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.,	)	**REDACTED - PUBLIC VERSION**
Defendants and Counterclaim-Plaintiffs.	)	

ANSWERING POST-TRIAL BRIEF
OF DEFENDANTS TEVA PHARMACEUTICALS USA, INC.
AND TEVA PHARMACEUTICAL INDUSTRIES LTD.
REGARDING NONINFRINGEMENT OF THE '321 PATENT

YOUNG CONAWAY STARGATT & TAYLOR LLP
Josy W. Ingersoll (No. 1088) [jingersoll@ycst.com]
Karen L. Pascale (No. 2903) [kpascale@ycst.com]
Karen E. Keller (No. 4489) [kkeller@ycst.com]
The Brandywine Building
1000 West St., 17th Floor
P.O. Box 391
Wilmington, Delaware 19899-0391
Phone: 302-571-6600

SUTHERLAND ASBILL & BRENNAN LLP
John L. North
Jeffrey J. Toney
Jeffrey D. Blake
Laura Fahey Fritts
999 Peachtree Street
Atlanta, Georgia 30309-3996
Phone: 404-853-8000

Attorneys for Defendants,
Teva Pharmaceuticals USA, Inc
and Teva Pharmaceutical Industries, Ltd.

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Defendants and Counterclaim-Plaintiffs Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. (collectively "Teva") respectfully submit this response to Plaintiffs Takeda's and TAP's Opening Post-Trial Brief Concerning Infringement of the '321 Patent (D.I. 163).

I. EXECUTIVE SUMMARY

Plaintiffs urge a construction of the critical "in contact . . . evenly" limitation that is nothing short of extraordinary. Plaintiffs ask the Court to construe "in contact . . . evenly" such that the limitation requires no physical contact between magnesium carbonate and lansoprazole. Plaintiffs assert that the claim limitation is met whenever the dosage form has a uniform "basic" or "alkaline" environment, irrespective of where the lansoprazole and magnesium carbonate may be found.

This argument is wholly unsupported by the patent specification or the law. It also begs the (factual) question: "What evidence proves a 'basic' environment in Teva's product?" The answer: none. Plaintiffs concede that they never tested the pH of a single sample of Teva's ANDA product. So Plaintiffs ask the Court to infer such an environment, invoking analogies of cell phone systems and a new "proton transfer" theory presented only at trial.

Teva respectfully submits that the trial evidence, when viewed in context of a proper construction of the claim limitations at issue, establishes that Plaintiffs' infringement arguments fail.

Claim construction: With respect to the construction of the "in contact . . . evenly" limitation, the inventors plainly advised the public what that term meant: a homogenous mixture of the lansoprazole and magnesium carbonate. The specification specifically states that the invention must be prepared through "homogenously admixing" the ingredients. In each

example, the ingredients are physically mixed. And the file history contains references showing that "even" and "homogenous" are interchangeable terms in the context of the alleged invention. There is no indication in the patent or file history – and absolutely no notice to the public – that the inventors intended to claim a pharmaceutical composition without physical contact between the lansoprazole and magnesium carbonate.

Infringement evidence: With respect to infringement, Plaintiffs failed to provide credible evidence that Teva's ANDA product contains the requisite homogenous mixture. It does not. Indeed, Plaintiffs' initial expert report of Dr. Bugay expressly described the Teva product as having layers. (Bugay Tr. at 261, ll. 17-19 ("Q. So when you wrote your report you referred to them as layers; is that right? / A. That general feature, yes.").) Plaintiffs since changed their theories. Plaintiffs now rely on Dr. Byrn's theory that the components in Teva's product accidentally mix during manufacturing. This is supported by nothing but the *ipse dixit* of Dr. Byrn, who admitted having only one prior experience with subcoats. This accidental mixing theory also was contradicted by the testimony of Teva's expert Dr. Chambliss,[1] who has decades of private industry experience making drugs with subcoats.

The Court received considerable evidence regarding the different tests the parties performed and the spatial relationship of the lansoprazole and magnesium carbonate in Teva's

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[1] Dr. Chambliss is a Professor of Pharmaceutics, the Director of Technology Management, and a Research Professor for the National Center for Natural Products Research at the University of Mississippi. He holds a B.S. in Pharmacy, a M.S. in Pharmaceutics, and a Ph.D. in Pharmaceutics. Dr. Chambliss, a drug formulator, has worked in formulation and process development throughout his career. Over his 17 years of private industry experience, Dr. Chambliss held positions at G. D. Searle, Bristol-Myers, and Schering-Plough where he performed hands-on formulation of granules and pellets with coatings and subcoatings and prepared NDAs and ANDAs for submission to the Food and Drug Administration. At Bristol-Myers, he also gained extensive experience formulating acid sensitive compounds. (Id. at 449, ll. 5-22.) Dr. Chambliss has developed or supervised the development of over 300 pharmaceutical products for the U.S. and international markets. (Chambliss Tr. at 446-52; see also DTX30, attached as Exhibit 1.)

ANDA product. Teva respectfully submits that its testing, including testing performed by the only "blinded" expert to appear before the Court, supports the ANDA's description of a layered product in which the lansoprazole and magnesium carbonate are never mixed, but rather are applied in different layers and further separated by yet another layer of talc. This evidence refutes any argument that the ANDA product contains a homogenous mixture of the lansoprazole and magnesium carbonate.

Further, key trial admissions by both Dr. Bugay and Dr. Byrn establish that Plaintiffs failed to meet their burden of proof. Both Dr. Bugay and Dr. Byrn admitted that they could not quantify their test results. Although they used qualitative terms such as "substantial" and "significant" to describe the alleged degree of mixing and contact, they could not tell the Court how much lansoprazole and how much magnesium carbonate were present in any given area of Teva's ANDA product. In other words, there is no proof that any "contact" is "even." As Dr. Byrn testified:

> Q. And so under your theory, there is a uniform basic environment in all portions of the granule, but you can't tell us in any particular portion of the granule how much magnesium carbonate and how much lansoprazole you have; correct?
>
> A. Correct.

(Byrn Tr. at 168, l. 22 – 169, l. 2.) Dr. Bugay made similar admissions:

> Q. As a result, I mean none of the techniques you used report how much mixing occurred, do they?
>
> A. They do not.

(Bugay Tr. at 257, ll. 15-17.)

Without quantification, Plaintiffs cannot prove by a preponderance of the evidence that Teva's ANDA product meets any reasonable construction of the "in contact . . . evenly"

limitation. And Plaintiffs must prove literal infringement, as they have presented no trial evidence or argument regarding infringement under a doctrine of equivalents theory.

Below, Teva briefly will outline the legal standards governing the infringement issues. (See Section II below.) Then it will address the limitations of claim 2 of the '321 patent that are at issue, beginning with the "in contact . . . evenly" limitation. (See Section III below.).

II. PERTINENT LEGAL STANDARDS

A. The Hatch-Waxman Act Permits Challenges to Drug Patents

Plaintiffs assert claims of infringement under Section 271(e)(2) of the Patent Code. 35 U.S.C. § 271(e)(2). The Hatch-Waxman Act, which gave rise to Section 271(e)(2), permits generic versions of previously approved innovator drugs to be marketed without requiring the submission of a New Drug Application ("NDA"). Apotex, Inc. v. Thompson, 347 F.3d 1335, 1338 (Fed. Cir. 2003); Merck & Co., Inc. v. Apotex, Inc., 488 F. Supp. 2d 418, 420-21 (D. Del. 2007). Instead, a generic version of an approved innovator drug can be marketed after submission of an Abbreviated New Drug Application ("ANDA"), which can rely on testing submitted during the NDA process and a previous FDA finding that the drug is safe and effective. Merck, 488 F. Supp. 2d at 421.

Hatch-Waxman gives a generic drug manufacturer an opportunity to challenge infringement and/or the validity of a patent covering an approved innovator drug by making a "Paragraph IV certification." A Paragraph IV certification permits a generic drug manufacturer to market a generic version of the drug before expiration of the challenged patents. In this case, Teva certified under Paragraph IV that the formulation it designed for its ANDA product would not infringe the '321 patent and that the '321 patent is invalid.

B. The Court First Construes the Patent Claims

1. The Court Construes All Limitations of the Asserted Claims

The starting point for any patent infringement case, including a case under Section 271(e)(2), is the construction of the claim(s) at issue. Abbott Labs. v. Novopharm Ltd., 323 F.3d 1324, 1329 (Fed. Cir. 2003). Plaintiffs then must show that the ANDA product at issue meets every limitation of the asserted claim(s). Id. Plaintiffs bear the burden of proving infringement by a preponderance of the evidence. Centricut, LLC v. Esab Group, Inc., 390 F.3d 1361, 1367 (Fed. Cir. 2004).

Claim construction is a matter of law for the Court. Exxon Chem. Patents, Inc. v. Lubrizol Corp., 64 F.3d 1553, 1556 (Fed. Cir. 1995). Teva set forth the current claim construction standards in its pre-trial claim construction brief. (DI 131.) Plaintiffs do not dispute these general legal standards. Teva highlights below certain specific legal points applicable to the limitations at issue here.

2. The Claim Language Must Be Read As a Whole

Claim limitations must be construed in light of the claim language as a whole. Pause Tech. LLC v. TiVo Inc., 419 F.3d 1326, 1331 (Fed. Cir. 2005). Plaintiffs' attempts to isolate certain words and phrases for construction outside the context of the language of the entire claim are legally invalid. (See, e.g., subsection IV.D(1) below regarding "Pharmaceutical Composition"; see, e.g., Plaintiffs' cell phone analogy.)

3. Claims Must Be Construed From the Perspective of a Person of Ordinary Skill in the Art ("POSITA")

With respect to the '321 patent, which is directed to a homogenously mixed formulation, Plaintiffs' expert Dr. Byrn testified that a "person of ordinary skill is a person with a Bachelor's

degree in chemistry or pharmacy and two to five years experience in a relevant field."[2] (Byrn Tr. at 102, l. 24 – 103, l. 1.) Dr. Byrn and Dr. Bugay have considerably more education and experience – indeed, every single witness to testify at trial, both experts and fact witnesses, had considerably more education and experience.

The relevant inquiry for claim construction does not take into account extraordinary theories such as Dr. Byrn's late-disclosed "proton transfer" theory, but the view of a POSITA when reading the patent and file history. Standard Oil Co. v. American Cyanamid Co., 774 F.2d 448, 454 (Fed. Cir. 1985) ("A person of ordinary skill in the art is . . . presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate . . . by extraordinary insights.").

4. The Claims Should Be Construed in Light of the Specification; Dictionaries and Other Extrinsic Evidence Are Disfavored

The Federal Circuit has re-affirmed the primacy of the specification in claim construction. See Phillips v. AWH Corp., 415 F.3d 1303, 1315 (Fed. Cir. 2005). The Phillips decision noted that claim construction had become a battle of competing dictionary definitions, and instructed that less significance should be placed on such extrinsic evidence because it "focuses the inquiry on the abstract meaning of words rather than on the meaning of claim terms within the context of the patent." Id. at 1321. Thus, abstractions and incongruous analogies – like comparing a drug to a cell phone system – cannot prevail over definitions rooted in the context of the specification.

[2] Teva will accept this definition of POSITA with respect to the '321 patent for purposes of this case only.

5. The Patent Must Give "Public Notice" of Its Metes and Bounds

The grant to a patent holder of the right to exclude is based on the patent holder's public disclosure of the metes and bounds of the invention. See PSC Computer Prods., Inc. v. Foxconn Int'l, 355 F.3d 1353, 1359 (Fed. Cir. 2004). The Federal Circuit underscores that claim language "must [also] be read consistently with the totality of the patent's applicable prosecution history." Biovail Corp. Int'l v. Andrx Pharms., Inc., 239 F.3d 1297, 1301 (Fed. Cir. 2001). The prosecution history "constitutes a public record of the patentee's representations concerning the scope and meaning of the claims, and competitors are entitled to rely on those representations when ascertaining the degree of lawful conduct, such as designing around the claimed invention." Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc., 222 F.3d 951, 957 (Fed. Cir. 2000). "The public notice function of a patent and its prosecution history requires that a patentee be held to what he declares during the prosecution of his patent." Spring Window Fashions LP v. Novo Indus., L.P., 323 F.3d 989, 995 (Fed. Cir. 2003). Teva properly relied on the inventors' representations made in the specification and file history when designing its own formulations to avoid the (properly construed) claims of the '321 patent; Plaintiffs' new "cell phone" and "proton transfer" theories played no role in prosecution of the patent and should have none here.

C. Plaintiffs Bear the Burden of Proving That Teva's Product Embodies Every Claim Limitation.

Plaintiffs must establish literal infringement by Teva. Plaintiffs neither argued infringement under the doctrine of equivalents at trial nor submitted any evidence of equivalents, and therefore waived any such claim. Aquatex Indus., Inc. v. Techniche Solutions, 479 F.3d 1320, 1329 (Fed. Cir. 2007) (requiring particularized testimony to a jury or other fact finder, on a limitation-by-limitation basis, describing the claim limitations and establishing that those skilled

in the art would recognize the equivalents); Network Commerce, Inc. v. Microsoft Corp., 422 F.3d 1353, 1363 (Fed. Cir. 2005).

To prove literal infringement, Plaintiffs must demonstrate that the accused product embodies each and every element and limitation of the asserted claim. Hutchins v. Zoll Med. Corp., 492 F.3d 1377, 1380 (Fed. Cir. 2007). Literal infringement cannot be found if "even one [asserted] claim limitation is missing or not met" by the allegedly infringing product. MicroStrategy. Inc. v. Business Objects, S.A., 429 F.3d 1344, 1352 (Fed. Cir. 2005). Teva therefore focuses on Plaintiffs' failure to prove that the Teva ANDA product meets the "in contact . . . evenly" limitation; Teva briefly establishes below that Plaintiffs' proof fails with respect to other limitations as well.

III. TEVA DOES NOT INFRINGE THE '321 PATENT

A. Asserted Claim 2 Includes Six Limitations

Plaintiffs assert only claim 2 of the '321 patent, and correctly parse the claim into six limitations. (DI 163 at 2-3.) Teva does not dispute that its ANDA product meets the third and fourth limitations regarding the presence of an effective amount of lansoprazole and the presence of magnesium carbonate; Teva's product, however, does not embody the four remaining limitations. Both parties focus on the sixth limitation, which requires that the lansoprazole and magnesium carbonate be "in contact . . . evenly."

