byrn Direct); Tr. 1651:21-1652:3 (DiCapua Dep.)). There is no dispute that 15 and 30 milligrams represent effective amounts of lansoprazole (Prevacid package insert) (PTX 453; Tr. 114:18-115:22 (Byrn Direct); Tr. 494:3-8 (Chambliss' Direct)). Indeed, Teva's entire ANDA submission is predicated on Teva's Product containing an effective amount of lansoprazole. There is also no dispute that Teva's Product contains magnesium carbonate. (Tr. 114:18-115:22 (Byrn Direct), Tr. 494:11-16 (Chambliss Direct), Tr. 519:7-11 (Chambliss Cross), PTX 445A, Byrn 034, TVL 6615).

Thus, determining infringement of the '321 Patent turns on construing the other four elements of claim 2 and determining whether they are found in Teva's Product. Because Plaintiffs previously submitted detailed claim construction briefs, D.I. 133 and 141, a detailed

discussion of all of those claim terms is not included here. Instead, Plaintiffs focus in this brief on their infringement proofs elicited at trial.

B. Teva's Product Satisfies Each Of Claim 2's Disputed Elements

1. Teva's Product Is A "Pharmaceutical Composition"

As detailed in Plaintiffs' claim construction briefs and confirmed by Professor Byrn at trial, "pharmaceutical composition" is a widely used term in the pharmaceutical and formulation sciences. (Tr. 103:13-15 (Byrn Direct)). Based on over 35 years in the pharmaceutical sciences, Professor Byrn concluded that a person of ordinary skill in the art, having read the '321 Patent and its prosecution history (PTX 4), would interpret the term consistent with its ordinary meaning, which is "a medicinal drug product in a state suitable for administration to a patient." (Tr. 103:5-22 (Byrn Direct)). Dr. Byrn's construction of "pharmaceutical composition" is consistent with the '321 Patent specification as well as with how the courts have construed the term.[4]

Teva proposes a completely unprecedented construction of the term. Teva contends that a "pharmaceutical composition" as claimed in the '321 Patent refers to a "mixture of lansoprazole with a basic inorganic salt of magnesium and/or calcium, which may contain any necessary additives that are used to make the tablet or granules but does not include any excipients used for coating the pharmaceutical composition." Thus, Teva's proposed construction is that the term "pharmaceutical composition" excludes the end product that is administered to a patient. (Tr. 478:9-479:3 (Chambliss Direct)). Teva's proposed construction is

[4] This includes a recent case where Teva's expert, Dr. Chambliss, testified. *See Abbott Labs. v. Sandoz, Inc.*, 500 F. Supp. 2d. 807, 830 (N.D. Ill., 2007) ("[E]ach term is assigned its plain and ordinary meaning as understood by a skilled artisan. The term 'pharmaceutical composition' means an aggregated product formed from two or more substances for use as a drug in medical treatment.")

not consistent with the term's plain and ordinary meaning, the plain language of the claims, or the specification of the '321 Patent. *See* D.I. 133, Plaintiffs' Claim Construction Brief, dated September 11, 2007, at 4-10.

It is indisputable that as properly construed, Teva's Product is a pharmaceutical composition. Teva's Product's package inserts describe lansoprazole as a "***drug for treatment***," and Teva's ANDA describes the generic capsules as a "formula ***composition***" for administration to a patient. (Tr. 111:17-112:3 (Byrn Direct), PTX 445A, Byrn 036, TVL 6617, Byrn 45). Teva's expert, Dr. Chambliss, admitted that Teva's Product is a "stable pharmaceutical composition," as that term is used by those of skill in the art:

> Q. Well, you would agree with me that Teva's proposed ANDA product is a stable pharmaceutical composition?
>
> A. Yes.

(Tr. 518:15-17 (Chambliss Cross)).

Teva's Product is a pharmaceutical composition.

2. Teva's Product Contains Granules

In their claim construction briefs, Plaintiffs construe the term "granules" as "small pellets that are typically combined with other granules into a tablet or capsule." This construction is consistent with the ordinary and plain meaning of the term, as defined in technical dictionaries,[5] and also with the way courts have consistently construed the term.[6] As explained by Professor

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[5] *See Grant & Hacks' Chemical Dictionary* 268 (5th ed. 1987) ("granules"…(2) Medicinal substances in small pellets"), a copy of which is attached as Ex. E to Byrn Declaration submitted in support of Plaintiffs' Claim Construction Brief, dated September 11, 2007, D.I. 134.

[6] *See Abbott Labs v. Teva Pharms. USA, Inc.*, No. 02-CV-1512-KAJ, 2005 WL 1026746, *9 (D. Del. Apr. 22, 2005)(*citing Webster's Unabridged Dictionary*, at 989, construing (Continued . . .)

Byrn at trial, it is also how a person of skill in the art, having read the '321 Patent and its prosecution history, would interpret the term "granules." (Tr. 105:9-18, Byrn 0015 (Byrn Direct)).

The evidence establishes that Teva's Product is made up of granules, as the term is properly construed. (Tr. 112:18-113:23 (Byrn Direct), PTX-386, Byrn 21). As shown in the picture below (PTX 386), Teva's Product is in the form of capsules filled with small, generally spherical pellets. Persons of skill in the art would readily identify these pellets as granules. (*Id*.)



Teva contends that the term "granules" should be defined as "an irregularly shaped or a spheroid shaped mass of particles made up of a pharmaceutical composition, which also may contain additives." (Tr. 105:19-106:7 (Byrn Direct)). In addition, Teva attempts to read its incorrect definition of pharmaceutical composition into its proposed "granule" construction:

> Q: What is your view regarding the limitation that, wherein the composition is made up into tablets or granules?

(. . . continued)
the similar term "granulate" as a synonym of "granule," and applying its ordinary definition of "one of a number of particles forming a larger unit.").

> A: Well, the literal reading of that claim is, the pharmaceutical composition which was just defined as being the mixture, and then I'm making it up into tablets or granules. So if the granule doesn't contain the pharmaceutical composition, it doesn't infringe. And Teva's product does not contain a granule which has a mixture of the lansoprazole and magnesium carbonate so it does not infringe.

(Tr. 493: 6-15 (Chambliss Direct)).

Teva's proposed construction is wrong. Nothing in the claim or specification requires that a "granule" have a particular shape at all. And nothing in the claim or specification requires anything specific to be contained within the granule. Teva's proposed construction is not how those of skill in the art would define "granules," and therefore it should be rejected. (Tr. 105:9-18 (Byrn Direct)).

