IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION, NOVARTIS AG, NOVARTIS PHARMA AG, NOVARTIS INTERNATIONAL PHARMACEUTICAL LTD. and LTS LOHMANN THERAPIE-SYSTEME AG, Plaintiffs, v. PAR PHARMACEUTICAL, INC., Defendant.	REDACTED PUBLIC VERSION FILED: MAY 30, 2014 Case No. 1:11-cv-01077-RGA Case No. 1:13-cv-01467-RGA [redacted]

PLAINTIFFS' OPENING POST-TRIAL BRIEF CONCERNING INFRINGEMENT

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I. Introduction

Par seeks FDA approval to market generic rivastigmine transdermal devices that infringe U.S. Patent No. 6,335,031 ("'031 Patent"). Asserted claim 7 of the '031 Patent recites a rivastigmine transdermal device containing an antioxidant. Par's infringement raises only two issues: (1) whether acetaldehyde is an "antioxidant," and (2) whether acetaldehyde will be present in Par's ANDA products in the claimed amount.

As to the first issue, there are two undisputed scientific facts: reducing agents can act as antioxidants, and acetaldehyde is a reducing agent. Dr. Davies confirmed that acetaldehyde is an "antioxidant," *i.e.*, an "agent that reduces oxidative degradation," using a controlled head-to-head stress test. While Par's experts disputed Dr. Davies's test, they conducted no testing to confirm their hypothetical criticisms. Par's experts also repeatedly ignored the Court's claim construction requiring only the *presence* of an "antioxidant," and instead argued that acetaldehyde would not *function* in Par's ANDA products. Par's experts relied on Par's stability tests, but by their own admissions, such tests do not resolve the first issue; Par's stability tests were not controlled head-to-head tests due to batch-to-batch and patch-to-patch variability, and did not show sufficient oxidation to reliably measure any reduction caused by acetaldehyde. Dr. Davies's stress test is the *only* experimental evidence that addressed the first issue and it confirmed the basic science that acetaldehyde is an "agent that reduces oxidative degradation."

As to the second issue, there is no factual dispute that Par's ANDA specification allows up to 0.1% acetaldehyde, which amount falls within the claimed range. Under Federal Circuit precedent, Par infringes that claim element as a matter of law.

II. The Law

In a Hatch-Waxman suit, the infringement analysis is conducted on the product for which the ANDA filer seeks FDA approval. *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731

F.3d 1271, 1278 (Fed. Cir. 2013). When the ANDA specification describes a product "within the scope of a valid patent, it is an infringement as a matter of law." *Id.* at 1278, 1280; *Meds. Co. v. Hospira, Inc.*, No. 09-750-RGA, 2014 WL 1292802, at *4-5 (D. Del. Mar. 31, 2014).

Plaintiffs have the burden of proving infringement by a preponderance of the evidence, *i.e.*, that it is "more likely than not" that the accused products meet the claim limitations. *Adams Respiratory Therap., Inc. v. Perrigo Co.*, 616 F.3d 1283, 1287 (Fed. Cir. 2010); *Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1314 (Fed. Cir. 2011). "A patentee may prove infringement by any method of analysis that is probative of the fact of infringement." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009) (quotation omitted); *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1219 (Fed. Cir. 2006).

III. Par's ANDA Products

Par's ANDA describes three different dosage strength rivastigmine transdermal devices (4.6, 9.5, and 13.3 mg/24 hour), each comprising a backing layer, a release liner, and a drug-in-adhesive layer ("Par's ANDA products"). (PTX 344 at 231; Tr. 65:4-19.) The drug-in-adhesive layer contains the drug rivastigmine, the tackifier isopropyl myristate, and the acrylate copolymer adhesive R-27149, which contains acetaldehyde. (*Id.*) The same infringement analysis applies to all three ANDA products. (*Id.*)

IV. Asserted Claim 7 Of The '031 Patent Is A Presence Claim

The '031 Patent comprises two categories of claims: presence and function claims. Each requires an "antioxidant," but the former category only requires the presence of "about 0.01 to about 0.5 percent by weight of an antioxidant," whereas the latter requires proof of stabilizing rivastigmine in the accused product. (*See, e.g.*, JTX 1 at 8:14-21, 9:10-15.) Claim 7, the only asserted claim, is a presence claim. (Tr. 66:12-67:4, 556:11-557:23; JTX 1 at 8:49-51.)

V. Acetaldehyde Is An "Antioxidant"

The term antioxidant requires the presence of an "agent that reduces oxidative degradation." (D.I. 250.) As a matter of basic chemistry, two scientific facts are undisputed: (1) reducing agents can act as antioxidants by undergoing preferential oxidation thereby protecting another compound from degradation; and (2) acetaldehyde is a known reducing agent. In a controlled head-to-head oxidative stress test, Dr. Davies confirmed that acetaldehyde reduces the oxidative degradation of rivastigmine. Acetaldehyde is therefore an "antioxidant."

A. Acetaldehyde Can Reduce Oxidative Degradation

First, there is no dispute that reducing agents are recognized in the literature and the '031 Patent as antioxidants. (Tr. 264:13-265:20, 496:10-19, 497:18-498:22; JTX 106 at 203.) The EMEA (the European counterpart to the FDA) highlights reducing agents as one class of antioxidants, and Modern Pharmaceutics explains that "some antioxidants, such as ascorbic acid [and] ascrobyl palmitate . . . act as reducing agents." (Tr. 79:7-81:4; JTX 105 at 1/4; JTX 106 at 203.) The antioxidants named in the '031 Patent include the known reducing agents ascorbyl palmitate and ascorbic acid. (Tr. 264:20-265:6, 437:3-22.) Reducing agents by their very nature are susceptible to oxidation and can act as antioxidants by undergoing sacrificial oxidation in preference to the drug or other compound they protect. (Tr. 79:7-81:4, 264:13-265:20, 497:9-498:22; JTX 105 at 1/4; JTX 106 at 203.)

Second, as Dr. Davies showed and Par's organic chemistry expert, Dr. Ganem agreed, the literature recognizes that acetaldehyde "is used as a reducing agent." (Tr. 76:24-77:13, 238:15-16; JTX 61 at 5.) Drs. Ganem and Davies further agreed that aldehydes generally, and acetaldehyde specifically (one of the simplest aldehydes), undergo oxidation in the presence of both oxygen and peroxides. (Tr. 77:15-79:5, 265:21-266:18; JTX 106 at 183.) During cross-examination, Dr. Ganem also acknowledged that "acetaldehyde can be oxidized, so that means . .

. it meets the minimal requirement that it could function as an antioxidant." (Tr. 267:10-18.)

