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.	C.A. No. 11-1077-RGA C.A. No. 13-1467-RGA

PAR PHARMACEUTICAL, INC.'S
REPLY POST-TRIAL BRIEF ON INVALIDITY

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Par	Defendant Par Pharmaceutical, Inc.
Plaintiffs	Plaintiffs Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd., and LTS Lohmann Therapie-Systeme AG
Novartis	Plaintiffs Novartis Pharmaceuticals Corporation, Novartis AG, Novartis Pharma AG, Novartis International Pharmaceutical Ltd.
LTS	Plaintiff LTS Lohmann Therapie-Systeme AG
'031 patent	U.S. Patent No. 6,335,031
ANDA	Abbreviated New Drug Application
FDA	Food and Drug Administration
PTX	Plaintiffs' admitted trial exhibit
DTX	Defendant's admitted trial exhibit
JTX	Joint admitted trial exhibit
Tr. __:__	The corresponding page and line of the trial transcript, May 1-2, 2014 (D.I. 398, 399)

Note: All emphases added throughout unless otherwise indicated.

I. INTRODUCTION

The public is entitled to know with reasonable certainty whether their products are inside or outside Claim 7, by reading the patent specification—not by having to consult with Plaintiffs or Dr. Davies. Par, a member of the public, did the standard test specified in the '031 patent specification to evaluate antioxidant behavior, and that test showed that acetaldehyde does not reduce oxidative degradation. Allowing Plaintiffs to override those test results with Dr. Davies' litigation-specific test would violate the reasonable certainty requirement of § 112.

As Plaintiffs would have it, any ingredient, impurity, or degradant in a product in minute quantities might ultimately turn out to be an antioxidant, if Plaintiffs and Dr. Davies can eventually devise the right test. Plaintiffs do not even try to explain how Par, a member of the public, would supposedly single out one compound (*e.g.*, acetaldehyde) from all the ingredients, impurities, and degradants in its product, then arrive at Dr. Davies' arbitrary testing conditions out of all the possible permutations in the references on which he relies. Nor do they explain why Par would even use the type of test Dr. Davies conducted, after the test in the '031 patent specification showed that none of the ingredients was an antioxidant, when it has never been described for identifying antioxidant behavior. Dr. Davies used extreme conditions and failed to include controls to confirm that his test could even detect antioxidant behavior. Without those controls, Plaintiffs have no idea how many compounds would test "positive" in Dr. Davies' study, nor how a "positive" result would translate to a pharmaceutical composition. If Dr. Davies' forced degradation study is sufficient to pronounce a compound to be an antioxidant under Claim 7, then an infinite number of alternative tests could be run, with no limits to what might be ensnared by the claim.

For infringement, Plaintiffs attempted to go well beyond a reasonable reading of the Court's construction of "antioxidant," to encompass any compound that has ever produced lower

oxidation of any other compound, in any single instance, using any testing conditions, with no evidence that those conditions are relevant to pharmaceutical formulations, and regardless of what the predominant properties of the purported antioxidant are. Plaintiffs' position is incompatible with controlling precedent under 35 U.S.C. § 112.

"It is axiomatic that claims are construed the same way for both invalidity and infringement." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1330 (Fed. Cir. 2003). When "antioxidant" in Claim 7 is given the same turgid scope that Plaintiffs insist on in their infringement analysis, the claim fails to meet the definiteness, enablement and written description requirements. Plaintiffs argue that the written description and enablement requirements are met because the '031 patent describes and enables a ***single*** example of a rivastigmine transdermal device using tocopherol as the antioxidant. But binding precedent requires that the ***full scope*** of the invention be described, enabled, and conveyed with reasonable certainty. In prevailing on non-obviousness of the '031 patent, Plaintiffs successfully argued that a person of ordinary skill would not have been motivated to use an antioxidant with rivastigmine, because the "compatibility of an excipient with a given pharmaceutical formulation cannot be predicted without experimentation because of the numerous possible chemical reactions." D.I. 414 at 33. Given that unpredictability, Plaintiffs cannot now contend that the single example in the patent describes and enables the vast number of potential compounds that heretofore are not known to be antioxidants, but might test "positive" in one of an infinite number of possible tests, like the forced degradation study Dr. Davies conducted.

II. PLAINTIFFS' INFRINGEMENT POSITION RENDERS CLAIM 7 INVALID UNDER 35 U.S.C. § 112

A. As Asserted by Plaintiffs, Claim 7 Is Indefinite

Plaintiffs, in their briefing, do not address the fundamental question of whether a person

of ordinary skill would understand the term "antioxidant" with reasonable certainty ***in light of their infringement positions***. *See Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014). The "presumption of validity does not alter the degree of clarity that § 112, ¶ 2 demands from patent applicants." *Id.* at 2130 n.10. Because Plaintiffs' asserted claim scope does not "appris[e] the public of what is still open to them" and creates a "zone of uncertainty" as to whether a compound falls inside or outside of the claims (*see id.* at 2129), Claim 7 is indefinite.