3. Teva's Product Is "Coated By A Coating Agent"

A person of skill in the art would understand the term "coated by a coating agent" to mean "covering a tablet or granule with a pharmaceutically acceptable coating." (Tr. 106:8-22 (Byrn Direct)).[7,8] Even Teva's expert, Dr. Chambliss, admits that if "coated by a coating agent" is construed consistent with its ordinary meaning, Teva's Product is coated with a coating agent. (Tr. 461:18, 462:5-13, 462:18-463:2 (Chambliss Direct), Tr. 518:21-24 (Chambliss Cross)).

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[7] Plaintiffs' construction is consistent with the ordinary dictionary definition of "coating," which is a "layer of any substance used as cover, protection, decoration, or finish." Webster's Unabridged Dictionary, at 433 (Byrn Decl., Ex. G), submitted with Plaintiffs' Opening Claim Construction Brief, dated September 11, 2007 (D.I. 134).

[8] Plaintiffs' construction is also consistent with the '321 Patent's specification, which states that "granules ***may be*** coated by a per se known method for the purpose of masking the taste or providing them with enteric or sustained release property." PTX 3 ('321 Patent, at col. 10, ll. 3-6) (emphasis added). The use of the word "may" and the reference to "per se known" methods in the sentence indicates the coating methods identified in the '321 Patent are illustrative rather than exclusive, which is consistent with Plaintiffs' construction.

As seen in the picture above (PTX 386), there is a white coating covering each of the granules contained within Teva's Product. The white coating is identified by Teva as an "Enteric Coating Dispersion," which contains the enteric polymer Eudragit L-30 D-55 (PTX 445A, at Byrn 0036; Tr. 113:24-114:17 (Byrn Direct)). Thus, Teva's Product satisfies the coating requirement of Claim 2 of the '321 Patent.

4. Teva's Product Contains Lansoprazole And Magnesium Carbonate In The Claimed Weight Ratio

The weight ratio of magnesium carbonate to lansoprazole in Teva's Product is 0.4 -- squarely within the claimed range of the '321 Patent. (Tr. 115:23-116:21 (Byrn Direct); PTX 445A, at Byrn 036). Dr. Chambliss admits that Professor Byrn properly calculated this ratio. (Tr. 494:20-495:4 (Chambliss Direct)).

A person of skill in the art, having read the '321 Patent and its prosecution history, would interpret the phrase "the amount of the basic inorganic salt relative to parts by weight of the benzimidazole [lansoprazole] being about 0.3-20 parts by weight" to mean that the ratio of magnesium carbonate to lansoprazole by weight in the entire pharmaceutical composition must be between 0.3 and 20. (Tr. 108:3-15 (Byrn Direct)). Plaintiffs' construction of this term is consistent with the ordinary meaning of the phrase, as well as the weight ratios in the '321 Patent's examples. (Tr. 108:6-15 (Byrn Direct)).

In an attempt to avoid this commonsense approach, Teva asserts that the term means "the weight of the inorganic salt that is in even contact with the benzimidazole" falls within the claimed range. (Tr. 494:20-495:12 (Chambliss Direct)). Yet on cross-examination, Teva's expert, Dr. Chambliss, admitted that the words "in even contact" do not appear in this claim element. (Tr. 527:13-528:7 (Chambliss Cross)). Dr. Chambliss also had to concede that the '321 Patent contains no discussion of how to measure a quantity of magnesium carbonate in the

formulation that is in even contact with the lansoprazole and does not include any examples reflecting such data. (Tr. 530:2-531:25 (Chambliss Cross)). Instead, consistent with Plaintiffs' proposed claim construction, the '321 inventors calculated the claimed ratio based simply on the amounts of lansoprazole and magnesium carbonate that were weighed out initially in order to prepare the formulation. (*Id.*) Notwithstanding these admissions, Teva improperly attempts to import the words "in contact evenly" from a separate and distinct limitation into its proposed construction of this weight ratio in an effort to avoid an otherwise clear-cut case of infringement.

5. Teva's Product Contains Lansoprazole In Contact Evenly With Magnesium Carbonate

When boiled down to its essence, the determination of infringement of this element turns on whether the purported 2-micron talc "layer" applied by Teva during manufacturing actually prevents mixing between the lansoprazole and magnesium carbonate. The evidence presented at trial establishes that it does not, and therefore the lansoprazole and magnesium carbonate are in contact evenly.

a. Construction of the Term "In Contact . . . Evenly"

A person of skill in the art, having read the '321 Patent and its prosecution history, would conclude that the term "the benzimidazole compound [lansoprazole] being in contact with the basic inorganic salt evenly" means "a mixture of the benzimidazole compound [lansoprazole] in contact with the basic (*i.e.*, alkaline) inorganic salt in a uniformly basic environment." (Tr. 109:19-110:5 (Byrn Direct)); D.I. 133, Plaintiffs' Claim Construction Brief, at p. 14-20.

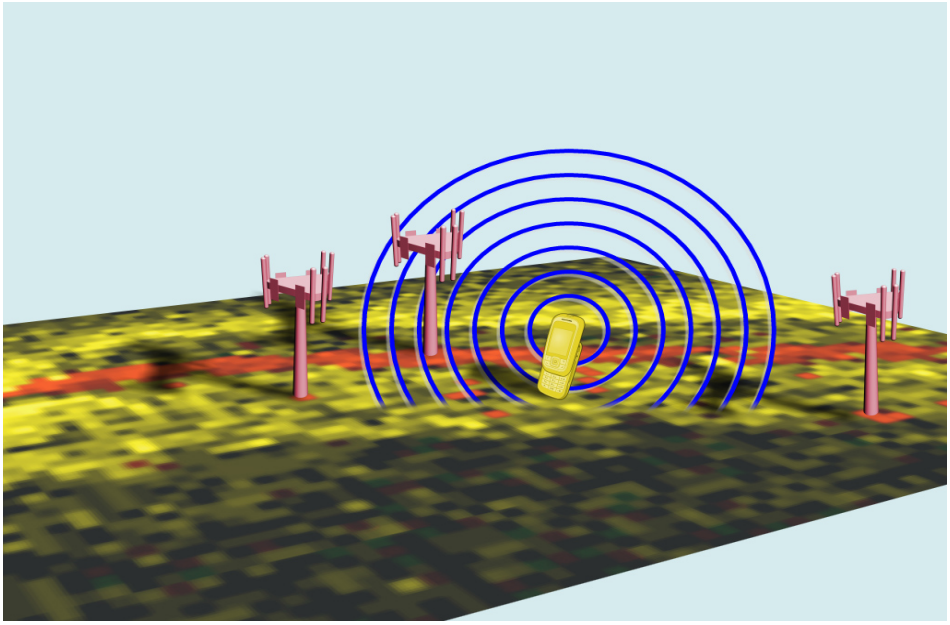
This construction is consistent with the stated purpose of the '321 Patent -- to stabilize lansoprazole, which is acid sensitive, by placing it "in contact with the basic inorganic salt [magnesium carbonate]." (Tr. 109:19-110:5 (Byrn Direct); *see also* Tr. 110:6-11 (Byrn Direct)). The magnesium carbonate contacts the lansoprazole, through physical touching and through

contact mediated by moisture and residual water, and creates a basic (*i.e.* alkaline) environment surrounding the lansoprazole. This basic environment insulates lansoprazole from any acids -- both those present in the formulation and those it may encounter in the stomach -- which would otherwise cause it to degrade. (Tr. 110:6-11 (Byrn Direct)).