B. The "In Contact . . . Evenly" Limitation Requires Uniform Physical Mixing

1. Claim Construction: "In Contact . . . Evenly" Requires Physical, Homogenous Mixing

Plaintiffs propose that the Court should construe the "in contact . . . evenly" limitation to mean "a mixture of the benzimidazole compound in contact with the basic (i.e., alkaline) inorganic salt in a uniformly basic environment." (DI 133 at 14.) The intrinsic record, however,

compels a different construction: that "the benzimidazole compound and the inorganic salt are mixed homogenously together." (DTX734.) As addressed in Teva's pre-trial claim construction briefs (DI 131; DI 140) and further addressed below, the heavy weight of the intrinsic evidence supports Teva's proposed construction.

a) The Intrinsic Evidence Requires Physical Contact Through a Homogenous Mixture of the Lansoprazole and Magnesium Carbonate

(1) The Inventors Described the Invention To Be a "Homogenous Mixture" During Prosecution to Distinguish Prior Art

The parties agree that the phrase "in contact . . . evenly" was not a term of art at the time Takeda filed for the '321 patent. Thus, Takeda's use of the phrase in the intrinsic record controls construction. Safas Corp. v. Etura Premier, L.L.C., 293 F. Supp. 2d 436, 438 (D. Del. 2003) (noting that the intrinsic record, including the claims themselves, is "of prime importance when claim language has no ordinary meaning in the pertinent art").

The intrinsic record clearly establishes the context and meaning of both the term "contact" and the term "evenly." The inventors specifically describe the "the composition of the invention" as follows:

> The composition of the invention is prepared by homogenously admixing the above benzimidazole compound, the basic inorganic salt of magnesium and/or basic inorganic salt of calcium, and the above additives.

(PTX3 at col. 9, ll. 45-48 (emphasis added).) This is not a description of just one embodiment. It unambiguously states a requirement "of the invention."

The entirety of the '321 patent file history likewise underscores the importance of the "in contact . . . evenly" limitation. The inventors repeatedly explain why the claimed technology requires sufficient mixing of the benzimidazole and the basic inorganic salt to achieve an "even distribution" or "homogenous mixture." Indeed, as originally filed, the claims of the '321 patent

lacked the "in contact . . . evenly" limitation. (PTX4, Patent Application, at Takeda 739470-739472.) Instead, the as-filed claims merely required the presence of the benzimidazole and a basic inorganic salt of magnesium and/or calcium. (Id. at Takeda 739470.)

Takeda added the "in contact . . . evenly" limitation through amendment and in response to an Office Action rejecting the patent claims for obviousness. (DTX4, see claim 19, Amendment, at Takeda 739670-739671.) Amongst other things, the examiner had rejected the application as obvious because the prior art also taught the use of basic inorganic salts to be "old stabilizing agents." Takeda amended its claims to avoid the prior art cited by the examiner. (DTX4, Amendment, at Takeda 739670-739676.) Takeda then differentiated its claimed technology from the examiner-cited references based on the extent of contact required between the benzimidazole and inorganic basic salt in its amended claims.

> However, the [Rainer] reference makes no comment or suggestion on stabilization of the benzimidazole compounds by contacting with magnesium aluminate or any other basic inorganic salt of magnesium and calcium evenly. It should be noted that in Rainer, et al., magnesium aluminate is contained in the pharmaceutical formulations as an antacid, and in such use as an antacid, the salt need not contact the benzimidazole compounds at all.

(Id. at Takeda 739674 (emphasis added).)[3]

Takeda also submitted a declaration from a named inventor, Dr. Shin-ichiro Hirai, to support patentability of its claimed technology. Takeda submitted the declaration to show that following the criteria set forth in U.S. Pharmacopeia (21st Revision) would result in "an even or homogenous mixture." (Id. at Takeda 739674-739675.) Thus, the contemporaneous

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[3] The Rainer reference cited by the Examiner during prosecution is U.S. Patent No. 4,686,230. (DTX016.) Defendants' Opening Brief discusses the Rainer reference as part of its obviousness case. The patent teaches a formulation of a benzimidazole and antacids, but does not disclose how the benzimidazole and antacids should be physically incorporated into the formulation. (Id. at col. 40, ll. 22-28.) It is undisputed that magnesium carbonate acts as an antacid. (Chambliss Tr. at 504, ll. 2-11.)

submissions of one of the inventors confirms the interchangeability of the concepts of "even" and "homogenous."

Ultimately, Takeda was unable to convince the examiner of the patentability of the claimed technology and was forced to appeal its patentability. (PTX4, Appeal Br. at Takeda 739749-739758.) On appeal, Takeda continued to assert that its claimed technology required sufficient mixing to obtain even contact. (Id. at Takeda 739755.) Explaining the patentability of the claimed technology, Takeda argued that "[n]o evidence of record suggests why one of ordinary skill would infer that the Rainer et al. antacids should be mixed evenly with the benzimidazole derivatives." (Id. (emphasis added).) "Rainer et al. fails to indicate that the benzimidazole derivatives should be mixed at all, much less mixed to the extent that even contact is present." (Id. at Takeda 739757 (emphasis added).)

Takeda on appeal again relied on the Hirai declaration to support patentability. "The experimental results reported therein demonstrate the importance of establishing even contact. Inadequate mixing, resulting in uneven contact, yielded unstable products. On the other hand, the products with even contacting showed stability." (Id. (emphasis added).)

Takeda ultimately prevailed on appeal, and the '321 patent issued. It cannot now claim that the invention covers combinations of lansoprazole and magnesium carbonate that are not "an even or homogenous mixture." Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995) ("Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers.").

(2) The Specification Describes the Invention As a Homogenous Mixture

Plaintiffs attempt to bypass the specification's description of the invention as a homogenous mixture (see supra) by arguing that this point is contradicted by other portions of the specification. (DI 163 at 26-27.) Plaintiffs rely on the following passage:

> 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 and the basic inorganic salt of magnesium and/or calcium as prepared by preliminary admixing, or the basic inorganic salt of magnesium and/or calcium may be added to a mixture of the benzimidazole compound and the additives as prepared by preliminary admixing.

(PTX3, col. 9, ll. 56-66 (emphasis added).) This passage in no way negates the notion that the resulting admixture must be homogenous. To the contrary, this language expressly states that the result must be "in contact . . . evenly," and that is precisely what the inventors previously had defined to be a "homogenous mixture" in the context of the invention.

The above passage simply stands for the unremarkable proposition that one can implement the invention through a number of methods of mixing and by adding the ingredients in a number of different sequences. Dr. Chambliss explained that a number of different methods for mixing pharmaceutical ingredients was known at the time. (Chambliss Tr. at 481, ll. 4-22.) While the method of mixing may vary, even Dr. Byrn conceded that there is physical mixing in every single example in the specification. (Byrn Tr. at 157, ll. 19-22.)

Plaintiffs rely on a recent Federal Circuit case, Acumed LLC v. Stryker Corp., 483 F.3d 800 (Fed. Cir. 2007), for the proposition that the use of both "in contact . . . evenly" and "homogenous mixture" in the specification "is consistent with there being 'different meanings of those phrases.'" (DI 163 at 25.) While Plaintiffs accurately recite the stark holding in Acumed, a more thorough reading reveals that Acumed is quite different from the case at hand. There, the

court attempted to determine whether the plaintiff's use of "perpendicular" in the specification equated to its use of "transverse" in claim language. Acumed, 483 F.3d at 807. The court ultimately decided that the ordinary meaning of "transverse" did not imply "perpendicular" because "there [was] very little indication that the patentees considered perpendicularity important to their invention." Id. In addition, the Acumed court noted that "perpendicular hole[s] . . . may not always be ideal." Id. at 807.

In contrast, Takeda repeatedly emphasized the importance of a homogenous mixture in its final product. (See PTX4, Amendment at Takeda 739674 (noting the need for "an even or homogenous mixture"), and at Takeda 739757 (stating that "[i]nadequate mixing, resulting in uneven contact[] yielded unstable products" while "products with even contacting showed stability").) Further, Takeda clearly stated that homogenous contact is more than ideal – it is required for a stable compound. (Id. at Takeda 739674-739675) Thus, just as the intrinsic evidence supported the Acumed conclusion to give "transverse" and "perpendicular" different meanings, the intrinsic evidence in the case requires the opposite result.

Plaintiffs also cite Dow Chemical Co. v. Sumitomo Chemical Co., 257 F.3d 1364 (Fed. Cir. 2001). (DI 140 at 5.) Dow, which Teva distinguished during claim construction (see DI 140 at 5), was decided prior to Phillips and is of little value for this analysis. The Dow court started with a technical dictionary definition and referenced intrinsic evidence only to confirm that definition. Id. at 1376-77 (noting that "boiling point" and "reaction temperature" cannot be synonymous because of an inherent technical difference in how they are measured). The parties here agree that the disputed term is not an ordinary term of art and, unlike in Dow, it does not have a universally accepted technical definition. As stated above, the intrinsic evidence in this case, reviewed as instructed by Phillips, cannot sustain the result advocated by Plaintiffs.

(3) "Homogenous Mixture" Describes the Final Product; It Is Not a Process Limitation

Plaintiffs suggest that Teva is improperly attempting to read a process limitation into a product claim. (See DI 163 at 25-26.) This is incorrect. Teva's proposed construction simply incorporates what the inventors claimed as the end product – a homogenous mixture, not any particular method of mixing. Teva's proposed construction in no way limits the process by which the homogenous mixing must occur. The patent discloses several different types of equipment that could be used ultimately to result in the homogenous mixture. (Chambliss Tr. at 481, ll. 15-22; PTX3, col. 12, l. 55 – col. 16, l. 15.) Takeda avoided obviousness objections by repeatedly arguing that sufficient mixing was necessary to obtain even contact and the benefits of the claimed technology.

Even if the Court were to view a homogenous mixture to refer not to the final product, but as reading in a process limitation, which is not the case, Teva submits that Takeda's arguments during prosecution of the '321 patent allow a process limitation to be read into the claim. Plaintiffs rely on AFG Indus. Inc. v. Cardinal IG Co. to support their contention that it is "well-established" that process limitations cannot be read into a product claim. 375 F.3d 1367 (Fed. Cir. 2004). Not true. An exception to this general rule arises when the process limitation is argued by the inventors to distinguish prior art:

> [E]xceptions may arise when the product's distinction from the prior art depends on how it was produced, for when the validity of the patent depends on use of a particular process, the claims are construed in the manner that will sustain their validity, when such construction is supported by the record.

AFG Indus. Inc. v. Cardinal IG Co., 224 Fed. Appx. 956, 958 (Fed. Cir. 2007) (citing Whittaker Corp. v. UNR Indus., Inc., 911 F.2d 709, 712 (Fed. Cir. 1990) and TorPharm, Inc. v. Ranbaxy Pharms., Inc., 336 F.3d 1322, 1329 (Fed. Cir. 2003)). The Federal Circuit ultimately found that

"the process by which a product is produced can limit a product claim when, as here, the process is relied on for patentability and validity." Id. at 958-59.

Plaintiffs cannot dispute that Takeda repeatedly argued that the patentability of its technology resulted from "sufficient mixing." As such, Takeda's arguments place construction of this claim term squarely within the exception identified in the second AFG Industries opinion. Therefore, while Teva maintains that its proposed construction refers to the claimed dosage form and does not import a process limitation into a product claim, Takeda's arguments during prosecution would make it proper to do so.

(4) In The Art, a "Homogenous Mixture" Need Only Be "Uniform"; Each Particle Need Not Be In Contact

Plaintiffs argue that Teva's proposed construction of "in contact . . . evenly" and definition of "homogenous mixture" contradict the specification, which contains examples where all of the lansoprazole is not touching all of the magnesium carbonate. (See DI 163 at 24.)

This is a straw man. Teva never suggests that all of the lansoprazole must be touching all of the magnesium carbonate for there to be a homogenous mixture. To the contrary, Dr. Chambliss testified that the concept of a homogenous mixture was well known by those in the art and understood to mean "uniform." (Chambliss Tr. at 475, ll.17-23; see also Hirai Dep. at 60, ll. 1-11 (defining "homogenous" to mean "well mixed.").) This is consistent with the ordinary meaning of the term "homogenous mixture": "any combination of substances that has uniform composition and properties; a mixture that is uniform throughout." Webster's New Millennium Dictionary of English, Preview Edition (v. 0.9.7), http://dictionary.reference.com/browse/homogeneous_mixture (last visited Jan. 10, 2008). (Attached as Exhibit 2.)

b) The Intrinsic Record Contradicts Plaintiffs' Construction

Plaintiffs' proposed construction of "in contact . . . evenly" – "a mixture of the benzimidazole compound in contact with the basic (i.e., alkaline) inorganic salt in a uniformly basic environment" – finds no support in the patent or file history.

(1) Plaintiffs Offer No Meaning for the Term "Mixture"

Plaintiffs pay lip service to the term "mixture" in their construction, but give that term no real meaning. Certainly the description of the requisite "mixture" set forth by Plaintiffs' expert differs substantially from that argued by the inventors during prosecution. Plaintiffs now eschew the standards set forth in the USP, expanding "mixture" to include the presence of only one percent lansoprazole in ninety-nine percent magnesium carbonate without regard to homogeneity. (Bugay Tr. at 258, ll. 1-5.) Put another way, applying Plaintiffs' experts' understanding of mixture, the requisite mixture exists as long as there is an alkaline environment. (See DI 163 at 24.) Plaintiffs no longer believe a true mixture is necessary.

(2) The Intrinsic Record Fails to Support a "Uniformly Basic Environment" Interpretation of "In Contact . . . Evenly"

Plaintiffs point to no reference in the file history that supports their "uniformly basic environment" interpretation. There is none.

Plaintiffs' references to the specification fare no better. While Plainitiffs attempt to cobble together specification references to water and pH levels, the references provide no support for Plaintiffs' conclusion. With regard to water, the bottom line is that the patent teaches that water is bad because lansoprazole is "susceptible to . . . moisture" and "poor in stability." (PTX3 at col. 1, ll. 33-36.) With respect to the specification's references to pH levels, the statements always refer to the basic nature of the basic inorganic salt of magnesium and/or calcium. (See DI 163) Nowhere in the specification did the inventors use the term "basic" to

describe anything but an basic inorganic salt. (Byrn Tr. at 151, l. 13 – 152, l. 6.) While Plaintiffs would like the Court to splice the word "basic" and place it before the word "solution" or "environment," the specification provides no rational basis for doing so. (See DI 163 at 22.)

Finally, the Examples teach away from Plaintiffs' proposed claim construction. The granules described in Examples 1, 2, and 7, contain no water. (PTX3 at col. 12, l. 55 – col. 13, l. 23 and col. 14, ll. 18-41.) The granules were prepared using a dry granulator. (Id.) Without the addition of water, a "uniform basic environment" and contact through proximity resulting from the proton transfer theory cannot exist. Thus, Examples 1, 2 and 7 do not support Plaintiffs' moisture-driven theory and, in fact, teach away from it.