B. Dr. Davies's Controlled Head-To-Head Stress Test Confirmed That Acetaldehyde Reduces Oxidative Degradation

Dr. Davies conducted a controlled head-to-head stress test in an oxidizing environment to confirm that acetaldehyde reduces oxidative degradation. (Tr. 63:5-64:7, 72:8-18, 73:21-75:18.) Stress tests are commonly used in the pharmaceutical industry; they use stress conditions, *e.g.*, an oxidizing environment, to accelerate degradation of a drug substance or drug product so that degradation can be studied in a relatively short time. (Tr. 88:12-18, 90:7-91:16, 396:1-5; JTX 75 at 60; JTX 221 at 141.) A controlled head-to-head test measures the effect caused by changing only one variable, such as the presence of acetaldehyde. (Tr. 73:21-74:16.) By changing only one variable, any difference between samples, such as a reduction in oxidative degradation, can be directly attributed to that one variable, *i.e.*, the presence of acetaldehyde. (*Id.*)

To conduct a controlled head-to-head stress test (PTX 103 at 9), Dr. Davies:

1. Prepared a single stock solution containing 0.36% rivastigmine and 1.3% of the peroxide t-butyl hydroperoxide ("TBHP") in ethyl acetate solvent to eliminate any variability that would result from multiple solutions (Tr. 103:1-105:13, 107:20-22);

2. Divided the stock solution into two identical parts, added 0.0017% acetaldehyde (an amount similar to that reported in some batches of Par's ANDA product) to only one half of the stock solution, and used the other half as a control (Tr. 110:4-111:6);

3. Divided each of the acetaldehyde-containing and control solutions into three samples (Tr. 111:7-18);

4. Stressed the samples at 60°C (Tr. 111:19-22); and

5. Measured the extent of oxidative degradation after 6, 15, and 21 hours by analyzing the samples using high performance liquid chromatography ("HPLC"), a common technique used in the pharmaceutical industry to identify and quantify different compounds of a mixture (Tr. 115:16-116:11, 117:19-119:17).

As shown in the scientific literature, the method used by Dr. Davies falls within the parameters typically used in the pharmaceutical industry for stress tests:

Dr. Davies's Parameters	Acceptable Parameters In Scientific Literature
1.3% TBHP (peroxide) (Tr. 106:21-108:7)	TBHP (JTX 74 at 5:61-65); TBHP (JTX 77 at 1058); 1-3% peroxides (JTX 75 at 67-68); peroxides, *e.g.*, TBHP (JTX 78 at 4)
60°C temperature (Tr. 114:11-115:14)	25°C to >50°C (JTX 75 at 67-68); about 60°C (JTX 74 at 5:61-65); 25°C to 100°C (JTX 77 at 1058; JTX 78 at 4)
21 hours (Tr. 117:5-17)	7.2 hours to 30 days (JTX 77 at 1058); *e.g.*, 1 or 7 days (JTX 75 at 67-68); *e.g.*, 1 to 24 hours (JTX 78 at 4)

In *Alsante*, 95% of pharmaceutical companies surveyed used peroxides in oxidative stress tests. (JTX 75 at 67.) And Dr. Michniak-Kohn admitted that peroxides, including TBHP, are used to "assess oxidative stability." (Tr. 390:19-391:20; JTX 74 at 5:61-65.) Dr. Davies knew that a peroxide would be an appropriate oxidizing agent because it is now known that peroxides cause oxidative degradation of rivastigmine. (Tr. 83:4-10, 85:15-86:10, 106:16-20, 390:14-18; PTX 125 at 33980.)

Dr. Davies also ran preliminary experiments to validate his method. (Tr. 103:21-104:19, 107:20-108:7, 111:23-113:20; JTX 170 at 6-7.) To test whether an agent reduces oxidative degradation, it is necessary to create an oxidizing environment that leads to appreciable oxidative degradation. (Tr. 96:3-21, 607:12-608:11.) Dr. Michniak-Kohn agreed that if the levels of oxidative degradation are too low, the test cannot determine whether an agent, such as acetaldehyde, has a statistically significant effect on oxidative degradation. (Tr. 404:4-18.) Dr. Davies's preliminary experiments demonstrated that 60°C provided sufficient oxidative degradation, but 25°C and 40°C did not. (Tr. 111:23-113:23.) Increasing the temperature did not change the chemistry or mechanism of oxidative degradation—the two key degradation products of rivastigmine, Impurity 4 and ECAV, were formed—it only increased the reaction rate allowing testing in a relatively short time. (Tr. 111:23-112:21.)

Dr. Davies found that, at each time point, the acetaldehyde-containing samples contained ***more*** rivastigmine and approximately 30% ***less*** rivastigmine oxidative degradation products than

the control samples without acetaldehyde. (Tr. 122:24-123:15, 126:3-127:13; JTX 66 at 11-12; PTX 365.) Because the only difference between the acetaldehyde-containing and the control samples was the presence of acetaldehyde, the reduction in oxidative degradation was directly attributable to acetaldehyde. (Tr. 127:24-128:9.) These results confirmed that acetaldehyde is an "antioxidant." (Tr. 127:14-19.)

1. Dr. Davies's Results Are Statistically Significant

Using two independent statistical analyses, Dr. Davies confirmed that acetaldehyde causes a statistically significant reduction in the oxidative degradation of rivastigmine. Dr. Davies's one-tailed T-test with equal variance demonstrated with greater than 95% confidence that acetaldehyde reduces the oxidative degradation of rivastigmine. (Tr. 128:10-129:11.) It is undisputed that a T-test was a proper statistical analysis to apply here. (Tr. 128:10-130:21, 372:8-373:7.) Because acetaldehyde is a known reducing agent, Dr. Davies expected that either acetaldehyde would have no effect or it would reduce the oxidation of rivastigmine; he thus used a *one-tailed* T-test, which is appropriate where the measured difference is expected in one direction. (Tr. 129:21-130:8.) Equal variance was also appropriate because Dr. Davies designed his test to ensure equal variance; he prepared the same number of acetaldehyde-containing and control samples from a single stock solution. (Tr. 133:8-134:11.)