1. A Person of Ordinary Skill in the Art Would Not Understand What Is or Is Not an "Antioxidant" With Reasonable Certainty

Plaintiffs assert that Claim 7 is definite because antioxidants are "well-known in the pharmaceutical industry," and it would be routine to determine whether a compound reduces oxidative degradation using the teachings in the '031 patent. D.I. 409 at 14-16. But Par did the routine, standard test described in the patent. Plaintiffs had to resort to a non-standard, litigation-driven test (a forced degradation study[1]) described nowhere in the patent. Nor does the literature provide any reference to, much less standards for, using a forced degradation study to determine antioxidant behavior. *See* D.I. 403 at 9 (admitting that Dr. Davies' test "has not been described in the literature"); Tr. 215:11-221:7 (Davies). The term "antioxidant" has no defined bounds under Plaintiffs' infringement positions. D.I. 401 at Section II.A. Plaintiffs have provided no standard for the public to determine whether a compound falls outside of the claim. Even if a compound enhances or has no effect on oxidative degradation in the vast majority of circumstances, it would become an antioxidant if Plaintiffs can contrive a single instance where

[1] Plaintiffs' newfound assertion that the patent discloses "stress ***or*** stability tests" (D.I. 409 at 15, 17) is incorrect. The '031 patent describes "standard" stress tests, which refer to a single category of "stress stability tests" on a pharmaceutical formulation—not separate "stress tests" and "stability tests." JTX 001 at 1:29-39; Tr. 175:23-176:14 (Davies); 440:9-443:14 (Buckton); 592:4-12 (Klibanov). Dr. Davies did not conduct such a stress stability test, or any standard test.

it reduces oxidative degradation of any other compound under any condition.

2. Different Testing Results in Different Outcomes

Plaintiffs argue that the multiple different tests it asserts can show antioxidant behavior would not produce significantly different results. D.I. 409 at 17. But that position is contradicted by (1) Par's stability testing showing acetaldehyde has no antioxidant effect, and (2) Plaintiffs' representation in this case that the identity of the antioxidant in Par's ANDA product would be revealed by testing taking "two to two and one-half months" (which they did not disclose in the litigation). DTX 568 at 11. Plaintiffs argue—with no evidentiary support—that Par's stability tests should be disregarded because the use of different batches of ingredients (as required by FDA) could have supposedly influenced the outcome. Plaintiffs' unsubstantiated argument fails, because Par used standard, FDA-sanctioned test conditions, including different batches of ingredients. *See* D.I. 414 at 14. The patent specification references "standard tests" and specifically identifies the conditions of the standard FDA-required tests Par ran.

None of Plaintiffs' witnesses testified that different forced degradation studies would be expected to give the same outcome, and it is difficult to reconcile Plaintiffs' position that minute variations in the different batches in Par's FDA manufacturing process would influence results, but a wholesale change in test conditions would not. Such a position would also not be credible in light of Plaintiffs' successful arguments on non-obviousness, that the compatibility of any excipient—including an antioxidant—with a given pharmaceutical formulation is unpredictable. D.I. 414 at 33. Even well-established antioxidants can increase oxidative degradation in some formulations, while reducing it or having no effect in others. D.I. 401 at II.A.3.a. Each of the numerous possible forced degradation tests represents a different set of conditions, and could give significantly different results, *i.e.*, whether a compound does or does not reduce oxidation. D.I. 401 at Section II.A.3.c; *Honeywell Int'l, Inc. v. ITC*, 341 F.3d 1332, 1339 (Fed. Cir. 2003)

(patent indefinite where choice of test was "critical to discerning whether a particular product… infringes"). Plaintiffs' citation to *Cadence Pharmaceuticals, Inc. v. Paddock Laboratories Inc.*, 886 F. Supp. 2d 445, 453 (D. Del. 2012), where multiple test methods led to results that did ***not*** vary significantly, is therefore inapposite.

In *Cadence*, the claims were directed to stable liquid formulations. The specification disclosed two methods for assessing stability: color change and HPLC. Both methods were well known in the art and had accepted industry standards. 886 F. Supp. 2d at 454. The district court found no evidence that these multiple methods for evaluating stability led to results that vary significantly; rather, the evidence indicated that a person of ordinary skill in the art would understand that there were multiple accepted methods to assess stability, each leading to measurable results. *Id.* at 453. In contrast, Dr. Davies' study is not an accepted method with accepted standards. And Dr. Davies' conclusion that acetaldehyde is an antioxidant is contradicted by the results from Par's standard stability testing. This is a "significant difference" causing reasonable uncertainty[2] in the scope of Claim 7.