Additional Examples also teach away from Plaintiffs' proposed claim construction. The granules prepared in Examples 3, 4, 5, 6, and 8 all require the addition of a small amount of water. (Id. at col. 13, l. 24 – col. 14, l. 15 and col. 14, ll. 45-69.) Each of these Examples, however, require that the mixtures be "dried in vacuum at 40º C for 16 hours" before forming the granule. (Id. (40º C is equivalent to 104º F).)[4] The inventors expressly teach that the mixture should be dried after mixing – yet again teaching a person of ordinary skill in the art that the amount of water in the formulation should be minimized. As such, Examples 3, 4, 5, 6, and 8 not only fail to support Plaintiffs' moisture driven theory, they teach away from it.

[4] At trial, Dr. Byrn dismissed the Examples as teaching a brief amount of drying. Respectfully, 16 hours of drying at over 100 degrees cannot constitute "dry[ing] them briefly." (Byrn Tr. at 97, l. 25 – 98, l. 5.)

c) The Court Should Not Consider Plaintiffs' Extrinsic Evidence

(1) The Court Should Not Resort to Extrinsic Evidence When the Intrinsic Evidence Unambiguously Defines the Limitations

Teva's proposed construction of the "in contact . . . evenly" limitation is supported by the unambiguous teachings of the intrinsic record. Accordingly, there should be no resort to extrinsic evidence. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583 (Fed. Cir. 1996) ("In most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term. In such circumstances, it is improper to rely on extrinsic evidence."). Plaintiffs' extrinsic evidence should be rejected for the following reasons as well.

(2) Dr. Byrn's Proton Transfer Theory Was Not Disclosed In His Expert Report, Would Have Been Rejected By a POSITA, And Is Wrong

Teva objected to Dr. Byrn's proton transfer theory for the alleged creation of the uniform basic environment on the basis that such theory had not been disclosed in his expert reports. (Byrn Tr. at 91, ll. 11-16 and 96, ll. 20-24.) Most telling is that, given Teva's objection to this new theory, Plaintiffs fail in their Opening Brief to point to any disclosure in the expert reports that the "in contact . . . evenly" limitation can be met by this "proton transfer" theory. Accordingly, the Court should bar consideration of this late developed theory. See Fed. R. Civ. P. 26(a)(2)(B) (An expert report "must contain . . . a complete statement of all opinions the witness will express and the basis and reasons for them.").

Moreover, this theory is irrelevant because there is no evidence that a POSITA reading the '321 patent would have considered that "proton transfer" might render two components of a drug formulation that were not only remote from each other, but in fact separated by an intervening layer, to be "in contact . . . evenly." Without some evidence that a POSITA would

have appreciated the proton transfer theory, it should not be considered. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 68 F. Supp. 2d 508, 531 (D.N.J. 1999) ("[E]vidence must be viewed from the position of a person of ordinary skill, not from the position of an expert."). Indeed, the evidence directly contradicted such a conclusion. Dr. Bugay, himself substantially more educated than the POSITA that Dr. Byrn described,[5] had not considered the new theory even as of the time he testified at trial. (Bugay at Tr. 278, ll. 4-8.)

Finally, for the reasons set forth by Dr. Meyer[6] and described below in subsection III.C.(3)(e), Dr. Byrn's proton transfer theory does not hold up under technical scrutiny.[7]

The foregoing explains why, even after listening to Dr. Byrn's testimony regarding his "proton transfer" theory and having a night to digest it, Dr. Bugay still was unable to explain, comment on, or even support Dr. Byrn's infringement theory. (Bugay Tr. at 277, l. 1 – 278, l. 8.)

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[5] Dr. Byrn testified that a POSITA would have "a bachelor's degree in chemistry or pharmacy and two to five years experience in the relevant field." (Byrn Tr. at 102, l. 24 – 103, l. 1.) Dr. Byrn's academic qualifications alone show that he is not a POSITA.

[6] Dr. Meyer is a Professor of Chemistry and Materials Science & Engineering at Johns Hopkins University, with a joint appointment in the departments of Chemistry and the department of Engineering. He holds a B.S. in Chemistry and Mathematics from the State University of New York at Albany. He received a Ph.D. in Chemistry from the University of Wisconsin at Madison, where his research focused on analytical and spectroscopic methods. He performed postdoctoral work at the University of North Carolina at Chapel Hill. And Dr. Meyer began teaching at Johns Hopkins in 1991. His research funding includes grants from the National Science Foundation to research the electronic interactions in hybrid organic nanoparticle materials. He also serves as a reviewer and an advisory board member of several journals of the American Chemical Society. (Meyer Tr. at 368-72; see also DTX66.)

[7] To the extent that the Court considers Dr. Byrn's late disclosed theory, Teva submits that it also should consider Dr. Meyer's response at trial, and Plaintiffs' motion to strike (see DI 163 at 39-41) should be denied.

(3) Plaintiffs' Dictionary Definitions Are Extrinsic Evidence Taken Outside the Context of the Patents and Should Not Be Considered

Plaintiffs rely upon non-technical dictionary terms to support a bizarre "cell phone" analogy to buttress Plaintiffs' proposed claim construction. (See DI 163 at 22-23.) Such dictionary definitions constitute extrinsic evidence. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1584 (Fed. Cir. 1996). Moreover, this is precisely the use of dictionary definitions that the Federal Circuit frowned upon in Phillips. Phillips v. AWH Corp., 415 F.3d 1303, 1321-22 (Fed. Cir. 2005). These definitions and the cell phone analogy as a whole are completely divorced from the alleged invention at issue and the teachings of the specification. See id.

(4) The Litigation Testimony of Takeda Inventors Should Be Given No Weight

Finally, Plaintiffs also rely upon deposition testimony of Takeda inventors in an attempt to support their proposed claim construction. See DI 163 at 6. Inventor testimony is extrinsic evidence. Vitronics, 90 F.3d at 1584. Moreover, hindsight and litigation-oriented testimony such as this should be given no weight. Finally, the testimony on which Plaintiffs rely does not support their moisture driven process: mechanochemical relates to the "conversion of chemical energy into mechanical work" and not contact mediated through water as Plaintiffs state. (Webster's New Collegiate Dictionary 713 (1977), attached as Exhibit 3.)

C. Teva's Product Does Not Infringe: The Lansoprazole and Magnesium Carbonate Are Not "In Contact . . . Evenly"

1. Summary: Teva Designed Around the '321 Patent By Formulating Its Product in Layers

Plaintiffs concede that Teva "attempted to design around the '321 Patent by purportedly physically separating lansoprazole and magnesium carbonate in the product." (See DI 163 at 2.) Indeed, Dr. Bugay conceded in his initial expert report – drafted as it was before Plaintiffs

retreated to "accidental mixing" as one of their primary theories – that mere optical inspection establishes that Teva's ANDA product contains multiple layers. (See DTX300, attached as Exhibit 4.) Paragraph 37 of that report describes Teva's layered product as follows:

> 37. A number of features are present in the optical image of the prepared granule surface. First, the cross-sectioned surface of the granule appears as a whitish solid having a generally layered appearance. There appears to be a core located in the center of the granule and a first layer annular to the core. The first layer appears to be approximately 40 • m in thickness as demonstrated in Exhibit 14 (Bugay 0026). There appears to be a second layer with a slightly darker shade of white within the optical image. Finally, there appears to be a third layer having a slightly whiter shade within the optical image. The three layers are approximately 100 • in thickness and for this particle cross-sectional area of this one granule, it appears that the first and third layers are nearly equivalent in thickness and slightly larger in thickness than the second layer. At the edge of the granule, a fourth layer is slightly visible based upon the darker image in this area. I believe the fourth layer to be the enteric coating of the granule. No smearing of the surface of the granule has occurred due to the sample preparation procedure.

(Id. (emphasis added).) At trial, both Dr. Bugay and Dr. Byrn tried to run away from the fact that the Teva product is layered. For instance, on cross examination, Dr. Bugay first tried to refer to the layers as "bars" (Bugay Tr. at 260, ll. 14-17), but then conceded that he considered the product to have "layers" when he drafted his report (Id. at 261, ll. 17-19). Dr. Byrn tried to characterize the layers as "dispersions," but still repeatedly referred to the product's "layers," at least on direct examination. (See, e.g., Byrn Tr. at 122, ll. 7-8 ("And we end up with a layer of talc, hypromellose and lansoprazole").)

Mere optical inspection and other strong evidence establish that Teva's product is layered – and that Teva applies the lansoprazole and magnesium carbonate in two different layers, separated by yet another layer of talc. Faced with these facts, Plaintiffs sought to avoid the inevitable legal conclusion (that Teva does not infringe) by conjuring a number of novel arguments and theories. Teva addresses these and other pertinent points regarding the "in contact . . . evenly" limitation in the subsections below.

2. Teva's ANDA Specifies a Layered Formulation Separating the Lansoprazole and Magnesium Carbonate

a) Teva's ANDA Specifies a Layered Formulation

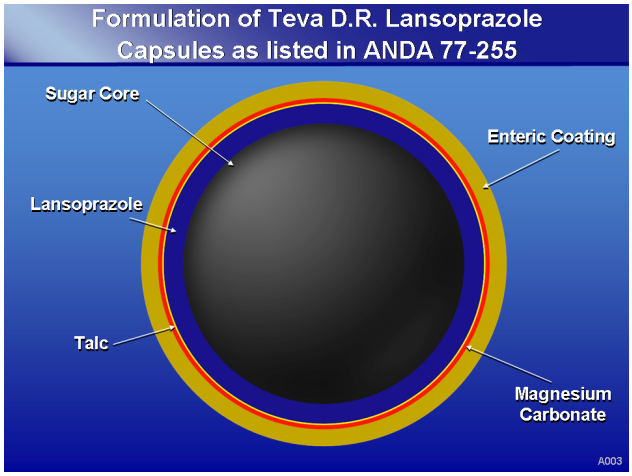
Teva's ANDA sets forth the manufacturing process that would be used for commercial production. The multi-step process plainly is aimed at creating a multiple layer product.

Teva's ANDA describes the manufacture of Teva's Product, which contains multilayer enteric coated pellets filled into capsules. (Chambliss Tr. at 462, l. 5 – 463, l. 10 and 465, l. 24 – 467, l. 16; DTX056; DTX303.) Teva's manufacturing process, as described in its ANDA, involves the application of four layers onto sugar spheres to form the multilayer pellet. (DTX056.) Teva applies each of the four layers in a separate manufacturing step. (Id. at TVL006856-99.) Each layer is dried before application of the next layer, a fact that Plaintiffs repeatedly have ignored at trial and in briefing. (Id.) Teva's automated drying process operates in a manner similar to the newer clothes dryers that turn off only when the clothes are dry. (Chambliss Tr. at 470, ll. 1-8.) Teva also includes hypromellose in the dispersion to protect the integrity of each layer. (Id. at 463, ll. 18-23.) Hypromellose is a film former that acts like Saran™ Wrap in protecting the layer from mixing with other layers. (Id.) The multilayer pellets are then filled into capsules to create the final dosage form for administration to patients. (DTX056 at TVL006900-07.)

Teva's manufacturing process seeks to minimize the presence of water, rather than encouraging its presence in the final formulation. As stated above, Teva uses its automated drying process to dry its product after application of each and every layer. (Id. at TVL006856-99; see also Chambliss Tr. at 468, l. 5 – 470, l. 8.) In fact, Teva's ANDA requires that water make up not more than 5.0% of its product, and testing disclosed that water comprised only 1.1% of the final product. (Chambliss Tr. at 465, ll. 3-11; PTX0445A at TVL007539.) In Dr.

Chambliss' words, a formulation with only 1.1% moisture is "very dry." (Chambliss Tr. at 465, l. 15.)

The below demonstrative shows the basic structure of the granule resulting from the above manufacturing process:



(See Chambliss at Tr. 463, l. 11 – 467, l. 8.)

Dr. Chambliss testified that he had seen NDA and ANDA descriptions such as the above "many times," and there was nothing out of the ordinary about it. (Id. at 467, ll. 17-23 and 474, ll. 12-21.) Dr. Byrn conceded on cross-examination that he had no basis to doubt that Teva can manufacture a pharmaceutical product with an effective subcoat. (Byrn Tr. at 150, ll. 5-9.)

b) Teva's Final Product Is A Layered Formulation In Which The Lansoprazole And Magnesium Carbonate Are Separate, Not Homogenously Mixed.

Dr. Bugay's initial report confirmed the layered nature of the ANDA product under visual inspection. (See supra in subsection III.C.(1).) Plaintiffs consequently turned to a number of avoidance arguments including that a two micron talc layer is not thick enough to be a separating layer and the research and development records show this to be the case; there is sufficient water in the manufacturing process to create a mixture and to facilitate Dr. Byrn's proton transfer theory; and the ANDA product is stable and, thus, must meet the "in

contact . . .evenly" limitation. Furthermore, Plaintiffs refused to commit to a single infringement theory in their brief. Plaintiffs argue both that no contact is necessary and that "even contact" can be achieved through their new proton transfer theory, yet Plaintiffs continue to exert substantial effort trying to show that contact is present. None of these arguments stands up under scrutiny, as set forth in the subsections below.

When evaluating the manufacturing-related arguments, Teva respectfully submits that the Court should consider the relative experience levels of Dr. Chambliss and Dr. Byrn as it specifically relates to the manufacture of pharmaceutical products that have subcoats. Dr. Chambliss' experience includes 17 years working at G. D. Searle, Bristol-Myers, and Schering-Plough. (Chambliss Tr. at 448, ll. 13-20; see also discussion in note 1.) Dr. Chambliss explained at trial that his substantial industry experience included work on formulations similar to Teva's ANDA product and many formulations that involved the use of subcoats. (Id. at 448, l. 4 – 450, l. 24.) Dr. Chambliss also has substantial experience with the machines that make these formulations: "My whole career I've worked with machines that make pharmaceutical products from the mixing of those to the tableting to the pelletization, drying, all the machines." (Id. at 451, l. 23 – 452, l. 2.) In stark contrast, Dr. Byrn candidly conceded on cross-examination that he only had one prior work experience relating to subcoats and that was in connection with a litigation:

> Q. Would you agree with me that the only one work experience you have before this litigation regarding subcoats was another litigation regarding subcoats?
>
> A. Yes.

(Byrn Tr. at 150, l. 25 – 151, l. 3.) Dr. Byrn also conceded that he never has been employed by a pharmaceutical company for the purposes of developing a product with subcoats.[8] (Id. at 150, ll. 10-13.)

Testing of samples made according to the ANDA process likewise supports the layered nature of the Teva ANDA product. Teva showed at trial that it prepared its samples in a manner most likely to avoid the generation of false data. Teva also used time of flight secondary ion mass spectroscopy ("ToF-SIMS") – the technique best able to analyze the structure of the bisected samples. Finally, correct interpretation of the Raman and EDS/SEM data shows that it supports Teva's positions and not Plaintiffs'.