The '321 Patent teaches that there should be substantial moisture or residual water present in the composition. (PTX 3, (Col. 9, ll. 54-56 ("[T]he moisture amount in the composition is preferably about 6-60%, and more preferably about 20-40%)); Tr. 90:22-25 (Byrn Direct)). The '321 Patent also teaches that the magnesium carbonate and other basic inorganic salts used in the invention must have the ability to create a basic solution or environment when there is moisture or water present. (PTX 3 ('321 Patent, Col. 9, ll. 21-24) (salts used in the invention must show "basicity (pH of not less than 7) when they are in the form of a 1% aqueous solution or suspension")). A drug formulator of ordinary skill in the 1980s would have understood these teachings to mean that the invention of the '321 Patent involved the creation of a basic environment to surround and stabilize lansoprazole. (Tr. 89:17-90:16, 99:10-18 (Byrn Direct)).

Professor Byrn explained in detail how a person of skill would understand the term "contact . . . [between lansoprazole and magnesium carbonate] evenly" in the context of the '321 Patent. (Tr. 97:18-99:18 (Byrn Direct)). The ordinary meaning of the word "contact" is "association or relationship (as in physical or … communication) <students or teachers in daily contact>" and "a condition or an instance of meeting, connecting, or communicating." *See* D.I. 133, Plaintiffs' Claim Construction Brief, at p. 16 (citing *Webster's Unabridged Dictionary*, at 490).

Contact does not require physical touching; the word includes "immediate proximity or association" and "to communicate with." *See* D.I. 133, Plaintiffs' Claim Construction Brief, at p. 16 (citing *The Random House Dictionary of the English Language, Unabridged* 437 (Stuart B. Flexner, ed., 2d ed. 1987). For example, two people on the telephone are said to be in contact even though they are not physically touching. As Professor Byrn explained, a cell phone is *in contact with* a cellular phone tower through radio waves even though the phone and tower are not physically touching, and a cell phone user remains *in contact* as long as he or she is within range of any cellular phone tower that can receive his or her radio transmissions and send him or her its radio waves. (Tr. 100:16-101:14 (Byrn Direct)).



As Teva acknowledges in its Opening Claim Construction Brief (D.I. 131), the dictionary defines "even" as "uniform in action, character, or quality." *Random House Dictionary of the English Language Unabridged*, at 670 (D.I. 131, Ex. 9). In the context of the '321 Patent, "in contact with the basic inorganic salt evenly" means that the environment is "uniformly basic" in

that all or substantially all of the lansoprazole is in a pH environment that can be characterized as basic (*i.e.*, pH of 7 or above). (Tr. 89:10-90:16, 109:19-110:11 (Byrn Direct)).

From the specification, one skilled in the art would understand that the invention of the '321 Patent includes both homogenous and non-homogenous mixtures of lansoprazole and magnesium carbonate, as long as "contact with the basic inorganic salt evenly" is achieved. (*See* '321 Patent, Col. 9, ll. 56-59, 62-65.) "Contact with the basic inorganic salt evenly "is achieved by lansoprazole/magnesium mixtures that create an alkaline environment." (Tr. 89:10-91:10, 91:23-92:14, 109:19-110:11 (Byrn Direct)). But it does not require that every particle of lansoprazole be physically touching a particle of magnesium carbonate; nor does it require homogenous mixing, to achieve an even or uniform alkaline environment. (Tr. 97:10-99:18, 101:15-102:17 (Byrn Direct)). Just as in the case of steak *au poivre*, a steak in "even contact" with pepper, the pepper can interact with and effectively complement the steak without being in a homogeneous mixture with the steak, as even Dr. Chambliss admits. (Tr. 525:3-10 (Chambliss Cross)).

Consistent with the foregoing, the '321 Patent explicitly contemplates embodiments in which the lansoprazole and magnesium carbonate are not physically touching. For instance, in Example 11 of the '321 Patent, the composition described includes a total of five different ingredients, two of which are lansoprazole and magnesium carbonate. (PTX 3, ('321 Patent, Col. 15, ll. 30 - Col. 16, ll. 15)), Tr. 195:19-197:13 (Byrn Re-Direct)). In such a system, the lansoprazole being "in contact with the basic inorganic salt evenly" does not and cannot require that all the lansoprazole be physically touching or homogenously mixed with the magnesium carbonate. (Tr. 195:19-197:13 (Byrn Re-Direct)). Even Teva's expert Dr. Chambliss admitted that under his proposed construction requiring a "homogeneous mixture," there will not

necessarily be physical touching between every particle of lansoprazole and magnesium carbonate. (Tr. 535:20-25 (Chambliss Cross)).

As Professor Byrn explained, and Dr. Chambliss implicitly conceded, a person of skill in the relevant art would understand that "contact" between two compounds in a pharmaceutical could occur through acid-base reactions or proton transfer, and could occur through chemical interactions mediated by moisture or residual water. (Tr. 91:23-92:14, 93:9-95:4, 94:13-22 (Byrn Direct)). In the 1980s, drug formulators understood that acid-base chemistry, including interactions involving the transfer of protons, routinely occurred between ingredients in solid pharmaceutical formulations. (Tr. 99:10-18 (Byrn Direct)). They also understood that acid-base chemistry and these proton transfers could be used to create a basic or alkaline environment, such as a uniform basic environment to surround and stabilize lansoprazole. (*Id.*).

Teva's contention that "contact … evenly" and "homogenous mixture" are synonymous is refuted both by the ordinary usage of those terms, as well as by their differing uses in the '321 Patent itself. (Tr. 519:24-520:19). The fact that the specification uses two different phrases for these concepts is consistent with there being "different meanings of those phrases." *Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 807 (Fed. Cir. 2007) ("[T]he evidence of the specification therefore suggests that the patentees knew how to restrict their claim coverage …. They could have used the word 'perpendicular …. Instead, they chose a different term that implies a broader scope."); *Dow Chem. v. Sumitomo Chem. Co.*, 257 F.3d 1364, 1377 (Fed. Cir. 2001). Indeed, if the '321 inventors wished to limit claim 2 to a "homogeneous mixture," they certainly could have used that term in the claim. Instead, they chose the broader "in contact . . . evenly" language and therefore did not limit the claim to a particular process. Teva is improperly attempting to read a process limitation into a product claim in contravention of well-established

Federal Circuit precedent. *See AFG Indus., Inc. v. Cardinal IG Co.*, 375 F.3d 1367, 1370 (Fed. Cir. 2004) (product claim covers structure of product "however it is made or however it is used").