Although "not offer[ed] . . . as a statistics expert, per se" (Tr. 354:13-22), Par relied on Dr. Michniak-Kohn's testimony in an effort to rebut Dr. Davies's statistical analysis. However, Dr. Michniak-Kohn made two improper *post hoc* assumptions. First, she incorrectly assumed that Dr. Davies should have conducted a two-tailed, not a one-tailed, T-test because, notwithstanding that acetaldehyde is a reducing agent, acetaldehyde allegedly could have promoted rather than reduced oxidation. (Tr. 129:12-130:21, 372:8-373:7, 375:8-21.) Even accepting Dr. Michniak-Kohn's flawed assumption, using a two-tailed T-test, Dr. Davies's

results demonstrate that acetaldehyde reduces the oxidative degradation of rivastigmine with greater than 90% confidence, which is statistically significant. (Tr. 132:23-133:7, 398:13-399:15, 411:1-12.) Dr. Michniak-Kohn's opinion that only p-values of 0.05 or better (*i.e.*, a 95% or greater confidence interval) are statistically significant was contradicted by the very textbook she relied on in forming her opinions. (Tr. 376:7-377:15, 398:1-399:15 (typical confidence intervals "are 90, 95 and 99 with 95 being the most common").)

Dr. Michniak-Kohn's second incorrect and unexplained assumption was that unequal variance should apply. (Tr. 133:8-134:19, 396:6-15.) But Dr. Davies designed his experiment to ensure equal variance and confirmed using an F-test that he had equal variance. (Tr. 133:8-134:19.) Ultimately, the combination of Dr. Michniak-Kohn's two flawed approaches resulted in a confidence interval of 87-94% (Tr. 133:8-134:19, 401:3-402:1), meaning the results still demonstrated with at least 87% confidence—a result far above the preponderance threshold needed to show infringement—that acetaldehyde reduces oxidative degradation. *See Adams Respiratory*, 616 F.3d at 1287 ("Requiring a 90% confidence interval [as in the FDA's bioequivalence guidelines] would inappropriately raise the bar for establishing infringement.").

Dr. Davies also used a linear regression analysis to compare the *rates of oxidation* in the presence and absence of acetaldehyde. (Tr. 134:20-135:7.) Using linear regression, Dr. Davies found with greater than 99% confidence that the presence of acetaldehyde reduced the oxidative degradation of rivastigmine; a result that was uncontested at trial. (*Id.*)

2. Dr. Davies's Stress Test Is Reliable And Satisfies The *Daubert* Requirements

Dr. Davies's stress test is based on "good grounds" and is helpful to the Court in determining whether acetaldehyde is an "antioxidant" sufficient to satisfy the *Daubert* requirements. Federal Rule of Evidence 702 embodies three restrictions on expert testimony:

"qualification, reliability and fit." *Schneider ex rel. Estate of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003). There is no dispute that Dr. Davies is a qualified expert on the subjects he testified: pharmaceutical formulations and analytical chemistry of pharmaceutical products. (Tr. 62:8-15.) Thus, Par can only challenge Dr. Davies's testimony under the *Daubert* "reliability" and "fit" prongs.

a. Dr. Davies's Stress Test Is Reliable

The "reliability" prong of *Daubert* requires that expert testimony "be based on the 'methods and procedures of science' rather than on 'subjective belief or unsupported speculation.'" *Schneider*, 320 F.3d at 404 (citations omitted). Expert testimony is reliable if it is based "on the methods and procedures of science," and "[t]he grounds for the expert's opinion merely have to be good, they do not have to be perfect." *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 461 F. Supp. 2d 271, 274-75 (D.N.J. 2006) (quoting *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 745 (3d Cir. 1994)). If the opinion is based on "good grounds," exclusion is not appropriate. *Schneider*, 320 F.3d at 406; *In re Paoli*, 35 F.3d at 741 (Rule 702 mandates a "liberal policy of admissibility"). When determining reliability, the Court should consider:

> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

United States v. Mitchell, 365 F.3d 215, 235 (3d Cir. 2004). Dr. Davies's testing and opinions meet all of the Third Circuit's "*Mitchell* factors" for *Daubert* reliability. *See id.*

First, Dr. Davies had a testable hypothesis that acetaldehyde would reduce the oxidative degradation of rivastigmine. (Tr. 63:5-64:7, 129:12-130:21.) He based that hypothesis on the scientific facts that reducing agents can act as antioxidants and that acetaldehyde is a known

reducing agent. (Tr. 71:11-72:18, 129:12-130:21.) To test his hypothesis, Dr. Davies conducted a controlled head-to-head stress test in an oxidative environment. (*See* Section V.B.)

Second, the type of test that Dr. Davies conducted has been subject to peer review and is routinely conducted in the pharmaceutical industry to assess the stability and compatibility of a drug and excipients, including antioxidants. (Tr. 88:12-18, 90:7-91:16, 97:16-98:17; JTX 75 at 60, 64; JTX 221 at 141.) While Dr. Davies's specific stress test on rivastigmine and acetaldehyde has not been published, the method he employed falls within the parameters that are described in the literature. (*See* Section V.B.) Also, the fact that Dr. Davies's specific stress test has not been described in the literature is irrelevant; "expert testimony does not have to obtain general acceptance or be subject to peer review to be admitted under Rule 702." *Schneider*, 320 F.3d at 406; *see also Astra Aktiebolag v. Andrx Pharms., Inc.*, 222 F. Supp. 2d 423, 489 (S.D.N.Y. 2002) ("[T]he mere fact that an expert's findings have not been peer-reviewed or published is not a sufficient reason to exclude it. Particularly in areas raising issues that may never have interested any scientist, the absence of peer review may not be surprising." (internal citation omitted)).

Third, Dr. Davies eliminated potential errors by conducting his stress test in triplicate and preparing a single stock solution thereby ensuring only one variable—the presence or absence of acetaldehyde. (*See* Section V.B.) Dr. Davies also used the standard technique of HPLC to separate and identify rivastigmine and its two oxidative degradation products using known standards and UV spectroscopy. (Tr. 117:19-121:20.) And he verified the reliability of his results by conducting statistical analyses demonstrating that acetaldehyde caused a statistically significant reduction in the oxidative degradation of rivastigmine. (*See* Section V.B.1.)

Fourth, Dr. Davies utilized proper controls in his stress test. He prepared samples with

and without acetaldehyde; the set without acetaldehyde operated as a negative control and baseline against which Dr. Davies could reliably measure the reduction in degradation by acetaldehyde. (Tr. 88:5-11.) Dr. Ganem's assertion that Dr. Davies should have implemented additional controls (Tr. 247:17-248:2) is unfounded. An additional control using a different antioxidant was not needed because it was already established that antioxidants reduce oxidative degradation caused by peroxides and reduce oxidative degradation of rivastigmine. (Tr. 77:15-78:14, 80:14-81:4, 226:3-227:2; JTX 1 at 1:34-39, 4:20-30.) Modern Pharmaceutics confirms that many oxidation reactions are initiated by peroxides and reducing agents can undergo sacrificial oxidation to reduce such oxidation. (Tr. 77:15-78:14, 80:14-81:2; JTX 106 at 183, 206.) Consistent with the literature, Dr. Davies observed less oxidative degradation in samples containing acetaldehyde. (Tr. 122:24-123:15.) The only possible scientific explanation for the observed reduction in Dr. Davies's controlled head-to-head stress test was the presence of acetaldehyde. (Tr. 126:3-128:9.) Par's experts offered no other explanation. Of course, Par's experts could have repeated Dr. Davies's stress test with the additional controls they alleged were necessary, but none did. (Tr. 267:3-5, 385:4-386:21, 514:12-24.)