Finally, even if the Court were to adopt Plaintiffs' uniformly basic environment interpretation of the "in contact . . . evenly" limitation, which Teva submits it should not for the reasons set forth above, Plaintiffs fail to meet their burden because they never tested the pH of the samples. Plaintiffs' surrogate argument was not disclosed in the expert reports and, otherwise, simply does not work.

c) Teva's Talc Subcoat Forms a Separating Layer

Plaintiffs suggest that the talc subcoat of about 2 microns is not thick enough to form an effective separating layer. (See DI 163 at 2; see also Byrn Tr. at 138, ll. 16-18 (stating that Teva's talc layer measures 2-8 microns in width).) Plaintiffs, however, present absolutely no scientific data or writings to support this assertion. The only basis is Dr. Byrn's unsupported testimony. (See Byrn Tr. at 143, ll. 8-14.) Moreover, Dr. Byrn, as Plaintiffs have done in other instances, mischaracterizes Teva's position as stating that the talc layer must be "impermeable."

[8] Dr. Byrn's true area of expertise appears to be the academic exploration of crystalline structures in pharmaceutical compositions, such as polymorphs. (PTX444.) Such issues, however, are not present in this case.

(Id.) Teva has never taken the position that the talc layer needs to be "impermeable" to form an effective separating barrier.

Dr. Chambliss, who has the superior credentials regarding subcoats, confirmed that this talc subcoat is sufficient to perform its intended purpose. (Chambliss Tr. at 532, ll. 12-24.) Mr. Hirt, an expert retained by Teva, has analyzed barriers as small as 1/1000 of a micron, and as small as one micron in the context of a pharmaceutical product:

> Q. Plaintiffs in this case suggest that a barrier that might be two to three microns thick is extremely small. Based on your background and experience, do you have any views on that?
>
> A. In particular, in granule formulations, I'm very familiar with layers that are on the order of one micron in size that are routinely applied in the pharmaceutical industry, and I have analyzed those specifically many times in just this type of analysis.

(Hirt Tr. at 293, ll. 17-24 and 294, ll. 3-11 (emphasis added).) Dr. Meyer likewise has examined barriers and layers far smaller than two microns. (Meyer Tr. at 371, l. 17 – 372, l. 15.)

In short, in our current technological environment where objects are analyzed in terms of nanometers (one billionth of a meter) and not just micrometers (or microns – one millionth of a meter), two microns simply is not that small. And, again, there simply is no scientific evidence in this case that the talc layer is insufficient to perform its role as a separating barrier.

3. Chemical Analysis Establishes That Teva's ANDA Product Does Not Contain an Infringing Mixture of Lansoprazole and Magnesium Carbonate.

a) Summary: Teva Presented Unbiased, "Blinded" Chemical Analysis to Determine Infringement

Teva retained Mr. Hirt – a professional materials scientist with a long roster of major engineering, pharmaceutical, and chemical company clients to his name – to analyze the ANDA

product. [9] Mr. Hirt was not informed that his analysis was for purposes of determining infringement of a patent; he was not aware of the patents at issue; he did not know the positions of the parties; and he was not told what impact his opinions might have on the outcome of the case. (Hirt Tr. at 284, ll. 11-17.) He was retained not as a "hired gun" but for his reputation and expertise, which included work with dozens of analytical tools, including Raman, ToF-SIMS, and SEM – work that encompassed more than two decades, and literally hundreds and thousands of such analyses every year. (Id. at 289, l. 7 – 293, l. 1 and 295, l. 12 – 296, l. 18.)

The assignment: Mr. Hirt was asked to select the appropriate techniques to determine the spatial relationship between magnesium carbonate and lansoprazole in Teva's ANDA formulation, using his own experience and the most appropriate and advanced analytical tools available to arrive at his conclusions. Based on this experience, Mr. Hirt chose ToF-SIMS to conduct his analysis of Teva's product, and he chose Raman and EDS/SEM to confirm that analysis. (Id. at 297, l. 1 - 298, l. 24.) He performed his initial analysis using ToF-SIMS because of its high molecular specificity and because it "ha[d] the highest spatial resolution . . . available for this type of analysis." (Id. at 297, ll. 12-25.) To perform the analysis, he first cross-sectioned the samples with a diamond knife; he chose a diamond knife because it was much sharper than a metal knife or a razor blade and helped ensure that particles were not smeared between layers during cutting. (Id. at 308, l. 16 – 310, l. 23.)

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[9] Mr. Hirt is the owner and Senior Scientist at Materials Research Laboratories, Inc., a firm that specializes in material analysis. He graduated from the Case Institute of Technology in 1977 with a bachelor's degree in physics. Mr. Hirt specializes in surface interface, thin film analysis and materials science, and teaches Ph.D. and master's degree level students in materials science and the operation and interpretation of surface analysis equipment. He has also written more than fifty publications relating to materials science, and has more than thirty years' experience using dozens of analytical instruments. (Hirt Tr. at 286-89; see also DTX58.)

The ToF-SIMS analysis was performed at Evans Analytical Group, "the premier laboratory worldwide for mass spectroscopy," and was closely supervised by Mr. Hirt. (Id. at 311, l. 20 – 312, l. 2.) To ensure reliability, Mr. Hirt also designed an experiment to test the samples using Raman spectroscopy. (Id. at 327, l. 11 – 328, l. 19.) Because Raman has lower spatial resolution than ToF-SIMS, Mr. Hirt used this technique for the limited purpose of verifying whether magnesium detected in the ToF-SIMS analysis was attributable to magnesium carbonate rather than the magnesium that appears in talc, another ingredient in Teva's formulation found in the layer that separates the lansoprazole and the magnesium carbonate. (Id. at 298, ll. 9–24; 300, l.18 – 301, l. 14; 330, ll. 4-23). The Raman data was collected using a Raman laser microscope at R.J. Lee Group, another leading analytical company that Mr. Hirt had worked with many times before. (Id. at 327, l. 11 – 328, l. 13.)

Finally, Mr. Hirt tested the samples using EDS/SEM. (Id. at 338, l. 19 – 339, l. 4.) He used this technique, which has a deep surface penetration, for the limited purposes of determining whether any smears or scratches were created by cutting the samples and to verify the ToF-SIMS data. (Id.)

b) ToF-SIMS Confirms That Teva's Product Does Not Have a Homogenous Mixture

(1) ToF-SIMS Is the Superior Technique for Surface Analysis

Mr. Hirt chose ToF-SIMS – and Dr. Meyer chose to rely on it – to evaluate the spatial relationship between the components of the ANDA product because of its precise, high resolution. (Hirt Tr. at 297, l. 1 – 298, l. 6; Meyer Tr. at 388, ll. 3-8 and 394, l. 17 – 395, l. 20; see also DTX902 at p. 922.) Peer-reviewed literature supports the superiority of ToF-SIMS for this purpose. (See, e.g., DTX903, DTX904.) ToF-SIMS confirmed what Dr. Bugay admitted he

saw through optical analysis – that Teva's ANDA product is layered and contains no homogenous admixture of lansoprazole and magnesium carbonate (see below).

ToF-SIMS is the best analytical tool for surface analysis because it provides the greatest spatial resolution. (Hirt Tr. at 297, ll. 12-25.) Spatial resolution describes how small a volume of analysis the technique can analyze at one time. (Id. at 299, ll. 6-12.) By analyzing smaller volumes, it is easier for a technique with greater spatial resolution to distinguish ingredients that are located close together than a technique that analyzes a larger sample volume. (Id. at 299, ll. 13-21) As discussed below, laser Raman's resolution is inferior to that of ToF-SIMS. Therefore, it is less accurate in distinguishing features across the face of the bisected granule sample. Its depth penetration also raises potential for erroneous conclusions regarding the structure of the granule.

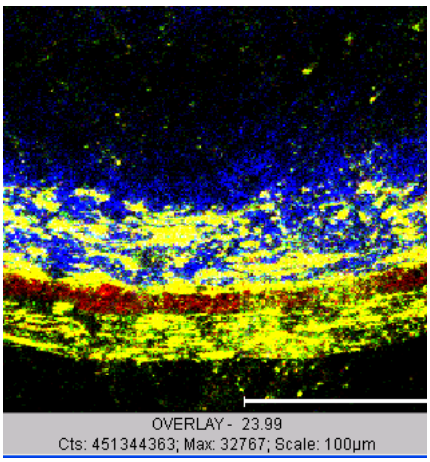
Plaintiffs admit that ToF-SIMS is superior to laser Raman and EDS for spatial analysis of a surface. Dr. Bugay conceded this on cross-examination as follows:

> Q. The spatial relationship, for example, of ToF-SIMS is vastly more precise. It's smaller resolution than is Raman; is that right?
>
> A. ToF-SIMS is much greater spatial relationship in the two dimensions of the surface only.
>
> Q. If you wanted to get information about what is at the surface of a sample, ToF-SIMS is the better implement to use, isn't it?
>
> A. If you mean the surface as being a monolayer, two monolayers, or what you can refer to as one molecule or two molecules – molecules, not particles, but molecules, then ToF-SIMs absolutely has the resolution to look at that where you are probing for a molecule, not for particles for the representative structure of the granule.

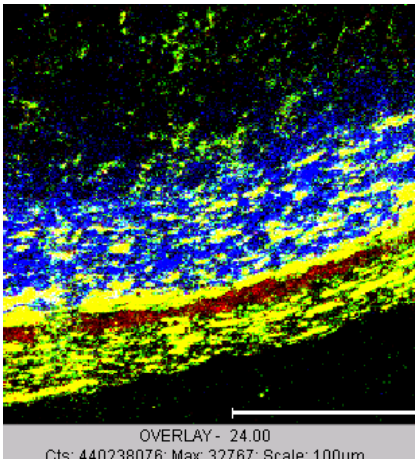
(Bugay Tr. at 254, ll. 8-21; see also id. at 264, l. 24 – 265, l. 3.)

(2) The ToF-SIMS Data Shows That Lansoprazole and Magnesium Carbonate in Teva's Product Are Separated, Not Mixed

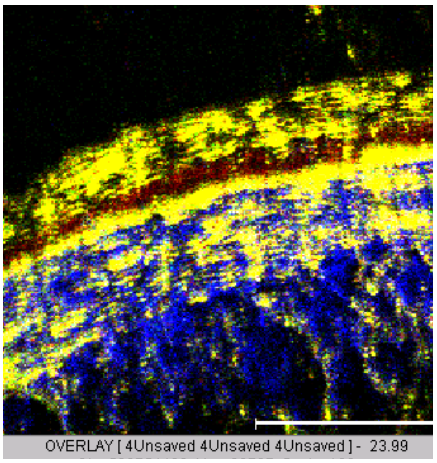
The ToF-SIMS testing confirmed that Teva's Product contains an intermediate talc layer separating the lansoprazole and magnesium carbonate layers.[10] (DTX063-2 (lansoprazole depicted by blue, talc depicted by yellow, and magnesium carbonate depicted by red).) The ToF-SIMS testing also confirms that the manufacturing process described in Teva's ANDA results in a multilayer formulation as explained at trial by Dr. Chambliss. (Hirt Tr. at 285, l. 17 – 286, l. 1; Chambliss Tr. at 462, l. 18 – 467, l. 16.) The images below pictorially show the cross-section of the multilayer product.



(DTX063-2, at HIRT022.)



(Id., at HIRT024.)



(Id., at HIRT027.)

ToF-SIMS identifies the chemical composition of a cross-section through molecular fragments and corresponding mass peaks. Ideally, a unique peak or set of peaks can be identified for each ingredient present in a cross section. (Hirt Tr. at 316, ll. 10-21.) Here, the only

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[10] Through subsequent EDS testing, Mr. Hirt confirmed that the yellow smear of talc across the red magnesium carbonate band resulted from cross-sectioning the pellet with a diamond knife during sample preparation. (Hirt Tr. at 341, ll. 3-14.) This smear did not result from mixing of talc with the magnesium carbonate during the manufacturing process. (Id.)

molecular fragment available to identify magnesium carbonate was magnesium, which is present in both talc and magnesium carbonate. (Id. at 321, ll. 6-16.) Because of this overlap, Mr. Hirt used Raman to confirm his chemical characterization of magnesium carbonate in the formulation. (Id. at 327, ll. 12-21; see also DTX903 at 5626 (recognizing the value of using Raman for chemical characterization).) Magnesium carbonate enjoyed a unique peak in laser Raman and confirmed the presence of the magnesium carbonate layer. (Hirt Tr. at 330, ll. 4-23.)

Plaintiffs criticize Teva's presentation of its ToF-SIMS data analysis for reporting the results without manipulation. (Bugay Tr. at 235, ll. 1-17.) Interestingly, Teva presented its data as a "direct visual representation of what [was] being presented." (Hirt Tr. at 324, ll. 2-3.) Teva's expert chose to report the data exactly as set forth during the test and without manipulation. (Id.) Certainly if the data had been manipulated, Plaintiffs would have cried foul as being misleading. Further, Plaintiffs had ample time and expertise to run their own analysis to counter the clear noninfringement evidence set forth in Teva's ToF-SIMS testing. (Bugay Tr. at 233, l. 25 - 234, l. 4 ("I've run about 30 different ToF-SIMS experiments myself.").) Not surprisingly, given the clear factual support of noninfringement gleaned by Teva, Plaintiffs chose not to do so.

(3) Peer-Reviewed Literature – Including a Paper By Dr. Bugay Himself – Confirms Mr. Hirt's Reliance on ToF-SIMS

The literature confirms that Mr. Hirt correctly chose ToF-SIMS for use as the lead tool for determining the spatial relationship of the components of Teva's product. Even Dr. Bugay has described ToF-SIMS as lending "itself to the spatial characterization of an API within a formulated product. Based upon a ToF-SIMS chemical image of the pharmaceutical product, the

location of different components incorporated into the formulation can be determined."[11] (DTX901 at 44.) "ToF-SIMS can provide a chemical image of a two-dimensional area," such as a plane of a cross-sectioned tablet. (Id. at 49.) This technique uses "a low energy, pulsed source of ions [to] irradiate[] the sample of interest" to create "a chemical image [of] the sampled area. . . . Sub-micron spatial resolution has been reported for ToF-SIMS." (Id. at 49.) Presumably based on his research into ToF-SIMS for this article, Dr. Bugay further opined that ToF-SIMS would "become an integral technique for pharmaceutical analysis in the very near future." (Id. at 59.)