At its core, Teva's construction relies on its position that Takeda made a "clear and unambiguous" surrender of subject matter in the '321 Patent specification or in the prosecution history which limits the scope of claim 2. Teva principally relies on one sentence to support its proposed claim construction:

> The composition of the invention is prepared by homogeneously admixing the above benzimidazole compound, the basic inorganic salt of magnesium …, and the above additives.

(PTX 3, ('321 Patent, col.9, ll. 45-48)). Teva contends that this sentence limits claim 2 and disclaims everything except a pharmaceutical composition prepared by homogeneous admixing of lansoprazole and magnesium carbonate. But as explained in Plaintiffs' Claim Construction briefs, D.I. 133 and 141, and as explained above, the '321 Patent goes on to say that magnesium carbonate may also be added to an already-prepared mixture of lansoprazole and other excipients, where the magnesium carbonate is not homogeneously admixed:

> The method of admixing is ***optional*** if the benzimidazole compound can finally be in contact with the basic inorganic salt of magnesium and/or of calcium evenly. Thus, for example, the additives may be admixed with a mixture of the benzimidazole compound lansoprazole and the basic inorganic salt of magnesium and/or calcium as prepared by preliminary admixing, ***or*** *the basic inorganic salt of* ***magnesium*** *and/or of calcium* ***may be added to*** *a mixture of* ***the benzimidazole compound lansoprazole*** *and the additives as prepared by preliminary admixing.*

See '321 Patent, col. 9, ll. 54-66 (emphasis added).

As the Federal Circuit recognized recently, where a purported surrender is contradicted by other statements in the patent or prosecution history, it should not be interpreted to constitute. *Elbex Video, Ltd. v. Sensormatic Elecs. Corp.*, No. 2007-1797, 2007 WL 4180138 at *6 (Fed.

Cir. Nov. 28, 2007) ("For a prosecution statement to prevail over the plain language of the claim, the statement must be clear and unmistakable such that the public should be entitled to rely on any 'definitive statements made during prosecution.'"); *see also MBO Labs., Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323, 1333 (Fed. Cir. 2007) ("Limiting claims from the specification is generally not permitted absent a clear disclosure that the patentee intended the claims to be limited as shown."); *Acumed*, 483 F.3d at 807. Given the full context, the '321 inventors' statements in the specification and prosecution history do not clearly and unmistakably limit the claim.

b. The Lansoprazole In Teva's Product Is In Contact Evenly With Magnesium Carbonate

Teva's ANDA and the testing performed by Plaintiffs' and Teva's own experts establish that Teva's Products contains "a mixture of the benzimidazole compound [lansoprazole] in contact with the basic (*i.e.*, alkaline) inorganic salt [magnesium carbonate] in a uniformly basic environment." (Tr. 119:18-124:3, 125:16-127:22, 128:12-129:4 (Byrn Direct)).

(i) Teva's Manufacturing Process Causes Lansoprazole To Be In Contact Evenly With Magnesium Carbonate

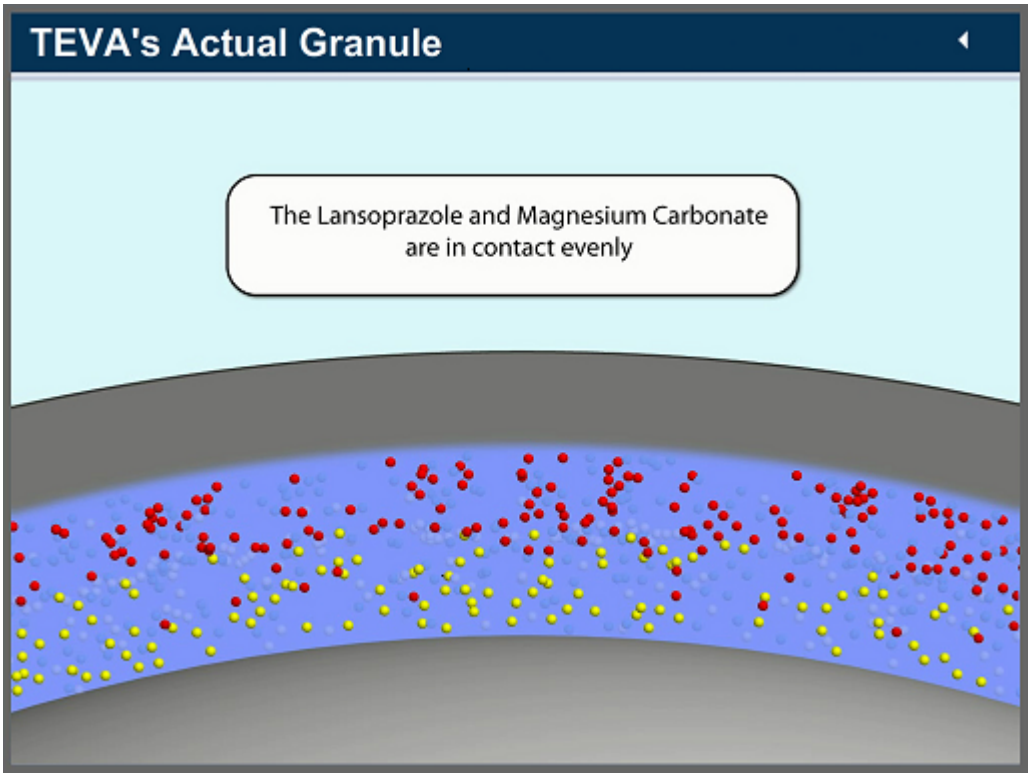
As described in greater detail above, Teva's manufacturing process involves spraying a series of four water-based dispersions (mixtures of ingredients dispersed within water) onto a sugar core. (PTX 445A, Byrn 0036, TVL 6617, Tr. 119:18-120:10 (Byrn Direct)). The first dispersion, a so-called "Drug Coating Dispersion," is a mixture of solid lansoprazole, talc, and hypromellose dispersed in a solution of water and ammonia. (PTX 445A, Byrn 0036, TVL 6617).

A "Subcoat 1 Coating Dispersion" containing a small amount of hypromellose and a small amount of talc dispersed in water, is sprayed on top of the first dispersion. (PTX 445A,

Byrn 0036, TVL 6617, Tr. 120:11-121:3, (Byrn Direct)). This "Subcoat 1 Coating Dispersion" is the extremely thin 2-micron talc layer that is supposed to separate lansoprazole and magnesium carbonate. (Tr. 138:10-24 (Byrn Direct)). However, because the "Subcoat 1 Coating Dispersion" is sprayed on with water and is so thin, there is blending and intermixing of the components of the Drug Coating Dispersion (containing the lansoprazole) and the Subcoat 1 Dispersion. (Tr. 122:5-123:10 (Byrn Direct)).