Fifth, the type of stress test that Dr. Davies conducted is generally accepted and routinely conducted in the pharmaceutical industry to assess the stability and compatibility of a drug and excipients, including antioxidants. (Tr. 88:12-18, 90:7-91:16, 97:16-98:17; JTX 75 at 60, 64; JTX 221 at 141.) Dr. Michniak-Kohn admitted that stress testing is routine within the pharmaceutical industry. (Tr. 395:15-396:5.) And as Dr. Davies explained, stress testing is a "critical component of drug development" that can aid in "solving . . . stability-related problems" and the design of more stable drug formulations. (Tr. 90:7-91:16; JTX 75 at 60; JTX 221 at 141.) Dr. Davies has previously conducted similar stress tests at the University of Nottingham

and Molecular Profiles including to determine the stabilizing effect of excipients. (Tr. 92:11-93:8.)

Dr. Michniak-Kohn, who acknowledged that the FDA's stability tests are not designed to establish that a compound is an antioxidant (Tr. 393:4-14), contradicted Dr. Buckton's argument that Dr. Davies should have performed FDA stability tests on final transdermal products (Tr. 445:17-446:15). And as Dr. Davies explained, he did not have access to transdermal products made with Par's ingredients that differed only in acetaldehyde content with which to conduct a head-to-head test. (Tr. 140:22-141:19.) Moreover, while some of the testing in the '031 Patent is similar to the FDA's stability tests, the patent also expressly recognized "stress tests" are appropriate and provides one example of a head-to-head stress test conducted at 60°C for two months—conditions which fall outside the confines of the FDA's stability tests. (JTX 1 at 4:20-25; Tr. 425:19-426:9, 441:21-442:18.) Finally, as a legal matter, Plaintiffs "may prove infringement by 'any method of analysis that is probative of the fact of infringement.'" *Martek*, 579 F.3d at 1372; *Liquid Dynamics*, 449 F.3d at 1219.

Sixth, Dr. Davies's use of a stress test to confirm that acetaldehyde is an antioxidant is consistent with the reliable use of stress testing in the pharmaceutical industry. *Alsante* describes the use of stress tests to conduct excipient compatibility studies, which includes studying the effect of an antioxidant on a drug. (Tr. 97:16-98:17; JTX 75 at 60, 64.) *Aubry* states that stress tests may be used to "facilitate . . . drug formulation design," which includes selecting suitable excipients, such as an antioxidant, to solve stability-related problems. (JTX 221 at 141; Tr. 90:22-91:16.) Thus Par's suggestion that there was no literature to support the use of stress tests to evaluate whether a compound is an antioxidant is unfounded. (Tr. 174:8-175:14.)

Likewise, Par's experts are incorrect that stress testing is conducted only on the active

pharmaceutical ingredient alone. (Tr. 395:12-24, 467:8-10, 472:1-8.) The literature repeatedly states that stress testing is conducted on both the drug substance and the drug product with excipients. (*See, e.g.*, Tr. 90:22-91:16 (citing JTX 221 at 141), 93:22-95:2 (citing JTX 75 at 67).) And Dr. Buckton admitted that formulators use "stress test[s] to see whether the excipient itself causes any degradation of the drug substance." (Tr. 477:14-23.) In addition, stress testing is conducted both in early stages of development and on the "drug product . . . as the final commercial formulation is developed." (JTX 75 at 62.)

Dr. Michniak-Kohn stated that oxidative stress testing is routinely conducted, but there is no single set of conditions for such testing. (Tr. 395:5-396:5.) As Dr. Buckton recognized, this variation exists because "[t]he detailed nature of the studies will depend on the individual drug substance and type of drug product." (Tr. 469:3-6; DTX 591 at 13.) Dr. Davies's stress test was necessarily specific to rivastigmine; for example, Dr. Davies used a peroxide as the oxidizing agent because he knew peroxides oxidatively degrade rivastigmine. (Tr. 85:24-86:10, 106:16-20.) Dr. Davies also knew that rivastigmine could undergo hydrolysis (degradation caused by water), so he selected a peroxide and solvent that were free from water to avoid hydrolysis. (Tr. 104:20-106:20, 108:8-19.) Specificity to the issues of this case is entirely acceptable within the *Daubert* framework because "[s]ome propositions . . . are too particular, too new, or of too limited interest to be published." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 593 (1993). Thus, Drs. Michniak-Kohn and Buckton's assertions that stress testing is "non-standardized" is irrelevant to its reliability. (Tr. 393:4-14, 395:12-24, 470:20-471:14.)

Dr. Buckton's further allegation that Dr. Davies's stress test is unreliable because it may demonstrate a "degradation process . . . which wouldn't actually happen" (Tr. 478:6-19) is also unfounded. Dr. Buckton's only literature support for this assertion was the FDA guidelines,

which caution that "under forcing conditions decomposition products may be observed which are unlikely to be formed under accelerated or long-term testing." (Tr. 516:3-517:16.) Such concerns are not applicable here. Dr. Davies observed the two known rivastigmine oxidative degradation products Impurity 4 and ECAV. (Tr. 121:4-122:23.) Dr. Buckton admitted that these are the same degradation products observed in Par's stability testing of its ANDA products. (Tr. 518:19-22.) Dr. Davies also found that rivastigmine and its two oxidative degradation products accounted for over 99% of the overall mass balance in his test samples. (Tr. 121:21-122:23.) And neither Dr. Buckton nor Dr. Ganem explained what other degradation products of rivastigmine, if any, allegedly formed in Dr. Davies's stress test. (Tr. 279:2-18, 517:17-518:18.) Thus, there is no credible dispute that Dr. Davies's stress test caused the same oxidative degradation products of rivastigmine observed in Par's ANDA products.

Seventh, Dr. Davies is well qualified in the field of pharmaceutical stress testing and routinely conducts stress tests as part of his work. (Tr. 92:11-24; *see* PTX 50A.) Even Dr. Buckton acknowledged that he respects Dr. Davies as a scientist and Dr. Davies is highly thought of by the scientific community. (Tr. 513:18-514:3.)