Dr. Bugay's above paper cites a 1999 article entitled "Characterization of Pharmaceuticals by ToF-SIMS"[12] to support his statement that "ToF-SIMS can also be used to chemically image a pharmaceutical product." (DTX901 at 59; DTX902.) This 1999 article explained: "Vibrational spectroscopy techniques such as Raman . . . are options, however, these techniques [do] not have sufficient spatial resolution for analyzing the distribution of ingredients or excipient within a system." (DTX902 at 919.) The submicron spatial resolution of ToF-SIMS makes the technique particularly well suited to analysis of multilayer pharmaceutical formulations. (Id. at 922.) ToF-SIMS is particularly useful in "evaluating the integrity of the

---

[11] In his article, Dr. Bugay identified the drawback to ToF-SIMS as "not permit[ting] the differentiation of anhydrous polymorphic forms of a drug substance (same molecular weight but different crystal structure)." (DTX901 at 44.) There are no issues relating to polymorphic forms of lansoprazole in this litigation.

[12] During his testimony, Dr. Bugay dismissed this article, alleging that it was not reliable because one of its authors sold ToF-SIMS equipment. (Bugay Tr. at 237, l. 9 – 238, l. 3.) Another red herring. First, the article was written by a combination of academic authors and members of the industry. (DTX902.) Second, Dr. Bugay himself relied on this article in his own, peer-reviewed journal without disclaimer. (DTX901 at 59 & 62; Byrn Tr. at 174, ll. 17-25.) Third, the substance of this article appeared in Analytical Chemistry, a peer-reviewed journal that Dr. Byrn admitted is reliable and not promotional in nature. (DTX903; Byrn Tr. at 179, ll. 2-11 and 266, ll. 3-6.) Finally, a subsequent article published in a peer-reviewed journal in 2007 that discussed the superiority of ToF-SIMS to Raman also cited the 2000 article. (DTX904 at 258; Byrn Tr. at 184, l. 20 – 185, l. 8.)

coatings of drug pellets as well as investigating the distribution of species within a particular layer." (Id.)

The authors of the 1999 article published another article that contained essentially the same views in the peer-reviewed journal Analytical Chemistry, published by the American Chemical Society. (DTX903.) Dr. Byrn conceded that this journal is reliable. (Byrn Tr. at 179, ll. 2-11.) Again pointing out the superiority of ToF-SIMS for spatial relationship analysis similar to the one at issue in this case, the authors Belu et al. stated:

> Vibrational spectroscopy techniques such as Raman microprobe and FT-IR microscopy are useful for chemical characterization; however, these techniques have limited spatial resolution for analyzing the distribution of ingredients or excipient within a system. Time-of-flight secondary ion mass spectrometry (TOF-SIMS) is a powerful method for characterizing cross sections of drug dosage forms, allowing imaging with high spatial resolution and spectroscopy for molecular chemical identification.

(DTX903 at 5626 (emphasis added).) Plaintiffs nevertheless criticize the ToF-SIMS technique.

When faced with these articles, Dr. Byrn attempted to dismiss ToF-SIMS as a fleeting area of interest. (Byrn Tr. at 184, ll. 16-19.) The 2007 article next shown to Dr. Byrn after this comment dispels any notion that the interest in ToF-SIMS in the technical community is fleeting. This article, entitled "Time-of-flight secondary-ion mass spectrometry for the surface characterization of solid-state pharmaceuticals," was published in the Journal of Pharmacy and Pharmacology, a peer-reviewed journal. (DTX904; Byrn Tr. at 185, ll. 6-8.) The article provides that Raman and EDS "both suffer from relatively low levels of surface specificity (i.e. they 'see' too much of the bulk material below the surface) and relatively low spatial resolution." (DTX904 at 252.) ToF-SIMS provides a better chemical mapping technique due to its significant improvement in surface sensitivity. "The surface chemical imaging capabilities of

ToF-SIMS provide new insight into drug distribution within solid dosage forms, offering significant improvements in spatial and elemental resolution over existing technologies." (Id. at 257 (emphasis added).) The 2007 article states that "ToF-SIMS provides an invaluable tool for formulation scientists, providing significant insight into drug and excipient distribution within a matrix." (Id. at 257.)

Dr. Byrn also attempted to dismiss ToF-SIMS as a spatial relationship analytical tool because two journals contained fewer citations to ToF-SIMS than Raman. (Byrn Tr. at 135, l. 15 – 136, l. 4.) Such a comparison is meaningless, however, unless each citation analyzed the benefits of Raman testing to analyze the spatial relationship of ingredients in pharmaceutical products. Dr. Byrn admitted that he did not know how many of these articles contained such an analysis. (Id. at 173, l. 15 – 174, l. 2.) Moreover, ToF-SIMS only recently became widely available to pharmaceutical scientists and formulators. (DTX904 at 252.) Its recent widespread availability does not negate its clear superiority to Raman when analyzing the spatial relationship of ingredients at higher spatial resolutions and surface sensitivity. (Id.) It is also noteworthy that Dr. Byrn admitted that he was not aware of any articles criticizing the use ToF-SIMS for identifying the spatial relationship of ingredients in a pharmaceutical product. (Byrn Tr. at 174, ll. 3-7.)

Plaintiffs further criticize the use of ToF-SIMS in this case because it supposedly does not provide adequate depth penetration. (Id. at 234, ll. 16-21.) Another red herring. It is the cross-sectioning of the granule that reveals the internal structure. Dr. Bugay testified:

> A. . . . In order to investigate the interior portion of the granule, we needed to actually expose that interior portion. And to do that, we actually utilized a metallic knife edge and subsequently cut . . . .

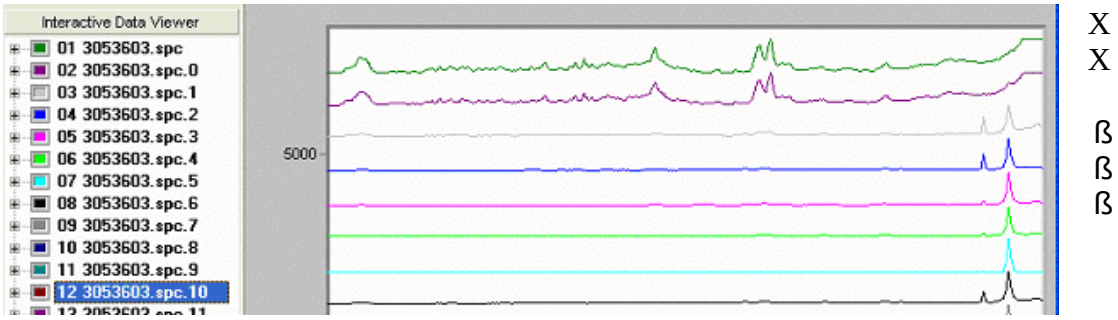
(Id. at 205, l. 23 – 206, l. 4.) These cut samples revealed a random view of the interior of the granules. (Hirt Tr. at 366, ll. 14-22.) The cutting technique employed by Teva resulted in a glass-like smooth surface suitable for surface analysis. (Id. at 306, l. 20 – 307, l. 25.)

By analogy, Plaintiffs' suggestion that ToF-SIMS lacks adequate depth penetration only makes sense if you were trying to look at the rings of a tree without cross-sectioning the tree; if you were trying to look at the layers of a cake without cutting a slice; or if you were trying to examine the structure of an onion without cross-sectioning it. Then you might need a tool that could penetrate through the bark, icing, or outside peel. But once the tree, cake, or onion is cross-sectioned, there is no need for penetration. Instead, you want the tool that gives you the clearest view of where one ring starts and where the next begins; where the chocolate layer of the cake stops and the vanilla begins; where one layer of the onion stops and the next begins. ToF-SIMS is such an analytical tool. Raman is not.

Mr. Hirt's Raman testing provided a vivid example of Raman's spatial resolution limitations. His Raman testing of Teva's product showed spectra that detected UV curable resin, which was indisputably present only outside the pellet, up to 10 to 15 microns inside the pellet.[13] (Hirt Tr. at 334, l . 1 - 334, l. 21.) The image below reflects the Raman spectra taken from just outside the cross-sectioned sample moving towards the sugar core. The measurements shown by the top two spectra (peaks 01 and 02, shown as green and purple, and marked by an X) were taken where the laser physically was located in the resin. The peaks in the middle of the spectra (the single and double peaks) indicate the presence of resin. (Id.) The next two to three layers (03, 04, and 05, shown as grey, blue, and pink, and marked with an ß) contain residual peaks

[13] Mr. Hirt selected the UV curable resin specifically because it would not penetrate into the pharmaceutical product. (Hirt Tr. at 308, ll. 1-3.) Subsequent testing showed that the UV curable resin material had not penetrated the pellet. (Id. at 334, ll. 22-25.)

indicating the presence of resin, even though the measurements were taken when the laser physically was located inside the sample in the enteric coat, which contained no resin. (Id.)



(DTX063-3, at HIRT031.)

Thus, the lack of specificity inherent in the Raman technique caused the Raman data to report the presence of UV resin some 10-15 microns away from where it actually was. In terms of the above analogy, Raman generates data that would confuse the location of rings on a tree, indicate that the layers of cake are mixed, and indicate that the meat of the avocado is in the core.

Plaintiffs and/or their experts simply neglected to consider (or at least to report on) the ToF-SIMS technique when attempting to prove infringement.[14] Neither Dr. Bugay nor Dr. Byrn even considered (or rejected) the technique when reaching their initial conclusions, and Plaintiffs' Opening Brief nowhere mentions ToF-SIMS, despite the fact it was a focus of the trial. This silence is quite telling..

[14] There is no evidence that Plaintiffs even considered ToF-SIMS at the time Dr. Byrn chose to use Raman and EDS. This may well be because Dr. Byrn's primary focus is on the analysis of crystalline structures, such as polymorphs, and that is one subject area where ToF-SIMS is not as strong as Raman. It may have been in a technical blindspot for Dr. Byrn, when considering analytical tools in a case like this that does not involve polymorph issues, and ToF-SIMS is certainly an expensive technique. In any event, ToF-SIMS plainly is the best analytical tool for addressing the spatial relationship issues in this case.

c) Laser Raman and EDS Analysis Confirmed the ToF-SIMS Data

(1) Sample Preparation: Mr. Hirt Properly Prepared Samples for Analysis; Plaintiffs Did Not

Sample preparation is the key to getting good data, and it must be done very carefully. (Meyer Tr. at 383, ll. 15-17.) Dr. Bugay acknowledged this in a 2001 article when he wrote: "Probably the most singly important aspect for any of the techniques is sample preparation." (DTX901 at 45.) Here, Teva carefully prepared its samples. Plaintiffs, however, did not and this resulted in clear damage to the samples being tested.

Teva's blinded expert, Mr. Hirt, designed each experiment performed on Teva's product, including how the individual pellets would be cross-sectioned. Mr. Hirt used a diamond knife, a "very standard technique for cutting a sample." (Meyer Tr. at 382, ll. 5-6.) For each sample prepared, Mr. Hirt used a new diamond knife to cross-section each pellet to expose the pellet's internal structure for analysis. (Hirt Tr. at 307, l. 23 – 308, l. 5.) Mr. Hirt selected the diamond knife microtome because the prepared surface would provide the most accurate reflection of the product's structure before cutting. (Id. at 297, ll. 14-25.) The nearly perfect edge of the diamond knife results in movement of very little material during preparation, and the resulting surface most closely represents the actual structure of the pellet before cutting. (Id.) Even Dr. Bugay testified that "[t]ypically the diamond blade is the most precise" cutting tool. (Bugay Tr. at 247, ll. 6-8.)

Plaintiffs, in contrast, used a razor to cross-section Teva's product for analysis, even though both glass knives and diamond blades were available for use. (Brostrom Dep. at 68, 85,

91, 93, 95; Bugay Tr. at 247, ll. 9-11.)[15] Mr. Lyle Brostrom, the technician charged with preparing and testing the 30 mg samples, selected the method for cross-sectioning Teva's Product without prior input from Plaintiffs' experts. (Bugay Tr. at 245, ll. 21-23.) Mr. Brostrom decided to cross-section the pellets using a razor blade on an apparatus that he had never used in this manner before. (Brostrom Dep. at 100.) Mr. Brostrom did not know the manufacturer of the razor blade used, nor did he know whether the razor blade used had been used before. (Id. at 95.) Mr. Brostrom used the same razor blade to cut multiple samples of Teva's product. (Id. at 104.) Mr. Brostrom testified that he visually inspected the razor blade before use for nicks, but no pictures were taken of the razor to memorialize the sharpness of the blade. (Id. at 97.) After the pellets had been cut, Plaintiffs' expert Dr. Byrn approved the use of the razor blade and the razor-cut pellets of Teva's product. (Id. at 68.)

Razor blades[16] do not provide the best quality cross-section available. For instance, the imperfect edges of the blade can move particles around as particles are caught in the imperfections and moved to other areas of the cross-section. (Hirt Tr. at 309, ll. 8-15.) The size of particles used in Teva's product were not measured; however, their size would not prevent the particles from being trapped in the grooves of the razor blade and pushed to another location in the cross-section. To put the difference between these cutting edges in perspective, many of the nicks and grooves on the cutting edge of the razor are thicker than the talc separating layer in

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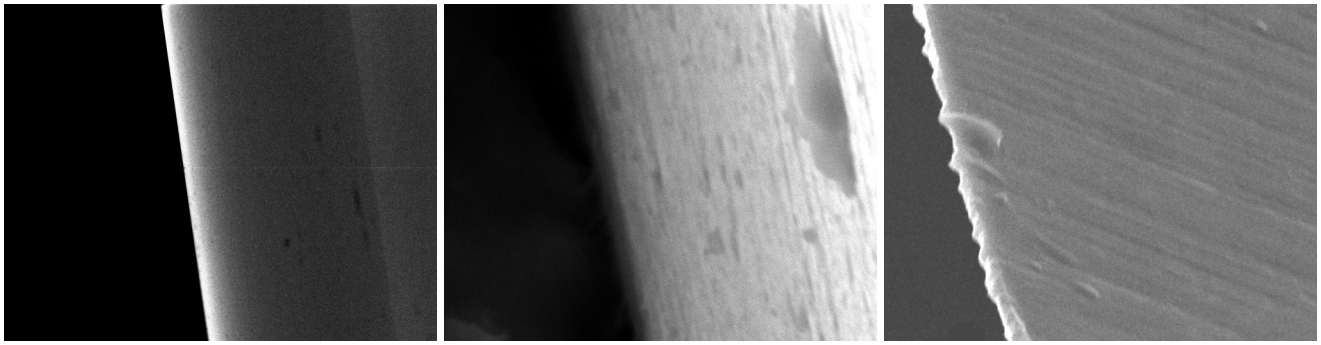
[15] Mr. Brostrom only cross-sectioned the 30-mg granules of Teva's ANDA product for analysis, but Plaintiffs have not introduced any evidence that the later cross-sections of Teva's 15-mg product were performed any differently than the product prepared by Mr. Brostrom.