B. The Full Scope of Claim 7 of the '031 Patent Is Not Enabled

Plaintiffs assert that the enablement requirement is met because the '031 patent enables at least one mode of making the claimed transdermal device. D.I. 409 at 8. But Plaintiffs never address whether the patent enables the ***full scope*** of the claim as they assert it, *i.e.*, whether it enables all of the antioxidants that would fall within the scope of the claim using any stress stability test, standard test, or ***any of the infinite variations of forced degradation studies that could be devised***. The limited examples in the '031 patent do not enable the full scope of

[2] Plaintiffs' reliance on *Alza Corp. v. Mylan Laboratories, Inc.*, 349 F. Supp. 2d 1002 (N.D. W. Va. 2004) is misplaced. D.I. 409 at 19-20. The district court in *Alza* expressly tied its finding of definiteness to the now-overruled "insolubly ambiguous" standard. *Nautilus*, 134 S.Ct. at 2124.

Plaintiffs' extreme interpretation of the claim.

1. Stabilization Is Required to Enable a Person of Ordinary Skill to Make and Use the Invention of Claim 7

Plaintiffs assert that stabilization is an "unclaimed feature" of Claim 7. D.I. 409 at 7. That assertion is irrelevant, because the specification must enable stabilization for the full claim scope using the claimed amount of antioxidant. While the term "antioxidant" itself does not require function under the Court's claim construction (D.I. 250), the prosecution history makes clear that the numerical range was added to Claims 1 and 7 to enable the amount of antioxidant to stabilize rivastigmine in the composition. DTX 249 at N1075, 1078. Plaintiffs' argument that stabilization does not apply to the "presence" claims (D.I. 409 at 2) is incorrect, because the applicants amended Claims 1 and 7 to overcome the enablement rejection. *Id.*

2. Plaintiffs' Single Successful Antioxidant Does Not Enable the Full Scope of Claim 7

A single embodiment ***may*** enable a claim, but only where disclosure of a single embodiment enables the full scope of the invention. *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). The stability data for tocopherol disclosed in the patent cannot plausibly be argued to enable the full scope of the invention as Plaintiffs have asserted it in this case. First, such a contention conflicts with Plaintiffs' successful non-obviousness positions, that a person of ordinary skill would not add an antioxidant unless necessary, because adding any excipient has an unpredictable effect. D.I. 414 at 33. Plaintiffs cannot now argue that any of the compounds that might produce a single "positive" result in a non-standard forced degradation study—but have never been shown to be an antioxidant in any pharmaceutical composition—can be used without undue experimentation to stabilize a rivastigmine patch. Further, the stability tests disclosed in the patent demonstrated that acetaldehyde does not reduce oxidative degradation. D.I. 403 at II.D.4. Therefore it is clear that

the single mode of making and using the invention described in the '031 patent does not enable the full scope of the claim.

Plaintiffs rely on *Takeda Pharmaceutical Co. v. Zydus Pharmaceuticals USA, Inc.*, 743 F.3d 1359 (Fed. Cir. 2014) for the proposition that the enablement requirement is met if the description enables *any* mode of making and using the invention. D.I. 409 at 8. But *Takeda* did not address ***full scope*** enablement. In *Takeda*, the claim at issue was directed to an orally disintegrable tablet comprising granules having an average particle diameter of 400 μm or less. The dispute centered around whether the patent disclosed a way to measure the claimed particle diameter. Zydus argued that a skilled artisan would not be able to determine the average particle diameter using the coulter counter method of measurement without undue experimentation. However, because the patent identified laser diffraction as a viable measurement technique, and there was no dispute that a skilled artisan would know how to use laser diffraction to measure particle diameter, the claim was not invalid for lack of enablement. 743 F.3d at 1369.

Plaintiffs do not address binding Federal Circuit case law that require that the specification "teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *See, e.g.*, *MagSil*, 687 F.3d at 1380. Plaintiffs have not shown that Claim 7 is enabled to the same extent that Plaintiffs extended the claim during their infringement analysis. *Acorda Therapeutics Inc. v. Apotex Inc.*, No. 07-4937 (GEB-MCA), 2011 WL 4074116, at *21 (D.N.J. Sept. 6, 2011), *aff'd*, 476 F. App'x 746 (Fed. Cir. 2012) ("A claim must be enabled to its full scope. This means that it needs to be enabled to the same extent that it is extended during the infringement analysis.").

In *Acorda Therapeutics*, the district court held that a single example disclosed in the patent was insufficient to enable the full scope of claimed multiparticulate compositions. *Id.* at

*25. Acorda sought a broad construction of "multiparticulate" to include a "plurality of discrete particles, pellets, mini-tablets, and mixtures or combinations thereof," so that it could argue that Apotex's formulation, a granulation, infringed the claim. But the patent specification disclosed only a single study on a bead formulation, and not any other kind of multiparticulate. *Id.* at *4. Because Acorda's infringement theory extended to ***all*** multiparticulates, including Apotex's granulation, the court looked to whether the full scope of multiparticulates was enabled.