Lastly, as explained above, stress testing is regularly used in the pharmaceutical industry for nonjudicial uses, including solving stability-related problems, designing more stable drug formulations, and determining excipient compatibility. In a survey of 20 pharmaceutical companies, 19 reported conducting oxidative stress tests on the drug, 13 reported conducting oxidative stress tests on the drug product, and 17 reported conducting stress tests to determine excipient compatibility. (Tr. 93:22-95:2, 97:16-98:17; JTX 75 at 64, 67.)

In sum, Dr. Davies's testing is based on good grounds and is admissible under *Daubert*.

b. Dr. Davies' Stress Test Is Helpful To The Trier Of Fact

Expert testimony meets the "fit" requirement under Rule 702 if it is "helpful to the trier

of fact," and courts "interpret the helpfulness standard broadly." *Am. Tech. Res. v. United States*, 893 F.2d 651, 655 (3d Cir. 1990); *Pfizer Inc. v. Mylan Labs., Inc.*, No. 02-cv-1628, 2006 WL 3354479, at *4 (W.D. Pa. Nov. 17, 2006). Dr. Davies's controlled head-to-head stress test meets the "fit" requirement under *Daubert* because it was specifically designed to address whether acetaldehyde is an "antioxidant" and it showed that acetaldehyde caused a statistically significant reduction in the oxidative degradation of rivastigmine. Dr. Davies's stress test therefore is admissible under *Daubert* because it is helpful to the Court.

3. Dr. Ganem's Criticisms Of Dr. Davies's Test Are Pure Speculation

Dr. Ganem's concerns regarding Dr. Davies's stress test are pure speculation that do not change the reality that Dr. Davies demonstrated that acetaldehyde reduces the oxidative degradation of rivastigmine. Dr. Ganem testified regarding three hypothetical concerns: (1) the potential for TBHP side reactions generating unknown components, (2) the co-elution of such hypothetical components, and (3) the normalization of the results hiding alleged errors. (Tr. 248:3-20.) Dr. Ganem's concerns ignore that Dr. Davies designed his test to eliminate variables other than acetaldehyde that could potentially affect the results. (Tr. 73:21-74:16.)

First, it is undisputed that TBHP causes the oxidation of rivastigmine. (Tr. 244:23-245:24.) Dr. Ganem readily admitted that the "dominant process" in Dr. Davies's stress test was TBHP's "direct oxidation" of rivastigmine into its two degradation products. (*Id.*) Dr. Ganem also never disputed that Impurity 4 and ECAV are the two prominent impurity peaks in Dr. Davies's stress test chromatograms. (Tr. 258:2-8, 262:19-264:12.) And Dr. Ganem provided no support for the hypothetical components that he alleged "***might*** be generated by side reactions with TBHP." (Tr. 244:23-245:24, 248:8-16, 253:9-254:1, 255:12-256:12 (emphasis added).) Nor did he conduct any testing to identify any of these hypothetical components. (Tr. 276:8-12, 279:2-18.) While Dr. Ganem speculated that the hypothetical side reactions "could" account for

20 percent of the degradation products, he never explained how he arrived at his figure. (Tr. 121:21-122:23, 255:12-256:19.) And it is contradicted by Dr. Davies's mass balance analysis showing that rivastigmine, Impurity 4, and ECAV accounted for over 99% of the compounds present in the test samples. (Tr. 121:21-122:23.)

Second, Dr. Ganem's concern that hypothetical side-reaction components could co-elute with Impurity 4 and ECAV is baseless because all test samples were *identical* except for acetaldehyde, and thus any side reactions would occur uniformly across *all* test samples. (Tr. 73:21-74:16, 103:8-20, 256:6-12.)[1] Dr. Davies prepared all the test samples from a single stock solution thereby ensuring the samples differed in only one way: the presence of acetaldehyde. (Tr. 73:21-74:16, 103:8-20.) Thus even if hypothetical side-reaction components co-eluted, they would not affect the *relative* differences in oxidative degradation between the control and acetaldehyde-containing samples—such a difference can only be attributed to acetaldehyde. (*Id*.)

Third, Dr. Ganem's criticism about Dr. Davies's normalization technique is meritless. (*See* Tr. 122:2-23, 126:3-127:19, 248:3-20.) Dr. Davies found that the oxidation reaction accounted for over 99% of compounds in the samples and normalized the data to compare the relative differences in oxidative degradation with and without acetaldehyde. (Tr. 122:2-23, 126:3-127:19; JTX 66 at 8-9.) Dr. Ganem identified the A3 test sample taken after 21 hours as the only alleged normalization error (Tr. 259:11-260:20), but this sample in fact demonstrates why it is helpful to normalize the data. As Dr. Davies explained, in this sample some sample

[1] Moreover, the very point of running an HPLC is to separate each compound such that it exits the column at a unique time allowing accurate identification. (Tr. 118:3-119:17.)

evaporated[2] causing the amount of rivastigmine (as well as its degradation products) to appear to increase. (Tr. 198:21-200:17.) After measuring that sample in triplicate to ensure accuracy, Dr. Davies normalized the results and was therefore able to determine that the relative amounts of rivastigmine and its oxidative degradation products were consistent with the other test samples and that the reduction in oxidative degradation was statistically significant. (*Id.*)

Finally, contrary to Dr. Ganem's assertion, the oxidation of acetaldehyde will not promote further oxidation. Oxidation of acetaldehyde can result in the formation of acetic acid (also referred to as the "normal" or "carboxylic" acid). (Tr. 132:1-17, 245:8-11, 275:17-19.) Acetic acid is not a free radical (Tr. 276:4-7) and does not cause the oxidation of rivastigmine, as demonstrated by Dr. Davies's controlled head-to-head stress test. (Tr. 131:3-132:17, 161:17-162:3; *see also* Tr. 276:8-277:3.) Dr. Ganem conceded that oxidation of acetaldehyde by TBHP can form acetic acid, yet he arbitrarily drew a distinction between the oxidation of acetaldehyde by oxygen versus peroxides. (*See* Tr. 240:20-241:3, 244:7-245:11.) Dr. Ganem alleged that, when oxidized by oxygen, acetaldehyde "can" form "a variety of reactive chemical radicals" that could cause oxidation. (Tr. 240:20-241:3; *see also* Tr. 237:6-16.) His sole support was *McNesby*. (Tr. 131:24-132:17, 265:24-266:8; JTX 86.) But the one study in *McNesby* on *acetaldehyde* showed that the chemical radicals and peracids were only "stable at minus 30 degrees centigrade and decomposed to [acetic acid] on heating." (Tr. 132:1-17; JTX 86 at 328.) *McNesby* thus teaches that free radicals from *acetaldehyde* only exist at extremely low temperatures and would not exist at room temperature or higher. (Tr. 132:1-17; JTX 86 at 328.) Dr. Ganem cited no other literature or testing for his opinion that "these radicals could occur at