A "Subcoat 2 Coating Dispersion," containing hypromellose and magnesium carbonate dispersed in water is sprayed onto the product after the talc and hypromellose dispersion. (PTX 445A, Byrn 0036, TVL 6617, Tr. 123:11-19 (Byrn Direct)). Once again, because the dispersion contains water, it will mix with the previously applied dispersions. Thus, there is mixing of the magnesium carbonate with lansoprazole and talc from the previous applications. (*Id.*)

Finally, an "Enteric Coating Dispersion," containing the enteric coating agent (Eudragit), talc, titanium dioxide and triethyl citrate, is applied. (PTX 445A, Byrn 0036, TV 6617, Tr. 123:20 (Byrn Direct)). The result is illustrated in the graphic representation of the Teva granule discussed by Dr. Byrn at trial:



This illustration, which depicts a portion of a cross-section of a granule, shows an innermost sugar core (shown in gray), a layer formed by the first three dispersions containing, *inter alia*, lansoprazole (shown in yellow), magnesium carbonate (shown in red), and moisture and/or residual water (shown in blue). (Tr. 122:5-123:19 (Byrn Direct)).

As can be seen in the illustration and as confirmed by tests described below, the supposed 2-micron talc "layer" or "subcoat" ("Subcoat 1 Coating Dispersion") does not serve as an impenetrable barrier between lansoprazole and magnesium carbonate. This is hardly surprising given its extreme thinness (roughly 1/50th of the width of a human hair). As Dr. Byrn testified, in his over 35 years in the field of pharmaceutical sciences, he does not "know of an impermeable layer that's that thin." (Tr. 139:5-6 (Byrn Direct)).

(ii) Numerous Raman Tests of Teva's Product Establish That There Is Contact and Mixing of Lansoprazole and Magnesium Carbonate

Extensive Raman spectroscopy (over 60 tests) carried out by both Plaintiffs' and Teva's experts establishes that the lansoprazole and magnesium carbonate in Teva's Product are in contact evenly. The results of these experiments indicate numerous regions throughout each granule of Teva's Product in which magnesium carbonate and lansoprazole were in contact and mixed with each other. (Tr. 216:15-217:5 (Bugay Direct), Tr. 126:19-127:22 (Byrn Direct)).

Raman spectroscopy is an analytical test used to identify a compound based upon its chemical structure. (Tr. 208:12-14 (Bugay Direct)). The Raman spectrum of each component of Teva's Product is a fingerprint of that component, which allows one to determine precisely where in the granule each particular component is found. (PTX 390-395; Tr. 208:1-209:16 (Bugay Direct)). By interfacing the Raman instrument with a microscope, a Raman spectrum can be acquired from a very small and specific area on Teva's Product. (Tr. 209:22-210:6 (Bugay Direct)).

In this case, Plaintiffs and Teva's experts performed independent Raman mapping analyses of Teva's Product. (Tr. 217:6-218:5 (Bugay Direct), PTX 408, PTX 413-414, PTX 433, PTX 926-927). Plaintiffs collected data from various granules within Teva's Products using "line maps." (*Id.*) Line maps were taken at positions outside the sugar core in the area where the dispersions of lansoprazole and other substances were applied to the core during the four spraying steps. (PTX 400, PTX 410; Tr. 212:8-213:3 (Bugay Direct)). In Plaintiffs' line map experiments, three lines of laser radiation were focused upon the surface of the sample granule.[9]

[9] The sample granules were "microtomed" -- *i.e.*, cut in half -- with a sharp blade to obtain a cross-sectional area of the granule to be studied.

These three lines were separated from each other by 3 microns, and each line was 2 microns wide and 72 microns long. The 72 micron lines were further divided into 12 separate "bins," with each bin being 2 microns wide by 6 microns long. (Tr. 210:9-211:1 (Bugay Direct)). The Raman laser penetrates into the sample to a depth of 5.6 microns. (Tr. 1409:1-1410:15 *citing* PTX 953 (Bugay Rebuttal)). Thus, the volume being observed in each bin is 2 x 6 x 5.6 microns -- a very small, finite volume.

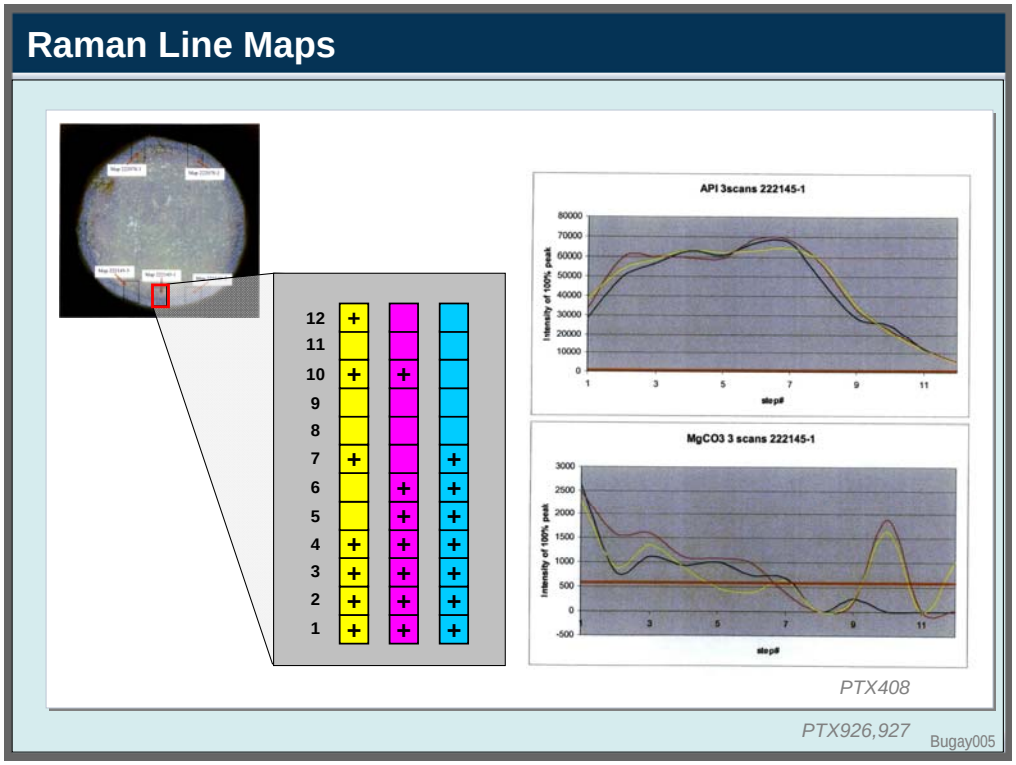
Teva's expert Dr. Meyer criticized Plaintiffs' use of Raman to determine even contact as unreliable because, in his words, "I would guess, I don't know for sure, that in the experiments that were done, some of the excitation light in the Raman experiment light passes through the entire sample." (Tr. 397:13-16 (Meyer Direct)). However, when pressed on cross, Dr. Meyer admitted that his testimony regarding the depth penetration of the Raman instrument was just speculation and that he actually did not know how deep the Raman beam penetrates. (Tr. 432:9-18 (Meyer Cross)).