The district court held that "the limited scope of the study supporting this invention, particularly in that it was only ever conducted with the bead formulation, and the extremely wide breadth of the claims… demonstrate that the invention was not enabled to its full scope." *Id.* at *20. The court found that the patent provided "very little guidance" based on one type of multiparticulate, which did not extend to other possible covered multiparticulates, and therefore the scope of the claims was not enabled. *Id.* at *22-25.

The analysis in *Acorda Therapeutics* applies here. Plaintiffs successfully pressed to have Claim 7 construed to include any "agent that reduces oxidative degradation," and then further asserted an extreme interpretation of that construction to mean any compound that lowers the oxidative degradation of any other compound, in any test, under any conditions. But Plaintiffs must then also show that the full scope of such supposed antioxidants is fully enabled. That broad scope is not reasonably supported by the scope of enablement in the specification. D.I. 401 at II.B. By extending the term "antioxidant" to include acetaldehyde, Plaintiffs have not enabled the full scope of antioxidants that are encompassed by Claim 7, a "problem of its own making." *MagSil*, 687 F.3d at 1384 (citing *Liebel–Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371, 1380 (Fed. Cir. 2007) ("The irony of this situation is that Liebel successfully pressed to have its claims include a jacketless system, but, having won that battle, it then had to show that

such a claim was fully enabled, a challenge it could not meet.")).

3. Plaintiffs' Fact Testimony Supports Non-Enablement

In response to Par's argument that the antioxidant ascorbyl palmitate failed, Plaintiffs assert that Par improperly incorporated a "commercial utility" limitation into Claim 7. D.I. 409 at 10. But Dr. Ogorka's cited testimony stated that ascorbyl palmitate was not suitable as an antioxidant for rivastigmine, and did not refer to commercial utility. Plaintiffs also assert that the testimony from Drs. Ogorka, Theobald, and Tiemessen was related to development work prior to the invention, and therefore does not take into account the teachings of the '031 patent. D.I. 409 at 12. But inventor Tiemessen, ***when looking at the patent specification***, could not conclude whether any of the antioxidants ***listed in the patent***, which Novartis never assessed, would work. Tr. 325:22-328:22 ("I think it have to be investigated" and "I have not seen these data"). Therefore, even after the disclosures of the '031 patent, it was unpredictable whether even established antioxidants would work with rivastigmine, and substantial experimentation was necessary. Tr. 548:3-529:22; 534:23-540:10 (Buckton). Going beyond established antioxidants (*i.e.*, discovering new antioxidants) plainly requires undue experimentation.

C. Claim 7 of the '031 Patent Fails To Meet The Written Description Requirement

Plaintiffs assert that the written description requirement is met because there is no requirement that the patentees actually reduce to practice all embodiments of the claim. D.I. 409 at 4. Plaintiffs further assert that the fact that acetaldehyde is not listed in the '031 patent "is irrelevant to the written description analysis." *Id.* at 6. But whether the patentees reduced to practice all embodiments, or specifically listed acetaldehyde, is not the issue. The specification does not convey that the patentees were in possession of antioxidants beyond the list in the '031 patent, much less myriad additional, undefined compounds that might be shown to affect

oxidation by conducting any non-standard test. D.I. 401 at II.C. Nowhere in the patent is there any disclosure or description of how to discover previously-unappreciated antioxidants for use in rivastigmine patches.

Plaintiffs' reliance on *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, 665 F.3d 1269 (Fed. Cir. 2012) is unfounded. In *Streck*, the issue was whether the patent sufficiently described the use of both "true" reticulocytes and reticulocyte analogs with the invention. Though the inventor had never attempted to use true reticulocytes, the court concluded that the patent provided written description of true reticulocytes because (1) the specification referred to true reticulocytes, and (2) the use of true reticulocytes was well-known in the prior art. *Id.* at 1287.

Here, the patent fails entirely to describe a scope of "antioxidant" that would encompass acetaldehyde. The '031 patent describes no antioxidants beyond those listed in column 4, even in general terms, and does not disclose the kind of methodology Dr. Davies used.[3] Nor is the use of acetaldehyde as an antioxidant, or Dr. Davies' methodology, known in the art.

III. CONCLUSION

For the reasons set forth herein and in Par's Opening Brief (D.I. 401), and based on the evidence presented at trial, Par requests that the Court find Claim 7 of the '031 patent invalid under 35 U.S.C. § 112.

[3] Plaintiffs assert that Dr. Davies' methodology is "generally referenced" in the '031 patent. D.I. 409 at 5. There is no such disclosure. *See* D.I. 401 at II.C.3.

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