[2] As Dr. Davies explained, the boiling point of the test samples was between the boiling points of pure acetaldehyde and pure ethyl acetate (the solvent) meaning that while the solution may evaporate, acetaldehyde was not preferentially removed and remained in solution during the test. (Tr. 228:2-18.)

room temperature." (Tr. 242:14-243:1, 265:24-266:8, 267:3-5, 276:4-277:3.) Indeed, neither Dr. Ganem nor Par's other experts ran any tests to validate any alleged flaws in Dr. Davies's test. (Tr. 267:3-5, 385:4-386:21, 514:12-15.) The Federal Circuit has considered a defendant's failure to conduct testing relevant in weighing the evidence of infringement. *See Electro Med. Sys., S.A. v. Cooper Life Scis., Inc.*, 34 F.3d 1048, 1055 (Fed. Cir. 1994); *In re Omeprazole Patent Litig.*, 84 Fed. Appx. 76, 82 (Fed. Cir. 2003) (infringer's failure to perform tests, present data or expert rebuttal testimony supported finding of infringement).

C. Par's Experts Ignored The Claim Construction Of "Antioxidant"

Drs. Buckton and Michniak-Kohn cited various reasons why they believed acetaldehyde is not an antioxidant, each of which ignores the Court's claim construction.

1. The Term "Antioxidant" Is Not Limited To Antioxidants Named In The '031 Patent Or Previously Used In Pharmaceuticals

Dr. Buckton's first argument that acetaldehyde is not an "antioxidant" because it is not named in the '031 Patent is irrelevant and contrary to the Court's construction. (Tr. 436:23-437:2; 540:17-542:4.) Dr. Buckton cited one passage in the '031 Patent that states stabilization "is surprisingly achieved when the antioxidant is selected from" the named antioxidants. (Tr. 436:23-437:16, 530:22-531:17; JTX 1 at 4:10-19.) He ignored that "[i]n one aspect, the invention provides a pharmaceutical composition comprising [rivastigmine] and an anti-oxidant" in general. (Tr. 543:3-15, 558:19-560:7; JTX 1 at 1:34-36.) Dr. Klibanov explained that a POSA[3] in January 1998 would have understood that there are many antioxidants and the '031 Patent does not attempt to list them all. (Tr. 560:9-561:7.) Indeed, Dr. Buckton admitted that pharmaceutical references, including Modern Pharmaceutics and the Handbook of Pharmaceutical Excipients ("HPE"), include known antioxidants that are not listed in the '031

[3] Dr. Klibanov's definition of a POSA (Tr. 555:13-556:8) was not disputed by Par's experts.

Patent. (Tr. 438:16-23, 542:5-543:2; *compare* DTX 505 at 857 *and* JTX 106 at 203 *with* JTX 1 at 4:10-19.) A POSA would thus understand that "antioxidant" is not limited to those named in the '031 Patent. (Tr. 560:9-561:10, 565:17-566:1.)

The '023 Patent[4] further confirms that the term "antioxidant" is not limited to those named in the specification. Independent claim 1 of the '023 Patent uses the general term "antioxidant," whereas dependent claims 2 and 3 recite *all* the antioxidants named in the patent specification. (Tr. 561:12-562:9; JTX 2 at 8:17-30.) Because independent claim 1 is presumed to be broader than dependent claims 2 and 3, the claim term "antioxidant" must be broader than the antioxidants listed in the specification or claims 2 and 3 of the '023 Patent. *Abbott Labs. v. Andrx Pharms., Inc.*, 473 F.3d 1196, 1209 (Fed. Cir. 2007). (Tr. 561:12-562:22.)

Dr. Buckton's second argument that acetaldehyde is not an "antioxidant" because it is not listed in the pharmaceutical literature as an antioxidant or as an excipient is also incorrect. (Tr. 437:23-438:4.) During claim construction, the Court rejected Par's proposed construction that an "antioxidant" must be a "pharmaceutically acceptable" ingredient. (*Compare* D.I. 250 at 1 *with* D.I. 224 at 17-18, 34.) Regardless, Par established that acetaldehyde is safe in its ANDA products at levels up to 1000 ppm or 0.1%. (Tr. 64:8-65:2; PTX 348 at 780; PTX 349 at 788; PTX 350 at 796; JTX 65 at 722.) Furthermore, the Specialty Chemicals Source Book states that acetaldehyde has been used in pharmaceuticals and in the manufacture of pharmaceuticals, and is generally recognized as safe. (Tr. 81:9-24; JTX 63 at 7.) Dr. Buckton's reliance on only the FDA inactive ingredient list and HPE is unduly restrictive because some antioxidants, *e.g.*, acetone sodium bisulfite and thioglycolic acid, recognized in Modern Pharmaceutics are not

[4] U.S. Patent No. 6,316,023 ("'023 Patent") is a continuation of the '031 Patent and shares the same specification; therefore it must be construed the same way. (D.I. 224 at 1-2.) *See NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005).

listed in the HPE. (Tr. 438:16-440:8; *compare* DTX 505 at 857 *with* JTX 106 at 203.)

Dr. Buckton's third argument that acetaldehyde is not an "antioxidant" because it has never been used or recognized as an antioxidant is incorrect too. (Tr. 439:9-14.) It is well known that reducing agents can be antioxidants. (*See* Section V.A.) And as Dr. Ganem admitted and Van Nostrand's Concise Encyclopedia of Science confirms, acetaldehyde "is used as a reducing agent" and thus "meets the minimal requirement that it could function as an antioxidant." (Tr. 76:24-77:6, 238:15-16, 266:19-267:18; JTX 61 at 5.) Dr. Buckton was also cross-examined on Chinese Patent No. ZL 92108440.4, which states that acetaldehyde is an antioxidant used to prevent degradation caused by the presence of oxygen. (Tr. 501:9-11, 503:8-20.)

2. The Term "Antioxidant" Does Not Require Proof That Acetaldehyde Functions In Par's ANDA Products

The Court has twice construed "antioxidant" in the '031 Patent to require only the presence of an "agent that reduces oxidative degradation." (D.I. 250 at 1; *Novartis Pharms. Corp. v. Alvogen Pine Brook, Inc.*, No. 13-cv-52-RGA (D. Del. Apr. 7, 2014) (D.I. 147).) Par agreed throughout the claim construction proceedings that an "antioxidant" reduces oxidative degradation but maintained that "antioxidant" also requires proof of function in the accused product. (D.I. 224 at 9, 34; D.I. 244 at 43:1-25.) The Court found it would be "improper to impute the antioxidant's stabilizing effect on [rivastigmine], explicitly claimed in some claims, into claims that do not contain that explicit limitation." (D.I. 250 at 2.) Claim 7 nowhere mentions "stabilizing" rivastigmine; rather, it is a presence claim and does not require proof of antioxidant function in Par's ANDA products. (JTX 1 at 8:14-21, 49-51; Tr. 557:16-23.)