[16] While at trial Dr. Bugay attempted to deny the use of a razor blade, but he cannot escape that his report specifically refers to the use of a razor blade: "After the [Super] glue hardened, the granule was cross sectioned using a rotating stage and a razor blade mounted in a stage support." (Bugay Tr. at 245, l. 8 – 246, l. 7; Bugay Report at ¶ 34 (emphasis added) (See DTX300, attached as Exhibit 4).)

Teva's product.[17] The pictures below show the difference in edge quality between the type of blade used by Teva and the type of blade used by Plaintiffs:



Diamond Knife Edge Surgical Scalpel Edge Safety Razor Edge

All at 2,000X (Demonstrative Hirt001.)

Plaintiffs' use of a razor blade to cross section Teva's sample granules plainly resulted in imperfect cross-sections. Defendants' scanning electron microscope ("SEM") images and electron dispersive microscope ("EDS") maps (discussed in detail in subsection III.C.(3)(c)(iii) below) demonstrate the damage caused to the pellets during sample preparation. By way of example, the SEM image below (on the left) shows damage to the top portion of the cross-sectioned pellet. (DTX336.3.) The corresponding EDS (on the right) map also shows damage to the top of the cross-sectioned pellet. (PTX423, Meyer Tr. at 406, ll. 4-21.) This type of damage was common to many of the cross-sectioned samples prepared by Plaintiffs and likely resulted from the cross-sectioning method employed by Plaintiffs' technician. (Meyer Tr. at 406, l. 4 – 408, l. 4.)

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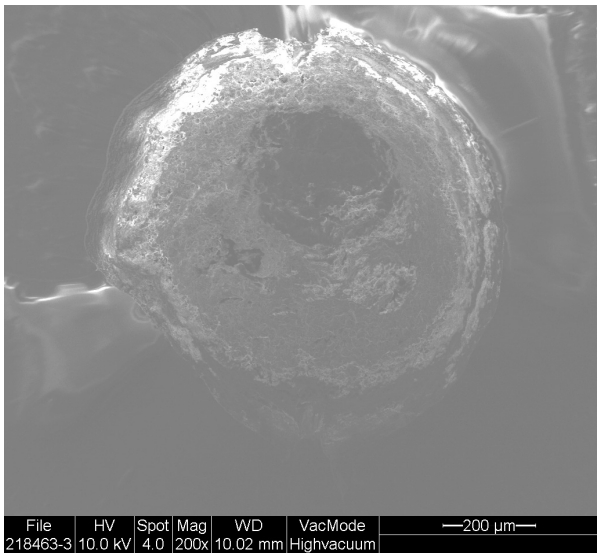
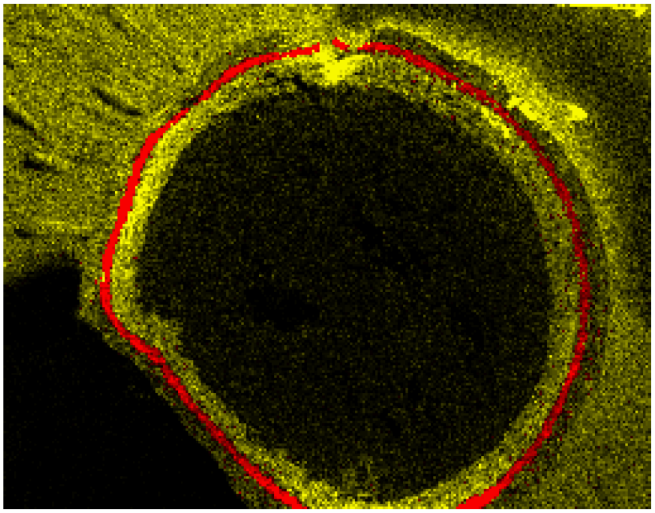
[17] The Court can readily measure these grooves on the image above using a ruler. The images are at magnification of 2000x. Multiplying the size of the nick in centimeters by 5 gives the actual size of the imperfection in microns. ([1,000,000 microns per meter]/[(100 cm per meter)x(2000 magnification)] = 5.)

A nick of 0.5 centimeters on the image above represents a nick that is 2.5 microns wide (0.5 x 5 = 2.5.) Teva's talc layer is 2-8 microns thick. (Byrn Tr. at 138, ll. 16-18.)



(DTX336.3.)



(PTX423.)

The EDS map on which Plaintiffs relied at trial not only shows damage to the pellet, it also shows that lansoprazole spread throughout the cross-sectioned sample. (Id. at 406, l. 4 – 408, l. 24.) The pattern of spreading shown by the lansoprazole indicates that the sample was cut toward the top left hand portion of the image, where the highest concentration of the lansoprazole appears to have been deposited. (Id. at 407, ll. 10-15.) Yellow indicia of lansoprazole can be seen within the red magnesium carbonate band where Teva applies the lansoprazole layer; immediately external to the red magnesium carbonate band, which would be in the enteric coat; and external to the enteric coat surrounding the pellet and scattered across the stage of the instrument.

Dr. Bugay recognized that damage to the pellet during sample preparation could spread lansoprazole throughout the sample, but he chose to believe that was not the case here. (Bugay Tr. at 274, ll. 4-18.) Despite evidence to the contrary, Dr. Bugay assumed the sample preparation was done correctly. (Id.) Dr. Bugay then selectively chose to interpret any yellow pigment outside of the red magnesium carbonate ring as background noise – although the "noise" was not spread across the entire background, but only in the direction of the cut – whereas he

treated any yellow pigment inside the magnesium carbonate layer as lansoprazole. (Bugay Tr. at 273, l. 7 – 274, l. 25.) Dr. Bugay provided no scientific basis for such treatment. He did no testing to confirm. And, he offered no evidence rebutting what appears to be damage his technician imposed on the sample during preparation. (Id. at 275, ll. 6-18.)

(2) Laser Raman Data Confirmed the ToF-SIMS Results

As noted above, Teva's expert Mr. Hirt selected laser Raman as a complement to the ToF-SIMS testing described above. (Hirt Tr. at 327, ll. 11-21.) He did not use it as his primary analytical tool because its resolution is poorer than ToF-SIMS. (See id. at 297, ll. 12-25.) In particular, Mr. Hirt used laser Raman to confirm that the red band ToF-SIMS identified in the multilayer pellet was in fact magnesium carbonate. (Id. at 327, ll. 11-21 and 330, ll. 7-10.) Mr. Hirt also used laser Raman to confirm the identification of the other layers through the ToF-SIMS testing. (Id. at 330, ll. 12-23.) In short, the Raman analysis confirmed Mr. Hirt's ToF-SIMS results. (Id. at 330, ll. 7-23.)

Plaintiffs repeatedly have misconstrued Mr. Hirt's statements and analysis, contending that Mr. Hirt has admitted finding lansoprazole and magnesium carbonate in the same physical space. (E.g., DI 163 at 34; Hirt Tr. at 348, l. 22 – 358, l. 15.) Absolutely false. As Mr. Hirt explained, because Raman has a weaker resolution than ToF-SIMS, the Raman data may reflect indications of a substance even where the substance is not physically present. (Hirt Tr. at 358, ll. 3-15 and 367, l. 10 – 368, l. 7.) Mr. Hirt specifically rebutted the contention that he had admitted lansoprazole and magnesium carbonate being in the same place as follows:

> The fact that the species all are seen to be present in the same spectrum is not an indication of intermixing of layers, but a demonstration of the actual volume of sample that is being analyzed in Raman instruments.

(Id. at 367, ll. 16-22 (confirming the consistency of the statement above, from his expert report, with his deposition and trial testimony).)

Plaintiffs also have mischaracterized Dr. Meyer's testimony regarding the Raman testing performed. (DI 163 at 34.) Dr. Meyer unequivocally testified that both Plaintiffs' and Teva's Raman data support a finding of noninfringement. Dr. Meyer based his opinion, among other things, on the poor spatial resolution of laser Raman.[18]

Even a marketing brochure from the manufacturer of Dr. Bugay's Raman microscope recognized that the instrument lacks the spatial resolution necessary to resolve a ten micron layer, much less a layer of less than ten microns. (See DTX70; Meyer Tr. at 401, l. 11 – 403, l. 13.) The manufacturer analyzed a prepared sample that contained alternating ten micron layers of alternating polymers using a laser with improved spatial resolution even more precise than that used on Dr. Bugay's machine. (Id.) Even the manufacturer, with superior spatial resolution than that used in this case, could not resolve a ten micron layer sample. Each Raman spectra generated by the manufacturer indicated the presence of both polymers in each layer – even though each layer contained only one polymer. (Meyer Tr. at 402, ll. 9-19.) At no time did the generated spectra fail to include at least a small peak indicating the presence of the other polymer. (Id.; see also DTX70 at Figure 3.) Dr. Meyer explained how the data generated could be misinterpreted to show that the polymers were in contact with each other – even mixed – even though the polymers existed solely in separate layers. (Meyer Tr. at 403, ll. 10-13.) The teachings in this brochure demonstrate that the mere presence of a small peak indicative of a

[18] Likewise, Plaintiffs mischaracterize Dr. Chambliss' testimony as implicitly conceding that a person of skill in the art would agree with Plaintiffs' new proton transfer theory. The passage to which Plaintiffs cite in no way supports their argument of an implicit concession. (DI 163 at 25; see also Chambliss Tr. at 535, ll. 20-25.)

chemical cannot conclusively determine the presence of an ingredient. (Id. at 404, ll. 5-12.) Dr. Bugay failed to consider this limitation of Raman when analyzing his data.

Even putting Mr. Hirt's analysis aside and considering only Dr. Byrn and Dr. Bugay's analysis, Plaintiffs still cannot show that the lansoprazole and magnesium carbonate are in a homogenous admixture. At most, Plaintiffs' evidence shows that, at certain points, Raman shows lansoprazole and magnesium carbonate both to be above the level of detection. (Byrn Tr. at 172, l. 16 – 173, l. 1.) Both Dr. Byrn and Dr. Bugay admit that they can make no quantification whatsoever regarding how much lansoprazole and how much magnesium carbonate are in any given location. (Byrn Tr. at 168, l. 22 – 169, l. 2; Bugay Tr. at 257, l. 15 – 258, l. 5.) With respect to any location on any granule, they have not and cannot tell the Court anything on a quantifiable basis regarding the spatial relationship of the lansoprazole and magnesium carbonate.

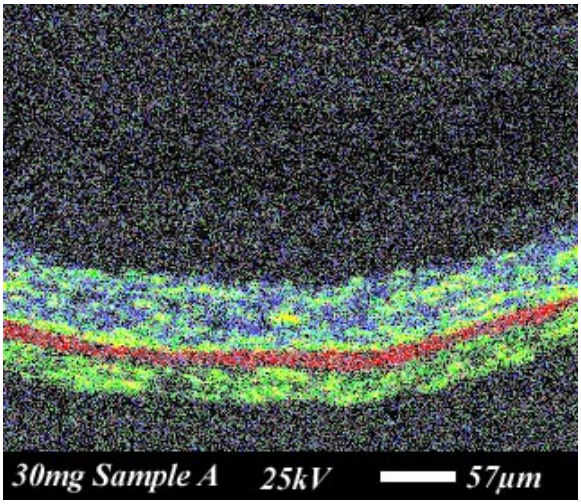
In short, Plaintiffs cannot make their case based off of their own data, which is why they try to side-step the absence of spatial relationship evidence through their "proton transfer" and "cell phone" theories.

(3) The EDS Data Confirms That Teva's ANDA Product Does Not Contain a Homogenous Mixture

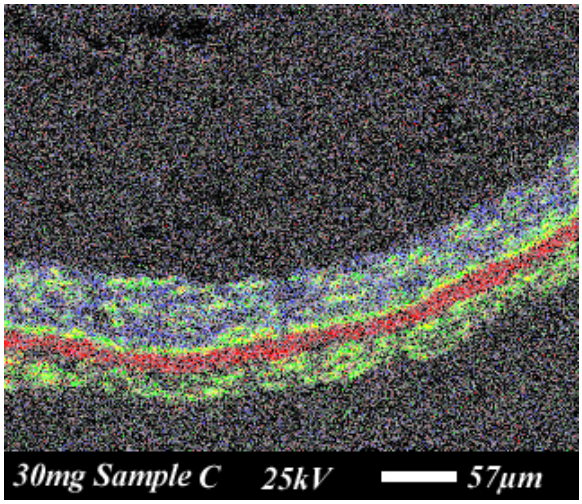
Teva's experts also used EDS to confirm the results obtained in the ToF-SIMS analysis. As explained at trial, a few of the ToF-SIMS images appeared to contain discrete smears of talc across the magnesium carbonate layer, suggesting that, despite Mr. Hirt's careful technique, talc from one layer had been deposited in the magnesium carbonate layer during sample preparation. (Hirt Tr. at 338, l. 19 – 339, l. 12; see also DTX63-2 at HIRT022 (Sample A from 30 mg Product).) Mr. Hirt used EDS to confirm that the indicia of talc found on the surface during his ToF-SIMS analysis was merely a surface smear of talc that occurred during sample preparation,

rather than an imperfection in Teva's manufacturing process. (Hirt Tr. at 339, l. 5 – 341, l. 14 (noting that here the depth penetration of EDS helped determine that the thin smear of talc over the magnesium carbonate was only a smear.).)

The EDS images confirm Teva's experts conclusions based on the ToF-SIMS data. The EDS images clearly indicate that Teva's Product contains a multilayer formulation and that a talc layer separates the lansoprazole and magnesium carbonate layers. (Id. at 341, l. 16 – 342, l. 12; DTX63-5.) Teva's EDS images mirror the teachings of Teva's ToF-SIMS images as discussed above in subsection III.C.(3)(b)(ii). Two representative EDS images generated by Teva's expert are shown below. Yellow/green represents talc, red represents magnesium carbonate, and blue represents lansoprazole. Certainly, this shows no homogenous mixture of lansoprazole and magnesium carbonate.



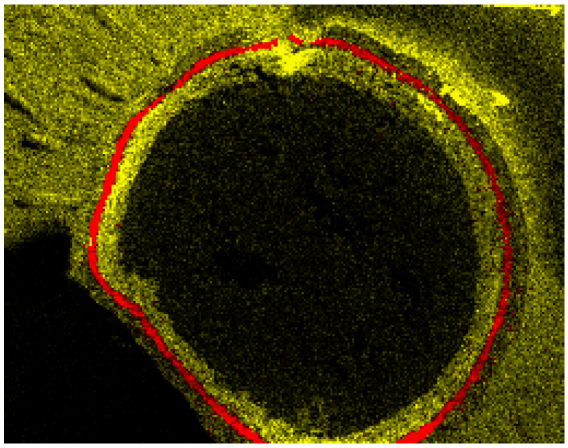
(DTX63-5 at HIRT041.)



(Id.)