Dr. Meyer's speculations were completely wrong. As Plaintiffs' expert Dr. David Bugay[10] testified in response to Dr. Meyer, the Raman light only penetrates 5.6 microns into the sample (in the configuration used in Plaintiffs' tests) -- which is completely insufficient to extend through multiple sections of Teva's granules. (Tr. 1409:1-1410:15 (Bugay Rebuttal), *citing* PTX-953).

For each 2 x 6 x 5.6 micron bin tested by Plaintiffs, a unique Raman spectrum was generated. (Tr. 210:18-24 (Bugay Direct)). Each bin was then analyzed using Raman to

[10] Dr. Bugay is the Managing Director of Aptuit Consulting, a contract research company that provides analytical chemistry and consulting services. He is an expert in analytical chemistry, including the use of Raman and EDS analyses. ***"Pharmaceutical Excipients: Characterization by IR, Raman, and NMR Spectroscopy***," *1998 and 1999 editions.* (PTX 385 (CV Bugay), Tr. 199:5-203:10 (Bugay Direct)).

determine whether that small volume contained both lansoprazole and magnesium carbonate particles. (Tr. 213:4-215:19 (Bugay Direct); PTX 408, 413, 414, 433, 926, and 927) Representative results are shown in PTX 408, which Dr. Bugay prepared and discussed at trial:



The signal for lansoprazole along each of the 3 line maps is shown in the upper graph of PTX 408, and the signal for magnesium carbonate is shown on the lower graph of PTX 408. (Tr. 213:13-214:11 (Bugay Direct)). The vertical axis corresponds to the intensity of the signal. (Tr. 214:6-11 (Bugay Direct)). The number on the horizontal axis corresponds to the bin along the line. (Tr. 214:4-6 (Bugay Direct)). Wherever the intensity is above the red line, called the limit of detection, magnesium carbonate or lansoprazole is present. (Tr. 214:12-215:2 (Bugay Direct)). The "+" sign in box in the graphic identifies the 2x6 micron positions along each line in which both magnesium carbonate and lansoprazole are present. Thus, both magnesium

carbonate and lansoprazole are present in the 2 x 6 x 5.6 micron volumes represented by bins 1, 2, 3, 4, 7, 10 and 12 in the first of three lines. (Tr. 215:3-19 (Bugay Direct)).

The Raman data collected by Plaintiffs confirm that (1) lansoprazole and magnesium carbonate are physically touching and in close proximity in many of the bins, and (2) the physical touching or close proximity occurs over significant adjacent portions of the granules in Teva's Product. A lansoprazole particle is about 10 microns in diameter, while magnesium carbonate ranges from about 10-40 microns. (Tr. 216:5-14 (Bugay Direct)). In other words, both particles are larger than the 2 x 6 x 5.6 micron bins being analyzed. (Tr. 216:5-14 (Bugay Direct)). Therefore, if both types of particles are present in the same bins, and both types of particles are present in a series of adjacent bins, the magnesium carbonate and lansoprazole are necessarily either physically touching and in extremely close proximity. (Tr. 216:15-217:5 (Bugay Direct)).

In the example set forth above, PTX 408, the physical contact and close proximity occurs over at least bins 1, 2, 3, 4, 5, 7 and 10. As noted, each bin is 6 microns in length, so on this particular line shown in PTX 408 the physical touching and close proximity occurs over a length of about 42 microns on the granule (7 bins multiplied by 6 microns). (Tr. 127:7-18 (Byrn Direct), Tr. 213:4 - 215:8 (Bugay Direct), Tr. 203:11-204:5 (Bugay Direct)). 42 microns is a significant distance relative to the size of the granule and the size of the 2 micron layer that Teva claims to separate lansoprazole and magnesium carbonate in Teva's Product. The results show that lansoprazole and magnesium extend in a mixture that goes far across the purported "impenetrable talc layer."

To be clear, these test results do not indicate that there is some incidental contact between lansoprazole and magnesium carbonate. Instead, they show contact and mixing of the two

substances spread across significant portions of Teva's granules thereby producing a mixture of lansoprazole and magnesium carbonate in Teva's Product. (Tr. 126:19-127:22 (Byrn Direct)).

Similar results were found along other line maps that were analyzed by Plaintiffs' expert Dr. Bugay. He performed line mapping on four of Teva's 30 mg granules and one of the 15 mg granules to obtain a total of 62 different lines. (Tr. 217:6-218:5 (Bugay Direct), PTX 408, PTX 413-414, PTX 433, PTX 926-927). Dr. Bugay found substantial contact between the lansoprazole and the magnesium carbonate, including physical touching, mixing, and close proximity in all 62 lines. (Tr. 218:3-8 (Bugay Direct)).

Furthermore, Teva's expert (Mr. Hirt) performed Raman testing on Teva's Product and obtained results consistent with Dr. Bugay's findings. Mr. Hirt found numerous portions of each line map in which both lansoprazole and magnesium carbonate were present. (PTX 942-943, Tr. 348:22-356:5 (Hirt Cross), Tr. 219:19-22, 221:9-223:14 (Bugay Direct). In fact, Mr. Hirt's Raman data found magnesium carbonate and lansoprazole present together in the same areas as Dr. Bugay. (PTX 378; PTX 688, PTX 924-925; Tr. 221:9-223:14 (Bugay Direct).

Teva's other expert, Dr. Gerald Meyer, admitted that Dr. Bugay and Mr. Hirt's Raman tests were largely in agreement. (Tr. 430:6-9 (Meyer Cross)). As Dr. Bugay noted in his testimony, the fact that he and Mr. Hirt, using two different Raman instruments at two different laboratories, both obtained the same results, demonstrates that this Raman data can be relied upon with a high degree of confidence. (Tr. 219:19-220:1, 222:13-224:14 (Bugay Direct)).

In total, the parties' respective expert laboratories (Aptuit and Materials Research Laboratories) tested eleven different granules and analyzed over 800 spectra. What they observed was "even contact" -- both physical touching and close proximity -- between lansoprazole and magnesium carbonate in substantially all of the areas that were tested.