Drs. Michniak-Kohn and Buckton, however, ignored the Court's claim construction and imputed a functional requirement into claim 7. In fact, Dr. Michniak-Kohn was not even aware

that claim 7 requires only the presence of an antioxidant and admitted that much of her testimony addressed whether acetaldehyde functioned in Par's ANDA products. (Tr. 386:22-388:7.) Dr. Buckton likewise testified that there was no infringement "because there is no material ***in Par's ANDA product*** that's ***functioning*** as an antioxidant." (Tr. 462:2-12 (emphasis added); *see also* Tr. 453:20-454:3.) Hence, Drs. Michniak-Kohn and Buckton's testimony is largely irrelevant.

For example, Dr. Michniak-Kohn argued that the reaction kinetics and the use of the peroxide TBHP in Dr. Davies's stress test do not model the conditions in Par's ANDA products. (Tr. 359:9-360:7; 365:22-366:9.) But reaction kinetics relate to how well acetaldehyde would function in Par's ANDA Products, not whether acetaldehyde is an antioxidant. (*See* Tr. 386:22-387:2.) And while Dr. Michniak-Kohn opined that Par's ANDA products are "substantially free of hydroperoxides" (Tr. 369:16-370:24), she admitted that even when a composition is substantially free of peroxides, adding an antioxidant may still improve stability. (Tr. 388:23-390:8; JTX 74 at 7:8-13.) Dr. Davies further explained that he simply used a peroxide to create an oxidizing environment, and whether oxygen or peroxides cause oxidative degradation of rivastigmine is immaterial because the degradation pathway is the same. (Tr. 82:13-83:24, 87:6-88:18, 105:1-13.) Dr. Davies's stress test did not change the chemistry, it merely accelerated the degradation and demonstrated that acetaldehyde is preferentially oxidized over rivastigmine. (*Id*.) The amount of peroxide in Par's ANDA products versus Dr. Davies's stress test thus relates only to acetaldehyde's function in Par's ANDA products and is irrelevant to infringement. Dr. Buckton's assertion that one cannot extrapolate from Dr. Davies's stress test to Par's ANDA products (Tr. 480:9-16) is irrelevant for the same reason.

Likewise, the deposition testimony that Par relied on is irrelevant because it relates to whether an antioxidant would have a sufficient stabilizing effect in a particular product. Dr.

Buckton relied on testimony from Dr. Joerg Ogorka to assert that the antioxidant ascorbyl palmitate did not work. (Tr. 485:20-486:12.) But Dr. Ogorka's testimony concerned whether ascorbyl palmitate was suitable for Plaintiffs' Exelon® Patch.[5] (Tr. 338:21-339:2.) Dr. Harry Tiemessen's testimony likewise concerned whether antioxidants listed in the '031 Patent "can be added to a formulation to ***stabilize that formulation***." (Tr. 327:5-14 (emphasis added).) Lastly, as Dr. Buckton admitted, Dr. Frank Theobald's testimony concerned whether an antioxidant is effective in a particular formulation. (Tr. 332:1-8, 511:7-20.) None of the deposition testimony related to the question of whether acetaldehyde is an antioxidant.

3. Par's Stability Testing Does Not Determine Whether Acetaldehyde Is An "Antioxidant"

Dr. Buckton's final argument that Par's stability data show that acetaldehyde is not an antioxidant (Tr. 440:9-14) is wrong by his own admission. Dr. Buckton admitted, as did Dr. Michniak-Kohn, that Par did not set up its stability tests to determine whether acetaldehyde is an antioxidant. (Tr. 393:15-395:3, 458:2-8.) Instead, Par's stability studies only address whether Par's ANDA products remain within stability specifications during the product's shelf-life. (Tr. 394:9-395:3, 506:9-21.)

Moreover, Par's stability testing lacked sufficient controls to determine whether acetaldehyde is an antioxidant. (Tr. 143:1-22.) To test whether acetaldehyde reduces oxidative degradation, it is important to conduct a controlled head-to-head study in which there is only one variable—acetaldehyde. (Tr. 73:21-74:16, 143:1-22, 280:14-284:14.) Par made each batch of its ANDA products, however, with different lots of components. (Tr. 143:1-145:17; PTX 364.)

[5] Dr. Buckton's assertion that Plaintiffs' testing with ascorbyl palmitate shows that antioxidants are formulation specific (Tr. 480:17-22, 483:4-485:12) is irrelevant as well because it ignores the Court's claim construction and imports function in the accused product into the claim term "antioxidant." Nonetheless, Dr. Klibanov showed that ascorbyl palmitate did reduce oxidative degradation, albeit to a lesser extent than tocopherol. (Tr. 568:17-572:14; JTX 182 at 24880.)

Such batch-to-batch differences introduce additional variables that can influence the stability data.[6] (Tr. 143:1-145:12, 146:6-17, 147:7-23.) Thus, there are no two batches of Par's ANDA products that differ only in the presence of acetaldehyde on which to conduct a proper head-to-head analysis to determine whether acetaldehyde is an antioxidant. (Tr. 143:1-22.)

Par's stability testing also is unreliable because Par tests *one patch* among thousands per batch to determine oxidative degradation at a given time point. (Tr. 148:1-150:3, 520:6-521:13; *e.g.* PTX 350 at 794.) As Dr. Michniak-Kohn admitted, testing on one patch is not "good statistics" and she "would [not] be making conclusions" from that data. (Tr. 405:15-408:14.) This is because such testing fails to account for patch-to-patch variability, as Dr. Davies illustrated by comparing Par's ANDA batch Nos. 110110 and 110177. (Tr. 148:1-150:3; *see also* Tr. 406:22-407:8.) Both of these batches comprise a drug-in-adhesive layer made from the same lots of excipients.[7] (Tr. 148:1-150:3; PTX 364.) Thus, the two batches should display similar stability results, yet after six months at 40°C batch 110177 showed 0.4% oxidation degradation while lot 110110 showed <0.1%. (Tr. 148:1-150:3; JTX 200 at 9357, 9355; DTX 586B.) This difference demonstrates why conclusions regarding the batch as a whole cannot be drawn from testing only a single patch and Par's stability data cannot be used to determine whether acetaldehyde is an antioxidant. (Tr. 148:1-150:3.)