Teva's EDS images also reflect the importance of good sample preparation. (See also discussion at subsection III.C.(3)(c)(i) above.) They confirm the presence of a multilayer formulation that conforms to the manufacturing process Teva disclosed to the FDA in its ANDA. (See discussion in subsection III.C.(2)(a) above.) Plaintiffs' EDS images, on the other hand, reflect how poor sample preparation can affect the quality of data generated. Plaintiffs' EDS,

shown below, shows a distribution of lansoprazole throughout the image – even off the sample, on the stage of the instrument – instead of distributed in a single layer. (See discussion in section III.C.(3)(c)(i) above.) Plaintiffs' EDS image indicates the presence of lansoprazole internal to the magnesium carbonate, in the enteric coat external to the magnesium carbonate, and present outside of the pellet itself. As noted above, while Dr. Bugay attempted to discount the presence of lansoprazole outside of the granule, he provided no scientific explanation for this data. Further, Teva's testing and ANDA show that Plaintiffs' data simply is not correct.



(PTX423.)

However, at the end of the day, Plaintiffs' EDS data still does not prove their case. At best, it shows a granule with imperfect layers and some scattering of some unquantified amount of lansoprazole across different layers. But this is hardly a homogenous mixture of the lansoprazole and the magnesium carbonate. This is not "in contact . . . evenly."

d) Plaintiffs Adduced No Evidence in Support of Their "Uniform Basic Environment" Construction

Plaintiffs ask the Court to hold that the "in contact . . . evenly" limitation can be met if Teva's product contains a "uniformly basic environment." Plaintiffs, however, never tested the pH of a single granule. (Bugay Tr. at 162, ll. 10-18.)

The omission is understandable. The concept of "pH" applies only to solutions; it is inapplicable to solids. (Amidon Tr. at 1096, l. 25 – 1097, l. 2.) There is no evidence regarding the pH of the Teva ANDA product, much less evidence establishing a uniform basic environment.

Plaintiffs attempt to fill this evidentiary hole in a number of ways, none of which work. Plaintiffs primarily point to a Takeda article that was attached to Dr. Byrn's expert report. This publication discloses that the pH of a 1% solution or suspension of pure magnesium carbonate to be 9.1 (PTX748 at 1442[19] and 1443[20]), and Plaintiffs use this for the basis for their conclusion that the pH of the Teva ANDA granule must be pH 9.1. (Byrn Tr. at 96, l. 18 – 97, l. 9.)

The first problem with this theory is that it nowhere was discussed in Dr. Byrn's report and it should be discarded on that basis alone. (Id. at 96, ll. 20-24.) Second, the article only addresses a suspension of the magnesium carbonate in water and not the pH of a suspension of a pharmaceutical granule containing lansoprazole, magnesium carbonate, and the many other components of Teva's formulation or a suspension thereof. (PTX748 at 1442-43.) Third, even if the article did address the pH of a granule as a whole, the composition of the granule addressed in the article is entirely different than the Teva formulation, putting lansoprazole and the magnesium carbonate aside. (Byrn Tr. at 166, l. 20 – 167, l. 10.) There is no evidentiary basis for concluding that two such different formulations (even in suspension) would have the same pH. Fourth and finally, if the pH of Teva's formulation actually was 9.1 as Dr. Byrn testified, the enteric coat that encapsulates the multilayer pellet would fall apart. (Chambliss Tr. at 466, l.

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[19] The asterisk after pH in Table 5 explains that the pH listed in the chart merely measures a 1% solution or suspension of the stabilizer tested listed in the table.

[20] "Table 5 also shows the pH of the 1% aqueous solution or suspension of the substances screened [magnesium carbonate]."

20 - 467, l. 8 and 492, ll. 1-10 (testifying that the Eudragit L-30 D-55 used in the enteric coat "falls apart at pH's above 5.5").)

Plaintiffs also point to Teva's ANDA in a misguided attempt to prove that Teva's Product was alkaline. (DI 163 at 38-39.) Teva's ANDA states that magnesium carbonate "imparts a slightly alkaline reaction" in water in the Certificate of Analysis for Magnesium Carbonate USP. (PTX956 at TVL006760.) Again, this statement refers solely to the pH of a solution containing only magnesium carbonate and water. This disclosure does not constitute competent evidence of the pH of Teva's Product in its final form with all of the ingredients included. This disclosure also presents no reliable evidence that Teva's Product enjoys a uniform alkaline environment.

In summary, Plaintiffs cannot meet their burden of proof with respect to the "in contact . . . evenly" limitation, without regard to which parties' proposed construction the Court adopts.

e) Plaintiffs Adduce No Evidence for Their New "Proton Transfer" Theory

At trial, Dr. Byrn advanced a theory that Teva's Product infringes because "proton transfer" between layers in its product puts lansoprazole and magnesium carbonate in remote "contact." This theory was new;[21] Dr. Byrn previously had never before presented data or opinion that proton transfer occurred in Teva's product or contributed to infringement.

Nor did he present any data at trial. Rather, Dr. Byrn testified that he could not test for proton transfer in Teva's product, and he presented no evidence in support of this conjecture:

[21] In his Declaration submitted in connection with claim construction, not infringement, Dr. Byrn suggested that "protons may freely move around in a sold state drug formulation, especially when there is water present. This movement of protons can result in the creation of an alkaline environment." (Byrn Decl. at 12 ¶ 48.) Nowhere did Dr. Byrn suggest before trial that such transfer occurs in Teva's product or proffer this theory in support of his infringement analysis.

Q. And, Dr. Byrn, in terms of the tests that you've described, do the ramen tests that you described and the EDS tests that you described, do they capture simply the solid substances that are in the area being studied or do they also capture the water that -- and the contact that's going on in water that you've been describing?

A. They capture only the solid. There's no – of course, we would have done a test if we could have, if there was one available to measure the water molecules and the proton transfer, but these are two small particles and they're moving too rapidly to be able to test and find them. They're moving, remember, at about a hundred million times per second, the protons are moving through this system, and so we don't have a method to analyze those protons.

(Byrn Tr. at 133, l. 12 – 134, l. 6.) Dr. Byrn further testified, however, that there were methods to measure such transfer; Manfred Eigen had managed the feat in 1967, some forty years ago:

Q. And where did the concept of proton transfer come from, Dr. Byrn?

A. Of course, chemists had been interested for as long as chemistry was in existence what happened in water and how protons moved through water. But it wasn't until the 60s that a famous German chemist named Manfred [Eigen] who won the Nobel Prize in 1967 described proton transfer and was able to measure the rate. And, like I said, it showed that proton transfer occurs at roughly the rate of 100 million times per second . . . .

(Byrn Tr. at 92, l. 22 – 93, l. 7 (emphases added).)

No other expert was able to agree with Dr. Byrn's new theory. Even Dr. Bugay, Plaintiffs' own expert, could not support Dr. Byrn's theory. The theory was as new to Dr. Bugay as it was to Teva, and Dr. Bugay testified that, even after Dr. Byrn's testimony, he did not have sufficient information to form an opinion:

Q. You do understand the [proton transfer] theory is magnesium carbonate on one hand and lansoprazole on the other hand are attracted to these two entities, is that the theory, hydroxides and protons?

A. In general, but I haven't studied it. I heard Dr. Byrn yesterday so I don't really have learned opinions on it with the limited information.

Q. You didn't hear his theory before yesterday either?

A. No.

(Bugay Tr. at 277, l. 25 – 278, l. 8.) Clearly, this is not a theory that leapt to the mind of at least Dr. Bugay, an expert who analyzed infringement of the '321 patent.

Dr. Meyer pointed out many of the theory's technical flaws. The first is that Dr. Byrn's new theory relies on "protons mov[ing] through water" (Byrn Tr. at 92 l. 22 – 93 l. 7), and water is necessary for transport of the protons and for acid-base chemistry to occur:

Q. Does this sort of acid based chemistry occur in the solid state?

A. Again, you can take, for example, citric acid, which is a solid, and you take magnesium carbonate, which is a solid, and if you put them together, there is no acid base reaction. The two of them can sit right next to each other. You can press pellets of them and the reaction doesn't occur. On the other hand, if you were to add some water to that solid sample, you could see rapid neutralization reactions of that type.

(See Meyer Tr. at 421, l. 21 – 422, l. 5.) Dr. Byrn presented no data that there was sufficient water in Teva's (dry) product for this reaction. Further, Dr. Meyer contradicted Dr. Byrn's assertion that the reactions were too fast to measure.

A. . . . . I also found it a little misleading to present a Nobel Prize in 1967 which was a very celebrated one. I'm particularly aware of the work of Norrish and Porter who shared the Nobel Prize in that year, 1967, for studying what were then very fast reactions. They invented the technique of nanoseconds, flash photolysis, for measuring fast reaction. And [Eigen], the one he measured, figured out these neutralization reactions were very fast. Well, that was 30 years ago. Zewell won the Nobel Prize two years ago for femtoseconds spectroscopy which is something that is about six orders of magnitude faster time resolution. Plus, the way that protons are conducted in water is very well understood much, much better than it was back in the time of [Eigen].

I'm familiar with the work from Berkley. For example, there was a science paper just a few years ago that described proton transfer in water using statistical mechanics and the most current approaches and to just put a cartoon up like that in the kind of detail that was presented without any scholarly references or anything of that type I found to be misleading and a little bit inappropriate for this setting.

(Meyer Tr. at 420, l. 14 – 421, l. 10 (emphasis added).) "Femtoseconds" are hundreds of thousands of times faster than the reactions that Dr. Byrn conjectured. Further, Dr. Meyer noted that the idea that "a very polar molecule like hydroxide" would congregate around a "very nonpolar molecule like benzimidazole" for protection is unsupportable by chemical theory. (Id. at 422, ll. 6-15.)

Dr. Chambliss also disagreed with this new theory; he pointed out that if it were valid, the same "proton transfer" that allegedly occurred in the (dry) drug layer would occur to a greater extent in the (MUCH more wet) enteric coat, causing the product to fail:

> Q. Now, you have been in the courtroom during the course of the '321 patent portion of the case. Have you heard any evidence that is contrary to the opinions you just gave?
>
> A. Not at all. I haven't seen any evidence that these coats don't appear, that they don't stay. They're not stable. I saw an animation from Dr. Byrn, which I do not understand or do not agree with at all, showing the subcoats all kind of merge together with the drug coat, but because there is a lot of water involved, that obviously doesn't occur from the data that we've seen from Dr. Bugay and Mr. Hirt and from the way the process was designed.
>
> Also, if that was occurring, the enteric coat layer would also merge in with the others and the product would totally fail. There is more water in the enteric coat layer than the subcoat layers the theory is just totally incorrect.

(Chambliss Tr. at 474, l. 22 – 475, l. 12 (emphasis added).)

In short, Dr. Byrn's conjecture about proton transfer was totally unsupported by scholarship, data, or the opinion of even Plaintiffs' other testifying expert. For these reasons, and because the theory was disclosed only at trial, Teva respectfully submits that the Court should reject the theory.

Having heard Dr. Byrn's new theory only the day before, Dr. Meyer[22] questioned whether sufficient water and protons exist in a solid state formulation to support this transfer theory. (Meyer Tr. at 421, 1.1 – 422, l. 5.) This concern is particularly relevant if the Court accepts Plaintiffs' unsupported assertion that the formulation has a uniformly basic pH of 9.1, which would result in a decreased number of protons.[23] In addition, the idea that "a very polar molecule like hydroxide" would congregate around a "very nonpolar molecule like benzimidazole" for protection is unsupportable by chemical theory. (Id. at 422, ll. 6-15.)

f) Plaintiffs Cannot Meet the Burden of Proving the "In Contact . . . Evenly" Limitation Merely By Showing That Teva's Product Is Stable

Plaintiffs place great weight on the fact that the Teva ANDA product (not surprisingly) is stable. (See, e.g., DI 163 at 12.) If the ANDA product was not stable, the FDA would not approve the ANDA. See 21 C.F.R. § 314.125(a), (b)(1) (2007) (noting that the FDA "will refuse to approve" an application if the method by which it is produced is "inadequate to preserve its . . . stability"); (Chambliss Tr. at 544, ll. 12-14.). Dr. Byrn goes so far as to suggest that stability

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[22] Dr. Meyer is a Professor of Chemistry and Materials Science & Engineering at Johns Hopkins University, with a joint appointment in the departments of Chemistry and the department of Engineering. (Meyer Tr. at 368, l. 25 – 370, l. 2.) He holds a B.S. in Chemistry and Mathematics from the State University of New York at Albany. He received a Ph.D. in Chemistry from the University of Wisconsin at Madison, where his research focused on analytical and spectroscopic methods. He performed postdoctoral work at the University of North Carolina at Chapel Hill. And Dr. Meyer began teaching at Johns Hopkins in 1991. (Id. at 370, ll. 5-22.) His research funding includes grants from the National Science Foundation to research the electronic interactions in hybrid organic nanoparticle materials. (Id. at 370, l. 25 – 372, l. 13.) He also serves as a reviewer and an advisory board member of several journals of the American Chemical Society. (Id. at 372, l. 16 - 373, l. 16.) (DTX66.)

[23] pH (also written p[H+]) is the negative log of concentration of H+ (protons) in an aqueous solution. Higher pH measurements show a lower concentration of protons than lower measurements. As such, a pH of 9.1 would have more than 100 times fewer protons than a neutral pH of 7 or an acidic pH of below 7.

itself can be used as surrogate proof that a uniformly basic environment exists in the Teva ANDA product, but provides no scientific support for his assertions. (Byrn Tr. at 132, l. 25 – 126, l. 11.) Finally, Plaintiffs incorrectly assert that Teva never addressed at trial how the stability is achieved. (DI 163 at 12.) This "stability" argument fails for a number of reasons.

First, although stability no doubt is a goal of the '321 patent, Plaintiffs still must establish that each limitation of the claim is met. Baxa Corp. v. McGaw, Inc., 981 F. Supp. 1348, 1351, 1360 (D. Colo.1997) (finding that even when the asserted invention and the accused products accomplished the same goal, there was no literal infringement because the accused products did not embody each and every limitation of the asserted claims), aff'd per curiam, 185 F.3d 883 (Fed. Cir. 1999) (unpublished table decision). The '321 patent claims a product with six limitations or features to realize the goal of stability. Products that achieve stability without meeting each of the six limitations do not infringe.