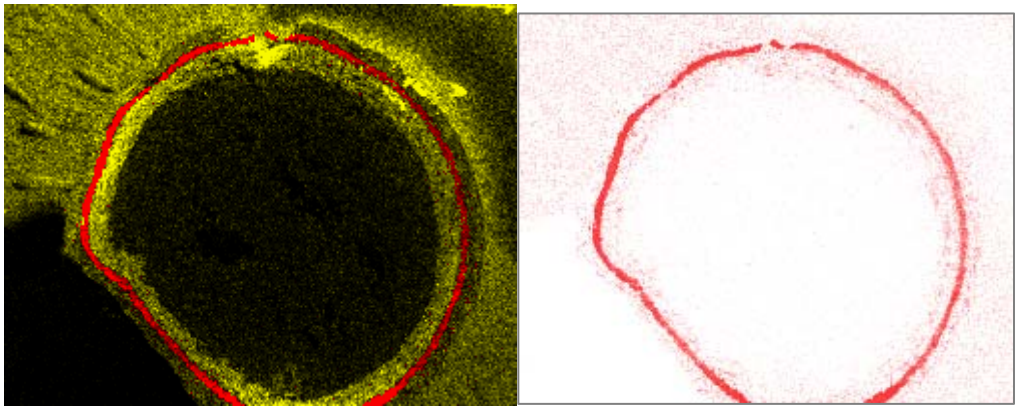
(Tr. 229:10-19 (Bugay Direct)). These spectra demonstrate the existence of a mixture of lansoprazole and magnesium carbonate in the Teva's Product. (Tr. 126:23-127:22 (Byrn Direct)).

(iii) EDX Spectroscopy Of Teva's Products Shows Physical Contact, Close Proximity And Mixing Of Lansoprazole And Magnesium Carbonate

Energy Dispersive X-ray Spectroscopy ("EDX" or "EDS," interchangeably) carried out by both Plaintiffs' and Teva's experts similarly demonstrates that lansoprazole and magnesium carbonate in Teva's Products are in even contact. EDX detects the elements (from the periodic table) that are contained within a chemical compound. (Tr. 229:4-230:16 (Bugay Direct)). And like Raman, EDX provides a fingerprint for identification of a material in a pharmaceutical formulation. (*Id.*). Also like Raman, EDX has high spatial resolution associated with the instrument, from which one can obtain a map of the components in a sample based on an array of four-by-four micron pixels. (Tr. 230:10-16 (Bugay Direct)).[11]

PTX 423 and 422 are representative examples of EDX images from one of Teva's granules. PTX 423 (below left) shows magnesium carbonate in red and lansoprazole in yellow. PTX 422 (below right) shows just magnesium carbonate.

[11] Similar to his unfounded criticisms of depth penetration in Raman, Teva's expert, Dr. Meyer criticized the EDX analysis for having a high depth penetration that "can be tens of microns large." (Tr. 384:7-12, 392:8-19 (Meyer Direct)). Once again, Dr. Meyer is wrong. Teva's other expert, Mr. Hirt, correctly identified the depth of penetration of EDX as being "from half a micron to about five microns." (Tr. 300:18-301:4 (Hirt Direct)). Mr. Hirt's testimony is consistent with that of Dr. Bugay and the scientific literature, which shows that the depth of penetration of EDX experiment used in this case is about two microns. (Tr. 1416:3-1417:5 (Bugay Rebuttal)).



The dark spot in the center of the left image is the sugar core. Just outside the sugar core but within the generally red band, yellow pixels are indicative of lansoprazole. If lansoprazole is subtracted by computer from that portion of the image (PTX 422, with a white background), magnesium carbonate is evident in the same portion of the granule as lansoprazole (*i.e.*, within the red band). (Tr. 230:24-231:12 (Bugay Direct)). These images show that substantial amounts of magnesium carbonate and lansoprazole are touching. (Tr. 232:2-13 (Bugay Direct)). The extent of this contact is evidence of mixing of lansoprazole and magnesium carbonate in Teva's Product. (Tr. 130:24-131:25 (Byrn Direct)). Further, Teva's own expert performed EDX analysis of Teva's granule, and the results of those experiments likewise show physical contact, close proximity, and mixing of lansoprazole and magnesium carbonate. (PTX 379, Tr. 232:21-233:20 (Bugay Direct)).

Between Dr. Bugay and Mr. Hirt, the parties' two expert labs analyzed 14 different granules using EDX, and found contact -- both actual physical touching and close proximity -- of magnesium carbonate and lansoprazole in all of those EDX maps.

(iv) The Evidence Proving Mixing Between Lansoprazole And Magnesium Carbonate Is Not Surprising Given Teva's Product Development History

As noted in detail above, throughout the product development history Teva was not able to develop an impenetrable subcoat. Teva's own determination that its layers and subcoats were porous and poorly defined is consistent with both parties' Raman and EDX results showing a mixture of lansoprazole and magnesium carbonate in Teva's Product.

At trial, Teva's trial counsel promised to prove to the Court that Teva could make subcoats that separated lansoprazole from magnesium carbonate:

> And plaintiffs will suggest to you that Teva is unable to create a product with a separate talc subcoat that separates the lansoprazole from the magnesium carbonate. And we'll explain to the Court why Teva has plenty of experience making such subcoats."

(Tr. 68:22-69:1 (Teva's Opening Statement)).

Despite its promise, Teva's never offered any such explanation and never produced a single witness that discussed Teva's purported experience in producing subcoats that rigidly separated lansoprazole from magnesium carbonate. Instead, Teva relied on Dr. Chambliss to suggest that the manufacture of such subcoats was within the purview of "a competent pharmaceutical company." (Tr. 474:17-21 (Chambliss Direct)). But Dr. Chambliss never reviewed or considered the development documents or deposition testimony that Teva's Ms. DiCapua provided and has no basis for any such opinion regarding Teva. (Tr. 461:4-10 (Chambliss Direct)).

Even today, Teva scientists are not aware of whether the lansoprazole mixes with the magnesium carbonate in Teva's Product, because Teva stopped doing the necessary tests to make this determination. (Tr. 1663:3-11 (DiCapua Dep.)). However, as set forth in detail above, tests

by Plaintiffs' and Teva's experts show that Teva did not solve the penetration problem it was experiencing during product development. In fact, lansoprazole and magnesium carbonate are mixed within Teva's Product.