Additionally, as Par's experts agreed, Par's stability studies failed to display sufficient oxidative degradation to demonstrate one way or another that acetaldehyde reduces the oxidative degradation of rivastigmine. (Tr. 404:2-18, 521:14-522:2, 527:1-15.) Dr. Buckton admitted that in Par's stability data there was "no meaningful evidence of oxidative degradation," so it was not

[6] The FDA encourages such variation during stability tests, but that is to see how it may affect the quality of the drug product during storage. (Tr. 459:1-21; DTX 591 at 6.)

[7] Lot Nos. 110110 and 110177 differ in lot numbers for the release liner and pouching material. (Tr. 148:1-150:3; PTX 364.)

possible to test whether acetaldehyde reduced oxidative degradation. (Tr. 451:15-21, 527:1-15.) And Drs. Klibanov and Davies explained to ascertain whether an agent reduces oxidation one needs to have a sufficiently oxidizing environment such that the oxidative degradation without an antioxidant is significant. (Tr. 96:3-21, 607:12-608:11.) In contrast to Par's stability tests, Dr. Davies's stress test obtained sufficient levels of oxidative degradation to make a proper comparison and confirm that acetaldehyde reduces oxidation.

Last, Par's experts did not conduct any statistical analysis of Par's stability data (Tr. 404:4-18, 521:14-522:2, 525:19-527:15), despite Dr. Michniak-Kohn's assertion that one needs to conduct "a proper statistical analysis of the data before you make any conclusions." (Tr. 372:8-22.) Given the batch-to-batch and patch-to patch variability, insufficient oxidative degradation, and lack of statistical analysis, Par's stability tests do not demonstrate whether or not acetaldehyde is an antioxidant. (Tr. 143:1-22, 146:6-17, 147:7-150:3.)

VI. Par's ANDA Products Contain "About 0.01 To About 0.5 Percent By Weight" Acetaldehyde

Par concedes that its ANDA specification for each dosage strength allows up to 0.1% of acetaldehyde. (D.I. 374-3 at ¶ 43; Tr. 64:8-65:2, 69:23-71:9; PTX 348 at 780; PTX 349 at 788; PTX 350 at 796.) Par's ANDA specification thus permits its products to contain 0.01 to 0.1% acetaldehyde and defines a product that falls squarely within the claimed range. (Tr. 151:14-152:10.) [redacted] And none of Par's experts disputed that Par's ANDA specification permits its products to contain up to 0.1%

acetaldehyde. Under *Sunovion*, a finding of infringement of the amount limitation must necessarily ensue. *See Sunovion*, 731 F.3d at 1278.

Dr. Buckton's reliance on batches of ANDA products containing amounts of acetaldehyde up to 30 ppm is also unavailing. (Tr. 446:21-448:22.) In *Sunovion*, the Federal Circuit found that the ANDA filer's "internal manufacturing guidelines" and certification to the district court that it would *only* produce products containing amounts of impurity outside the claimed range was misplaced. *Sunovion*, 731 F.3d at 1278. Rather, the ANDA specification, which permitted amounts of impurity within the claimed range, "mandate[d] a finding of infringement." *Id.* at 1278, 1280. As in *Sunovion*, Par's ANDA specification mandates a finding of infringement of the amount limitation because Par's ANDA specification allows 0.01 to 0.1% acetaldehyde—amounts within the claimed range. (Tr. 151:14-152:17.)

If Par did not intend to sell products containing between 0.01 and 0.1% acetaldehyde, Par "should not have requested . . . approval to market a product within the scope of the claim." *See Sunovion*, 731 F.3d at 1279. And if Par truly believed that it would not manufacture or sell products containing between 0.01 and 0.1% acetaldehyde, Par could have amended its ANDA specification accordingly but Par has not. *See id.* at 1280 ("Simply saying 'But I won't do it' is not enough to avoid infringement.").

Par's reliance on *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562 (Fed. Cir. 1997), is misplaced. The drug at issue in *Glaxo* existed in two different crystalline forms: Forms 1 and 2. *Id.* at 1564. The patent at issue claimed Form 2 as defined by a specific set of 29 peaks on an infrared ("IR") spectrum, whereas, the ANDA applicant sought FDA approval for Form 1 with 90% purity. *Id.* The ANDA specification revealed the presence of one impurity with one of the claimed IR peaks, and the plaintiff argued that this indicated Form 2 was present in the ANDA

product. *Id.* at 1566. The Federal Circuit disagreed finding that "the single peak analyzed was not sufficient to substitute for the claimed 29-peak spectrum." *Id.* The Federal Circuit thus "endorsed the district court's reference to evidence including biobatch data and actual samples of the generic composition . . . as relevant to the infringement inquiry because the ANDA specification itself did not resolve the question of infringement in the first instance." *Sunovion*, 731 F.3d at 1279-80 (citing *Glaxo*, 110 F.3d 1562). Here, it does.

The present dispute, just as in *Sunovion*, simply requires a comparison of the numerical ranges in claim 7 of the '031 Patent and Par's ANDA specification.[8] Par's ANDA specification alone resolves infringement of this limitation in the first instance because it describes a product that contains acetaldehyde in the claimed range "about 0.01 to about 0.5 percent by weight."

VII. Par's ANDA Products Meet The Undisputed Claim Elements

Par does not dispute infringement of the remaining elements of claim 7: (a) transdermal device (Tr. 156:1-9; PTX 343 at 170), (b) pharmaceutical composition (Tr. 65:4-19, 156:21-157:6; PTX 343 at 171; PTX 344 at 231), (c) therapeutically effective amount of rivastigmine (Tr. 157:7-15; PTX 343 at 170), (d) diluent or carrier (Tr. 65:4-19, 157:16-158:6; PTX 344 at 231, 245), and (e) supported by a substrate (Tr. 65:4-19, 158:7-17; PTX 344 at 231).

VIII. Conclusion

For the reasons discussed above, Par infringes claim 7 of the '031 Patent. Plaintiffs respectfully request that judgment of infringement be awarded in their favor and the Court issue a permanent injunction restraining Par from manufacturing its ANDA products until the expiration of the '031 Patent, and any additional relief the Court deems just and proper.

[8] *See Ferring B.V. v. Apotex, Inc.*, No. 3:13-cv-595-RCJ-VPC, 2014 WL 1379758, at *4 (D. Nev. Apr. 7, 2014) (citing *Sunovion*, 731 F.3d at 1279) ("Here we have a simple matter of comparing mathematical ranges . . . under the Patents and the ANDA. Under *Sunovion*, a district court need not conduct a *Glaxo* inquiry if it is clear that the ANDA permits infringement.").

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