Second, Teva did address how the Teva ANDA product achieves stability without satisfying each of '321 patent's six limitations. Dr. Chambliss explained that the Teva ANDA product achieves stability through a multilayer product as opposed to one where the lansoprazole and magnesium carbonate are mixed. (Chambliss Tr. at 463, ll. 3-10.)

g) Plaintiffs Cannot Base Their Infringement Case on Evidence of Teva's Prior, Discarded Formulations

Plaintiffs point to various research and development documents to support the point that magnesium carbonate is a stabilizer in Teva's ANDA product, and that there is no separation between the lansoprazole and magnesium carbonate. (See DI 163 at 10-12.) Teva objected to Dr. Byrn's testimony on this point because there was no foundation that established that Teva's early tests were formulations similar to Teva's final ANDA product. (Byrn Tr. at 139, l. 25 – 140, l. 2.) Plaintiffs never laid such a foundation and, therefore, the early R&D documents are

not probative of any issue in dispute. See Fed. R. Evid. 402; Abbott Labs. v. Novopharm Ltd., 323 F.3d 1324, 1329 (Fed. Cir. 2003) (To show infringement, Plaintiffs must demonstrate that the accused product meets the limitations of the claims asserted) (emphasis added).

Teva developed dozens of different formulations during the research and development process. (DiCapua Dep. at 87, ll. 4-16.) The early formulations contained different ingredients and varying numbers of subcoats from the final formulation. (PTX0446A, PTX0446B, PTX0446C; PTX0446D; PTX0446E.) In fact, the exhibits on which Plaintiffs rely fail to describe a single formulation where a sublayer separates magnesium carbonate from lansoprazole (id.) and have no relevance to this case. As in almost all research and development projects, these early formulations did not work for a variety of reasons.

Plaintiffs acknowledge in their Opening Brief that Teva's goal was to design around the '321 patent. (DI 163 at 2.) Teva tested its earlier formulations but stopped the testing because Teva "realized that this testing was inconclusive." (DiCapua Dep. at 109, ll. 18-24.) Thus, any attempt by Plaintiffs to suggest that Teva "just stopped looking for problems" simply has no credibility. (DI 163 at 14.)

D. Plaintiffs Failed to Prove Teva's Product Meets Other Claim Limitations.

The limitations of the '321 patent that remain in dispute all require that the lansoprazole and magnesium carbonate exist as a homogenous mixture. Teva refers to its Pre-Trial Markman submissions in this regard. (DI 131, 140.) For that reason, these limitations as used in the '321 patent cannot be met if the Court finds that Teva's product does not contain a homogenous mixture of lansoprazole and magnesium carbonate.

1. "Pharmaceutical Composition"

The phrase "pharmaceutical composition" was given a specific meaning in the context fo the '321 patent; it means "the 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." (DI 131 at 12-14; DTX734; Chambliss Tr. at 478, ll. 9-17.) This phrase, while often used, has no single accepted meaning to those of ordinary skill in the art. Thus, the context in which the phrase is used in the patent must be considered to determine its proper meaning. Here, the patentees described the pharmaceutical composition to cover the mixture of lansoprazole and magnesium carbonate specifically. (Chambliss Tr. at 517, ll. 12-18.)

The evidence submitted at trial failed to establish that Teva's product contains a "pharmaceutical composition" as used in the patent. As discussed in detail above, Teva's product does not contain the mixture of lansoprazole and magnesium carbonate required for a finding of infringement. Instead, Teva's product contains magnesium carbonate in a subcoat that is physically separated from the lansoprazole. Plaintiffs, therefore, have not met their burden of proving that Teva's product contains a pharmaceutical composition.

2. "Wherein the Composition is Made Up Into Tablets or Granules and Then Coated by a Coating Agent"

The phrase "coated by a coating agent" should be construed to mean "the tablets or granules containing the pharmaceutical composition are coated with a material that masks the taste or provides enteric or sustained release properties." (DI 131 at 15-16; DTX734.) This language, which Takeda added to the claim through amendment, makes it clear that the pharmaceutical composition must be made up into a tablet before it can be coated by a coating agent. Because Plaintiffs have failed to establish a "pharmaceutical composition," Plaintiffs failed to meet this limitation at trial.

3. "Amount of the Basic Inorganic Salt Relative to Parts by Weight of the Benzimidazole Compound Being About 0.3 – 20 Parts by Weight"

Properly construed, this claim phrase means "the weight of the basic inorganic salt that is in even contact with the benzimidazole falls between about 0.3 to 20 parts by weight." (DI 131 at 16-17; DTX734.) Plaintiffs' suggestion that the ratio be met by any lansoprazole and any magnesium carbonate anywhere in the granule has no support. Because Plaintiffs failed to quantify the amount of magnesium carbonate alleged to be in contact evenly with the lansoprazole (Byrn Tr. at 168, l. 22 – 169, l. 2) or otherwise measure the extent of mixing, if any exists, in Teva's product (Bugay Tr. at 257, l. 15 – 258, l. 5) Plaintiffs cannot meet their burden as to this limitation.

IV. PLAINTIFFS ARE NOT ENTITLED TO THE INJUNCTIVE RELIEF REQUESTED

For the reasons discussed above, Teva respectfully requests that the Court find that Teva's proposed delayed-release lansoprazole capsule products covered by ANDA No. 77-255 do not infringe claim 2 of the '321 patent. As such, and for the reasons stated in Teva's opening brief on unenforceability and invalidity of the '098 patent, (DI 165) Teva submits that the Court should decline to enter any judgment preventing the FDA from granting final approval of Teva's ANDA No. 77-255 prior to expiration of the patents.

Teva further submits that Plaintiffs' Relief Requested is overbroad to the extent that it is not limited to products covered by ANDA No. 77-255. The Hatch-Waxman Act encourages companies to file Paragraph IV certifications by providing an incentive to the first ANDA filer of a 180-exclusivity period. Merck & Co., Inc. v. Apotex, Inc., 488 F. Supp. 2d 418, 420-21 (D. Del. 2007) (identifying the strong public policy favoring availability of lower priced generic drugs). Patentees are then given the option of filing suit to challenge the Paragraph IV

certification. Issuing an injunction that covers products that are not at issue in this action would directly undermine the structure and incentives set up by the Act. Further, Plaintiffs' relief potentially would apply to Teva's orally-disintegrating tablet lansoprazole products covered by ANDA No. 78-730, even though such products are the subject of a separate action pending before the Court. See Takeda Pharm. Co., et al. v. Teva Pharms. USA, Inc., et al., C.A. No. 07-331-SLR (D. Del. filed May 25, 2007).

Teva further requests that the Court decline to issue an injunction under 35 U.S.C. § 271(3)(4)(B) preventing Teva from making, using, selling, offering for sale or importing products covered by ANDA No. 77-255 prior to the expiration of the '321 and '098 patents. If the court holds in Teva's favor on both parents, of course, Plaintiffs would have no legal basis for an injunction. Should the Court rule in Plaintiffs' favor on either patent, however, Plaintiffs still cannot demonstrate factual circumstances warranting an injunction. Specifically, Plaintiffs have not met their burden of introducing evidence sufficient to satisfy the four-factor injunction test:

1. they have suffered irreparable injury;
2. remedies at law, such as monetary damages, are inadequate to compensate for any such injury;
3. considering the balance of hardships between the Plaintiffs and Teva, a remedy in equity is warranted; and
4. the public interest would not be disserved by an injunction.

See eBay Inc., v. MercExchange, LLC, 126 S. Ct. 1837, 1389 (2006).

Plaintiffs will not suffer irreparable injury by the introduction of Teva's Product into the PPI market. First, the PPI market already contains two generic products – generic omeprazole and pantoprazole. Those two products are available to physicians as a generic alternative to Plaintiffs' lansoprazole product. As Teva's expert gastroenterologist Dr. Solny and the peer-

reviewed clinical literature explain, "A PPI is a PPI." (Solny Tr. at 583, ll. 4-19.) Further, Plaintiffs' gastroenterologist Dr. Fennerty testified that he considers the various PPIs interchangeable whenever he needs to take one. (Fennerty Tr. at 865, ll. 7-10.) Plaintiffs thus should not be heard to claim that the existence of third generic PPI would constitute irreparable injury. Indeed, this may explain why Plaintiffs have not put forth any sales or market data purporting to show such injury if Teva's Product comes on the market. See Praxair, Inc. v. ATMI, Inc., 479 F. Supp. 2d 440, 444 (D. Del. 2007) (Robinson, J.) (denying motion for a permanent injunction in part because patentee did not provide sales or market data demonstrating irreparable injury.)

Second, Plaintiffs have had over two years to prepare for the eventuality of generic lansoprazole – whether at the expiration of Plaintiffs' patents or earlier. Teva put Plaintiffs on notice of its intention to market a generic lansoprazole product through a Detailed Statement sent to Plaintiffs on December 5, 2005. Less than three weeks later, TAP announced that it had licensed Novartis to develop and sell lansoprazole as an over-the-counter product upon expiration of the '098 patent. (See attached Ex. 5.)[24] Plaintiffs also recently announced their intention to launch dexlansoprazole, a successor product to lansoprazole, prior to the expiration of the '098 patent, and they expect dexlansoprazole to be successful. (See attached Ex. 6.) Thus, it appears that Plaintiffs are well-prepared for changes in the availability of lansoprazole.

Third, the fact that Plaintiffs market lansoprazole in countries other than the United States and a variety of other products in both the United States and abroad, including Lupron® and Rozerem™, mitigates against a claim of irreparable injury.

[24] Teva submits the attached Exhibits 5 and 6 in response to Plaintiffs' request for an injunction. Teva is mindful of the Court's desire not to receive additional exhibits. However, the injunction issue was raised for the first time in Plaintiffs' Opening Brief and not at trial.

Plaintiffs likewise have not shown that monetary damages would fail to compensate Plaintiffs for any alleged injury or that Teva, the largest generic pharmaceutical company in the world, would be unable to pay any such damages. Given this remedy at law, the balance of hardships leans towards Teva's ability to serve the public interest by providing increased access to affordable drug products, and away from Plaintiffs' desire to extend a lansoprazole monopoly that has already rewarded them with $34 billion in sales. (Cole Tr. at 1057, l. 19 – 1058, l. 1.)

Teva also requests that the Court decline to enjoin Teva from filing additional ANDAs on lansoprazole products. Practically speaking, even if Teva filed an additional lansoprazole ANDA with a Paragraph IV certification tomorrow, the resulting lawsuit and thirty month stay would prevent Teva from marketing the additional products until after the expiration of the '321 and '098 patents. Moreover, any lansoprazole products covered by additional ANDAs might be colorably different from the lansoprazole products involved in this action, and thus not subject to any injunction. Plaintiffs' citation to Abbott Labs. v. Torpharm, Inc., 503 F.3d 1372 (Fed. Cir. 2007) is not to the contrary. The Abbott court did not enjoin the filing of additional ANDAs; it held only that the existing injunction in that case prohibited the making, using, selling, offering for sale or importing of additional infringing products. See 503 F.3d at 1382-83.

Teva submits that it will request its costs if it prevails in this action. Teva also intends to seek a ruling that this is an exceptional case entitling Teva to attorneys' fees under 35 U.S.C. §285. See Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1350 (Fed. Cir. 2004) (explaining that attorneys' fees may be awarded to a defendant if the patentee engaged in inequitable conduct or "vexatious litigation," and that attorneys' fees were awarded to the patentee in Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339 (Fed. Cir. 2000) only because the defendant made "numerous baseless filings supporting its fruitless and meritless arguments.")

As suggested in Plaintiffs' Opening Brief, the exceptional case issue should be addressed by the Court after ruling on the non-infringement and/or invalidity of the '321 patent and the invalidity and/or unenforceability of the '098 patent.

V. CONCLUSION

For the foregoing reasons, Teva submits that the Court should hold that Teva's Product does not infringe claim 2 the '321 patent and should deny Plaintiffs' requested relief.

YOUNG CONAWAY STARGATT & TAYLOR LLP

/s/ Karen L. Pascale

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Josy W. Ingersoll (No. 1088) [jingersoll@ycst.com]
Karen L. Pascale (No. 2903) [kpascale@ycst.com]
Karen E. Keller (No. 4489) [kkeller@ycst.com]
The Brandywine Building
1000 West St., 17th Floor
P.O. Box 391
Wilmington, Delaware 19899-0391
Phone: 302-571-6600

-and-

SUTHERLAND ASBILL & BRENNAN LLP
John L. North
Jeffrey J. Toney
Jeffrey D. Blake
Laura Fahey Fritts
999 Peachtree Street
Atlanta, Georgia 30309-3996
Phone: 404-853-8000

Attorneys for Defendants,
Teva Pharmaceuticals USA, Inc., and
Teva Pharmaceutical Industries Ltd.

CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on January 18, 2008, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

Mary B. Graham [mgraham@mnat.com]
Rodger D. Smith II [rsmith@mnat.com]
James W. Parrett, Jr. [jparrett@mnat.com]
MORRIS, NICHOLS, ARSHT & TUNNEL LLP
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19899-1347
(302) 658-9200

I further certify that on January 18, 2008**,** I caused a copy of the foregoing document to be served by e-mail on the above-listed counsel of record and on the following non-registered participants in the manner indicated:

By E-Mail

Dillon Kim [dkim@hhlaw.com]
HOGAN & HARTSON LLP
875 Third Avenue
New York, NY 10022
(212) 918-3000

Melissa Mandrgoc [mmandrgoc@pbwt.com]
PATTERSON BELKNAP WEBB & TYLER LLP
1133 Avenue of the Americas
New York, NY 10036
(212) 336-2000

By E-Mail

Eric J. Lobenfeld [ejlobenfeld@hhlaw.com]
Tedd W. Van Buskirk
[twvanbuskirk@hhlaw.com]
Arlene L. Chow [alchow@hhlaw.com]
HOGAN & HARTSON LLP
875 Third Avenue
New York, NY 10022
(212) 918-3000

Philippe Y. Riesen [pyriesen@hhlaw.com]
HOGAN & HARTSON LLP
Shinjuku Center Building, 46th Floor
25-1 Nishi-Shinjuku 1-chome
Shinjuku, Tokyo 163-0646
Japan
(81) 3-5908-0470

Richard de Bodo [rdebodo@hhlaw.com]
HOGAN & HARTSON LLP
1999 Avenue of the Stars, Suite 1400
Los Angeles, CA 90067
(310) 785-4600
Attorneys for Plaintiffs Takeda Pharmaceutical Company Ltd.

William F. Cavanaugh, Jr. [wfcavanaugh@pbwt.com]
Stuart E. Pollack [sepollack@pbwt.com]
Chad J. Peterman [cjpeterman@pbwt.com]
PATTERSON BELKNAP WEBB & TYLER LLP
1133 Avenue of the Americas
New York, NY 10036
(212) 336-2000
Attorneys for Plaintiff TAP Pharmaceutical Products Inc.

YOUNG CONAWAY STARGATT & TAYLOR, LLP

/s/ Karen L. Pascale

Karen L. Pascale (No. 2903) [kpascale@ycst.com]
The Brandywine Building
1000 West Street, 17th Floor
Wilmington, Delaware 19801
(302) 571-6600
Attorneys for Defendants and Counterclaim Plaintiffs, Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.