(v) The Magnesium Carbonate And Moisture Or Residual Water In Teva's Product Creates A Uniformly Basic Environment

There is no dispute that Teva's Product contains moisture and residual water. (PTX 445A, Byrn 0034, TVL 6615). As part of post-manufacturing testing, Teva measures its Product's residual water content by a Loss-on-Drying (LOD) Test. The LOD test involves heating the Products for a certain length of time and measuring how much weight loss occurs (Tr. 132:7-10 (Byrn Direct)). Any weight loss is attributable to water that was in the Product and was caused to evaporate. In its specifications, Teva permits up to 5% weight loss measured by the LOD test. (PTX 445A, Byrn0184, TVL7163). In practice, Teva observes a 1.1 % weight loss attributable to water. (*Id.*).

In fact, as Dr. Byrn testified, there is substantially more moisture and residual water actually present in Teva's Product. The 1.1% weight loss represents the minimum amount of moisture and residual water that could be present in the Product. (Tr. 132:11-24 (Byrn Direct)). As Professor Byrn, explained, the enteric coat physically holds additional water in the granule during the LOD test. Therefore, Teva's test understates the amount of moisture and residual water actually present. (PTX 445A, Tr. 132:1-24 (Byrn Direct)).

In the presence of moisture and residual water, the magnesium carbonate and lansoprazole mixture in Teva's Product creates a unique uniformly basic environment surrounding lansoprazole. (Tr. 132:1-24 (Byrn Direct)). Teva's ANDA shows that while magnesium carbonate is practically insoluble in water, it creates an alkaline environment when

suspended in water. (PTX 956). This is also taught by the Handbook of Pharmaceutical Excipients, a highly regarded treatise in the pharmaceutical formulation sciences. (Tr. 1406:24-1407:10 (Bugay Rebuttal), *citing* PTX 954).

In a paper published by Takeda scientist Dr. Tabata, following the invention of the '321 Patent, the pH of the magnesium carbonate environment was determined to be 9.1, which is a basic pH. (PTX 748, Tr. 97:3-9 (Byrn Direct)). Based on the teachings of Tabata and the fact that Teva's Product is stable through the use of magnesium carbonate, the environment created by the magnesium carbonate is basic. As Dr. Byrn explained, absent a uniformly basic environment created by the mixture of lansoprazole and magnesium carbonate, there is no other explanation as to why the magnesium carbonate in Teva's Products functions as a stabilizer. (Tr. 116:25-117:12, 132:25-133:11 (Byrn Direct). Teva's response to this was silence. Teva's expert provided no explanation as to how the magnesium carbonate stabilizes the lansoprazole. In fact, as described above, Teva claims that it does not "have a full understanding of the mechanism of stabilization." (Tr. 1653:16-17 (DiCapua Dep.)).

Based on the foregoing, Teva's Product satisfies the requirement that the "benzimidazole compound [lansoprazole be] in contact with the basic inorganic salt evenly."

II. DR. MEYER'S TESTIMONY ON PH AND UNIFORMLY BASIC ENVIRONMENT SHOULD BE STRICKEN

As early as June 22, 2007, Plaintiffs' expert, Dr. Byrn disclosed his opinion that, with respect to the '321 Patent, he understood the claim term "contact evenly" to mean "a mixture of the benzimidazole compound [lansoprazole] in contact with the basic (*i.e*. alkaline) inorganic salt in a uniformly basic environment." Byrn Expert Report, p. 22, ¶ 71 (*emphasis added*), attached hereto as Exhibit 1. Defendants' expert, Dr. Meyer, did not address any of Dr. Byrn's opinions

about a uniformly basic environment in his rebuttal expert report. (Tr. 425:11-426:1 (Meyer Cross)).

On September 11, 2007, in a declaration submitted in support of Plaintiffs' claim construction brief, Dr. Byrn again addressed the concept of a "uniformly basic environment," explaining that proton transfer between components of a solid-state drug formulation in the presence of moisture or residual water results in creating a basic environment. (Byrn Decl., ¶ 48, D.I. 134; Tr. 425:8-13 (Meyer Cross)). Nine days later, on September 20, Plaintiffs took the deposition of Dr. Meyer. At his deposition, Dr. Meyer testified that he did not intend to offer any opinions at trial that were not contained in his expert report:

> Q: . . . [D]oes your report contain all the opinions you intend to offer at trial?
>
> A: Yes.
>
> Q: Do you intend to do any other work on this case before trial?
>
> A: Not that I'm aware of.

Meyer Dep. 124:19-25 (attached hereto as Exhibit 2).

Based on these disclosures, Plaintiffs reasonably expected that Dr. Meyer would not testify on the issues of uniformly basic environment, proton transfer, and pH at trial. Nonetheless, Meyer testified at length about all these issues. *See* Tr. 419:2-423:24. Plaintiffs request that this portion of Dr. Meyer's testimony be stricken.

Defendants provided no justification for their failure to disclose the subject matter of Dr. Meyer's testimony either at trial or deposition. As such, Dr. Meyer's testimony on these issues went beyond the scope of his expert report, and should be stricken under Rule 37(c)(1) of the Federal Rules of Civil Procedure.

III. RELIEF REQUESTED

Pursuant to 35 U.S.C. § 271(e)(4)(B), Plaintiffs request that the Court enjoin Teva (and related individuals and entities) from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of 15 mg or 30 mg lansoprazole products, or products that are not colorably different from these two infringing products, that infringe either '321 Patent claim 2 or '098 Patent claim 10. In addition, Plaintiffs request that the Court enjoin Teva from filing additional ANDAs for products that not colorably different with respect to the '321 and '098 Patents from the two infringing products. *Cf. Abbott Labs. v. Torpharm, Inc.*, 503 F.3d 1372, 1381 (Fed. Cir. 2007) (holding that an injunction against filing further ANDAs was appropriate). Moreover, Plaintiffs will request their costs if they prevail.

Finally, Plaintiffs seek their attorneys' fees under 35 U.S.C. § 285, and a ruling that Teva's filing of the ANDA was without merit, and thus, this case was exceptional. *See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1347 (Fed. Cir. 2000). Plaintiffs believe that this issue should be addressed only after the Court has made a decision in its favor regarding infringement, and will propose a briefing schedule at that time if necessary.

CONCLUSION

For the reasons set forth above, Plaintiffs respectfully request that this Court find that Teva's Product, if made, used or sold, would infringe claim 2 of the '321 Patent. Further, in light of Teva's admission that its Product would, if made, used or sold, infringe claim 10 of the '098 Patent, Plaintiffs respectfully request that the Court enter a judgment that approval of Teva's ANDA No. 77-255 be made no earlier than the expiration of the '098 patent, including any extensions that may apply.

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December 10, 2007
1331716

CERTIFICATE OF SERVICE

I hereby certify that on December 10, 2007, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send electronic notification of such filing to the following:

Karen L. Pascale, Esquire
YOUNG CONAWAY STARGATT & TAYLOR, LLP

Additionally, I hereby certify that true and correct copies of the foregoing were caused to be served on December 10, 2007, upon the following individuals in the manner indicated:

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